Low Bone Mineral Density is Associated with Increased Risk of Incident Fracture in HIV-infected Adults

COLORADO SCHOOL OF MINES

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#230

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BACKGROUND

- Low bone mineral density (BMD) is linked to increased fracture risk in the general population.[1]
- Low BMD is common among people living with HIV.[2]
- Increased bone fracture rates have been seen in HIV-infected cohorts.[3]
- To date, no data link low BMD to incident fracture risk in HIV-infected populations.

Table 1: Patient characteristics by study data source (N=1,008)

Patient characteristics: n or median (% or IQR)	Overall (n=1,008)	SUN (n=666)	HOPS-DIDC (n=342)
Median age*	42 (35-48)	40 (34-46)	44 (38-50)
Sex			
Male	838 (83.1)	513 (77.0)	325 (95.0)
Female	170 (16.9)	153 (23.0)	17 (5.0)
Race/ethnicity			
Non-Hispanic white	674 (66.9)	393 (59.0)	281 (82.2)
Non-Hispanic black	212 (21.0)	192 (28.8)	20 (5.9)
Hispanic	92 (9.1)	56 (8.4)	36 (10.5)
Other/unknown	30 (3.0)	25 (3.8)	5 (1.5)
HIV Risk			
IDU	58 (5.8)	50 (7.5)	8 (2.3)
MSM	690 (68.5)	388 (58.3)	302 (88.3)
Heterosexual	198 (19.6)	175 (26.3)	23 (6.7)
Other	62 (6.2)	53 (8.0)	9 (2.6)
Insurance*			
Private	590 (58.5)	301 (45.2)	289 (84.5)
Public	264 (26.2)	225 (33.8)	39 (11.4)
Other/unknown payer	154 (15.3)	140 (21.0)	14 (4.1)
Median CD4+ cell count/mm^3*	408 (254-598)	374 (232-562)	466 (316-642)
Nadir CD4+ cell count/mm^3	188 (71-299)	178 (71-275)	221 (73-335)
Viral load < 400 copies/mL*	560 (55.6)	338 (50.8)	222 (64.9)
Current/prior tobacco smoker	546 (54.2)	394 (59.2)	152 (44.4)
14+ alcoholic drinks/week	34 (3.4)	30 (4.5)	4 (1.2)
HAART type*			
Boosted PI	292 (29.0)	168 (25.2)	124 (36.3)
NNRTI	422 (41.9)	298 (44.7)	124 (36.3)
Other	260 (25.8)	172 (25.8)	88 (25.7)
None	34 (3.4)	28 (4.2)	6 (1.7)
TDF-containing HAART	468 (46.4)	260 (39.0)	208 (60.8)
HCV co-infection (DX or +Lab)	123 (12.2)	102 (15.3)	21 (6.1)
Normal bone density (hip T-score ≥ -1.0)	613 (60.8)	403 (60.5)	210 (61.4)
Osteopenia (hip T-score < -1.0)	366 (36.3)	245 (36.8)	121 (35.4)
Osteoporosis (hip T-score < -2.5)	29 (2.9)	18 (2.7)	11 (3.2)
Prevalent fracture (before date*)	60 (6.0)	41 (6.2)	19 (5.6)
Years follow-up, mean	4.99	5.99	3.05
Incident fracture	95 (9.4)	66 (9.9)	29 (8.5)

* At or closest to 3/1/2004 for SUN, 1/1/2008 for HOPS.
Abbreviations: IQR, interquartile range; IDU, intravenous drug use; MSM, men who have sex with men; PI, protease inhibitor; NNRTI, non-nucleoside analog reverse transcriptase inhibitor; TDF, tenofovir difumarate; HCV, hepatitis-C virus; DX, diagnosis.

Table 1 results: Among 1,008 participants who contributed 5,030 person-years of follow-up, 83% were male, 67% were non-Hispanic white, median age at date of DEXA scan was 42 years [interquartile range (IQR) 35-48], and median CD4+ cell count was 408 cells/mm^3 (IQR 255-600).

OBJECTIVE

- **Characterize association between baseline BMD determined by Central dual-energy X-ray absorptiometry (DEXA, GE Lunar or Hologic) defined as hip T-score normal (>-1.0), osteopenia (-2.5 to -1.0), and osteoporosis (< -2.5)[4] and any first incident fracture in HIV-infected adults. (The reference standard from which the T-score is calculated is the female, white, age 20-29 years, NHANES III database).**

Table 2: Factors associated with low bone mineral density (N=1,008)

