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Proteinuria is Associated with Increased Risk of Fragility Fracture in Men With or at Risk for HIV infection:

Proteinuria and Fracture Risk Association

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Abstract

Background: Proteinuria has been associated with bone loss and fractures in general population but data in HIV-infected population is lacking.

Setting: Prospective, multicenter cohort study of men with or at risk for HIV infection.

Methods: Between 2006 and 2015, urine protein measurements and bone fracture histories were ascertained semi-annually in 947 HIV-infected (HIV+) and 969 HIV-uninfected (HIV-) men ≥ age 40. Proteinuria was defined as protein-to-creatinine ratio ≥ 200 mg/g at ≥ 2 consecutive visits. Outcome measures: 1) all fractures (excluding fractures of skull, face, digits) 2) fragility fractures (fractures of vertebral column, femur, wrist, humerus). Multivariable Cox proportional hazards models assessed the association between proteinuria and fracture after adjusting for additional risk factors.

Results: The overall period prevalence of proteinuria was higher among HIV+ than HIV- (29% vs 6%, $p<0.001$). Men with proteinuria had a significantly higher risk of fragility fracture compared to men without proteinuria (aHR=2.29 [1.12–4.66]), and did not differ by HIV-serostatus (p-interaction=0.83). The risk of all fractures was not statistically different between men with or without proteinuria (aHR=1.31 [0.84–2.05]). Among HIV+ men, the association between confirmed proteinuria and fragility fracture was attenuated (aHR=2.12 [0.95–4.73]) after additional adjustment for $CD4^+$ T cell count/mm^3, history of AIDS, the presence of detectable plasma HIV-1 RNA, and cumulative exposure to tenofovir disoproxil fumarate.

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Conclusion: Proteinuria was more common in HIV+ than HIV- men and was a strong independent risk factor for fragility fracture regardless of HIV serostatus. Proteinuria should prompt consideration of a thorough evaluation for bone disease among HIV+ persons.

Keywords

HIV; fracture; fragility fracture; proteinuria; protein-to-creatinine ratio

INTRODUCTION:

The risk of bone loss is greater in persons infected with HIV (HIV+) compared to those without HIV infection (HIV-) (1) and translates into a higher risk of fracture among people living with HIV (PLWH)(2–4). The etiology of metabolic bone disease in PLWH is multifactorial, with contributions from a high prevalence of traditional osteoporotic risk factors in this population, certain antiretroviral therapies, and the effects of chronic systemic inflammation.

Proteinuria has been associated with bone loss and increased risk of fracture in the general population (5–7) and among patients with diabetes (8), even after controlling for additional risk factors including kidney function. The mechanisms underlying this relationship are largely unknown and probably multifactorial. Albuminuria has been associated with endothelial dysfunction, reduced bone blood flow resulting in decreased bone remodeling and bone loss, as well as decreased bone quality via inflammation and oxidative stress (9–10). Additional factors frequently associated with albuminuria, such as hypertension (HTN) and use of anti-hypertensive medications (11–14), have also been linked to higher risk of fracture (15–16). While albuminuria (glomerular proteinuria) is a marker of glomerular disease, proteinuria includes both glomerular and tubular proteins and can be a marker of both tubulo-interstitial as well as glomerular disease, both prevalent in treated HIV+ individuals. Unlike most of the prior studies that used albumin-to-creatinine ratios, we defined proteinuria based on urine protein-to-creatinine ratios. Nevertheless, proteinuria has been previously shown as a reliable test for the presence of microalbuminuria (17). HIV infection is a known independent risk factor for excessive urinary protein loss in several studies (10,18–20). Whether proteinuria is associated with an increased risk of fracture in HIV+ individuals has not been studied and data from the general population may not permit extrapolation to PLWH, given the unique contributors to proteinuria in this population. We used prospectively collected data from the Multicenter AIDS Cohort Study (MACS) to assess the relationship between proteinuria and incident fracture in men with or at risk for HIV infection.

