

Increased Rates of Bone Fracture among HIV-Infected Persons in the HIV Outpatient Study (HOPS) Compared with the US General Population, 2000–2006

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Background. Among persons with HIV infection, low bone mineral density is common and has raised concerns about increased risk of fracture.

Methods. We analyzed data from the HIV Outpatient Study (HOPS), an open prospective cohort study of HIV-infected adults who were followed up at 10 US HIV clinics. We assessed rates of first fractures at any anatomic site during the period 2000–2008. We indirectly standardized the rates of fracture in the HOPS to the general population by age and sex, using data from outpatients in the National Hospital Ambulatory Medical Care Survey (NHAMCS-OPD). We examined factors associated with fractures using Cox proportional hazards modeling.

Results. Among 5826 active HOPS patients whose data were analyzed (median baseline age, 40 years; male sex, 79%; white race, 52%; exposure to antiretroviral therapy, 73%), 233 patients had incident fractures (crude annual rates, 59.6–93.5 fractures per 10,000 persons). Age-standardized fracture rates increased from 2000 to 2002 ($P = .01$) and stabilized thereafter. Among persons aged 25–54 years, both fracture rates and relative proportion of fragility fractures were higher among HOPS patients than among patients in the NHAMCS-OPD. In addition to older age and substance abuse, nadir CD4+ cell count <200 cells/mm³ (adjusted hazard ratio [aHR], 1.60; 95% confidence interval [CI], 1.11–2.31), hepatitis C infection (aHR, 1.61; 95% CI, 1.13–2.29) and diabetes (aHR, 1.62; 95% CI, 1.00–2.64) were associated with incident fractures.

Conclusions. Age-adjusted fracture rates among HOPS patients were higher than rates in the general US population during the period 2000–2006. Clinicians should regularly assess HIV-infected persons for fracture risk, especially those with low nadir CD4+ cell counts or other established risk factors for fracture.

Low bone mineral density (BMD) is common among persons with human immunodeficiency virus (HIV) infection [1–4]. A recent meta-analysis estimated that 67% of HIV-infected persons exhibited reduced BMD, and 15% had osteoporosis [5]. The increased prevalence of low BMD among HIV-infected patients has

raised concerns that as cohorts of HIV-infected patients age, bone fracture rates will increase [6]. Although multiple analyses have reported decreased BMD in HIV-infected persons, there are few data regarding incidence rates of fractures [7–9]. One US report found that fracture prevalence was increased significantly in both HIV-infected men and HIV-infected women, compared with persons whose HIV status was negative or unknown [7]. A study of antiretroviral (ART)-treated HIV-infected persons in France from 1997 through 2007 found an increasing incidence of fractures, but this study did not include a general population comparison group [8].

In this report, we compared rates of bone fracture among a large and demographically diverse cohort of ambulatory HIV-infected adults with rates of bone

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^aMembers of the HOPS group are listed in the Appendix.

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Table 1. Baseline Characteristics of Active Patients in the HIV Outpatient Study (HOPS) Followed-up during 2000–2008

Characteristic	Patients (n = 5826)	
Median age, years (IQR)	40	(34–46)
Sex		
Female	1223	(21.0)
Male	4603	(79.0)
Race/ethnicity		
White	3015	(51.8)
Black	1924	(33.0)
Hispanic	684	(11.7)
Other/unknown	203	(3.5)
Antiretroviral therapy exposure		
Naive	1302	(22.4)
Experienced	4237	(72.7)
Unknown	287	(4.9)
BMI, median value (IQR)	24.4	(22.3–27.4)
<18.5	137	(2.4)
18.5–24.9	2757	(47.3)
25–29.9	4475	(28.8)
≥30	712	(12.2)
Missing	542	(9.3)
CD4+ cell count, median cells/mL (IQR)	372	(196–579)
<200	1380	(23.7)
200–350	1169	(20.1)
>350	2881	(49.5)
Missing	396	(6.8)
Nadir CD4+ cell count, median cells/mL (IQR)	245	(90–417)
<200	2359	(40.5)
200–350	1345	(23.1)
>350	1880	(32.3)
Missing	242	(4.2)
Plasma viral load, median copies/mL (IQR) ^a	1305	(<400 to 35,560)
<1000	2590	(44.5)
1000–9999	879	(15.1)
10,000–100,000	1166	(20.0)
>100,000	744	(12.8)
Missing	447	(7.7)
Duration of HIV infection, median years (IQR)	5.3	(1.3–9.9)

NOTE. Data are no. (%) of patients unless otherwise indicated. Characteristics are given as of 1 January 2000 or the first HOPS visit thereafter. BMI, body mass index, calculated as the weight in kilograms divided by the square of the height in meters; HIV, human immunodeficiency virus; IQR, interquartile range.

