Title
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Increased fracture incidence in middle-aged HIV-infected and uninfected women: updated results from the Women's Interagency HIV Study

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Abstract

Background—We previously reported that fracture incidence rates did not differ by HIV status among predominantly premenopausal Women's Interagency HIV Study (WIHS) participants. We now conduct a follow-up study with 5 additional observation years, to further characterize fracture risk associated with HIV infection in women as they age.

Methods—We measured time to first new fracture at any site in 2375 (1713 HIV-infected, 662 HIV-uninfected) WIHS participants, with median 10 years follow-up. Fractures were self-reported semiannually. Proportional Hazards models assessed predictors of incident fracture.

Results—At index visit, HIV-infected women were older (median age 40 yrs (IQR 34–46) vs. 35 (27–43), p<0.0001) and more likely to be postmenopausal, HCV-infected, and weigh less than

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HIV-uninfected women. Among HIV-infected women, mean CD4+ count was 480 cells/μL and 63% were taking HAART. Unadjusted incidence rates of any fracture were higher in HIV-infected than uninfected women (2.19/100 person-years (py) vs 1.54/100py, p=0.002). In multivariate models, HIV status, older age, white (vs. black) race, prior fracture, history of cocaine use, and history of injection drug use were significant predictors of incident fracture. Among HIV-infected women, age, white race, prior fracture, smoking, and prior AIDS were predictors of new fracture.

Conclusion—Middle-aged HIV-infected women had a higher adjusted fracture rate than uninfected women. Cocaine use and injection drug use were also associated with a greater risk of incident fracture. Further research is needed to understand whether the risk of fracture associated with cocaine use relates to increased rate of falls, or direct effects on bone metabolism.

Keywords

HIV; women; bone; fracture; fragility fracture

INTRODUCTION

Reduced bone mineral density (BMD) is common in persons living with HIV. It is estimated that HIV-infected adults have over three times the risk for osteoporosis and almost 7 times the risk of osteopenia as their uninfected counterparts [1]. Traditional risk factors such as tobacco use, age, and low body weight have been implicated in bone loss among HIV-infected individuals, as have direct effects of HIV infection, inflammation, and antiretroviral therapy [2–7]. Initiation of highly active antiretroviral therapy (HAART) in treatment naïve patients has been consistently associated with a marked and clinically significant loss of BMD (2–6%) independent of regimen [8–11]. Most longitudinal studies show stable or increasing BMD on established HAART [3, 4, 12], although the SMART Body Composition substudy suggested that continuous antiretroviral use may be associated with decline in BMD and greater fracture risk relative to intermittent antiretroviral therapy [13].

Some large cohort studies have found higher incidence of fractures in HIV-infected than uninfected individuals [14–16], while others have not [17–19.] In our previous analysis in the Women's Interagency HIV Study (WIHS), we found that fracture rates were similar in predominantly premenopausal HIV-infected and uninfected women (1.8/100 py vs 1.4/100 py, p=0.13) with a median age of 40 years for HIV-infected women and 36 years for HIV-uninfected women at index and follow-up of 5.5 years [17]. Given the concern for increased rates of fracture in older HIV-infected women, especially as they transition through menopause, we now compare rates and determinants of fracture in the same cohort of HIV-infected and uninfected women after 5 additional years of observation.

METHODS

Study Population

The WIHS, an ongoing, multicenter prospective cohort study of the natural and treated history of HIV infection in women, enrolled 3,766 women (2,791 HIV-infected and 975 HIV-uninfected) in 1994–95 (n=2,623) and 2001–02 (n=1,143) from six sites (Bronx/Manhattan NY, Brooklyn NY, Chicago IL, Los Angeles CA, San Francisco CA and

Washington DC). WIHS methods and baseline cohort characteristics have been described previously [20]. HIV-uninfected women in the WIHS were recruited from groups known to have high risk for HIV infection. The HIV infected and uninfected recruits were comparable for a wide array of characteristics, including drug use, history of chronic illness, perceived health status, reproductive history and income [20]. At semiannual visits, participants complete physical examinations and provide biological specimens; they also undergo extensive assessment of clinical, behavioral and demographic characteristics. Informed consent was obtained using procedures approved by committees on human research at each of the collaborating institutions.

