An Increased Rate of Fracture Occurs a Decade Earlier in HIV+ Compared to HIV- men in the Multicenter AIDS Cohort Study (MACS)

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Abstract

Objectives: To determine the incidence and age-related fracture risk among HIV-infected (HIV+) and uninfected men (HIV-). To evaluate factors independently associated with fracture risk.

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

Methods: Outcome measures: 1) all fractures (excluding skull, face, digits) and 2) fragility fractures (vertebral column, femur, wrist, humerus) were collected semiannually in 1221 HIV+ and 1408 HIV- men ≥ age 40. Adjusted incident rate ratios (aIRR) with an interaction term for age (40-49, 50-59, ≥60 years) and HIV serostatus were estimated with Poisson regression models accounting for additional risk factors.

Results: Fracture incidence increased with age among both HIV+ and HIV- men. While there was no significant difference in fracture incidence by HIV serostatus among men aged 40-49 years, the HIV+ men aged 50-59 years had a significantly higher incidence of all fractures (aIRR=2.06 [1.49, 2.84]) and fragility fractures (aIRR=2.06 [1.21, 3.50]) compared with HIV- participants of similar age. HIV modified the effect of age on all fractures (p=0.002) but did not significantly modify the effect for fragility fractures (p=0.135). Hypertension increased the rate of all fractures by 32% after adjustment for covariates (aIRR=1.32 [1.04, 1.69]).
Conclusions: Fracture incidence increased with age among HIV+ and HIV- men but was higher among HIV+ men. A significant increase in fracture incidence was found among 50-59-year-old HIV+ men, highlighting the importance of osteoporosis screening for HIV infected men above the age of 50.

Keywords: HIV, osteoporosis; fracture; antiretroviral therapy; fragility fracture
INTRODUCTION

Osteopenia and osteoporosis are more prevalent in HIV+ men and women compared with HIV- controls (1) and young HIV+ individuals are also at higher risk of bone loss (2,3,4). Low bone mineral density (BMD) translates into a higher risk of fracture (5,6) which is higher in HIV+ individuals. Triant et al. reported higher prevalence of vertebral, hip and wrist fractures in HIV+ men and higher prevalence of vertebral and wrist fractures in HIV+ women compared to HIV- controls (7). Higher rates of fracture in young HIV+ men have been previously reported (3,7) while studies in young HIV+ women have shown conflicting results (8,9). Among HIV+ patients, several risk factors have been associated with bone loss and higher incidence of fracture, including traditional risk factors such as age, sex, race, body mass index (BMI), smoking, alcohol and drug use (10,11), HIV-specific factors (3,12,13,14,15) and specific antiretroviral therapy (ART) agents, especially protease inhibitors (PI) and tenofovir disoproxil fumarate (TDF) containing combinations (15,16,17,18). Coinfection with hepatitis C virus (HCV) increased fracture risk in several reports (3), while others found no association (9).

Early screening for fracture risk in HIV+ individuals has been recommended (19, 20) but the exact age when screening should start remains controversial. There is still extensive variation in the approach to screening for osteoporosis in HIV+, not only in the USA but also worldwide (21).

In this study, we aimed to compare the incidence of fracture in HIV+ with HIV- men who participated in the Multicenter AIDS Cohort Study (MACS) and to determine the predictors of fracture. Our a priori hypothesis was that HIV modified the effect of age on fractures.
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 centers in U.S. (Baltimore, Maryland/Washington, DC; Chicago, Illinois; Los Angeles, California and Pittsburgh, Pennsylvania). MACS design and methods have been described previously (22-24). 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 (25). 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.

Self-reported fracture data were extracted from the MACS database using The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. At visit 36 (in 2001) and all subsequent visits, participants were asked if they had any bone-related diagnoses, including any new broken or fractured bones since the last visit. Additionally, in 2010 (visit 53 and 54), participants were asked retrospectively about personal history of fractures. A total of 2,283 men responded to the historical questions at visit 53 and 54; 1,935 men who were 40 years or older and had at least one follow-up visit were included. For men who did not respond to the historical questions, bone outcomes were ascertained in 1141 participants at and after visit 36. Of these, 865
men who were 40 years or older and had one additional visit were considered eligible for this study. The first MACS visit at which an individual came under observation for fracture outcomes was designated the index visit. HIV+ participants who never received ART before they were last seen in the MACS by March 2015 were excluded. The final study population included 2629 men.

