AIDS

DOI: 10.1097/QAD.0000000000001493

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

Anda Gonciulea[a], Ruibin Wang[b], Keri N Althoff[b], Frank J Palella[c], Jordan Lake[d], Lawrence A Kingsley[e], Todd T Brown[a]

[a]Johns Hopkins University School of Medicine, Baltimore, MD [b]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, [c]Northwestern University Feinberg School of Medicine, Chicago, Il, [d]University of California Los Angeles, Los Angeles, CA, [e]University of Pittsburgh School of Public Health, Pittsburgh, PA

Author responsible for correspondence and to whom requests for reprints should be addressed: Todd Brown MD, PhD 1830 East Monument Street, Suite 333, Baltimore, Maryland 21287, Phone: 410-502-2327 Fax: 410-367-4114, e-mail: tbrown27@jhmi.edu

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 is 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 ≥126 mg/dL or a self-reported diabetes diagnosis with the use of glucose-lowering medications. High blood pressure was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 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 recommending 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

1. Brown TT, Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. AIDS. 2006 Nov 14;20(17):2165-74.

2. Mulligan K, Harris DR, Emmanuel P, Fielding RA, Worrell C, Kapogiannis BG, et al. Low bone mass in behaviorally HIV-infected young men on antiretroviral therapy: Adolescent Trials Network Study 021B. Clin Infect Dis. 2012 Aug;55(3):461-8.

3. Young B, Dao CN, Buchacz K, Baker R, Brooks JT, HIV Outpatient Study (HOPS) Investigators. Increased rates of bone fracture among HIV-infected persons in the HIV Outpatient Study (HOPS) compared with the US general population, 2000-2006. Clin Infect Dis. 2011 Apr 15;52(8):1061-8.

4. Battalora L, Buchacz K, Armon C, Overton ET, Hammer J, Patel P, et al. Low bone mineral density and risk of incident fracture in HIV-infected adults. Antivir Ther. 2016;21(1):45-54.

5. Arnsten JH, Freeman R, Howard AA, Floris-Moore M, Lo Y, Klein RS. Decreased bone mineral density and increased fracture risk in aging men with or at risk for HIV infection. AIDS. 2007 Mar 12;21(5):617-23.

6. McComsey GA, Huang JS, Woolley IJ, Young B, Sax PE, Gerber M, et al. Fragility fractures in HIV-infected patients: need for better understanding of diagnosis and management. J Int Assoc Physicians AIDS Care (Chic). 2004 Jul-Sep;3(3):86-91.

7. Triant VA, Brown TT, Lee H, Grinspoon SK. Fracture prevalence among human immunodeficiency virus (HIV)-infected versus non-HIV-infected patients in a large U.S. healthcare system. J Clin Endocrinol Metab. 2008 Sep;93(9):3499-504.

8. Yin MT, Shi Q, Hoover DR, Anastos K, Sharma A, Young M, et al. Fracture incidence in HIV-infected women: results from the Women's Interagency HIV Study. AIDS. 2010 Nov 13;24(17):2679-86.

9. Sharma A, Shi Q, Hoover DR, Anastos K, Tien PC, Young MA, et al. Increased Fracture Incidence in Middle-Aged HIV-Infected and HIV-Uninfected Women: Updated Results From the Women's Interagency HIV Study. J Acquir Immune Defic Syndr. 2015 Sep 1;70(1):54-61.

10. Brown TT, McComsey GA. Osteopenia and osteoporosis in patients with HIV: a review of current concepts. Curr Infect Dis Rep. 2006 Mar;8(2):162-70.

11. Womack JA, Goulet JL, Gibert C, Brandt C, Chang CC, Gulanski B, et al. Increased risk of fragility fractures among HIV infected compared to uninfected male veterans. PLoS One. 2011 Feb 16;6(2):e17217.

12. Yong MK, Elliott JH, Woolley IJ, Hoy JF. Low CD4 count is associated with an increased risk of fragility fracture in HIV-infected patients. J Acquir Immune Defic Syndr. 2011 Jul 1;57(3):205-10.