METHODS

Study population

The MACS is an ongoing, prospective multicenter cohort study of the natural and treated history of HIV infection in men. As of March 2015, 3,898 HIV+ and 3,439 HIV- men who have sex with men (MSM) had been enrolled [1984–1985 (N=4,954); 1987–1991 (N=668); 2001–2003 (N=1,350); 2010+ (N=365)] at four sites in U.S. (Baltimore, Maryland/

Washington, DC; Chicago, Illinois; Los Angeles, California and Pittsburgh, Pennsylvania). The MACS design and methods have been described previously (21–23). In brief, at each semiannual study visit, participants complete a standardized questionnaire soliciting information about their medical history, HIV treatment, behaviors, depression and daily activities; undergo physical examinations; and have blood and urine specimens collected for laboratory testing and storage (24). Study questionnaires are available at http://aidscohortstudy.org/. Informed consent was obtained from all participants. Study protocols were approved by the Institutional Review Boards at each study site.

Between October 2006 and March 2015, urine protein and creatinine levels were measured at semiannual study visits using a spot urine test (Quest Diagnostics). A urine protein-to-creatinine ratio (UPCR) was reported if both measurements were taken and values were above the assay-specific lower limit of detection (4 mg/dL for urine protein; 20 mg/dL for urine creatinine). Individuals ≥40 years old with ≥2 UPCR measurements and no self-reported fracture before the first available UPCR (defined as index visit) were included in the present study. We excluded HIV + participants who were naïve to antiretroviral therapy (ART) before March 2015.

Exposure definition

Proteinuria was defined as having a UPCR ≥200 mg/g and confirmed at the following visit. Participants were considered exposed from the first visit of the visit-pairs at which proteinuria was determined without regard for subsequent reversal of proteinuria status prior to the endpoint (last seen in the MACS before March 2015 or occurrence of fracture).

Outcome definition

From October 2001 onwards, self-reported bone-related diagnoses (including any new broken or fractured bones) in the preceding 6 months were collected at each study visit. In addition, retrospective data collection on self-reported history of fracture occurred at two study visits in 2010. The date of incident fracture was estimated as the midpoint between the dates of last report of no fracture and first report of fracture (if ascertained prospectively), or estimated using the self-reported age of incident fracture (if ascertained retrospectively). The occurrence and types of fracture were determined using The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. Similar to our previous analysis (25), in the present study, we examined two composite fracture outcomes: 1) all fractures, except for face, skull or digits (ICD-9: 805–815, 817–825, 827–829) and 2) fragility fractures, which includes fractures that occurred at vertebral column, wrist, femur and humerus ICD-9: 805, 812, 813, 814, 820, 821).

Covariate Definitions

Date of birth and race were collected at enrollment into the MACS. Time-varying covariates included self-reported cigarette smoking and alcohol use, body mass index (BMI), hepatitis C virus (HCV) infection, diabetes mellitus and HTN; all were assessed at 6-month intervals. Heavy drinking was defined as having ≥3 drinks per day more than once a month and lagged by one study visit to account for the effect of drinking cessation among sicker individuals. BMI was calculated as body weight (kg)/ height (m^2) and categorized into normal (<25

kg/m^2) and overweight/obese (≥25 kg/m^2). The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to estimate glomerular filtration rate (eGFR) from serum creatinine (26). HCV infection was determined by the presence of HCV RNA. Diabetes was defined as a fasting glucose ≥126 mg/dL or a self-reported or clinical history of diabetes with the receipt of diabetic medications. HTN was defined as a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg, or self-reported or clinical history of diagnosis with the receipt of anti-hypertensive medications. For HIV-infected participants, CD4$^+$ T lymphocyte cell count/mm^3(CD4) and plasma HIV-1 RNA concentrations were measured using standard assays.