**Outcome: Incident fracture**

In this study, we considered two self-reported fracture outcomes that occurred among men of 40 years and over: 1) all fractures except for those occurring at the face, skull or digits and 2) fragility fractures, defined as fractures at vertebral column, femur, wrist and humerus (26).

**Exposure of interest: Age and HIV**

Self-reported date of birth was obtained at enrollment into the MACS. HIV seropositivity was determined using an enzyme-linked immunosorbent assay (ELISA) confirmed by Western blot. Standardized tests were used for measuring CD4+ T lymphocyte counts (cells/microliter$^3$) (CD4+) and plasma HIV-1 RNA concentrations.

**Confounders:**

Race was obtained at enrollment into the MACS. Self-reported cigarette smoking and alcohol use, BMI, co-morbidities, T lymphocyte counts (cells/microliter$^3$)(CD4+) and plasma HIV-1 RNA concentrations were assessed at each semi-annual visit. Estimated glomerular filtration rate (eGFR) in mL/min/1.73m$^2$ was calculated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. HCV was determined by reactive HCV antibody or detectable plasma HCV
RNA levels. Diabetes mellitus was defined as a fasting glucose \( \geq 126 \text{ mg/dL} \) or a self-reported diabetes diagnosis with the use of glucose-lowering medications. High blood pressure was defined as systolic blood pressure \( \geq 140 \text{ mmHg} \), diastolic blood pressure \( \geq 90 \text{ mmHg} \), or self-reported diagnosis with use of anti-hypertensive medication. Viremia copy-years (VCY) was calculated as the area under the viral load curve from the index visit or the first available viral load after seroconversion, whichever occurred later, by applying the trapezoidal rule (27). Other HIV-specific factors that were considered include the history of AIDS diagnosis, any ART use, and cumulative use of TDF and PI per 5 years.

**Statistical analyses**

Demographic and clinical characteristics at the index visit were compared by HIV serostatus using Wilcoxon rank-sum test for continuous variables and Fisher’s exact test for categorical variables. Incident fracture was defined as the first self-reported fracture after age 40 while under observation for bone outcomes in the MACS. Individuals contributed person-time from the index visit to the time of incident fracture or the last time they were seen in MACS before March 31, 2015. Incidence rates (IR) were calculated as the number of new fractures (or fragility fractures) that occurred per 1000 person-years (PY). Crude (IRR) and adjusted (aIRR) incidence rate ratios and 95\% confidence intervals ([,]) were estimated with Poisson regression models. To test the *a priori* hypothesis, a nested models approach with a likelihood ratio tests to determine the better fit (the model with or without the interaction term) was used. The final model included a test for interaction between HIV serostatus and age and adjustment for
confounders: race, BMI, hypertension, diabetes, HCV, eGFR, smoking and alcohol use. We also explored the associations between fractures and HIV-related factors including CD4+ T-cell count and plasma HIV-1 RNA level at index visit, VCY, ART use (time updated), AIDS diagnosis prior to index visit, and cumulative use of TDF and PIs among the HIV-infected men. Missing predictor data were handled by multiple imputation using the Markov Chain Monte Carlo (MCMC) methods. Ten imputations were carried out for the entire study population and after stratification by HIV serostatus. A p-value <0.05 guided statistical interpretation. All statistical analyses were performed using SAS version 9.4. Plots were produced using R statistical software.

RESULTS

Participant Characteristics at Index Visit

The study population included 1221 HIV+ and 1408 HIV- men (Table 1). The two groups were similar with respect to age, BMI, eGFR and moderate/heavy alcohol consumption. The presence of comorbidities such as diabetes and hypertension was similar by HIV serostatus. A greater proportion of HIV+ than HIV- participants were non-white, HCV-infected as well as current smokers.