13. Grijsen ML, Vrouenraets SM, Steingrover R, Lips P, Reiss P, Wit FW, et al. High prevalence of reduced bone mineral density in primary HIV-1-infected men. AIDS. 2010 Sep 10;24(14):2233-8.

14. Cotter EJ, Malizia AP, Chew N, Powderly WG, Doran PP. HIV proteins regulate bone marker secretion and transcription factor activity in cultured human osteoblasts with consequent potential implications for osteoblast function and development. AIDS Res Hum Retroviruses. 2007 Dec;23(12):1521-30.

15. Brown TT, McComsey GA, King MS, Qaqish RB, Bernstein BM, da Silva BA. Loss of bone mineral density after antiretroviral therapy initiation, independent of antiretroviral regimen. J Acquir Immune Defic Syndr. 2009 Aug 15;51(5):554-61.

16. Grund B, Peng G, Gibert CL, Hoy JF, Isaksson RL, Shlay JC, et al. Continuous antiretroviral therapy decreases bone mineral density. AIDS. 2009 Jul 31;23(12):1519-29.

17. Hansen AB, Gerstoft J, Kronborg G, Larsen CS, Pedersen C, Pedersen G, et al. Incidence of low and high-energy fractures in persons with and without HIV infection: a Danish population-based cohort study. AIDS. 2012 Jan 28;26(3):285-93.

18. Bedimo R, Maalouf NM, Zhang S, Drechsler H, Tebas P. Osteoporotic fracture risk associated with cumulative exposure to tenofovir and other antiretroviral agents. AIDS. 2012 Apr 24;26(7):825-31.

19. Aberg JA, Gallant JE, Ghanem KG, Emmanuel P, Zingman BS, Horberg MA, et al. Primary care guidelines for the management of persons infected with HIV: 2013 update

by the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis. 2014 Jan;58(1):1-10.

20. McComsey GA, Tebas P, Shane E, Yin MT, Overton ET, Huang JS, et al. Bone disease in HIV infection: a practical review and recommendations for HIV care providers. Clin Infect Dis. 2010 Oct 15;51(8):937-46.

21. Alvarez E, Belloso WH, Boyd MA, Inkaya AC, Hsieh E, Kambugu A, et al. Which HIV patients should be screened for osteoporosis: an international perspective. Curr Opin HIV AIDS. 2016 Feb 18.

22. Detels R, Jacobson L, Margolick J, Martinez-Maza O, Munoz A, Phair J, et al. The multicenter AIDS Cohort Study, 1983 to ... Public Health. 2012 Mar;126(3):196-8.

23. Dudley J, Jin S, Hoover D, Metz S, Thackeray R, Chmiel J. The Multicenter AIDS Cohort Study: retention after 9 1/2 years. Am J Epidemiol. 1995 Aug 1;142(3):323-30.

24. Kaslow RA, Ostrow DG, Detels R, Phair JP, Polk BF, Rinaldo CR,Jr. The Multicenter AIDS Cohort Study: rationale, organization, and selected characteristics of the participants. Am J Epidemiol. 1987 Aug;126(2):310-8.

25. Jacobson LP, Phair JP, Yamashita TE. Update on the Virologic and Immunologic Response to Highly Active Antiretroviral Therapy. Curr Infect Dis Rep. 2004 Aug;6(4):325-32.

26. Gazzola L, Comi L, Savoldi A, Tagliabue L, Del Sole A, Pietrogrande L, et al. Use of the FRAX equation as first-line screening of bone metabolism alteration in the HIV-infected population. J Infect Dis. 2010 Jul 15;202(2):330,1; author reply 331-2.

27. Mugavero MJ, Napravnik S, Cole SR, Eron JJ, Lau B, Crane HM, et al. Viremia copy-years predicts mortality among treatment-naive HIV-infected patients initiating antiretroviral therapy. Clin Infect Dis. 2011;53(9):927-35.

