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Fracture incidence is increased in aging HIV-infected women

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Abstract

Background: Low bone mineral density (BMD) is common among HIV-infected individuals. Some studies find higher fracture incidence in HIV+ than HIV- individuals. There is particular concern for increased rates of fracture in older HIV-infected women as they continue to age.

Methods: We analyzed a cohort of 2375 (1713 HIV+, 662 HIV-) women enrolled in the Women's Interagency HIV Study (WIHS) to evaluate the effects of HIV infection on time to first self-reported fragility and non-fragility fracture, and determine risks for incident fracture, between 2003-2013. Incident fractures were assessed at semiannual visits. Associations of traditional fracture risk factors and HIV disease characteristics measured at index visit with subsequent incident fracture were estimated using proportional hazards models.

Results: HIV+ women were older than HIV- (median 40 vs 35 yrs) and had lower body mass index (28 vs 30kg/m2), but were racially similar (59% vs 62% black). HIV+ women were more likely to be post-menopausal (19% vs 11%), HCV infected at study entry (24% vs 15%), and use vitamin D at index visit (42% vs 28%), but less likely to smoke (45% vs 51%). Among HIV+, mean CD4+ count was 480 cells/μL and 63% were taking HAART at index visit. New fractures occurred in 300 (17.5%) HIV+ women and 90 (13.6%) HIV- women, including new fragility fractures in 82 (4.8%) HIV+ and 24 (3.6%) HIV- women. Unadjusted fracture incidence rates were higher in HIV+ versus HIV- women (2.19 vs 1.54/100py, p=0.002); however, unadjusted incidence rates of fragility fractures did not statistically differ (0.56/100py vs. 0.39/100py, p=0.13). Adjusted for age, race, prior fracture, and history of cocaine and injection drug use, HIV+ women had significantly higher incidence rate of any fracture compared with HIV- women (aHR1.30; 95% CI 1.02-1.66). Among HIV+ women, older age, white race, prior fracture, smoking, and prior AIDS defining illness(aHR=1.56; 95% CI: 1.22-1.98) significantly predicted new fracture, while CD4+ count and antiretroviral exposure did not.

Conclusions: Fracture rates were higher among HIV+ than HIV- women. Cocaine and injection drug use were also significant predictors 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. Our data support optimizing musculoskeletal health in older HIV-infected women.

Introduction

- Reduced bone mineral density (BMD) is common in persons living with HIV
- Some large cohort studies have found higher incidence of fractures in HIV-infected than uninfected individuals, while others have not
- 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
- 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 is a multicenter prospective cohort study established in 1994 to investigate the progression of HIV in women with and at risk for HIV.
- HIV- women in the WIHS were recruited from groups known to have high risk for HIV infection.
- Semiannual research visits included standardized interviews, phlebotomy, and physical examinations
- Starting in 2002 (visit 17) and each subsequent visit, 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 was determined: fragility (resulting from fall from standing height or less) and non-fragility.

Measurements

Primary Predictors

HIV status

Secondary Predictors

Age, race/ethnicity, history of prior fracture, smoking, alcohol use, opiate use, cocaine use, injection drug use, menopause status, body mass index (BMI), Hepatitis C infection, estimated glomerular filtration rate (eGFR). HIV-specific variables: current and nadir CD4+ counts, history of AIDS-defining illness, HAART use at index visit, cumulative HAART exposure, as well as cumulative exposure by each antiretroviral class and tenofovir.

Outcome

Time to self-reported fracture event, defined as any fracture (fragility or non-fragility) at any 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.

Statistical Analysis

Proportional hazards models determined predictors of fracture incidence. A stepwise selection strategy with a p-value of ≤0.05 used to determine which variables remained in the final multivariate model. Subgroup analyses assessed associations between HIV disease-specific factors and fracture.

Results

Table 1. WIHS Participant Characteristics

	HIV- (N=662)	HIV+ (N=1713)
Age (yr), median (IQR) *	35 (27-43)	40 (34-46)
Race (%) *		
White	143 (22%)	406 (24%)
Black	410 (62%)	1010 (59%)
Hispanic/Other	109 (17%)	297 (17%)
BMI (kg/m2) (mean± SD) *	30.2 ± 8.3	28.5 ± 7.4
Current smoking at index (%) *	336 (51%)	772 (45%)
Ever injection drug use (%) *	141 (21%)	478 (28%)
Ever cocaine use (%)	128 (19%)	304 (18%)
HCV RNA positive at study entry (%) *	96 (15%)	409 (24%)
Self-reported menopause *	74 (11%)	331 (19%)
Previous fracture*	35 (5%)	73 (4%)
Estimated GFR< 60 (MDRD), at index visit *	31 (5%)	140 (8%)
Calcium supplementation *	21 (3%)	94 (6%)
Vitamin D supplementation *	184 (28%)	717 (42%)
AIDS defining illness ever, prior to index visit		666 (39%)
CD4 + count at index visit, (mean± SD)		479.7 ± 289.8
HAART at index visit		1074 (63%)