Among the HIV+ men at index visit, the median CD4 count was 490 cells/µL, median HIV-1 RNA level was 342 copies/mL and 10% had a clinical AIDS diagnosis prior to the index visit. At the last follow-up visit, 798 (61%) HIV-infected men were using TDF and the median (IQR) cumulative TDF use at last follow-up visit was 3.4 (0.3-7.2) years. The proportion of men using PI at the last follow-up visit was 44% (N=581); median cumulative PI use was 4.5 (IQR 0.3-9.4) years.
Incidence of all fractures

New fractures occurred in 379 patients during 33,957 PY with an IR=11.2 [10.1, 12.4] per 1000 PY. Of those, 182 fractures occurred in HIV+ (IR=12.8 [11.1, 14.8] per 1000 PY) and 197 in the HIV- (IR=10.0 [8.7, 11.5] per 1000 PY). The IRs of all fractures were similar among HIV- men aged 40-49 and 50-59 with an increase among those aged ≥ 60 years. Among HIV+, the increase in IRs was seen among men aged 50-59 and ≥ 60 years (Figure 1 and Table 1 (supplementary, http://links.lww.com/QAD/B83)).

Figure 2 and Table 2 (supplementary, http://links.lww.com/QAD/B83) are showing risk factors associated with increased fracture risk. Only hypertension remained significantly associated with increased risk of all fractures after multiple adjustments (aIRR=1.32 [1.04, 1.69]) (Figure 2 and Table 3 (supplementary, http://links.lww.com/QAD/B83)).

The test of interaction showed evidence that HIV modified the effect of age on fracture risk (p=0.002). There was a significant increase in the incidence of all fractures in the HIV- aged ≥ 60 (aIRR=1.51 [1.06, 2.16]) and in the HIV+ aged 50-59 (aIRR =1.92 [1.41, 2.61]) as compared to the HIV- aged 40-49 years. Neither the HIV- aged 50-59, nor the HIV+ aged 40-49 had a significantly different fracture risk compared to the reference group (HIV- aged 40-49 years). A higher incidence of all fractures was seen in the HIV+ aged ≥ 60 although with only marginal significance (aIRR=1.56 [0.98, 2.49]).

Comparisons by HIV serostatus within each age group revealed a higher incidence of all fractures in the HIV+ aged 50-59 years compared with HIV- of similar age (aIRR=2.06 [1.49, 2.84]). We found no significant difference in the incidence of all fractures by HIV
serostatus among men aged 40-49 years (aIRR=0.92 [0.65, 1.29]) or ≥ 60 years (aIRR=1.03 [0.65, 1.65]). Sensitivity analysis restricted to the group aged ≥ 60 revealed no significant difference in the incidence of all fractures by HIV serostatus among men aged 60-69 (aIRR=1.19 [0.72, 1.97]) or ≥ 70 years (aIRR=0.45 [0.10, 2.01]).

In analyses restricted to HIV+ there was a significantly higher rate of fractures in men aged 50-59 compared to 40-49 years (aIRR=1.66 [1.18, 2.34]). Receipt of ART was associated with an increased risk of fracture (aIRR=2.11 [1.22, 3.63]), whereas having BMI ≥ 25 kg/m^2 was protective (Table 2). When current HIV-1 RNA > 400 copies/mL was replaced by VCY in the multivariable model, higher VCY was associated with all fractures (IRR 1.14 per log10 increase in VCY (1.01, 1.30); p=0.042) (Table 4 supplementary, http://links.lww.com/QAD/B83). Neither cumulative TDF use, nor cumulative PI use was associated with a higher rate of all fractures (Table 2).

**Incidence of fragility fractures**

A total of 140 fragility fractures occurred during 36,050 PY (IR=3.9 [3.3, 4.6] per 1000 PY). Of those, 70 fractures occurred in HIV+ [IR=4.6 [3.6, 5.8] per 1000 PY) and 70 in the HIV- [IR=3.4 [2.7, 4.3] per 1000 PY). When stratified by age categories and HIV serostatus, the incidence rates of fragility fracture in HIV- were 2.9/1000 PY in both the 40-49 and 50-59 year old groups and 5.1/1000 PY in the group aged ≥ 60 years. Within HIV+ the incidence rate of fragility fracture increased from 2.6 to 6.3 and 7.6 per 1000 PY in those aged 40-49, 50-59 and ≥ 60 years respectively (Table 2 (supplementary, http://links.lww.com/QAD/B83) and Figure 1). There was no evidence of an interaction between HIV and age on fragility fracture (p=0.135).
The unadjusted risk of fragility fracture is shown in Table 3 (supplementary, http://links.lww.com/QAD/B83) and Figure 2. In the multivariate analysis, compared to HIV- aged 40-49 years, a higher rate of fracture was only seen in the HIV+ aged 50-59 (aIRR=2.1 [1.24, 3.55]) and ≥ 60 years (aIRR=2.51 [1.26, 5.01]). Comparisons by HIV-serostatus within each age group revealed a higher incidence of fragility fracture in HIV+ aged 50-59 years compared with HIV- of similar age (aIRR=2.06 [1.21, 3.50]). We found no significant difference in fragility fracture incidence by HIV serostatus within the groups aged 40-49 (aIRR=0.92 [0.51- 1.66]) or ≥ 60 years (aIRR=1.46 [0.74, 2.87]). In sensitivity analysis restricted to the older group aged ≥ 60 years, although the rate of fracture was two-fold higher in HIV+ versus HIV- men aged 60-69 years, the difference was not statistically significant (aIRR=2.01 [0.94- 4.31]).