28. Shiau S, Broun EC, Arpadi SM, Yin MT. Incident fractures in HIV-infected individuals: a systematic review and meta-analysis. AIDS. 2013 Jul 31;27(12):1949-57.

29. Guerri-Fernandez R, Vestergaard P, Carbonell C, Knobel H, Aviles FF, Castro AS, et al. HIV infection is strongly associated with hip fracture risk, independently of age, gender, and comorbidities: a population-based cohort study. J Bone Miner Res. 2013 Jun;28(6):1259-63.

30. Wada H, Hirano F, Kuroda T, Shiraki M. Breast arterial calcification and hypertension associated with vertebral fracture. Geriatr Gerontol Int. 2012 Apr;12(2):330-5.

31. Vestergaard P, Rejnmark L, Mosekilde L. Hypertension is a risk factor for fractures. Calcif Tissue Int. 2009 Feb;84(2):103-11.

32. Yang S, Nguyen ND, Center JR, Eisman JA, Nguyen TV. Association between hypertension and fragility fracture: a longitudinal study. Osteoporos Int. 2014 Jan;25(1):97-103.

33. McCarron DA, Pingree PA, Rubin RJ, Gaucher SM, Molitch M, Krutzik S. Enhanced parathyroid function in essential hypertension: a homeostatic response to a urinary calcium leak. Hypertension. 1980 Mar-Apr;2(2):162-8.

34. Bergland A, Jarnlo GB, Laake K. Predictors of falls in the elderly by location. Aging Clin Exp Res. 2003 Feb;15(1):43-50.

35. Tinetti ME, McAvay GJ, Fried TR, Allore HG, Salmon JC, Foody JM, et al. Health outcome priorities among competing cardiovascular, fall injury, and medication-related symptom outcomes. J Am Geriatr Soc. 2008 Aug;56(8):1409-16.

36. Ghosh M, Majumdar SR. Antihypertensive medications, bone mineral density, and fractures: a review of old cardiac drugs that provides new insights into osteoporosis. Endocrine. 2014 Aug;46(3):397-405.

37. Fried LF, Biggs ML, Shlipak MG, Seliger S, Kestenbaum B, Stehman-Breen C, et al. Association of kidney function with incident hip fracture in older adults. J Am Soc Nephrol. 2007 Jan;18(1):282-6.

38. Dooley AC, Weiss NS, Kestenbaum B. Increased risk of hip fracture among men with CKD. Am J Kidney Dis. 2008 Jan;51(1):38-44.

39. Dong HV, Cortes YI, Shiau S, Yin MT. Osteoporosis and fractures in HIV/hepatitis C virus coinfection: a systematic review and meta-analysis. AIDS. 2014 Sep 10;28(14):2119-31.

40. Hansen AB, Lohse N, Gerstoft J, Kronborg G, Laursen A, Pedersen C, et al. Cause-specific excess mortality in siblings of patients co-infected with HIV and hepatitis C virus. PLoS One. 2007 Aug 15;2(8):e738.

41. Yin MT, Kendall MA, Wu X, Tassiopoulos K, Hochberg M, Huang JS, et al. Fractures after antiretroviral initiation. AIDS. 2012 Nov 13;26(17):2175-84.

42. Womack JA, Goulet JL, Gibert C, Brandt CA, Skanderson M, Gulanski B, et al. Physiologic frailty and fragility fracture in HIV-infected male veterans. Clin Infect Dis. 2013 May;56(10):1498-504.

43. Yin MT, Shiau S, Rimland D, Gibert CL, Bedimo RJ, Rodriguez-Barradas MC, et al. Fracture prediction with modified-FRAX in older HIV-infected and uninfected men. J Acquir Immune Defic Syndr. 2016 Mar 19.

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.

Funding/Acknowledgements: JEL has received funding from the National Institutes of Health, National Institute of Allergy and Infectious Diseases (K23 AI110532). TTB has received funding from the National Institutes of Health, National Institute of Allergy and

Infectious Diseases (K24 AI120834; R01AI093520). AG received support from the Clinical Research and Epidemiology in Diabetes and Endocrinology Training Grant T32DK062707. KNA has received funding from the National Institutes of Health, National Institute of Allergy and Infectious Diseases (K01AI093197).