Statistical Analyses

Descriptive statistics were summarized by HIV serostatus at the index visit (i.e. first UPCR measurement after age 40). Wilcoxon rank-sum test and Fisher's exact test were performed to compare the distributions of continuous and categorical variables, respectively. Survival analysis was carried out to determine the association between proteinuria and risk of fractures. We used age as the time scale and anchored the origin of analysis at age 40. Individuals with first UPCR measured after age 40 were treated as late entries and contributed to analysis time only after the first UPCR measurement. Individuals who remained fracture-free throughout the analytical period were censored at the time they were last seen in the MACS before March 31, 2015. Multivariable Cox proportional hazard models were used to assess the relationship between proteinuria and fracture outcomes. Potential risk factors considered in these models included HIV serostatus, age, race, BMI, hypertension, diabetes, hepatitis C virus infection, eGFR, current smoking and alcohol use. We also considered HIV-specific risk factors including recent CD4, recent, HIV-1 RNA level, clinical AIDS diagnosis and cumulative tenofovir disoproxil fumarate (TDF) use (per 1 year). The proportional hazards assumption was checked by graphical exploration of Schoenfeld residuals and assessed by incorporation of a time interaction term in models. A p-value <0.05 guided interpretation of statistical significance. Missing covariates data (22%) were multiply imputed using the Markov Chain Monte Carlo (MCMC) methods. Ten imputations were carried out for the entire study population and after stratification by HIV serostatus. All statistical analyses were performed using SAS version 9.4 (SAS Institute). Unadjusted Nelson-Aalen cumulative incidence curves were created using Stata/SE 13.1 (College Station, TX).

RESULTS

Participant Characteristics at Index Visit

The study population included 947 HIV+ men and 969 HIV- men (Table 1). At the index visit, the HIV+ men were younger (median age 49 versus 53 years old, p<0.001) and had lower BMI (median 25 versus 26 kg/m^{2,} p<0.001) and higher eGFR (median 92 in HIV+ versus 87 mL/min/1.73m^2 in controls, p<0.001). The two groups were similar with respect to presence of comorbidities such as diabetes and HTN, as well as moderate/heavy and binge alcohol consumption. A greater proportion of HIV+ men were non-white (45% versus 27%, p<0.001), HCV-infected (10% versus 5%, p<0.001) as well as current smokers (34% versus 22%, p<0.001). Median UPCR was higher in the HIV+ men (100 versus 70 mg/g

creatinine, p<0.001). Throughout the follow-up period, proteinuria was more common in HIV+ than in HIV- men (29% versus 6% in controls, p<0.001)

Among the HIV+ men, at the index visit, the median $CD4^+$ T cell count was 535 cells/μL, 68% had HIV-1 RNA < 50 copies/mL, 14% had AIDS before the index visit, and median cumulative TDF use was 1 year.

Crude incidence rates of all fractures and fragility fractures

The median (interquartile range [IQR]) follow-up time was 7.4 (3.9–8.0) years. The crude incidence rates per 1000-person years (IR/1000 PYR) of all fractures and fragility fractures by HIV serostatus and proteinuria are summarized in Table 2. Among the HIV- men, the incidence rates of all fractures were 14.4/1000 PYR among men without proteinuria and 14.4/1000 PYR among men with proteinuria. HIV+ men without proteinuria had an IR of all fractures of 14.8/1000 PYR, which increased to 23.4/1000 PYR in those with proteinuria. The incidence rates of fragility fractures were 4/1000 PYR and 9.6/1000 PYR among the HIV- men without and with proteinuria, respectively, and 4.2/1000 PYR and 10.2/1000 PYR among the HIV+ without and with proteinuria. For the outcomes of all fractures and fragility fractures, the log rank test indicates significantly different event curves based on proteinuria status (p=0.026 for all fractures and p=0.003 for fragility fractures) (Figure 1).