^a Among antiretroviral therapy–experienced persons, the median viral load was 2.3 log₁₀ copies/mL, and 53.8% had a viral load <400 copies/mL; Among antiretroviral therapy–naïve persons, the median viral load was 4.6 copies/mL.

fracture among adult outpatients in the general US population and explored risk factors for incident fractures among HIV-infected adults.

METHODS

The HIV Outpatient Study (HOPS) is an open, prospective observational cohort study of HIV-infected adults followed at 10 specialty clinics in 8 US cities and has been described elsewhere [10, 11]. We analyzed data from HOPS patients with at least 2 clinical encounters during the period from 1 January 2000 through 31 December 2008 using HOPS data updated as of 13 March 2009.

Identification of Fractures among HOPS Patients

Since 2000, HOPS electronic databases have specifically captured data on fracture events and their anatomic site. Fractures that were treated at facilities outside of a HOPS site were recorded when a discharge summary was available or from patient self-report. Subjects were not systematically queried as to whether they had experienced a fracture between outpatient encounters. For our analyses, we included only the first bone fracture (at any anatomic site) during the observation period. We defined as fragility fractures those occurring at the following sites: wrist, vertebra, and femoral neck of the hip.

Identification of Bone Fractures among Adults in the US General Population

We compared fracture rates among HOPS patients with rates estimated for the US general population using data from the Centers for Disease Control and Prevention–funded National Hospital Ambulatory Medical Care Survey of outpatient departments (NHAMCS-OPDs), which were available through 2006 at the time of this analysis [12]. Specific methodology for data acquisition for NHAMCS has been described elsewhere [13–15]. Any fractures were identified by first-listed or primary *International Classification of Diseases, Ninth Edition*, discharge codes 800–829, as recorded in charts or in discharge records.

Classification of Risk Factors in the HOPS

Risk factors for fracture in the contemporary HAART era (2002–2008) were defined according to status as of 1 January 2002 or at first HOPS visit thereafter (defined as baseline). Potential risk factors included basic demographic and clinical factors (eg, age, sex, HIV transmission risk group, AIDS status, body mass index [BMI, calculated as the weight in kilograms divided by the square of height in meters]); known risk factors for low BMD (eg, current tobacco smoking, alcohol use, substance abuse, certain co-morbid conditions, use of certain prescribed medications); baseline CD4+ cell count and plasma HIV RNA level; and exposure to highly active antiretroviral therapy (HAART). We defined patients as hepatitis C virus (HCV) infected if their medical record contained a diagnosis of HCV infection, evidence HCV seropositivity, or detectable plasma HCV RNA.