In 2003 (visit 18), all WIHS participants were asked about personal history of fracture of the hip, wrist and spine, both ever and within the prior 6 months. In those with a fracture history, fracture type(s) was determined, i.e., fragility (resulting from fall from standing height or less) and non-fragility. In all subsequent semi-annual study visits, participants were asked if they had fractures of the hip, wrist, spine and/or other site since the last visit. Two investigators reviewed and adjudicated all fracture reports, and excluded non-fractures. Of the 3,766 participants enrolled, 2393 had at least one additional core visit after the index visit (visit 17, October 2002 – March 2003), 18 participants who seroconverted during follow up were excluded, and the remaining 1713 HIV-infected, and 662 HIV-uninfected participants were included in the analysis. Visit 17 was designated as the index visit because participant report of incident fractures was not collected prior to visit 17. We considered fragility fractures, non-fragility fractures and all fractures (fragility and non-fragility combined) at any body site as study outcomes given recent data that high-trauma fractures are associated with lower BMD and are similar to fragility fractures in predicting future fractures [21]. This analysis includes fracture data from semiannual observations from October 2002 (visit 17) to September 2013 (visit 38). Our prior publication included data up to September 2008 (visit 28) [17]; therefore, this analysis increases the observation time by approximately 5 years.

Demographics, medical history, HIV treatment history, and laboratory data were extracted from the WIHS database at the index visit and subsequent visits. Presence of previously identified prognostic factors for fracture [22] at the index visit were quantified from the database: including age, menopause (no menses for greater than one year), personal history of fracture, parental history of hip fracture, body mass index (BMI, in kg/m^2), race/ethnicity, current use of cigarettes, greater than 2 alcoholic drinks per day, glucocorticoid use (ever/never), and history of rheumatoid arthritis or other cause of secondary osteoporosis. In addition, at the index visit we obtained: self-reported history of diabetes; current calcium use or multivitamin supplementation; any use of injection drugs (IDU), opiates or cocaine, statins, hormonal contraception, or hormone replacement therapy; and estimated glomerular filtration rate (eGFR) was determined using the Modification of Diet in Renal Disease (MDRD) calculation [23]. Chronic Hepatitis C virus (HCV) infection status was determined by the presence of HCV seropositivity and detectable HCV RNA level. We also considered the following HIV-specific variables: current and nadir CD4+ lymphocyte counts, history of AIDS-defining illness (ADI), any HAART use at index visit, protease inhibitor (PI)-based HAART or non-nucleoside reverse transcriptase inhibitor (NNRTI)-based HAART at index visit, and cumulative HAART exposure as well as cumulative exposure by each

antiretroviral class (total years of exposure to nucleoside reverse transcriptase inhibitors (NRTI), NNRTIs, PIs, and tenofovir from initiation, whether before or after enrollment into WIHS, to either last visit or fracture event.

STATISTICAL METHODS

Means, medians, standard deviations, interquartile ranges, and proportions were derived to summarize study variables, depending upon whether they were continuous or categorical. The primary outcome was time to self-reported fracture event, defined as any fracture (fragility or non-fragility) at any body site. Incidence rates were calculated as the number of participants with a new fracture divided by the total time (in person-years) at risk for new fracture during the study period. Visit 17 was considered the start time; the end of follow-up was either the visit at which the first fracture event was observed or, if no fracture was observed, the last visit prior to October 2013 for each participant. For women reporting multiple fractures, only the first fracture was included in these analyses.

Proportional hazards models were constructed to determine predictors of incidence of new fracture. Testing for HCV was performed at study entry, and cumulative ART exposure was calculated from time of ART initiation to time of fracture event or last visit; all other covariates were assessed at the index visit. Bivariate analyses evaluating each predictor in association with the outcome were considered for HIV-infected and uninfected participants together, and for HIV-infected participants separately. All variables were entered into multivariate models and a stepwise selection strategy with a p-value of ≤ 0.05 used to determine which variables remained in the final model. A p-value < 0.05 was considered statistically significant. A separate multivariate model, restricted to HIV-infected women, was constructed using similar methodology, to evaluate the contribution of measures of HIV disease severity and effects of antiretroviral therapy on fracture. Crude and adjusted proportional hazards curves were also constructed. The Kalbfleisch-Prentice approach was used to estimate baseline hazards and were fit twice, with all variables (except HIV) set to their mean values and HIV infection status set to negative and positive [24].