Data in this manuscript were collected by the Multicenter AIDS Cohort Study (MACS). MACS (Principal Investigators): Johns Hopkins University Bloomberg School of Public Health (Joseph Margolick), U01-AI35042; Northwestern University (Steven Wolinsky), U01-AI35039; University of California, Los Angeles (Roger Detels), U01-AI35040; University of Pittsburgh (Charles Rinaldo), U01-AI35041; the Center for Analysis and Management of MACS, Johns Hopkins University Bloomberg School of Public Health (Lisa Jacobson), UM1-AI35043. The MACS is funded primarily by the National Institute of Allergy and Infectious Diseases (NIAID), with additional co-funding from the National Cancer Institute (NCI), the National Institute on Drug Abuse (NIDA), and the National Institute of Mental Health (NIMH). Targeted supplemental funding for specific projects was also provided by the National Heart, Lung, and Blood Institute (NHLBI), and the National Institute on Deafness and Communication Disorders (NIDCD). MACS data collection is also supported by UL1-TR001079 (JHU ICTR) from the National Center for Advancing Translational Sciences (NCATS) a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. The research was also supported by the HIV Prevention Trials Network (HPTN) sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute on Drug Abuse (NIDA), the National Institute of Mental Health (NIMH), and the Office of AIDS

Research, of the National Institutes of Health (NIH), Dept. of Health and Human Services (DHHS) (UM1 AI068613).

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

		HIV-infected men (N=1221)	HIV-uninfected men (N=1408)	P-value
Demographics				
Age, median (IQR)		40 (40-46)	40 (40-45)	0.743
Race, n (%)	White	718 (59)	1023 (73)	<0.001
	Black	326 (27)	285 (20)	
	Hispanic/other	177 (14)	100 (7)	
Center, n (%)	Baltimore	299 (25)	371 (26)	<0.001
	Chicago	276 (23)	224 (16)	
	Pittsburgh	265 (22)	377 (27)	
	Los Angeles	381 (31)	436 (31)	
BMI, kg/m^{2,} median (IQR)		25 (23-28)	25 (23-27)	0.547
Medical history				
Hypertension, n (%)		319 (31)	352 (32)	0.816
Diabetes, n (%)		56 (9)	38 (8)	0.588
HCV infection, n (%)		110 (10)	77 (6)	<0.001
eGFR, mL/min/1.73m^2, median (IQR)		102 (87-109)	99 (87-109)	0.923
Current smoker, n (%)		454 (38)	431 (31)	<0.001
Moderate-heavy/Binge drinking (≥3 drinks/d, ≥1 month), n (%)		350 (29)	439 (32)	0.171
HIV-related characteristics				
AIDS ever before index visit, n (%)		124 (10)		
CD4 T cell count, cells/uL, median IQR)		490 (319-704)		
Viral load, copies/mL, median (IQR)		342 (40-14722)		
ART use, n (%)		666 (55)		
Cumulative TDF use, years, median (IQR)		0 (0-0)		
Cumulative PI use, years, median (IQR)		0 (0-3)		

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.