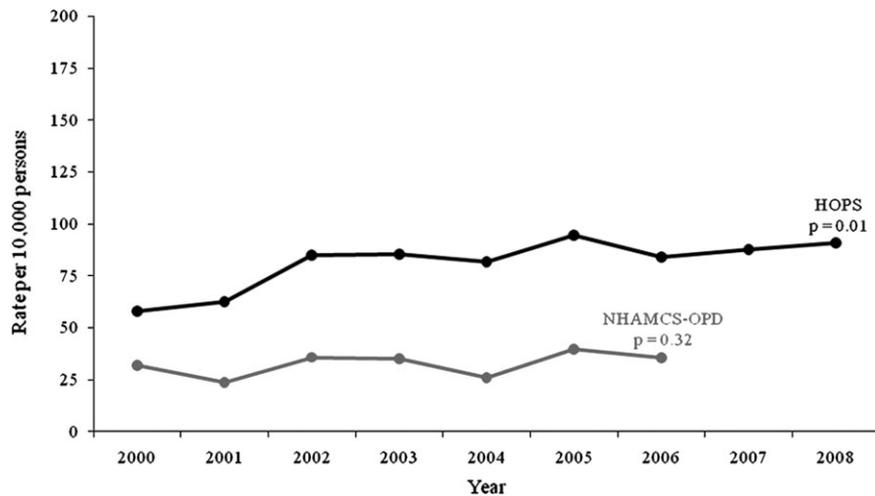


Figure 1. Rates of bone fracture among patients in the HIV Outpatient Study (HOPS), compared with rates among patients in the National Hospital Ambulatory Medical Care Survey of Outpatient Departments (NHAMCS-OPD) for adults aged 25–54 years. HOPS rates were indirectly standardized by age and sex using rates from NHAMCS-OPD. *P* values represent statistical significance of trends in annual values 2000–2008 for HOPS and 2000–2006 for NHAMCS-OPD.

Statistical Analysis

We first calculated overall and age-specific annualized rates (per 10,000 persons) of bone fracture among HOPS patients and among US adults using the NHAMCS-OPD [12, 13]. For a given year, only HOPS patients with ≥ 1 clinical encounter during that year were included. We indirectly standardized fracture rates among HOPS patients using fracture rates from NHAMCS-OPD and applying the age and sex distribution of the HOPS patients as weights [16]. We assessed trends in the annual fracture rate using linear regression, and we assessed the differences in the proportions of fractures focusing on subjects 25–54 years of age using the χ^2 test.

We used Cox proportional hazards modeling to examine risk factors for fracture. Observations were censored at date of fracture, patient's last contact with the HOPS, death, or 31 December 2008, whichever occurred first. Factors associated with fracture at the $P < .20$ level were evaluated in multivariable models that adjusted for sex and age. We used SAS, version 9.2, for analyses of HOPS data and SUDAAN for analyses of NHAMCS data. Associations with a P value $\leq .05$ were considered statistically significant.

RESULTS

Trends in Fracture Incidence

Of 5826 HOPS patients with data analyzed (median age, 40 years), 79.0% were male, 51.8% were non-Hispanic white, and 72.7% were exposed to ART (Table 1). During a median follow-up period of 3.8 years (interquartile range [IQR], 1.5–7.4 years), 233 patients experienced a first fracture, of whom 32 (13.7%) were hospitalized. In the HOPS, sex- and age-standardized

fracture rates per 10,000 persons increased from 57.7 during 2000 to 84.8 during 2002 ($P = .01$) and stabilized thereafter, measuring 89.9 during 2008; among NHAMCS-OPD patients, rates of fracture during 2000–2006 did not change significantly (Figure 1).

Crude fracture rates, as well as age- and sex-adjusted fracture rates, among HOPS patients and in the general US population surveyed by the NHAMCS-OPD are shown in Table 2. Differences in standardized rates were statistically significant (ie, there was no overlap between 95% CIs) in most years overall and for men, although not for women (Table 2). Among all HOPS patients and among those ages 25–54 years, who constituted 87% of all the HOPS patients included in this analysis, standardized rates of fracture increased significantly during the period 2000–2008 ($P = .01$, Figure 1) and were consistently higher than rates in NHAMCS-OPD during 2000–2006 (95% CIs not shown).

HOPS men aged 25–54 years experienced proportionally more fractures at the wrist and vertebra ($P < .01$, Table 3). HOPS women aged 25–54 years experienced proportionally more fractures at vertebra and femoral neck sites ($P < .01$ and $P = .04$, respectively). Both HOPS men and women experienced relatively fewer fractures at nonfragility sites, compared with NHAMCS-OPD patients (Table 3).

