Incident fractures in HIV-infected individuals: a systematic review and meta-analysis

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Objective(s): Some but not all studies indicate that individuals with HIV infection are at an increased risk of fracture. We systematically reviewed the literature to investigate whether incidence of fracture (both overall and fragility) differs between individuals with and without HIV.

Design: A systematic review and meta-analysis.

Methods: Medline, Scopus and the Cochrane Library databases for all studies ever published up to 28 September 2012 and electronically available conference abstracts from CROI, ASBMR, IAS and AIDS were searched. All studies reporting incidence of all fracture and fragility fracture in HIV-infected adults were included. A random effects model was used to calculate pooled estimates of incidence rate ratios (IRRs) for studies that presented data for HIV-infected and controls. For all studies, incidence rates of fracture and predictors of fracture among HIV-infected individuals were summarized.

Results: Thirteen eligible studies were analysed, of which seven included controls. Nine studies reported all incident fractures and 10 presented incident fragility fractures. The pooled IRR was 1.58 [95% confidence interval (CI) 1.25–2.00] for all fracture and 1.35 (95% CI 1.10–1.65) for fragility fracture. Smoking, white race and older age were consistent predictors for fragility fractures.

Conclusion: Our results indicate that HIV infection is associated with a modest increase in incident fracture. Future research should focus on clarifying risk factors, designing appropriate interventions and the long-term implications of this increased risk for an ageing HIV-infected population.

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Keywords: bone, fracture, fracture incidence, fragility fracture, HIV

Introduction

Low bone mineral density (BMD) and decreased bone mass have been reported in HIV-infected men and women as well as children and adolescents [1–3]. Multiple factors appear to be involved, including effects of HIV-1 viral proteins, inflammatory cytokines and antiretroviral therapy (ART) on bone cells and bone turnover, and the effect of HIV infection on traditional determinants of BMD such as body weight [4–8]. However, whether HIV infection and/or ART increase fracture incidence has not been clearly established. Two large database studies [9,10] suggest that the prevalence of International Statistical Classification of Diseases (ICD)-9 coded or self-reported fracture is higher among HIV-infected individuals than among the general population, particularly among older individuals. In several large cohort studies, incidence of fracture among HIV-infected individuals was compared with incidence in prospectively enrolled HIV-uninfected individuals [11,12], individuals within the same clinic system [13] or the general population [14,15]. Other cohorts have reported incidence and

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predictors of fracture limited to HIV-infected individuals [16–18]. Complicating the comparison of these studies and the interpretation of their results are their contrasting study samples and differing research methodologies. Nevertheless, as the HIV-infected population continues to age, a sophisticated understanding of the relative impact of HIV and/or ART on fracture risk is needed to better inform clinical practice and future research.

We conducted a systematic review to investigate whether incidence of fracture (both overall and fragility) differs in individuals with and without HIV. The primary objective of the study was to conduct a meta-analysis to estimate an incidence rate ratio (IRR) of incident fractures and incident fragility fractures in HIV-infected compared with controls. A secondary goal was to compare and contrast the reported incidence rates of fracture among HIV-infected individuals and to summarize predictors of fracture from available studies.

Materials and methods

Search process

We conducted a literature search of Medline, Scopus and the Cochrane Library for all studies ever published of fracture incidence in HIV-infected individuals up to 28 September 2012. Studies that were electronically published ahead of print publication during this time period were eligible for inclusion. In addition, published abstracts from the Conference on Retroviruses and Opportunistic Infections (CROI; 1997–2012), the scientific meeting of the American Society for Bone and Mineral Research (ASBMR; 2000–2011), the Conference on HIV Pathogenesis and Treatment of the International AIDS Society (IAS; 2001–2011) and the International AIDS Conference (AIDS; 2002–2012) were searched online. Specific search terms are provided in Table 1.

Study selection and data collection

A study was eligible for inclusion if it reported data from adult participants (≥16 years) and reported fracture incidence data for HIV-infected individuals. We included studies with, as well as those without a control group. Randomized clinical trials were eligible for inclusion. Studies were excluded if they were not in English, reported only prevalence data or failed to report incidence rates in person-years. Two investigators (E.C.B., S.S.) independently screened all studies by title or abstract followed by a full text evaluation and abstracted all data. Any discrepancy regarding a study's eligibility after initial screening or data abstraction was further adjudicated by review by two other investigators (M.T.Y., S.M.A.). The following was abstracted from each study: study name, authors, year of publication, study location, number of total participants, number of HIV-infected participants, number of controls (if applicable), fracture classification method (self-report, ICD codes, discharge summary), fracture type (all fractures or fragility fractures), number of fractures and person-years of observation. When available, sex, race/ethnicity, age, BMI and ART exposure status of study participants were also collected.