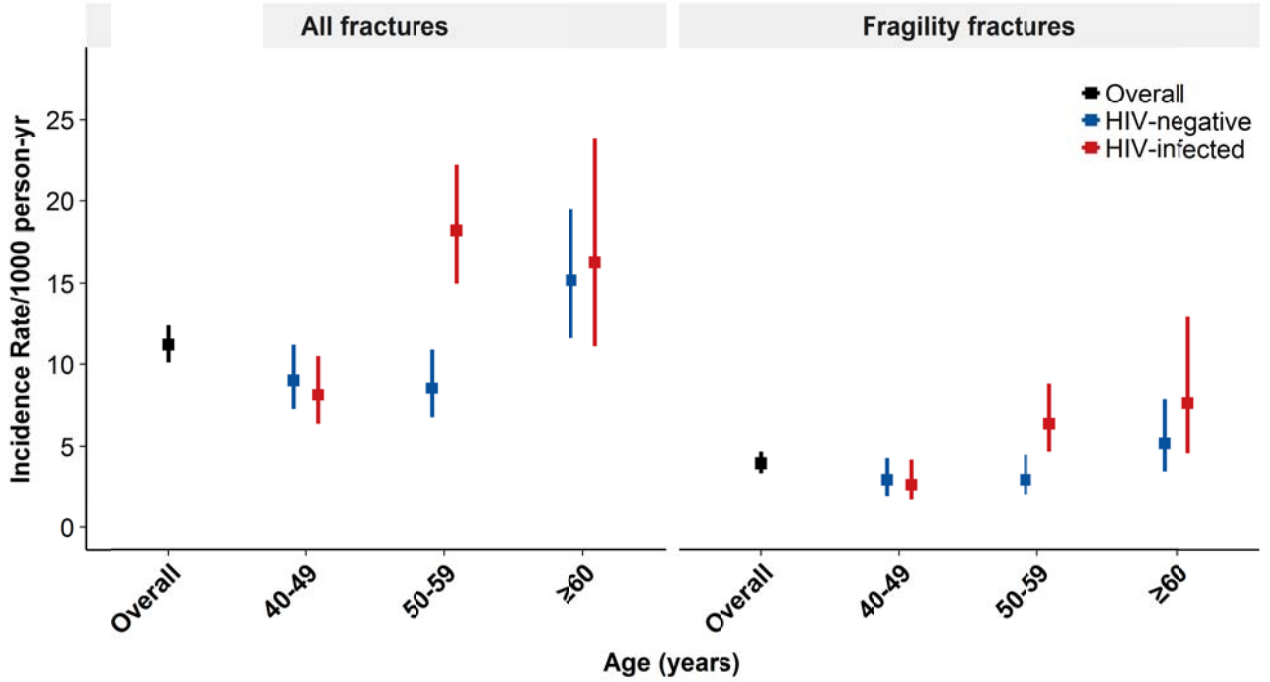
Table 2. Adjusted Incidence Rate Ratio of all fractures and fragility fractures in the HIV-

		Adjusted IRR All fractures	95% CI			Adjusted IRR Fragility fractures	95% CI		
			LL	UL	P-value		LL	UL	P-value
Age group	40-49	1	1	1	.	1	1	1	.
	50-59	1.66	1.18	2.34	**0.004**	1.85	1.04	3.28	**0.037**
	≥ 60	1.16	0.7	1.94	0.564	2.08	0.97	4.48	0.059
Non-Caucasian		0.76	0.53	1.08	0.127	0.83	0.46	1.47	0.513
BMI ≥ 25		0.71	0.51	0.99	**0.046**	0.72	0.41	1.26	0.251
Hypertension		1.34	0.97	1.87	0.079	1.03	0.57	1.84	0.931
Diabetes		0.76	0.42	1.36	0.343	0.6	0.2	1.79	0.353
Hepatitis C		0.81	0.42	1.57	0.531	1.48	0.61	3.63	0.386
eGFR < 60		1.48	0.87	2.52	0.142	0.8	0.29	2.2	0.665
Current smoking		0.98	0.69	1.4	0.929	1.05	0.6	1.85	0.857
Moderate-Heavy/Binge drinking		1.18	0.81	1.7	0.387	0.66	0.32	1.36	0.258
CD4+ < 500 cells/uL		1.22	0.88	1.69	0.233	0.94	0.54	1.65	0.834
Viral load ≥ 400 copies/mL		0.73	0.45	1.17	0.19	0.76	0.35	1.68	0.499
History of AIDS		1.04	0.71	1.53	0.831	1.3	0.73	2.34	0.375
Cumulative TDF/5 years		1.11	0.86	1.45	0.422	0.95	0.62	1.44	0.793
Cumulative PI/5 years		1.14	0.95	1.38	0.171	1.25	0.94	1.67	0.131
Current ART use		2.11	1.22	3.63	**0.007**	2.54	0.97	6.61	0.057

infected men.