Risk Factors Associated with Fractures in HOPS Patients

In univariate Cox proportional hazards analyses, age > 47 years, CD4+ cell count nadir < 200 cells/mm³, baseline AIDS diagnosis, current tobacco use, HCV infection, diabetes, substance abuse, and peripheral neuropathy were associated ($P < .05$) with increased fracture risk in the contemporary HAART era

Table 2. Rates of Fracture among HIV Outpatient Study (HOPS) Patients Indirectly Standardized to Rates of Fracture among Adults Age ≥18 Years in the US General Population Treated at Outpatient Departments

Sex, year	HOPS				NHAMCS-OPD			
	No. of fractures	Total no. of patients	Crude fracture rate per 10,000 population	Standardized fracture rate per 10,000 population (95% CI)	No. of fractures	Total population, ×10 ³	Fracture rate per 10,000 population (95% CI)	Standard error
Overall^a								
2000	19	3189	59.6	57.7 (41.6–108.0)	607,463	208,631	29.1 (10.1–44.1)	0.20
2001	21	3267	61.3	62.4 (46.3–114.4)	544,521	211,490	25.8 (17.7–37.2)	0.16
2002	29	3316	87.5	84.8 (68.1–146.1)	835,607	214,231	38.1 (24.5–48.9)	0.21
2003	29	3294	88.0	95.2 (68.5–146.8)	544,521	216,517	25.8 (28.4–52.4)	0.19
2004	27	3209	84.1	81.1 (64.1–141.6)	570,133	219,138	26.0 (18.4–37.1)	0.16
2005	31	3183	97.4	93.8 (76.5–159.8)	893,912	221,727	40.3 (27.7–58.7)	0.26
2006	26	3004	86.6	83.2 (65.2–146.3)	806,317	224,485	35.9 (24.1–53.5)	0.21
2007	26	2875	90.4	86.8 (68.0–152.5)
2008	25	2673	93.5	89.9 (69.8–159.2)
Men^b								
2000	17	2540	66.9	68.7 (40.0–109.9)	333,881	100,314	33.3 (26.5–39.8)	0.36
2001	16	2580	62.0	63.9 (36.5–103.7)	318,801	101,847	31.3 (27.1–35.3)	0.29
2002	24	2613	91.9	94.7 (60.7–140.9)	467,241	103,282	45.2 (36.6–52.9)	0.48
2003	21	2586	81.2	83.7 (52.9–130.6)	461,686	104,582	44.1 (36.3–51.7)	0.36
2004	18	2528	71.2	73.2 (43.4–115.7)	310,091	105,977	29.3 (25.1–33.4)	0.28
2005	21	2498	84.0	86.5 (53.5–132.1)	400,901	107,360	37.3 (30.9–44.0)	0.35
2006	20	2342	85.4	87.9 (53.6–135.6)	428,799	108,778	39.4 (33.4–45.3)	0.36
2007	20	2276	87.9	90.3 (55.1–139.4)
2008	20	2128	94.0	97.1 (59.3–149.9)
Women^b								
2000	2	649	30.8	31.4 (3.8–113.18)	273,582	108,317	25.3 (19.2–31.6)	0.15
2001	5	687	72.8	73.3 (23.8–170.9)	225,720	109,643	20.6 (16.9–24.5)	0.11
2002	5	703	71.1	71.0 (23.0–165.5)	275,291	110,949	24.8 (17.7–32.9)	0.14
2003	8	708	113.0	111.9 (49.6–226.6)	373,921	111,935	33.4 (26.4–40.7)	0.15
2004	9	681	132.2	129.5 (59.2–245.6)	260,042	113,161	23.0 (19.1–26.9)	0.14
2005	10	685	146.0	141.9 (68.0–260.7)	493,011	114,367	43.1 (36.8–49.2)	0.25
2006	6	662	90.6	87.1 (32.0–189.5)	377,518	115,707	32.6 (27.1–38.3)	0.15
2007	6	599	100.0	95.7 (35.1–208.1)
2008	5	545	91.6	87.2 (28.3–203.3)

NOTE. CI, confidence interval; NHAMCS-OPD, National Hospital Ambulatory Medical Care Survey.

^a HOPS rates were age- and sex adjusted.

^b HOPS rates were age-adjusted.

(Table 4). There were no observed associations between risk of fracture and sex, race/ethnicity, age, BMI, ART exposure, and use of selective serotonin reuptake inhibitors (SSRIs), proton pump inhibitors, or thiazolidinediones. In multivariable analyses, factors associated with increased fracture risk included age >47 years, nadir CD4+ cell count <200 cells/mm³, HCV infection, diabetes, and substance abuse (Table 4).