RESULTS

Participant characteristics at index visit

Table 1 presents participant characteristics at the index visit. HIV-infected women were older, had lower body weight, and more likely to be HCV-infected, report postmenopausal status, and use hormone replacement therapy (HRT), statins, and calcium and vitamin D supplements. HIV-infected women were also less likely than uninfected women to report heavy alcohol consumption or current smoking.

Among the 1,713 HIV-infected women at the index visit, 39% reported a prior ADI and 63% reported taking HAART; 49% of HAART regimens were PI-based, 47% were NNRTI-based, and 4% were neither PI- nor NNRTI-based. Mean (+/− SD) duration of HAART exposure at the index visit (including self-reported HAART use prior to enrollment in WIHS) was 4.31 +/− 3.4 yrs. Among the 37% of HIV-infected women not receiving

antiretroviral therapy at the index visit, half were antiretroviral-naïve, and half reported prior antiretroviral use.

Incident Fractures

During the study period, new fractures occurred in 390 of 2375 (16%) participants, with new fragility fractures occurring in 106/2375 (4%). At the time of fracture, the median ages of HIV-infected and uninfected women were 42 vs. 40 years (p=0.07) and 57% vs 47% (p=0.09) were postmenopausal, respectively. Fractures occurred more commonly at the hip in HIV-infected than uninfected women (2% vs 1%, p=0.06) but were similar at the spine and wrist. Fractures also occurred more commonly for HIV-infected women at other sites not associated with fragility fractures (14% vs 11%, p=0.08), including: foot, toe, hand, finger, ankle, and knee (Table 2.) Unadjusted incidence rates of fracture at any site were higher in HIV-infected women than uninfected women (2.19/100py vs. 1.54/100py, p=0.002) (Figure 1, Table 2).

Among the 390 fractures, 106 (27%) were self-reported as fragility fractures. The number of fragility fractures did not differ in HIV-infected vs. uninfected women (5% vs. 4%, p=0.22) (Table 2). Unadjusted incidence rates of fragility fractures were similar between HIV-infected and uninfected women (0.56/100py vs. 0.39/100py, p=0.13) as were rates of fracture limited to the hip, spine or wrist (Table 2).

Correlates of incident fracture

In bivariate analyses of all participants, traditional risk factors that were statistically associated with incident fracture were older age, self-report of menopause, history of fracture prior to index visit, HCV infection, reduced eGFR, diabetes mellitus, smoking, history of IDU, and cocaine or opiate use (Table 3). Use of statins, HRT and calcium supplementation were also associated with new fracture. HIV infection was a significant predictor of incident fracture (HR=1.45; 95% CI: 1.14–1.83). In multivariate analysis, HIV infection remained a statistically significant predictor of incident fracture, as were older age, white race, history of fracture prior to index visit, and history of IDU and cocaine use (Table 3).

Survival curves depicting incident fractures among HIV-infected and uninfected women are presented without adjustment (Figure 1A). The rate of incident fracture among HIV-infected women was significantly higher than that for HIV-uninfected women (p=0.002). After adjustment for significant covariates (age, race, fracture before index, cocaine use ever, and injection drug use ever), the HIV-infected group remained at greater risk for new fracture throughout the study period (p=0.037) (Figure 1B).

In bivariate analyses restricted to HIV-infected participants, older age, postmenopausal status, prior fracture, HCV infection, smoking, cocaine use, history of IDU, as well as CD4 nadir and history of AIDS were associated with incident fracture (Table 4). In contrast, race, BMI, HAART use at index or cumulative use, including tenofovir use, were not associated with incident fracture in bivariate analysis. In multivariate analyses restricted to HIV-infected participants, older age, white race, smoking, and history of fracture prior to index

visit were associated with greater fracture incidence, as was prior AIDS defining illness (aHR=1.57; 95% CI 1.24, 1.99; p=0.0002) (Table 4).