In analyses of fragility fractures restricted to HIV+, there was a higher rate of fracture with increasing age (aIRR=1.85[1.04, 3.28] for the 50-59 yo and 2.08 [0.97, 4.48] for the ≥ 60 year old group respectively) when compared to the 40-49 year old group. Current ART used was associated with a higher risk of fracture, although this was marginally significant (aIRR=2.54 [0.97,6.61]) (Table 2). Neither HIV-1 RNA > 400 copies/mL nor VCY were associated with higher incidence of fragility fractures (Table 2 and Table 4 (supplementary, http://links.lww.com/QAD/B83)). Cumulative PI use and cumulative TDF use were not associated with incident fragility fracture.

DISCUSSION:

In this cohort of MSM we found that the fracture incidence increased with older age among both the HIV+ and HIV- participants, however, the fracture rate was higher in
HIV+ aged 50-59 compared to HIV- men of the same age. Our findings support the Infectious Diseases Society of America (19) and the European AIDS Clinical Society guidelines, reinforcing the importance of baseline bone densitometry (DXA) screening for osteoporosis in HIV-infected men aged 50 and above.

Fracture rates are higher among HIV+ compared to HIV- persons and increase proportionally with advancing age (28). Among HIV+ persons in the HIV Outpatient Study (HOPS), age > 47 years was associated with increased fracture risk even after adjusting for multiple factors (HR 1.43 per 10 years for fragility fractures) (3). In a population-based retrospective cohort study conducted in Spain, age stratified analyses demonstrated significant associations between HIV infection and fractures only in the HIV+ participants aged 59 years and above (29). In the Veterans Aging Cohort Study Virtual Cohort (VACS-VC) there was a significant increase in the risk of fragility fracture with advancing age (HR 1.52 per 10 year increments) even after adjustment for multiple factors (11). In our analysis, we found an increase in the incidence of all fractures and fragility fractures among HIV+ men starting at age 50. The fracture incidence rates we observed in MACS are somewhat different from those reported by others. In the Danish population, Hansen at al reported a fracture incidence of 21 per 1000 PY in the HIV+ and 13.5 per 1000 PY in the HIV-. The incidence of fragility fracture among male veterans from VACS-VC was slightly lower, with 2.5 per 1000 PY for HIV+ and 1.9 per 1000 PY for HIV- persons. It is possible that our study population is unique in several aspects. Additionally, the HIV- comparison group in the MACS are drawn from a population of MSM with very similar underlying risk factors to the HIV+ men, which is a major strength of our study.
Amongst several risk factors investigated, we found that hypertension was an independent predictor of all fractures with similar trends for the outcome of fragility fracture. Although data are sparse, there is some clinical evidence, mainly from observational studies, supporting an increased fracture risk in hypertensive people. While some studies found only an increased risk of vertebral fractures in hypertensive patients (30), others demonstrated a higher risk of any fracture (31). An observational cohort study of Australians aged 50 years and above, found hypertension to be associated with an increased risk of fragility fractures in women but not in men (32). While the exact underlying mechanism remains uncertain, several potential explanations for the effect of hypertension on fracture risk exist. High blood pressure has been associated with increased urinary calcium loss, secondary hyperparathyroidism and loss of calcium from bone (33). In addition, hypertensive patients tend to be older and more prone to falls (34). Furthermore, antihypertensive medications, apart from increasing the risk of fall injuries by causing or worsening orthostatic hypotension (35), may also exert direct effects on bone (36). Data on falls, frailty and markers of calcium metabolism were not available for the entire period covered by this analysis, therefore we could not assess potential mechanisms for the observed hypertension/fracture association.