* P<0.05 for Chi-square test or two sample t-test

Table 2. Fracture incidence rates among HIV-infected and uninfected women

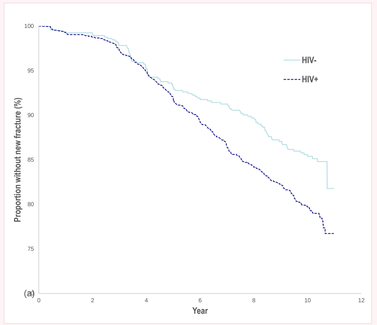
Fractures: number & site distribution	HIV- (N=662)		HIV+ (N=1713)		P value
	Fractures N (%)	Fracture/ 100 PY	Fractures N (%)	Fracture/ 100 PY	
Subjects	90 (13.6)	1.54	300 (17.5)	2.19	0.002
All fractures	24 (3.6)	0.39	82 (4.8)	0.56	0.13
Fragility fracture					
Fracture sites	11 (1.7)	0.18	27 (1.6)	0.18	0.96
Spine	4 (0.6)	0.07	27 (1.6)	0.18	0.05
Hip	15 (2.3)	0.24	52 (3.0)	0.35	0.20
Wrist	73 (11.0)	1.23	235 (13.7)	1.67	0.01
Other	90 (13.6)	1.54	300 (17.5)	2.19	0.002

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

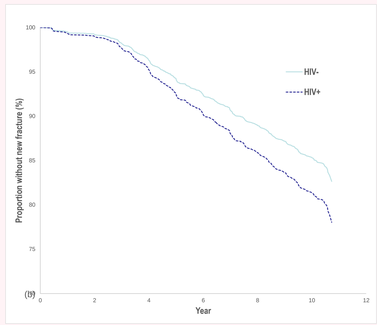
Table 3. "Other" fractures in HIV+ and HIV- women

Other fracture site (listed below)	HIV- (N=662) 73 (11.0)	HIV+ (N=1713) 235 (13.7)
Ankle	4	15
Clavicle	2	4
Elbow	0	4
Foot (includes heel, toes)	13	32
Hand (includes fingers)	4	14
Knee	3	8
Leg	2	7
Nose	1	2
Pelvis	0	1
Ribs	2	4
Shoulder/arm	1	5
Miscellaneous	0	4
Missing	40	135

Figure 1. Fracture Incidence in HIV+ and HIV+ Women



Unadjusted incidence of new fracture at any site, in HIV+ (dashed line) and HIV- (solid line) women (P=0.002).



Incidence of new fracture at any site adjusted for age, race, fracture before index, cocaine use (ever) and injection drug use (ever) in HIV+ (dashed line) and HIV- (solid line) women (P=0.04).

Table 4. Incident Fractures in HIV+ and HIV- women

	Multivariate Model HR (95% CI)	P value
HIV infection	1.32 (1.04, 1.69)	0.02
Age (per 10 yr increase)	1.28 (1.14, 1.44)	<0.0001
Race		
Black (Ref)	1.0	
White	1.25 (0.99, 1.57)	0.06
Hispanic/Other	0.71 (0.53, 0.97)	0.03
Fracture before index	1.87 (1.30, 2.69)	0.007
Cocaine use (ever)	1.56 (1.22, 1.99)	0.0003
Injected Drugs (ever)	1.38 (1.09, 1.75)	0.007

Table 5. Incident fractures in HIV+ women only

	Multivariate Model HR (95% CI)	P value
Age (per 10 year increase)	1.25 (1.10, 1.43)	0.0007
Race		
Black (Ref)	1.0	
White	1.37 (1.06, 1.78)	0.02
Hispanic/Other	0.71 (0.50, 1.02)	0.06
Fracture before index	2.11 (1.39, 3.20)	0.0004
Cigarette use (index)	1.44 (1.14, 1.81)	0.002
AIDS defining illness	1.57 (1.24, 1.99)	0.0002

Conclusions

- In this cohort of predominantly premenopausal women of color, HIV+ women had higher incidence of fracture than HIV- women over a 10 year follow up period
- History of cocaine use, but not HCV infection remained predictive of fracture in multivariable analysis.
- Fracture rates have increased in our HIV+ women over the last 5 years as the cohort has aged
- Our data support optimizing musculoskeletal health in older HIV-infected women