Associations between proteinuria and risk of all fractures

Table 3 displays the unadjusted [HR] and adjusted hazard ratios [aHR] of proteinuria and other covariates for all fractures. In the univariable model, proteinuria was associated with 1.53 (95% confidence interval [,]: [1.05, 2.24]) times increase in the risk of all factures. However, after adjusting for potential confounders including HTN, BMI and eGFR, this association was no longer statistically significant (aHR =1.31 [0.84,2.05]). BMI ≥ 25 kg/m^2 (aHR=0.67 [0.48, 0.95]) was protective against all fractures, whereas HTN was associated with a higher risk of all fractures (aHR=1.54 [1.10, 2.15]) (Table 3).

Associations between proteinuria and risk of fragility fracture

Table 4 shows the associations between proteinuria and the risk of fragility fracture. In the univariable model, proteinuria was associated with higher risk of fragility fractures (HR=2.43 [1.34, 4.39]) while HIV infection trended towards significance (HR=1.60 [0.92, 2.78]). BMI ≥ 25 kg/m^2 was protective against fragility fractures (HR=0.55 [0.31, 0.96]) (Table 4). After multivariable adjustments, proteinuria remained significantly associated with higher risk of fragility fractures (aHR=2.29 [1.12, 4.66]). None of the other variables included in the adjusted model were significantly associated with the risk of fragility fractures (Table 4).

Proteinuria and Fracture in HIV-infected Men

In analysis restricted to HIV-infected men, only HTN was associated with a higher risk of all fractures (aHR=1.68 [1.04, 2.70]), while the association between proteinuria and fragility fractures trended towards significance (aHR= 2.12 [0.95, 4.73]) (Table 1. Supplementary). A formal test of the interaction between HIV serostatus and proteinuria for the risk of fractures

was performed. P-values were not statistically significant for either type of fractures (0.56 for all fractures; 0.83 for fragility fractures).

DISCUSSION:

Similar to recently published data (20), in this cohort of MSM followed prospectively in the MACS, we found that proteinuria was more common among HIV+ men. Proteinuria was also associated with a significantly higher risk of fragility fracture, regardless of HIV serostatus and independent of confounders like GFR, HTN, diabetes or HCV infection. Qualitatively similar results were seen among HIV+ men, independent of TDF use and HIV disease severity. To our knowledge, this is the first study to find that proteinuria is a potent risk factor for fractures among HIV+ persons. Our findings highlight the importance of screening for bone loss in HIV+ adults with proteinuria.

Albuminuria has been associated with increased risk of fracture in several studies of diabetic and non-diabetic patients. In the Atherosclerosis Risk in Communities (ARIC) study, albuminuria was independently associated with fracture hospitalization (27). Doubling of albuminuria was associated with an increased risk of hip fracture in a cohort of 3110 adults from the Cardiovascular Health Study who were followed for up to 9.5 years, even after adjustment for osteoporosis-related factors, frailty, and falls. (28). In another study from the same group examining people at risk for cardiovascular disease, baseline albuminuria was associated with higher risk of pelvic and hip fractures (HR=2.01 [1.21–3.35]). In the adjusted model, the association was apparent for macroalbuminuria (HR=1.71 [1.007–2.91]), but not for microalbuminuria (HR=1.28 [0.92–1.78]) (29). Other studies have evaluated the association of both proteinuria and albuminuria with fracture risk. Several potential mechanisms for proteinuria's association with fracture risk have been proposed. Albuminuria is a marker of endothelial dysfunction and has been associated with diminished blood flow supply to the bone, which directly impairs bone remodeling, resulting in bone loss (9, 30). In a sub-cohort of 1208 participants from the Cardiovascular Health Study with available bone mineral density (BMD) measurements, increased urine albumin levels were associated with decreased hip BMD in men (27). Another hypothesis is that albuminuria is associated with impaired bone quality via inflammation and oxidative stress (31). In support of this theory are data from diabetic patients, who have a higher prevalence of proteinuria and in whom, despite higher BMD, increased rates of fractures are observed (32). More recently, albuminuria has been associated with elevation in parathyroid hormone (PTH) levels, independent of kidney function (33). High PTH levels are associated with higher risk of fracture in patients with primary hyperparathyroidism (34) and patients undergoing hemodialysis (35). The rise in PTH is generally preceded by increases in fibroblast growth factor 23 (FGF-23), a hormone associated with important roles in phosphorus homeostasis. Among PLWH who participated in the Mr Bean study, higher baseline FGF23 levels were associated with a higher risk of progressive albuminuria (36). Moreover, inflammation increases FGF23 levels (37).