DISCUSSION

In our middle-aged cohort, HIV-infected women had higher incidence of fracture than HIV-uninfected women over a 10 year follow up period. The difference remained statistically significant in multivariate models, in contrast to our earlier findings, where fracture rates were similar in HIV-infected and uninfected women [17]. We also found that incidence of fragility fracture remained similar between HIV-infected and uninfected women, however, the proportionate increase in fragility fracture risk is similar to that seen with overall fracture incidence, suggesting that this may reflect a lack of power to detect differences in fragility fracture incidence in this cohort. Traditional risk factors for fracture including older age, white race, and history of fracture prior to index visit were significant predictors of incidence of new fracture, as was calcium supplementation, and history of IDU and cocaine. Compared to our previous study which only had 5 years of follow-up data, fractures at any site occurred in twice as many women (17.5% vs 8.6%) and the incidence rate was 22% higher (2.19/100 py vs. 1.79/100py) [17]. These differences in number and fracture incidence may reflect the higher age of the women under study, or a greater ability to detect differences between the groups due to increased observation time with five years additional follow-up.

Our findings are similar to a number of other published studies that have found associations between HIV infection and fracture occurence; however many of these studies are limited by case-control design [25–27], use of general population data as an HIV-uninfected comparison group [15, 19], or have been conducted in predominantly male subjects [16, 27]. In a population-based nationwide cohort study using Danish health registries, HIV-infected patients had a 50% increase in risk of fracture compared with population controls, and among those HIV-infected, this increased fracture risk was seen only for low-energy (osteoporotic) fracture in HAART-exposed persons [14]. A Spanish population-based retrospective cohort study found a significant increase in overall fracture risk in HIV-infected compared with uninfected adults (aHR 1.75, 95% CI: 1.24–2.48) as well as for hip fracture risk (aHR 4.72, 95% CI: 2.35–9.47); however when analyses were stratified by age <59 years vs. 60 and older, the risk of fracture associated with HIV status was significantly increased in the older group only, among whom HIV more than doubled fracture risk (HR 2.11, CI :1.05–4.22) [28]. Our data suggest that fracture rates will increase over time in HIV-infected women as they age. In particular, rates may increase among non-black women and in women with history of substance use. This could be explained by a greater prevalence of reduced BMD in HIV-infected women combined with a differential increase in fall risk with age perhaps related to disorders that are more common in HIV-infected persons, such as multiple comorbidities, peripheral neuropathy, neurocognitive deficits, central nervous system effects of medications or illicit drugs, or functional impairment [29].

In our previous report, we found that in addition to white race and renal insufficiency, HCV infection was associated with fracture [17], yet in this report, HIV but not HCV remained associated with fracture in a multivariate model, after adjusting for race/ethnicity, and

history of cocaine use. Our findings differ from several other cohort studies of HIV-infected individuals in which HCV remains a significant predictor of fracture even after adjustment for traditional risk factors including some measure of drug use [15, 30]. The finding that HCV is no longer significant after adjustment could mean that the association between HCV and fracture is due to true confounders or that given the multicollinearity in our variables, we cannot ascertain the true association between HCV and fracture. For example in our cohort, HCV-infected women were older and more likely to have used illicit drugs. Because both HIV and HCV infection are often associated with substance use, studies that investigate the relation between HCV and fracture must specifically consider the role of substance abuse, including not only opioid use, but additionally cocaine and alcohol use, in risk of both falls and fracture. In addition, factors that influence fall risk such as muscle strength and balance can influence fracture rates independently of bone strength; therefore, models including independent assessments of fall risk and bone strength are necessary to determine the true relationships between HCV infection, and HIV infection and fracture.

We were surprised to find that a history of cocaine use remained strongly associated with fracture in our multivariate model. While cocaine use has not been shown to have a direct effect on bone cells or bone metabolism, cocaine use may have indirect effects on nutritional/hormonal factors that might impact upon bone mass or muscle strength. Additionally, cocaine use may lead to increased fall risk resulting in increased fracture. Interestingly, other variables associated with substance use (injection drug use, opiate use, alcohol) were not associated with fracture. It is also possible that cocaine use is a true confounder in this model since it is associated with both HCV status and older age. Without cocaine use in the model, age becomes a significant predictor but HCV is still not a significant predictor of fracture.