Outcome and data analysis

The primary outcomes in this review were the all-fracture and fragility fracture IRRs of the HIV-infected group compared with the control group. Secondary outcomes were the all-fracture and fragility fracture incidence rates in HIV-infected individuals. Fracture incidence rate was calculated by dividing the number of fractures by the period of risk for all included patients during the study period expressed as per 1000 person-years of follow-up. Exact confidence intervals (CIs) were calculated for studies that did not provide a CI but did provide the number of individuals (*N*) and person-years of follow-up. Requests for additional data were made to all authors of eligible studies that did not present results for both all fractures and fragility fractures. A pooled estimate of the IRR comparing HIV-infected with controls for

Table 1. Search terms used for systematic review.

Database or conference	Years	Search terms
Medline	Up to 28 September 2012	['HIV' (MeSH Terms) OR 'HIV' (All Fields)] AND ['fractures, bone' (MeSH Terms) OR ['fractures' (All Fields) AND 'bone' (All Fields)] OR 'bone fractures' (All Fields) OR ['bone' (All Fields) AND 'fracture' (All Fields)] OR 'bone fracture' (All Fields)
Scopus	Up to 28 September 2012	'HIV' AND 'Fracture'
Cochrane Library	Up to 28 September 2012	'HIV and fracture'
Conference on Retroviruses and Opportunistic Infections (CROI)	1997–2012	'fracture'
American Society for Bone and Mineral Research (ASBMR)	2000–2011	'HIV'
Conference on HIV Pathogenesis and Treatment of the International AIDS Society (IAS)	2001–2011	'fracture'
International AIDS Conference (AIDS)	2002–2012	'fracture'

both all fractures and fragility fractures was calculated. To account for heterogeneity between studies, a random effects model was used to calculate the combined effect sizes. Statistical heterogeneity was assessed using the I^2 coefficient. Funnel plots were not assessed for publication bias, as there were fewer than 10 studies [19]. Analyses were conducted using SAS version 9.1.3 (SAS Institute, Cary, North Carolina, USA) and RevMan (Version 5.2; The Cochrane Collaboration, Oxford, UK).

Results

Selection of studies

Figure 1 shows results from the literature search and study selection process. We identified 179 articles from the Medline database, 338 from Scopus, and two from the Cochrane library. We also identified a total of 128 abstracts, including 39 from CROI, 44 from ASBMR, 29 from AIDS and 16 from IAS. After exclusion of duplicate records and studies that did not meet our inclusion criteria, 36 articles remained and we further evaluated the full texts of these publications. Twenty-three studies were excluded because they did not contain fracture incidence data or because they did not report fracture incidence rates in person-years of observation. Authors of four studies were contacted for additional data, and all responded to data or clarification requests (i.e. providing either CIs or numbers for all fractures and/or fragility fractures and person-years) [12–14,17]. We used the provided estimated person-years for the two groups in Grund *et al.* (7500 person-years) [20]. A total of 13 studies met all inclusion criteria. A manual search of references cited by these studies did not yield any additional eligible articles.

The study by Young *et al.* [14] reported subgroup data for each year in the study, and different sampling weights were used for each year to produce population estimates and standard errors in the National Hospital Ambulatory Medical Care Survey of outpatient departments (NHAMCS-OPD). Therefore, we only used data from the most recent year (2006) containing information for both the HIV-infected group and the control group [14]. Both the CROI abstract by Volk *et al.* [21] and the