In our unadjusted model, proteinuria was associated with higher risk of all fractures and fragility fractures. Adjustment for additional risk factors including HIV serostatus, HTN, and kidney function attenuated the association, which remained significant only for fragility

fractures. This suggests that the effect of proteinuria on fracture risk could be mediated through factors associated with skeletal fragility not measured in our population. Of note, BMD measurements were not collected for the entire MACS cohort, so whether low BMD partially explains the observed association between proteinuria and fragility fractures cannot be answered in our study. Moreover, the aHR for all fractures and fragility fractures among HIV+ participants was attenuated when proteinuria was added to the model (aHR decreased from 1.2 to 1.14 for all fractures and from 1.43 to 1.16 for fragility fractures) suggesting that the high risk of fragility fracture observed among HIV+ individuals could be partly explained by the high prevalence of proteinuria in this population.

We found no association between eGFR and risk of all fractures or fragility fractures. Previous studies have variably demonstrated an association between eGFR and risk of fracture. Some have reported a graded increase in fracture incidence with lower eGFR (38), while others found a higher risk of fracture only with moderate to severe chronic kidney disease (26, 39), and yet others reported no significant association (40). The lack of an association between eGFR and fractures in our study population may be explained by the small number of participants with moderate and severe kidney function impairment.

In the multivariable analysis, BMI ≥25 kg/m^2 and non-Caucasian race were protective against all fractures. An unexpected finding was the protective effect of moderate/heavy alcohol consumption on all fractures. We conducted additional data analysis by lagging the drinking variable by 1 study visit to account for the unexpected protective effect on fracture. We found that sicker individuals (with comorbidities like low eGFR, diabetes and hypertension) were more likely to quit drinking. The apparent protective effect of heavy drinking observed in our analysis may actually be reflective of a lower risk of fracture among individuals who were healthy enough to be drinking excessively.

Consistent with data from prior studies (41), the prevalence of proteinuria observed in our cohort was higher in men with HIV compared to men without HIV (29% versus 6%). See comment in PubMed Commons below HIV- related kidney disease is multifactorial, resulting from direct HIV infection and damage of the renal epithelial cells (41–42), ART-related renal tubular toxicity (43–45), comorbidities such as HCV (46), diabetes mellitus or HTN, as well as low CD4 (47). In the multivariable analysis restricted to HIV+ men, proteinuria was associated with higher risk of fragility fracture independent of other HIV-specific and non-specific risk factors such as HTN and eGFR. A higher risk of all fractures was significantly associated with HTN and low CD4. We found no associations between the incidence of all or fragility fractures and other factors such as HCV infection, TDF use, HIV-1 RNA level or history of an AIDS diagnosis. Variable associations between fracture risk and low CD4 cell count (45, 25) and HCV infection have been reported in previous studies (25, 48). TDF use has been associated with higher risk of proteinuria (20, 43, 47) and fractures in several studies (49), while others failed to demonstrate such associations (45, 25). Since the median TDF exposure at the index visit was only of 1 year we further examined the distribution of cumulative TDF use at visits after the index visit. At the last study follow-up visit, the median (IQR) TDF use was of 4.88 (1.58–8.02).

Our study has several strengths, including a large sample size, incidence of all fractures and fragility fractures as main outcomes, and data on several fracture risk factors. The MACS population includes HIV- men who have similar risk behaviors as HIV+ men and who were similarly followed semiannually, completed the same fracture questionnaires and whose data regarding HIV-specific risk factors collected at semiannual visits. We accounted for multiple urine protein and creatinine levels measured at semiannual study visits, and we used two sequential elevated UPCR measurements to define proteinuria.