Risk factors associated specifically with fragility fractures during the period 2002–2008 (*n* = 42) in univariate analysis included increasing age (hazard ratio [HR], 1.44 per 10 years; 95% CI, 1.05–1.98), HCV infection (HR, 2.18; 95% CI, 1.12–4.26), BMI <18.5 compared with all other BMI categories (HR,

3.24; 95% CI, 1.00–10.48), peripheral neuropathy (HR, 2.34; 95% CI, 0.98–5.55), and use of SSRIs (HR, 2.01; 95% CI, 0.96–4.20). In multivariable analyses, 3 factors remained independently associated with experiencing a fragility fracture: increasing age (adjusted HR [aHR], 1.43 per 10 years; 95% CI, 1.03–1.98), HCV infection (aHR, 1.99; 95% CI, 1.01–3.90), and BMI <18.5 (aHR, 3.72; 95% CI, 1.14–12.09).

DISCUSSION

In this large and diverse cohort of HIV-infected US adults, incident first fracture rates increased slightly during the period

Table 3. Number (%) of Fractures by Anatomic Site among Adults 25–54 Years of Age, 2000–2006

Characteristic	No. (%) of subjects		P
	HOPS (n = 152)	NHAMCS-OPD (n = 2,842,221)	
Men			
No. of subjects	113	1,705,433	
Wrist	9 (8)	49,495 (3)	<.01
Vertebra	11 (10)	17,438 (1)	<.01
Femoral neck	5 (4)	30,051 (2)	.06
Nonfragility site	84 (74)	1,608,449 (94)	<.01
Women			
No. of subjects	39	1,136,788	
Wrist	3 (8)	92,358 (8)	0.92
Vertebra	7 (18)	48,075 (4)	<.01
Femoral neck	2 (5)	15,437 (1)	0.04
Nonfragility site	27 (69)	980,918 (86)	<.01

NOTE. HOPS, HIV Outpatient Study; NHAMCS-OPD, National Hospital Ambulatory Medical Care Survey.

2000–2008, with the increase occurring mostly during 2000–2002. Age-adjusted fracture rates among HIV-infected men and women ages 25–54 years in the HOPS were consistently higher than those in adults in the US general population captured by the NHAMCS-OPD during the study period. Moreover, the relative proportion of fractures at fragility sites (spine, hip, and wrist) was higher among HOPS patients than among participants surveyed in the NHAMCS-OPD. Among HOPS patients, increasing age, HCV co-infection, and BMI <18.5 were independently associated with fragility fractures.

Our finding that incident fracture rates among HIV-infected HOPS patients were greater than rates among predominantly HIV-uninfected counterparts in the general population confirms similar findings from prior reports [7]. The slight annual increase in fracture rates among the HOPS patients might reflect a true increase as HIV-infected patients experience improved survival or an improved capture of fracture data within the HOPS because of increasing awareness of bone health issues, or both.

We confirmed that several established risk factors for fracture (ie, older age, substance abuse, HCV co-infection and diabetes) were associated with incident fractures among HOPS patients. The Veterans Aging Cohort Study documented that incident fragility fractures were independently associated with HIV infection, as well as with cachexia, white race/ethnicity, alcohol abuse, and increasing age [17]. The Women’s Interagency HIV Study (WIHS) found that fractures were associated with white race/ethnicity, increasing age, a history of AIDS-defining illness, and a history of prior fracture [18] but found no association with HIV infection in this generally young cohort of mostly premenopausal women [18]. Although previous studies have linked advanced HIV disease and its markers to low BMD, we believe that our analysis is the first to highlight a possible association of

low nadir CD4+ cell count with incident fracture rates. The causal mechanism by which low nadir CD4+ cell count is associated with low BMD and fracture risk is unclear and warrants further investigation.

The optimal clinical management of bone health in HIV-infected individuals is not well defined and remains controversial. Screening HIV-infected adults for fracture risk has been recommended for individuals aged ≥40 years by the European AIDS Clinical Society and ≥50 years by McComsey and colleagues [19, 20]. Our findings suggest that younger HIV-infected adults are also at significant risk for fragility fractures and should be considered for similar screening interventions.