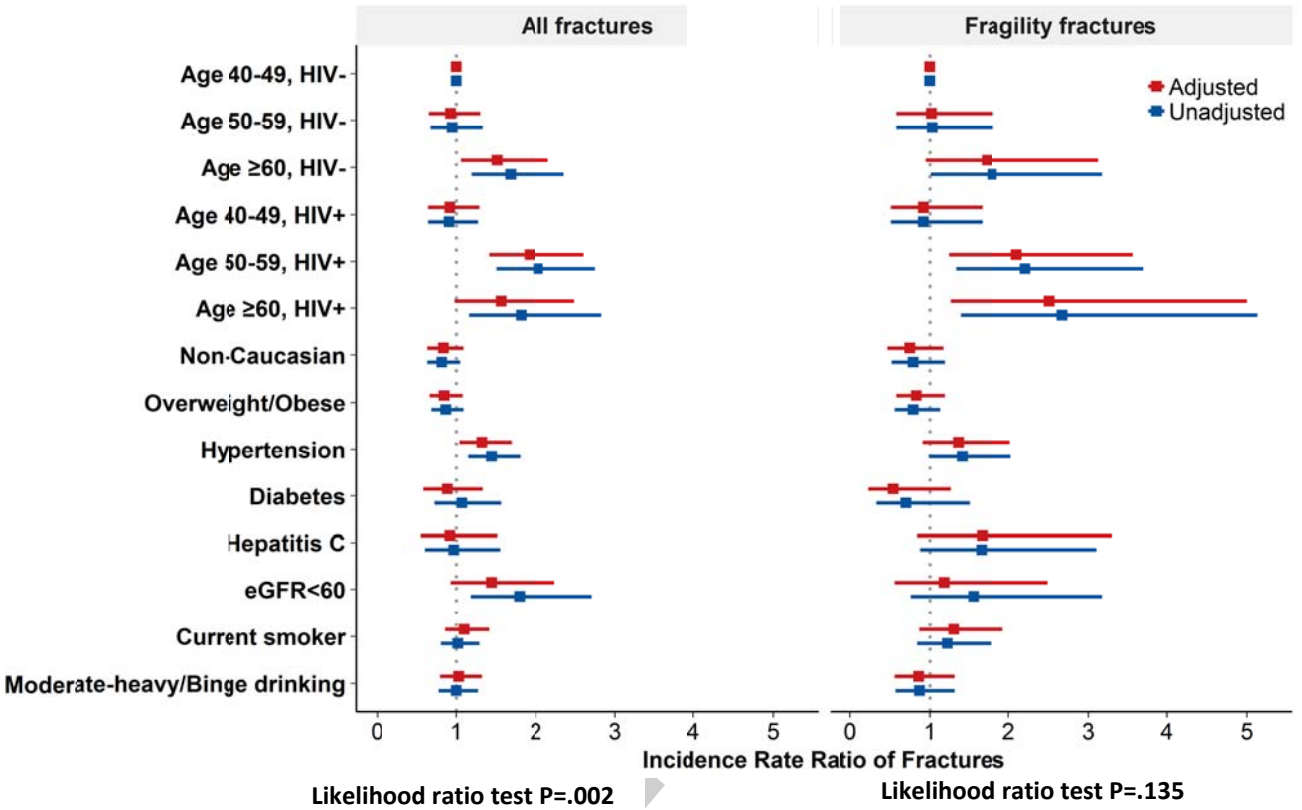
Adjusted Incidence Rate Ratio of all fractures and osteoporotic fractures in the HIV-infected cohort was estimated using Poisson regression model adjusting for age, BMI, race, eGFR, hypertension, diabetes, HCV-infection, tobacco smoking, alcohol use, CD4 count, viral load, AIDS history, 5 year cumulative 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 caregories (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