We also recognize several limitations to our study. First, fractures were self-reported without confirmation by medical chart review or radiographic evaluation, although some studies suggest that fractures tend to be reliably self-reported by patients (50). We have no data on use of calcium and vitamin D supplementation, and we did not adjust for use of other drugs potentially affecting bone health, such as proton pump inhibitor use. Additionally, specific information regarding testosterone and glucocorticoid use was unavailable for the time period represented in this analysis but has been introduced in the MACS questionnaire only more recently. Finally, the MACS includes only men, therefore our findings cannot be generalized to women. Sex differences in BMD and fracture risk have been reported in some studies, while others reported similar results regardless of sex. In the Cardiovascular Health Study, albuminuria was associated with higher risk of hip fracture in women (HR= 1.12 [1.001–1.25]) but not in men (HR= 1.02 [0.89–1.17]) (28), and increased urine albumin-to-creatinine ratios were associated with non-vertebral fractures in women only (11). In a study of people at risk for cardiovascular disease, albuminuria was associated with higher risk of pelvic and hip fractures irrespective of sex (29).

In conclusion, proteinuria was more common among HIV+ men in the MACS, and was associated with a higher risk of fragility fracture independent of other risk factors, including HTN and kidney function. To our knowledge, this is the first study demonstrating the association between proteinuria and higher fracture risk in an HIV-infected population. These data highlight the importance of osteoporosis screening and treatment in PLWH with proteinuria. Further investigation is required to understand underlying mechanisms common to both processes, such as chronic inflammation or microvascular disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Conflicts of Interests and Source of Funding:

JEL has served as a consultant for Gilead Sciences, Merck, and GSK. TTB has served as a consultant to Gilead Sciences, ViiV Healthcare, Merck, Theratechnologies, EMD-Serono, and Bristol Myers Squibb. FJP has served as a consultant and on the Speakers Bureau for Gilead Sciences Janssen Pharmaceuticals, Merck and Co and Bristol Meyers Squibb. KNA has served as a consultant to TrioHealth.

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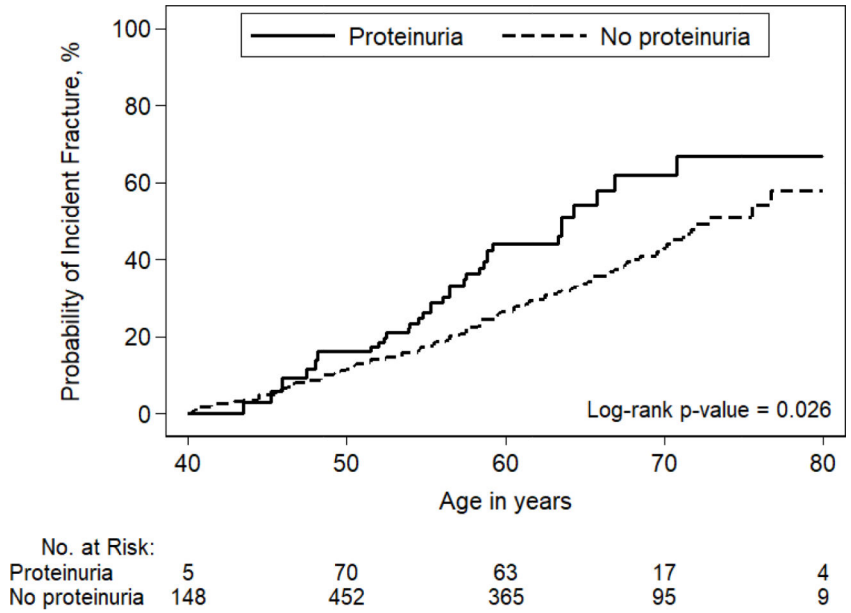
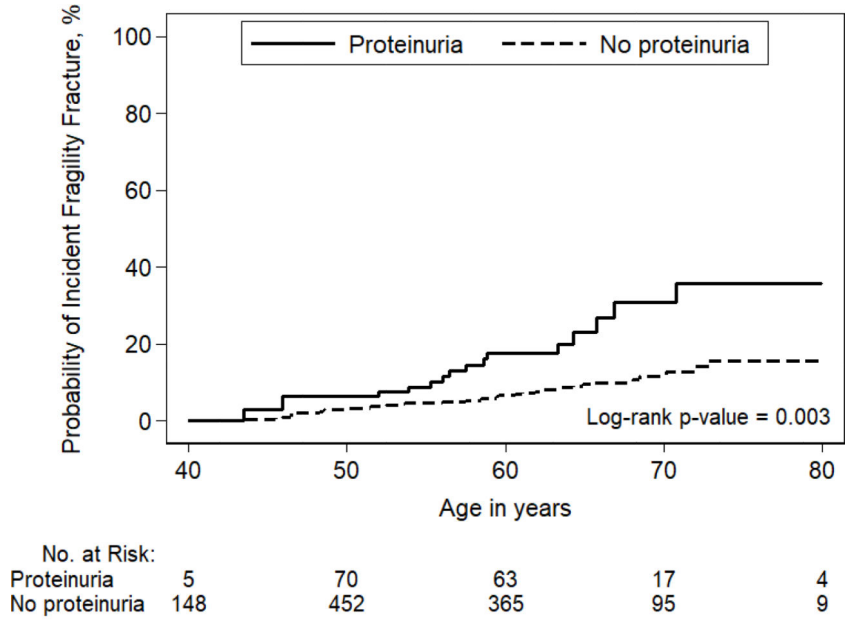