This analysis has several important limitations. First, bone fractures were ascertained from diagnoses of clinical events charted by HIV care providers and were not confirmed by review of radiographic findings or central adjudication. Second, subjects were not routinely queried about bone fractures that occurred outside of the HOPS clinic, which could have led to under-reporting of events that biased our analysis towards underestimation of fracture incidence. Third, for a majority of HOPS patients, we were not able to systematically determine the clinical venue where they initially presented for treatment of their fracture and thus could not restrict comparisons of HOPS data with national datasets by place of initial treatment (ie, hospital, outpatient clinic, or emergency department). Nevertheless, we believe that, despite methodological differences in fracture ascertainment, NHAMCS-OPD was our best available source of comparative data on fracture rates in the general population. Like the HOPS, the NHAMCS-OPD captures fractures among adults who initially present to outpatient departments for treatment of a fracture, who present to outpatient departments for follow-up treatment of a fracture, or who report a fracture to their health care provider, at which point this event is captured in their medical record and abstracted. Fourth, in

Table 4. Risk Factors for Bone Fracture among 5054 HOPS Patients Followed during the Contemporary HAART Era, 2002–2008

Baseline characteristic	No. (%) of patients	No. of fractures	Univariable analysis		Multivariable analysis ^a	
			Hazard ratio (95% CI)	<i>P</i>	Adjusted hazard ratio (95% CI)	<i>P</i>
Sex						
Male	1058 (20.9)	144	1.00		1.00	
Female	3996 (79.1)	49	1.30 (0.92–1.76)	.15	1.21 (.86–1.71)	.28
Race/ethnicity						
White	2636 (52.2)	106	1.00			
Black	1649 (32.6)	56	1.00 (0.72–1.38)	>.99		
Hispanic	604 (12.0)	26	1.26 (0.82–1.94)	.29		
Other	165 (3.3)	5	0.89 (0.36–2.19)	.81		
Age quartile, years						
≤35	1258 (24.9)	31	1.00		1.00	
36–40	1190 (23.6)	44	1.35 (0.85–2.14)	.20	1.29 (.80–2.06)	.30
41–46	1246 (24.6)	49	1.41 (0.90–2.21)	.14	1.15 (.72–1.85)	.56
≥47	1360 (26.9)	69	1.88 (1.23–2.87)	.004	1.58 (1.01–2.49)	.05
BMI^b						
<18.5	114 (2.5)	7	1.46 (0.68–3.13)	.33		
18.5–24.9	2515 (51.9)	94	1.00			
25–29.9	3993 (32.0)	49	0.81 (0.58–1.13)	.22		
≥30	4623 (13.6)	22	0.89 (0.56–1.40)	.62		
Baseline CD4+ cell count^c						
≥350 cells/mm ³	2732 (58.1)	106	1.00			
200–349 cells/mm ³	987 (21.0)	38	1.07 (0.74–1.55)	.71		
<200 cells/mm ³	980 (20.9)	37	1.28 (0.88–1.86)	.20		
Nadir CD4+ count						
≥350 cells/mm ³	1551 (32.0)	41	1.00		1.00	
200–349 cells/mm ³	1228 (25.3)	43	1.31 (0.86–2.01)	.21	1.25 (0.8–1.92)	.31
<200 cells/mm ³	2076 (42.8)	97	1.72 (1.20–2.48)	.004	1.60 (1.11–2.31)	.01
Baseline viral load						
<400 copies/mL	2534 (50.1)	107	1.00			
≥400 copies/mL	2520 (49.9)	86	0.97 (0.73–1.29)	.85		
AIDS status						
Without AIDS	2354 (46.6)	71	1.00			
With AIDS	2700 (23.4)	122	1.43 (1.07–1.92)	.02		
Current tobacco smoking						
No	2925 (57.9)	96	1.00			
Yes	1907 (37.7)	89	1.57 (1.17–2.10)	.002		
Unknown	222 (4.4)	8	1.04 (.51–2.14)	.92		
Current alcohol use						
No	2398 (47.5)	88	1.00			
Yes	2367 (46.8)	92	0.97 (0.73–1.30)	.85		
Unknown	289 (5.7)	13	1.09 (0.61–1.94)	.78		
ARV exposure						
Naive	967 (19.1)	29	1.00			
Experienced	3856 (76.3)	160	0.98 (0.66–1.46)	.91		
Unknown	231 (4.6)	4	0.64 (0.23–1.83)	.41		
HAART exposure						
No	1305 (25.8)	30	1.00			