Low eGFR has been associated with increased fracture risk (37). In our study, eGFR was no longer associated with fractures after adjusting for age, BMI and hypertension. This finding suggests that the association of eGFR and fracture may be due to other confounders or that the lack of an association was due to the small number of participants with moderate and severe kidney impairment in our study population. Several studies
evaluating the association between chronic kidney disease (CKD) and fractures have reported increased fracture risk only with moderate to severe CKD (38).

We found no associations between the incidence of fractures and other factors like BMI, race, current smoking, moderate-heavy or binge alcohol consumption, diabetes or HCV. Several studies have reported significantly higher rates of fractures in patients with HIV and HCV co-infection compared to those with HIV mono-infection (3,39), while others have not reproduced this finding (9). HCV has been shown to be a marker of intravenous drug use (40) and the higher risk of fracture in HIV-HCV co-infected patients has thus been attributed to direct consequences of drug use such as higher risk of trauma, falls and nutritional deficiencies (17). The small percentage of MACS participants reporting use of intravenous drugs (2%) might explain why no association was detected in our analysis.

The role of HIV specific factors in fracture risk remains uncertain. While no association with ART exposure have been reported in several studies (3,9), others found higher rates of fractures associated with ART exposure (11,17). Using data from the ACTG Longitudinal-Linked Randomized Trial (ALLRT), Yin et al. found a significantly higher fracture rate in the first 2 years after ART initiation that declined in subsequent years (41). We found that current ART use was associated with an increased risk of fracture. These findings are consistent with results from the Strategies for Management of Antiretroviral Therapy (SMART) sub-study in which continuous administration of ART results in losses in BMD, whereas ART interruption was associated with BMD stabilization or increases (16). Taken together these findings suggest that ART treatment, regardless of the ART regimens used has detrimental effects on bone health.
Specific ART medications, including TDF and PIs have been associated with loss of BMD and increased fracture risk in some (11,18) (42), but not all studies (9). In our multivariate analysis, neither cumulative PI use, nor TDF was associated with increased incidence of all or fragility fractures, although our study was not specifically designed to assess effects of specific medications, in that the relatively small number of events may have limited the statistical power to detect associations.

We found no associations between CD4+ T-cell count and history of AIDS with fracture risk. While some studies have reported increased fracture rates in individuals with low CD4+ T-cell count (3) and a history of AIDS-defining illness, others have not (17, 42). We did, however, find an association between cumulative viremia and fracture independent of receiving ART. This finding suggests that the legacy of poorly controlled HIV infection in the past may have important future clinical consequences with respect to fracture risk and that patients who have a long history of uncontrolled viremia may benefit from more aggressive osteoporosis screening and treatment.

Our study has several strengths including a relatively large sample size, incidence of all fractures and fragility fractures as main outcomes and data on several fracture risk factors. Additionally, the MACS includes HIV- men with similar risk behaviors as the HIV+ and regardless of HIV serostatus, men were followed semiannually and completed the same fracture questionnaires. We performed risk analyses stratified by age and HIV serostatus allowing us to demonstrate age strata specific increases in fracture rates. Furthermore, data on HIV specific risk factors were collected at semiannual visits.

We also recognize several limitations. Fractures were self-reported without confirmation by medical chart review or radiographic evaluation although fractures are adverse events
that patients tend to remember and reliably self-report (43). We were not able to
determine specifically whether fractures occurred in the setting of major trauma, which
might have resulted in the overestimation of fragility fractures. Additionally, since
histories of fractures were retrospectively collected through questionnaires, recollection
bias might be an important limitation. Furthermore, we have no data on calcium and
vitamin D supplementation and we did not account for drugs that may have an impact on
bone health, such as the proton pump inhibitors. Specific information on testosterone and
glucocorticoid use was introduced in the MACS questionnaire only recently. Missing
data was an issue particularly for variables only later routinely collected in the MACS but
we addressed this limitation by using multiple imputation analysis to fill in missing
covariates data.