There are several strengths to our study. WIHS has a comparison group of HIV-uninfected women that were enrolled based upon having similar risk behaviors as HIV-infected women, detailed data regarding fractures as well as fracture risk factors collected semiannually, and excellent participant retention. In addition fracture estimates from our study may differ from others because of more complete ascertainment resulting from use of a dedicated fracture questionnaire at semi-annual visits, and the use of the same questionnaire in prospectively enrolled HIV-infected and uninfected controls. Several other studies, have reported lower fracture incidence rates, perhaps in part be due to differences in methods of fracture ascertainment. In a French cohort of antiretroviral treated adults, fracture incidence was 0.33/100PY, however only serious adverse events that were reported were included in analyses, specifically including only fractures leading to severe or complete limitation of activity and/or hospitalization [19]. Similarly, a retrospective analysis of the ACTG A5001 [ACTG Longitudinal-Linked Randomized Trial (ALLRT)] database reported fracture incidence was 0.40/100 PY among all participants; yet because the parent studies included did not specify the reporting of fractures, fractures were likely underreported [31]. The fracture incidence rates we observed in the WIHS cohort are comparable to those reported by Hansen in a population-based nationwide cohort study using Danish registries, with mean age 37.6 and 76% male sex, and an incidence rate of 2.10/100 PY in the HIV-infected population and 1.35/100 PYR in the general Danish population [14]. By linking data from the population-based Danish HIV Cohort Study with the Danish Civil Registration System

and Danish National Hospital Registry, all fractures diagnosed at hospital admissions and at outpatient or emergency visits for both HIV-infected persons and matched general population controls were captured, and the authors note a high positive predictive value of the registry diagnoses, which is as high as 93% for hip fracture. Limitations include collinearity of HCV with substance use variables, and use of self-report for fracture ascertainment without radiographic confirmation or medical record verification. We also did not assess BMD, vitamin D levels, muscle strength and balance which are other potential determinants of falls and fracture. Since the majority of women in WIHS are African-American and overweight, our results may not be generalizable to all HIV-infected women (although our enrolled cohort is representative of the HIV epidemic among US women).

In conclusion, after 10 years of median follow up in predominantly premenopausal women of color, we found that HIV-infected women had higher fracture rates than HIV-uninfected women. History of cocaine use, but not HCV infection remained predictive of fracture in multivariable analysis. Our data also suggest that fracture rates have increased in our HIV-infected women over the last 5 years as the cohort has aged. Further research may be warranted to delineate the mechanisms by which cocaine use could predispose women to fracture, and/or whether cocaine affects either bone strength or fall risk, but in the meantime, these data support optimizing musculoskeletal health in older HIV-infected women.