Table 4. (Continued)

Baseline characteristic	No. (%) of patients	No. of fractures	Univariable analysis		Multivariable analysis ^a	
			Hazard ratio (95% CI)	<i>P</i>	Adjusted hazard ratio (95% CI)	<i>P</i>
Yes	3749 (74.2)	163	1.39 (0.94–2.06)	.10		
Hypogonadism						
No	4926 (97.5)	190	1.00			
Yes	128 (2.5)	3	0.69 (0.22–2.14)	.52		
Hepatitis C infection						
No	4235 (83.8)	142	1.00		1.00	
Yes	819 (16.2)	51	1.95 (1.41–2.69)	<.0001	1.61 (1.13–2.29)	.01
Diabetes						
No	4755 (94.1)	174	1.00		1.00	
Yes	299 (5.9)	19	1.81 (1.13–2.91)	.01	1.62 (1.00–2.64)	.05
Lipodystrophy						
No	4510 (89.2)	174	1.00			
Yes	544 (10.8)	19	0.66 (0.41–1.06)	.08		
Substance abuse						
No	4533 (89.7)	163	1.00		1.00	
Yes	521 (10.3)	30	1.82 (1.23–2.68)	.003	1.52 (1.00–2.32)	.05
Peripheral neuropathy						
No	4754 (94.1)	172	1.00			
Yes	300 (5.9)	21	1.68 (1.07–2.65)	.02		
Antidepressant ^d						
No	4455 (88.2)	163	1.00			
Yes	599 (11.8)	30	1.33 (0.90–1.97)	.15		
Proton pump inhibitor ^e						
No	4646 (91.9)	173	1.00			
Yes	408 (8.1)	20	1.25 (0.79–1.99)	.34		
Thiazolidinedione ^f						
No	4646 (91.9)	191	1.00			
Yes	408 (8.1)	2	1.52 (0.38–6.12)	.56		

NOTE. All characteristics were defined as of 1 January 2002 or first HOPS visit thereafter. ARV, antiretroviral; BMI, body mass index, calculated as the weight in kilograms divided by the square of height in meters; CI, confidence interval; HAART, highly active antiretroviral therapy.

^a The final model obtained by backward step-wise elimination included nadir CD4+ cell count, hepatitis C, diabetes, and substance abuse, and adjusted for sex and age.

^b Missing BMI data for 428 HOPS patients.

^c Missing baseline CD4+ cell count data for 355 HOPS patients.

^d Included fluoxetine, sertraline, paroxetine, citalopram, and escitalopram oxalate.

^e Included omeprazole, lansoprazole, rabeprazole, esomeprazole magnesium, and pantoprazole sodium.

^f Included rosiglitazone and pioglitazone.

both the HOPS and NHAMCS-OPD, we were unable to assess the completeness with which fracture events were captured; however, we have no a priori reason to believe that completeness would differ meaningfully between these datasets in a direction that would have biased against the null hypothesis. Fifth, although our analysis of HOPS data included >5800 patients, fractures are rare events, and rates in the HOPS are thus subject to considerable variability, which limited our ability to stratify by age, sex, and race/ethnicity. Sixth, we had no data on BMD for HOPS patients and were thus unable to assess its

contribution to the risk of fracture. Finally, we did not have adequate data on use of tobacco, alcohol, or other substances of abuse among HOPS patients to explore a dose-response association of exposure to these agents with the risk of fracture.

In summary, our study suggests that HIV-infected adults, particularly adults age 25–54 years of age, are at an increased risk of bone fracture, compared with the general population. In light of this finding and the established relationship between low BMD and increased fracture risk in the general adult population, we recommend that screening for and correcting reversible causes of

low BMD and fall risk be incorporated into routine clinical care of HIV-infected patients, as has been recently argued [20].