A.



B.

Figure 1: Cumulative incidence of fractures

Figure 1A. Cumulative incidence of all fractures

Figure 1B. Cumulative incidence of fragility fractures

Table 1.

Demographic and Clinical Characteristics at index visit

Characteristics* **at index visit median (IQR) year: 2007(2006–2007)**	**HIV-infected men (N=947)**	**HIV-uninfected men (N=969)**
Age, years	**49 (43–54)**	**53 (47–59)**
Caucasian	**55**	**73**
BMI, kg/m^2	**25 (23–28)**	**26 (24–30)**
Hypertension	40	43
Diabetes	12	10
HCV infection	**10**	**5**
eGFR, mL/min/1.73m^2	**92 (79–105)**	**87 (76–98)**
Current smoker	**34**	**22**
Moderate-heavy/Binge drinking (≥3 drinks/d, ≥1 month)†	19	22
Proteinuria		
UPCR, mg/g creatinine	**100 (70–160)**	**70 (53–90)**
Period prevalence of proteinuria (2 consecutive UPCR≥200 mg/g)	**29**	**6**
HIV-related characteristics		
AIDS ever before index visit	14	
CD4+ cell count, cells/uL	535 (359–721)	
HIV RNA level <50 copies/mL	68	
Cumulative TDF use, years	1 (0–3)	

All differences in characteristics by HIV serostatus were statistically significant (p<0.001) with the exception of hypertension (p=0.213), diabetes (p=0.268), and moderate-heavy/binge drinking (p=0.201).

*Showing median (IQR) and % for continuous and categorical variables, respectively

†Drinking variable was lagged by one study visit.

Abbreviations: HIV, human immunodeficiency virus; BMI, body mass index (calculated as weight in kilograms divided by height in square meters); eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus; AIDS, acquired immunodeficiency syndrome; TDF, tenofovir disoproxil fumarate; IQR, interquartile range.

Table 2.

Incidence rates (IR) of fractures by HIV status and proteinuria

	All Fractures	Person years	IR per 1000 person-years (95% CI)
HIV−, No proteinuria	83	5780	14.4 (11.6, 17.8)
HIV−, Proteinuria	3	208.9	14.4 (4.60, 44.5)
HIV+, No proteinuria	63	4265	14.8 (11.5, 18.9)
HIV+, Proteinuria	30	1279.9	23.4 (16.4, 33.5)
	Fragility Fractures	**Person years**	**IR per 1000 person-years (95% CI)**
HIV−, No proteinuria	23	5780	4.00 (2.60, 6.00)
HIV−, Proteinuria	2	208.9	9.60 (2.40, 38.3)
HIV+, No proteinuria	18	4265	4.20 (2.70, 6.70)
HIV+, Proteinuria	13	1279.9	10.2 (5.90, 17.5)

Abbreviations: CI, confidence interval.