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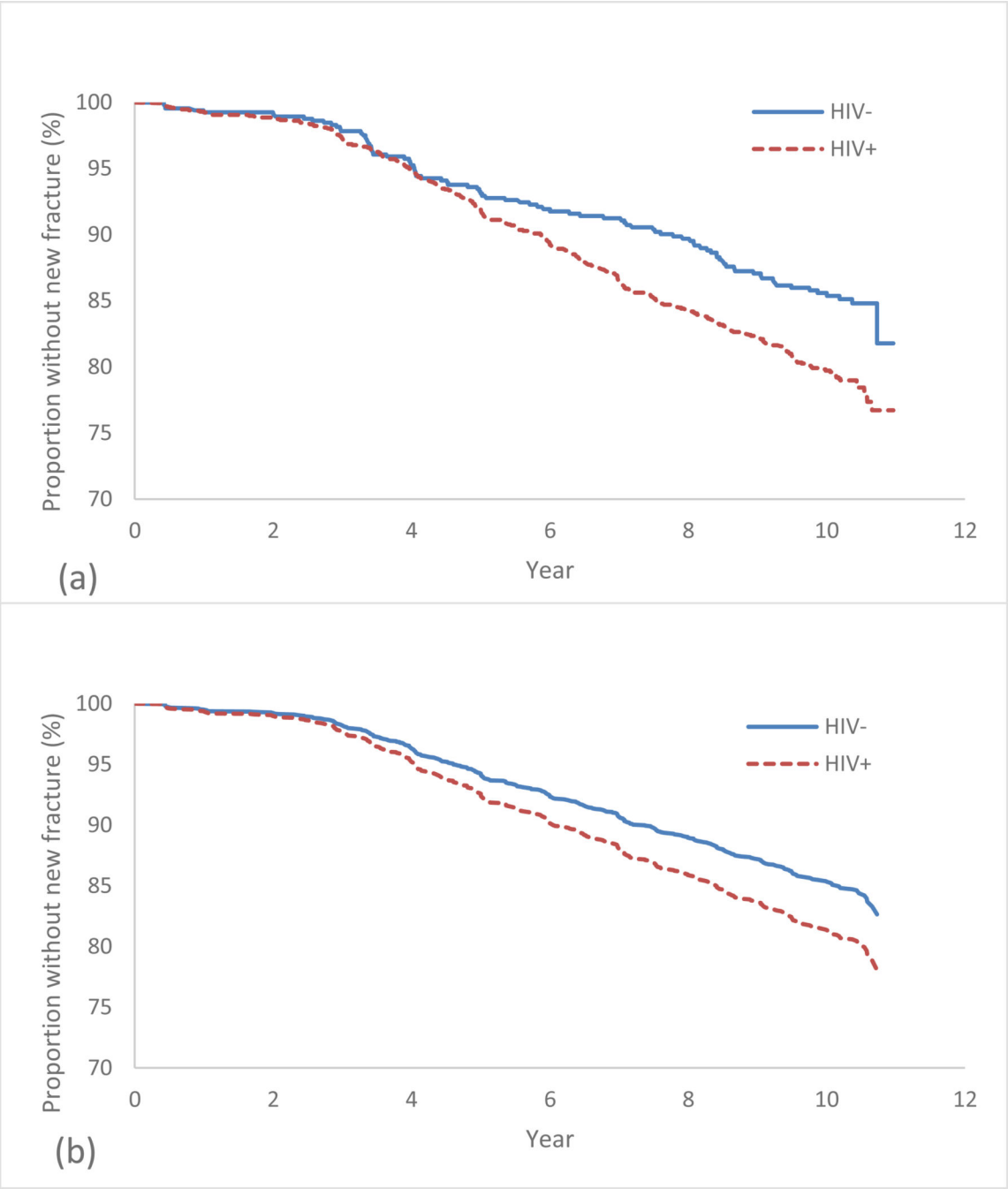

Figure 1.

(a). Incidence of new fracture (fragility or non-fragility) at any site, unadjusted in HIV-infected (dashed line) and uninfected (solid line) women (P=0.002). **(b)**. Incidence of new fracture (fragility or non-fragility) at any site adjusted for age, race, fracture before index, cocaine use (ever) and injection drug use (ever) in HIV-infected (dashed line) and uninfected (solid line) women (P=0.04).