Patient characteristics: n or median (% or IQR)	Osteoporosis (n=29)	Osteopenia (n=366)	Normal BMD (n=613)	p-value*
Median age†	47 (43-52)	44 (38-49)	39 (33-45)	< 0.001
Sex				< 0.001
Male	27 (93.1)	324 (88.5)	487 (79.5)	
Female	2 (6.9)	42 (11.5)	126 (20.5)	
Race/ethnicity				0.004
Non-Hispanic white	16 (55.2)	268 (73.2)	390 (63.6)	
Non-Hispanic black	6 (20.7)	61 (16.7)	145 (23.7)	
Hispanic	7 (24.1)	30 (8.2)	55 (9.0)	
Other/unknown	0 (0.0)	7 (1.9)	23 (3.8)	
HIV risk				0.012
IDU	2 (6.9)	23 (6.3)	33 (5.4)	
MSM	21 (72.4)	265 (72.4)	404 (65.9)	
Heterosexual	4 (13.8)	50 (13.7)	144 (23.5)	
Other/unknown	2 (6.9)	28 (7.7)	32 (5.2)	
Insurance†				0.12
Private	12 (41.4)	213 (58.2)	365 (59.5)	
Public	14 (48.3)	92 (25.1)	158 (25.8)	
Other/unknown payer	3 (10.3)	61 (16.7)	90 (14.7)	
Median CD4+ cell count/mm^3†	392 (168-624)	398 (247-598)	414 (258-594)	0.62
Nadir CD4+ cell count/mm^3	92 (15-274)	177 (57-285)	200 (87-305)	0.008
Viral load < 400 copies/mL†	17 (58.6)	230 (62.8)	313 (51.1)	0.001
Current/prior tobacco smoker	17 (58.6)	209 (57.1)	320 (52.2)	0.12
HAART type†				0.11
Boosted PI	3 (10.3)	104 (28.4)	185 (30.2)	
NNRTI	14 (48.3)	155 (42.4)	253 (41.3)	
Other	12 (41.4)	96 (26.2)	152 (24.8)	
None	0 (0.0)	11 (3.0)	23 (3.8)	
TDF-containing HAART	11 (37.9)	165 (45.1)	292 (47.6)	0.26
HCV co-infection (DX or +Lab)	8 (27.6)	53 (14.5)	62 (10.1)	0.003
Prevalent fracture	6 (20.7)	24 (6.6)	30 (4.9)	0.009
Incident fracture	9 (31.0)	37 (10.1)	49 (8.0)	0.003

* Yates corrected chi-square test for multiple categorical variables, Jonckheere-Terpstra test for individual continuous variables, Cochran-Armitage test for individual categorical variables.
† At or closest to 3/1/2004 for SUN, 1/1/2008 for HOPS.
Abbreviations: IQR, interquartile range; BMD, bone mineral density; IDU, intravenous drug use; MSM, men who have sex with men; HAART, highly active antiretroviral therapy; PI, protease inhibitor; NNRTI, non-nucleoside analog reverse transcriptase inhibitor; TDF, tenofovir difumarate; HCV, hepatitis-C virus; DX, diagnosis.

Table 2 results: In univariate analyses, low baseline BMD was significantly associated with older age, male sex, lower nadir CD4+ cell counts, HCV co-infection, history of fracture, and inversely associated with heterosexual HIV transmission risk.

METHODS, continued

Study Populations (SUN=Study to Understand the Natural History of HIV Infection, HOPS=HIV Outpatient Study):

- **SUN: Prospective cohort study (CDC-funded) with enrollment in 2004-2006, with 7 clinics in 4 US cities; patients followed from enrollment to last contact with DEXA scans every 6 months, up to June 2012.**
- **HOPS: Open prospective cohort study (CDC-funded) started in 1993, with 9 clinics in 6 US cities. Only 1 HOPS site, Denver Infectious Disease Consultants (DIDC), was included in this analysis, as it offered and performed DEXA scans as part of routine clinical care—these patients were followed from 2008 or later to last contact, up to 30 September 2012.**

Table 3: Characteristics of patients with and without incident fracture in the cohort (N=1,008)

Patient characteristics: n or median (% or IQR)	Fracture (n=95)	No Fracture (n=913)	p-value*
Median age†	43 (38-50)	41 (34-47)	0.007
Sex			0.47
Male	82 (86.3)	756 (82.8)	
Female	13 (13.7)	157 (17.2)	
Race/ethnicity			0.86
Non-Hispanic white	65 (68.4)	609 (66.7)	
Non-Hispanic black	18 (19.0)	194 (21.3)	
Hispanic	10 (10.5)	82 (9.0)	
Other/unknown	2 (2.1)	28 (3.1)	
HIV risk			0.051
IDU	8 (8.4)	50 (5.5)	
MSM	67 (70.5)	623 (68.2)	
Heterosexual	19 (20.0)	179 (19.6)	
Other/unknown	1 (1.1)	61 (6.7)	
Insurance†			0.22
Private	51 (53.7)	539 (59.0)	
Public	32 (33.7)	232 (25.4)	
Other/unknown payer	12 (12.6)	142 (15.6)	
Median CD4+ cell count/mm^3†	427 (276-660)	406 (253-588)	0.26
Nadir CD4+ cell count/mm^3	189 (51-300)	188 (72-299)	0.83
Viral load < 400 copies/mL†	57 (60.0)	503 (55.1)	0.42
Current/prior tobacco smoker	62 (65.3)	484 (53.0)	0.030
HAART type†			0.16
Boosted PI	20 (21.1)	272 (29.8)	
NNRTI	49 (51.6)	373 (40.9)	
Other	22 (23.2)	238 (26.1)	
None	4 (4.2)	30 (3.3)	
TDF-containing HAART	42 (44.2)	426 (46.7)	0.73
HCV co-infection (DX or +Lab)	19 (20.0)	104 (11.4)	0.023
Prevalent fracture	12 (12.6)	48 (5.3)	0.008
Bone density			0.002
Normal (hip T-score ≥ -1.0)	49 (51.6)	564 (61.8)	
Osteopenia (hip T-score < -1.0)	37 (39.0)	329 (36.0)	
Osteoporosis (hip T-score < -2.5)	9 (9.5)	20 (2.2)	