In conclusion, we found that HIV+ MACS participants had higher incidence of all
fractures and fragility fractures compared to the HIV- controls and that the rate of
fracture was higher among the HIV+ men aged 50-59 years compared with HIV-
participants of similar age. Our findings support the current available guidelines
recommendating baseline DXA screening for HIV+ men starting at age 50. Hypertension
remained consistently associated with higher incidence of all fractures even after
adjustment for additional fracture risks. To our knowledge, this is the first report in which
an association between hypertension and increased fracture incidence among HIV+
persons has been noted. The exact mechanism underlying the association between BMD,
fracture, hypertension and antihypertensive agents remains largely unknown and warrants
further exploration.
References


Conflicts of Interest:

JEL has served as a consultant for Gilead Sciences and GSK. TTB has served as a consultant to Gilead Sciences, 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 for Gilead Sciences, Inc.

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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 (NIH), Johns Hopkins ICTR, or NCATS. The MACS website is located at http://aidscohortstudy.org/.

**Table 1.** Demographic and Clinical Characteristics at index visit
<table>
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<tr>
<th>Demographics</th>
<th>HIV-infected men (N=1221)</th>
<th>HIV-uninfected men (N=1408)</th>
<th>P-value</th>
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<td>Age, median (IQR)</td>
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<td>40 (40-45)</td>
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<td>Race, n (%)</td>
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<td>White</td>
<td>718 (59)</td>
<td>1023 (73)</td>
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<td>Black</td>
<td>326 (27)</td>
<td>285 (20)</td>
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<tr>
<td>Hispanic/other</td>
<td>177 (14)</td>
<td>100 (7)</td>
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<td>Center, n (%)</td>
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<tr>
<td>Baltimore</td>
<td>299 (25)</td>
<td>371 (26)</td>
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<td>Chicago</td>
<td>276 (23)</td>
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<td>Pittsburgh</td>
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<td>Los Angeles</td>
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<td>BMI, kg/m², median (IQR)</td>
<td>25 (23-28)</td>
<td>25 (23-27)</td>
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<th>Medical history</th>
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<th>HIV-uninfected men (N=1408)</th>
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<tr>
<td>Hypertension, n (%)</td>
<td>319 (31)</td>
<td>352 (32)</td>
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<td>Diabetes, n (%)</td>
<td>56 (9)</td>
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<td>HCV infection, n (%)</td>
<td>110 (10)</td>
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<td>eGFR, mL/min/1.73m², median (IQR)</td>
<td>102 (87-109)</td>
<td>99 (87-109)</td>
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<td>Current smoker, n (%)</td>
<td>454 (38)</td>
<td>431 (31)</td>
<td>&lt;0.001</td>
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<tr>
<td>Moderate-heavy/Binge drinking (≥3 drinks/d, ≥1 month), n (%)</td>
<td>350 (29)</td>
<td>439 (32)</td>
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<th>HIV-uninfected men (N=1408)</th>
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<tr>
<td>AIDS ever before index visit, n (%)</td>
<td>124 (10)</td>
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<tr>
<td>CD4 T cell count, cells/uL, median (IQR)</td>
<td>490 (319-704)</td>
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<td>Viral load, copies/mL, median (IQR)</td>
<td>342 (40-14722)</td>
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<td>ART use, n (%)</td>
<td>666 (55)</td>
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<tr>
<td>Cumulative TDF use, years, median (IQR)</td>
<td>0 (0-0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative PI use, years, median (IQR)</td>
<td>0 (0-3)</td>
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</tbody>
</table>

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; PI, protease inhibitors (PI); IQR, interquartile range.
Table 2. Adjusted Incidence Rate Ratio of all fractures and fragility fractures in the HIV-