Table 1

Demographic and clinical characteristics

	HIV-infected (N=1713)	HIV-uninfected (N=662)	P value
Demographics			
Age, median (IQR)	40 (34–46)	35 (27–43)	<0.0001
Race White Black Hispanic/Other	406 (24%) 1010 (59%) 297 (17%)	143 (22%) 410 (62%) 109 (17%)	0.40
Weight (kg) (mean ± SD)	74.5 ± 20.7	79.7 ± 22.9	<0.0001
BMI (kg/m^2) (mean ± SD)	28.5 ± 7.4	30.2 ± 8.3	<0.0001
Current smoking at index visit	772 (45%)	336 (51%)	0.01
Ever injection drug use	478 (28%)	141 (21%)	0.001
Ever opiate use	299 (18%)	126 (19%)	0.37
Ever cocaine use	304 (18%)	128 (19%)	0.37
Heavy alcohol use (≥ 2 drinks/day)	37 (2%)	25 (4%)	0.03
Menstrual history			
Self-reported menopause	331 (19%)	74 (11%)	<0.0001
Hormone replacement therapy at index visit	183 (11%)	38 (6%)	0.0002
Medical history			
Previous fracture	73 (4%)	35 (5%)	0.35
Diabetes at index visit	161 (9%)	66 (10%)	0.67
HCV RNA positive at study entry	409 (24%)	96 (15%)	<0.0001
Serum creatinine (mg/dL) (mean ± SD)	1.02 ± 1.13	1.07 ± 1.32	0.43
Estimated GFR< 60 (MDRD), at index visit	140 (8%)	31 (5%)	0.003
Calcium supplementation	94 (6%)	21 (3%)	0.02
Vitamin D supplementation	717 (42%)	184 (28%)	<0.0001
Statin use	105 (6%)	16 (2%)	0.0002
HIV disease related characteristics			
AIDS defining illness ever, prior to index visit	666 (39%)		
CD4+ cell count, at index visit (cells/μl)	479.7 ± 289.8		
CD4+ cell count, nadir (cells/μl), at index visit	214.2 ± 174.5		
HAART at index visit	1074 (63%)		
PI-based HAART at index visit	524 (31%)		
NNRTI-based HAART at index visit	509 (30%)		

Abbreviations: HIV: human immunodeficiency virus; IQR: interquartile range; SD: standard deviation; BMI: Body Mass Index (calculated as weight in kilograms divided by height in meters squared); HCV: Hepatitis C Virus: GFR: glomerular filtration rate; MDRD: Modification of Diet in Renal Disease; HAART: highly active antiretroviral therapy; PI: protease inhibitor; NNRTI: non-nucleoside analog reverse transcriptase inhibitor

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Table 2

Fracture incidence rates among HIV-infected and uninfected women

Fractures: number & site distribution	HIV-infected (N=1713)		HIV-uninfected (N=662)		
	Fractures N (%)	Fractures/ 100 PY	Fractures N (%)	Fractures/ 100 PY	p-value
Subjects					
All fractures*	300 (17.5)	2.19	90 (13.6)	1.54	0.002
Fragility fracture	82 (4.8)	0.56	24 (3.6)	0.39	0.13
Fracture sites**					
Spine	27 (1.6)	0.18	11 (1.7)	0.18	0.96
Hip	27 (1.6)	0.18	4 (0.6)	0.07	0.05
Wrist	52 (3.0)	0.35	15 (2.3)	0.24	0.20
Other (listed below)	235 (13.7)	1.67	73 (11.0)	1.23	0.01
Ankle	15		4		
Clavicle	4		2		
Elbow	4		0		
Foot (includes heel, toes)	32		13		
Hand (includes fingers)	14		4		
Knee	8		3		
Leg	7		2		
Nose	2		1		
Pelvis	1		0		
Ribs	4		2		
Shoulder/arm	5		1		
Miscellaneous	4		0		
Missing	135		40		

*Includes only one fracture per person.

**Includes multiple fractures per person.

There were a total of 300 fractures in 1713 HIV-infected women and a total of 90 fractures in 662 HIV-uninfected women. (%) Percent of total fractures occurring at body site. P value is shown for comparison of incidence rates between HIV-infected and HIV-uninfected women.

Table 3

Bivariate and multivariate models for incident fractures in HIV-infected and uninfected women