* Univariate analyses: Yates corrected chi-square test for categorical variables, Kruskal-Wallis test for continuous variables.
† At or closest to 3/1/2004 for SUN, 1/1/2008 for HOPS.
Abbreviations: IQR, interquartile range; IDU, intravenous drug use; MSM, men who have sex with men; PI, protease inhibitor; NNRTI, non-nucleoside analog reverse transcriptase inhibitor; TDF, tenofovir difumarate; HCV, hepatitis-C virus; DX, diagnosis.

Table 3 results: Factors associated with incident fracture in univariate analyses included older age, being a prior/current tobacco smoker, having HCV co-infection, having a prior fracture, and having osteopenia or osteoporosis.

Table 4: Factors associated with incident fracture among the cohort (N=1,008 patients, 95 incident fractures)

Independent variables	Univariate HR (95% CI)	Multivariable HR (95% CI)
Age (per 10 years)	1.41 (1.13-1.76)*	1.35 (1.07-1.70)*
CD4+ count (per 100 cells/mm^3)	1.04 (0.97-1.11)	
Nadir CD4+ count (per 100 cells/mm^3)	1.00 (0.88-1.14)	
Female sex	0.66 (0.37-1.19)	
IDU HIV risk (vs. MSM HIV risk)	1.38 (0.66-2.87)	
Public insurance (vs. private/other)	1.26 (0.82-1.93)	
Hepatitis C	1.64 (0.99-2.71)	
Current/prior tobacco smoker	1.60 (1.05-2.44)*	1.53 (1.01-2.34)*
Osteopenia (hip T-score < -1.0)	1.21 (0.79-1.85)	1.04 (0.67-1.62)
Osteoporisis* (hip T-score < -2.5)	3.98 (1.96-8.11)*	3.03 (1.46-6.29)*

* p-value < 0.05
Abbreviations: HR, hazard ratio; CI, confidence interval; IDU, intravenous drug use; MSM, men who have sex with men.

Table 4 results: In multivariable analysis, DEXA score indicative of osteoporosis, increasing age, and being a prior/current tobacco smoker were associated with incident fracture, but HCV co-infection and current or nadir CD4+ cell count were not.

Figure 1: Hip BMD T-score distribution by incident fracture (N=1,008)

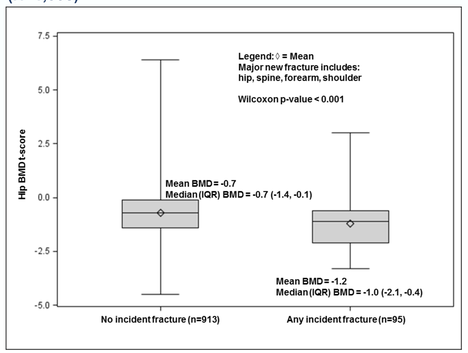

Figure 1 results: Baseline hip BMD T-scores were significantly lower among patients with incident fracture compared with those without an incident fracture.

METHODS, continued

Statistical Methods:

- **Descriptive statistics comparing patients by cohort and BMD at baseline (defined as closest to 3/1/2004 for SUN and 1/1/2008 for HOPS cohort patients).**
- **Univariate and multivariable analyses: Cox proportional hazards models, with backward selection for multivariable model.**

LIMITATIONS

- **Fractures occurring before entry into HOPS or SUN studies may be missing from medical records.**
- **Incident fractures may be incompletely captured, if not diagnosed in or reported to HOPS or SUN clinics.**
- **Incomplete reporting of anatomical site of fracture and limited number of fragility fractures (n=25) precluded site-specific analyses.**
- **Relatively few women were studied.**

CONCLUSIONS

- **In a large convenience sample of relatively young HIV-infected adults in the US, low baseline BMD, increasing age, and current or prior tobacco smoking were strongly associated with elevated risk of incident fracture.**
- **Presence of baseline osteoporosis was strongly associated with increased risk of incident fracture in this population of relatively young HIV-infected adults.**
- **Similar to previous analysis (Young 2011), fracture risk was associated with age.[5]**
- **Early detection of low BMD or risk of low BMD may provide an opportunity for earlier intervention to prevent fractures in HIV-infected patients.**

REFERENCES

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