Appendix 1

The HIV Outpatient Study (HOPS) Investigators

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References

1. Tebas P, Powderly WG, Claxton S, et al. Accelerated bone mineral loss in HIV-infected patients receiving potent antiretroviral therapy. *AIDS* 2000; 14:F63-7.
2. Carr A, Miller J, Eisman JA, Cooper DA. Osteopenia in HIV-infected men: association with asymptomatic lactic acidemia and lower weight pre-antiretroviral therapy. *AIDS* 2001; 15:703-9.
3. Moore AL, Vashisht A, Sabin CA, et al. Reduced bone mineral density in HIV-positive individuals. *AIDS* 2001; 15:1731-3.
4. Overton ET, Mondy K, Bush T, et al. Factors associated with low bone mineral density in a large cohort of HIV-infected US adults: baseline results from the SUN study [abstract 836]. In: Programs and abstracts of the 14th Conference on Retroviruses and Opportunistic Infections. Los Angeles, CA. February 25-28, 2007.

5. Brown TT, Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. *AIDS* 2006; 20:2165-74.
6. Brown TT, McComsey GA. Osteopenia and osteoporosis in patients with HIV: a review of current concepts. *Curr Infect Dis Rep* 2006; 8:162-70.
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; 93:3499-504.
8. Collin F, Duval X, Le Moing V, et al. Ten-year incidence and risk factors of bone fractures in a cohort of treated HIV1-infected adults. *AIDS* 2009; 23:1021-4.
9. 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; 21:617-23.
10. Moorman AC, Holmberg SD, Marlowe SI, et al. Changing conditions and treatments in a dynamic cohort of ambulatory HIV patients: the HIV outpatient study (HOPS). *Ann Epidemiol* 1999; 9:349-57.
11. Buchacz K, Baker RK, Moorman AC, et al. Rates of hospitalizations and associated diagnoses in a large multisite cohort of HIV patients in the United States, 1994-2005. *AIDS* 2008; 22:1345-54.
12. Centers for Disease Control and Prevention. CfDcCaP. NHAMCS Macro-file data documentation. National Center for Health Statistics. Available at: ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Dataset_Documentation/NHAMCS/. Accessed 20 November 2010.
13. Centers for Disease Control and Prevention. CfDcCaP. National hospital discharge Survey Public use data File Documentation. National Center for Health Statistics. Available at: ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Dataset_Documentation/NHDS/NHDS_2006_Documentation.pdf. Accessed 20 November 2010.
14. Centers for Disease Control and Prevention CfDcCaP. Emergency department patient record Form- NHAMCS Survey Instruments. National Center for Health Statistics. Available at: http://www.cdc.gov/nchs/data/ahcd/nhamcs100ed_2009.pdf. Accessed 20 November 2010.
15. Centers for Disease Control and Prevention. CfDcCaP. Outpatient department patient record. Available at: http://www.cdc.gov/nchs/data/ahcd/nhamcs100opd_2009.pdf. Accessed 20 November 2010.
16. Teutsch SM, Churchill RE. Principles and practice of public health surveillance, 2nd ed. Oxford, New York: Oxford University Press, 2000.
17. Womack J, Goulet J, Gibert C, Brandt C, Mattocks K, Rimland D, M Rodriguez-Barradas M, Tate J, Yin M, Amy J, and Veterans Aging Cohort Project Team. HIV-infection and fragility fracture risk among male veterans [abstract 129]. In: Programs and abstracts of the 17th Conference on Retroviruses and Opportunistic Infections. San Francisco, CA, February 16-19, 2010.
18. Yin M, Shi Q, Hoover D, et al. Fracture rates are not increased in younger HIV+ women [abstract 130]. In: Programs and abstracts of the 17th Conference on Retroviruses and Opportunistic Infections. San Francisco, CA. February 16-19, 2010.
19. Society EAC. Clinical management and treatment of HIV-infected adults in Europe. Available at: <http://www.europeanaidscinicalsociety.org/Guidelines2009/index.htm>. Accessed December 1.
20. McComsey GA, Tebas P, Shane E, et al. Bone disease in HIV infection: a practical review and recommendations for HIV care providers. *Clin Infect Dis* 2010; 51:937-46.