Table 3.

Unadjusted and adjusted hazard ratios for all fractures

	HR (95% CI)	P-value	aHR (95% CI)
Proteinuria (2 UPCR ≥200 vs <200 mg/g)	**1.53 (1.05, 2.24)**	**0.028**	1.31 (0.84, 2.05)
HIV infection (vs. uninfected)	1.30 (0.96, 1.76)	0.09	1.14 (0.82, 1.58)
Non-Caucasian (vs. Caucasian)	0.84 (0.59, 1.19)	0.32	0.84 (0.58, 1.21)
BMI≥25 (vs, <25) kg/m^2	**0.69 (0.50, 0.97)**	**0.032**	**0.67 (0.48, 0.95)**
Hypertension (vs. none)	**1.45 (1.05, 1.99)**	**0.023**	**1.54 (1.10, 2.15)**
Diabetes (vs. none)	1.03 (0.63, 1.67)	0.91	0.93 (0.56, 1.54)
HCV infection (vs. uninfected)	0.66 (0.33, 1.30)	0.23	0.62 (0.30, 1.26)
eGFR<60 (vs. ≥60) mL/min/1.73 m^2	1.55 (0.95, 2.53)	0.08	1.23 (0.72, 2.09)
Current (vs. not current) smoker	1.02 (0.71, 1.46)	0.91	1.02 (0.70, 1.49)
Moderate-Heavy/Binge (vs. low or no binge) drinking	0.97 (0.66, 1.41)	0.87	0.94 (0.64, 1.38)

Bold indicates p<0.05.

Abbreviations: (a)HR, (adjusted) hazard ratio; CI, confidence interval; BMI, Body mass index; HCV, hepatitis C virus; eGFR, estimated glomerular filtration rate; UPCR, Urine protein-to-creatinine ratio.

Table 4.

Unadjusted and adjusted hazard ratios for fragility fractures

	HR (95% CI)	P-value	aHR (95% CI)
Proteinuria (2 UPCR ≥200 vs. <200 mg/g	**2.43 (1.34, 4.39)**	**0.003**	**2.29 (1.12, 4.66)**
HIV infection (vs. uninfected)	1.60 (0.92, 2.78)	0.09	1.16 (0.63, 2.13)
Non-Caucasian (vs. Caucasian)	1.22 (0.67, 2.22)	0.52	1.07 (0.56, 2.04)
BMI≥25 (vs. <25) kg/m2	**0.55 (0.31, 0.96)**	**0.035**	0.57 (0.32, 1.02)
Hypertension (vs none)	1.41 (0.76, 2.61)	0.28	1.54 (0.81, 2.96)
Diabetes (vs. none)	0.92 (0.35, 2.38)	0.86	0.72 (0.26, 2.02)
HCV infection (vs. uninfected)	1.38 (0.56, 3.44)	0.48	0.98 (0.37, 2.60)
eGFR<60 (vs. ≥ 60) mL/min/1.73 m^2	0.92 (0.33, 2.60)	0.88	0.55 (0.18, 1.63)
Current (vs. not current) smoker	1.49 (0.81, 2.72)	0.20	1.31 (0.69, 2.46)
Moderate-Heavy/Binge (vs. low or no binge) drinking	0.81 (0.40, 1.64)	0.56	0.75 (0.37, 1.54)

Bold indicates p<0.05. *Abbreviations*: (a)HR, (adjusted) hazard ratio; CI, confidence interval; BMI, Body mass index; HCV, hepatitis C virus; eGFR, estimated glomerular filtration rate; UPCR, Urine protein-to-creatinine ratio.