<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>1</td>
<td>1.66</td>
<td>1.85</td>
<td>1.04</td>
<td>3.28</td>
<td>0.037</td>
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<tr>
<td>Non-Caucasian</td>
<td>0.76</td>
<td>0.53</td>
<td>1.08</td>
<td>0.127</td>
<td>0.83</td>
<td>0.46</td>
<td>1.47</td>
<td>0.513</td>
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<tr>
<td>BMI ≥ 25</td>
<td>0.71</td>
<td>0.51</td>
<td>0.99</td>
<td>0.046</td>
<td>0.72</td>
<td>0.41</td>
<td>1.26</td>
<td>0.251</td>
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</tr>
<tr>
<td>Hypertension</td>
<td>1.34</td>
<td>0.97</td>
<td>1.87</td>
<td>0.079</td>
<td>1.03</td>
<td>0.57</td>
<td>1.84</td>
<td>0.931</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.76</td>
<td>0.42</td>
<td>1.36</td>
<td>0.343</td>
<td>0.6</td>
<td>0.2</td>
<td>1.79</td>
<td>0.353</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>0.81</td>
<td>0.42</td>
<td>1.57</td>
<td>0.531</td>
<td>1.48</td>
<td>0.61</td>
<td>3.63</td>
<td>0.386</td>
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<tr>
<td>eGFR &lt; 60</td>
<td>1.48</td>
<td>0.87</td>
<td>2.52</td>
<td>0.142</td>
<td>0.8</td>
<td>0.29</td>
<td>2.2</td>
<td>0.665</td>
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<tr>
<td>Current smoking</td>
<td>0.98</td>
<td>0.69</td>
<td>1.4</td>
<td>0.929</td>
<td>1.05</td>
<td>0.6</td>
<td>1.85</td>
<td>0.857</td>
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<tr>
<td>Moderate-Heavy/Binge drinking</td>
<td>1.18</td>
<td>0.81</td>
<td>1.7</td>
<td>0.387</td>
<td>0.66</td>
<td>0.32</td>
<td>1.36</td>
<td>0.258</td>
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<tr>
<td>CD4+ &lt; 500 cells/uL</td>
<td>1.22</td>
<td>0.88</td>
<td>1.69</td>
<td>0.233</td>
<td>0.94</td>
<td>0.54</td>
<td>1.65</td>
<td>0.834</td>
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<td></td>
</tr>
<tr>
<td>Viral load ≥ 400 copies/mL</td>
<td>0.73</td>
<td>0.45</td>
<td>1.17</td>
<td>0.19</td>
<td>0.76</td>
<td>0.35</td>
<td>1.68</td>
<td>0.499</td>
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</tr>
<tr>
<td>History of AIDS</td>
<td>1.04</td>
<td>0.71</td>
<td>1.53</td>
<td>0.831</td>
<td>1.3</td>
<td>0.73</td>
<td>2.34</td>
<td>0.375</td>
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<tr>
<td>Cumulative TDF/5 years</td>
<td>1.11</td>
<td>0.86</td>
<td>1.45</td>
<td>0.422</td>
<td>0.95</td>
<td>0.62</td>
<td>1.44</td>
<td>0.793</td>
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</tr>
<tr>
<td>Cumulative PI/5 years</td>
<td>1.14</td>
<td>0.95</td>
<td>1.38</td>
<td>0.171</td>
<td>1.25</td>
<td>0.94</td>
<td>1.67</td>
<td>0.131</td>
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</tr>
<tr>
<td>Current ART use</td>
<td>2.11</td>
<td>1.22</td>
<td>3.63</td>
<td>0.007</td>
<td>2.54</td>
<td>0.97</td>
<td>6.61</td>
<td>0.057</td>
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</table>
infected men.

Adjusted Incidence Rate Ratio of all fractures and osteoporotic fractures in the HIV-infected cohort was estimated using Poisson regression model adjusting for age, BMI, race, eGFR, hypertension, diabetes, HCV-infection, tobacco smoking, alcohol use, CD4 count, viral load, AIDS history, 5 year cumulative TDF and PI use. Multiple imputation was carried out to fill in missing covariates.
Figure 1. Incidence rates of all fractures and osteoporotic fractures

Incidence rates of all fractures (left side) and fragility fractures (right side) stratified by HIV status and age categories (40-49, 50-59, ≥ 60)
Figure 2. Unadjusted and adjusted IRR of all fractures and osteoporotic fractures

Unadjusted and adjusted Incidence Rate Ratio (IRR) of all fractures (left side) and fragility fractures (right side) by age categories and HIV status, race, BMI, hypertension, diabetes mellitus, hepatitis C co-infection, eGFR, current smoking status and moderate-heavy/binge alcohol consumption. Poisson regression models were used for calculation and multiple imputation was carried out to fill in missing covariates data. The p-value for interaction between HIV serostatus and age for all fractures was 0.002, and for osteoporotic fractures 0.135.