	Bivariate Model HR (95% CI)	P value	Multivariate Model* HR (95% CI)	P value
HIV infection	**1.45 (1.14, 1.83)**	**0.002**	**1.32 (1.04, 1.69)**	**0.02**
HCV infection	**1.72 (1.37, 2.14)**	**<0.0001**		
Age (per 10 year increase)	**1.43 (1.29, 1.58)**	**<0.0001**	**1.28 (1.14, 1.44)**	**<0.0001**
Race Black (Ref) **White** **Hispanic/Other**	1.0 1.23 (0.98, 1.54) **0.73 (0.54, 0.99)**	0.08 **0.04**	1.0 **1.25 (0.99, 1.57)** **0.71 (0.53, 0.97)**	**0.06** **0.03**
BMI, kg/m^2	0.99 (0.98, 1.01)	0.41		
Post-Menopausal	**1.91 (1.52, 2.41)**	**<0.0001**		
Fracture before index	**2.21 (1.55, 3.16)**	**0.005**	**1.87 (1.30, 2.69)**	**0.007**
eGFR <60ml/min	**1.60 (1.13, 2.25)**	**0.007**		
HBV infection	0.96 (0.43, 2.16)	0.93		
Diabetes Mellitus	1.28 (0.93, 1.75)	0.13		
Smoking (index)	**1.55 (1.27, 1.89)**	**< 0.0001**		
Heavy Alcohol Use (≥2 drinks/day) (index)	**1.89 (1.13, 3.17)**	**0.02**		
Cocaine use (ever)	**1.98 (1.58, 2.47)**	**<0.0001**	**1.56 (1.22, 1.99)**	**0.0003**
Injected Drugs (ever)	**1.95 (1.59, 2.40)**	**<0.0001**	**1.38 (1.09, 1.75)**	**0.007**
Opiate Use (ever)	**1.74 (1.37, 2.20)**	**<0.0001**		
Calcium use (index)	**1.65 (1.13, 2.40)**	**0.01**		
Vitamin D use (index)	0.96 (0.78, 1.17)	0.67		
HRT (ever)	**1.61 (1.21, 2.15)**	**0.001**		
Statin Use (ever)	**1.45 (0.99, 2.13)**	**0.06**		

* All variables listed in table were considered in the multivariate model and eliminated if they did not meet stepwise selection criteria of p-value ≤0.05.

Table 4

Bivariate and multivariate models for incident fractures in HIV-infected women only

Variable	Bivariate Model HR (95% CI)	P value	Multivariate Model* HR (95% CI)	P value
Age (per 10 year increase)	**1.36 (1.20, 1.53)**	**<0.0001**	**1.25 (1.10, 1.43)**	**0.0007**
Race Black (Ref) **White** Hispanic/Other	1.0 1.28 (0.99, 1.65) 0.71 (0.50, 1.01)	0.06 0.06	1.0 **1.37 (1.06, 1.78)** 0.71 (0.50, 1.02)	**0.02** 0.06
BMI (kg/m^2)	1.00 (0.99, 1.01)	0.93		
Post-Menopausal	**1.71 (1.32, 2.22)**	**<0.0001**		
Fracture before index	**2.53 (1.67, 3.81)**	**<0.0001**	**2.11 (1.39, 3.20)**	**0.0004**
HCV coinfection	**1.68 (1.31, 2.16)**	**<0.0001**		
Cigarette use (index)	**1.52 (1.21, 1.91)**	**0.0003**	**1.44 (1.14, 1.81)**	**0.002**
Cocaine use (ever)	**1.93 (1.11, 3.36)**	**0.02**		
Injection drug use (ever)	**2.35 (1.35, 4.09)**	**0.003**		
CD4+ (per 100 cells/μL increase)	0.97 (0.93, 1.01)	0.12		
Nadir CD4+ (per 100 cells/μL)	**0.91 (0.84, 0.98)**	**0.008**		
AIDS defining illness	1.77 (1.41, 2.22)	**<0.0001**	**1.57 (1.24, 1.99)**	**0.0002**
NRTI use (index)	1.01 (0.77, 1.33)	0.92		
Tenofovir use (index)	1.24 (0.98, 1.56)	0.08		
PI use (index)	1.10 (0.98, 1.39)	0.40		
NNRTI use (index)	0.10 (0.78, 1.27)	0.97		
Cumulative HAART (yrs)	1.02 (0.99, 1.05)	0.14		
Cumulative NRTI (yrs)	1.02 (0.99, 1.05)	0.14		
Cumulative PI (yrs)	1.02 (0.99, 1.05)	0.28		
Cumulative NNRTI (yrs)	1.01 (0.98, 1.05)	0.49		
Cumulative Tenofovir (yrs)	1.00 (0.95, 1.05)	0.98		

*All variables listed in table were considered in the multivariate model and eliminated if they did not meet stepwise selection criteria of p-value ≤0.05.