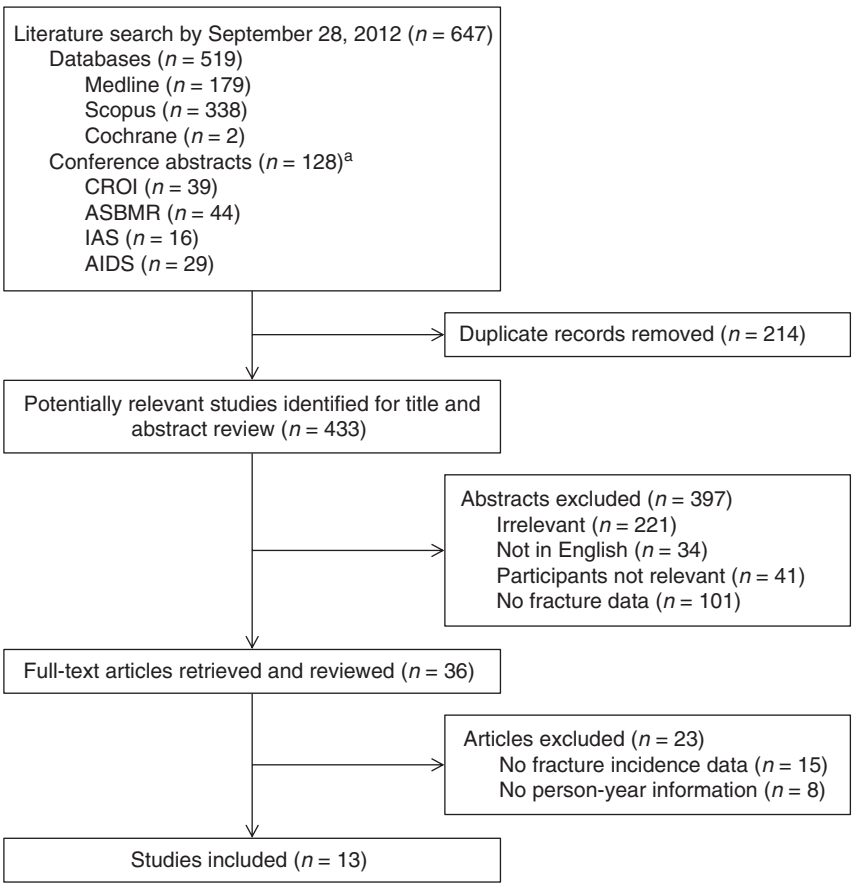

Fig. 1. Literature search and study selection. [a]Conferences included: Conference on Retroviruses and Opportunistic Infections (CROI, 1997–2012), the scientific meeting of the American Society for Bone and Mineral Research (ASBMR, 2000–2011), the Conference on HIV Pathogenesis and Treatment of the International AIDS Society (IAS; 2001–2011), and the International AIDS Conference (AIDS; 2002–2012).

manuscript by Lo Re *et al.* [22] were included in the analyses. As the abstract contained data for fracture at the spine and hip and the published manuscript contained data only for fractures at the hip, we utilized the spine data from the abstract and the hip data from the manuscript.

Study characteristics

Table 2 summarizes the characteristics of the 13 studies, published between 2007 and 2012, included in this systematic review. The meta-analysis includes only the seven studies with a control group [11–15,21–23]. Among the 13 selected studies, eight were conducted in the United States [11–14,16,21–24] and one each in France [18], Denmark [15], Australia [17] and Switzerland [25]. Grund *et al.* [20] conducted their study in multiple countries. The sample sizes of HIV-infected individuals varied widely across the studies, from 317 in the Cohort of HIV at-risk Aging Men's Prospective Study (CHAMPS) [23] to 95 827 in the study by Lo Re *et al.* [21,22] of the United States Medicaid population. Approximately half of the studies identified incident fractures using the ICD codes [13,15–17,20–22], whereas others relied on patient reports [11,12,18,23–25]. Young *et al.* [14] used discharge summaries or patient self-report to identify fractures for HIV-infected individuals, and ICD codes recorded in charts or discharge records for controls. Of the 10 studies that reported fragility fractures, four defined fragility fractures in terms of trauma (fall from standing height or less, low-energy trauma, atraumatic or low trauma, and inadequate trauma) [11,15,17,25], and six studies defined them by location (hip and vertebral, and either forearm or humerus) [12–14,16,21,22,24].

Among the seven studies with a control group, three studies utilized prospectively enrolled HIV-uninfected individuals [11,12,23]. Two studies selected controls from the same healthcare system as HIV-infected individuals: Womack *et al.* [13] used controls matched by age, race, sex and site from the Veterans Aging Cohort Study Virtual Cohort (VACS-VC) and Lo Re *et al.* [21,22] used hepatitis C virus (HCV)-uninfected/HIV-uninfected Medicaid recipients as controls. Two studies had general population controls: Hansen *et al.* [15] linked data from the Danish HIV Cohort study with the national Danish Civil Registration System and Danish National Hospital Registry to obtain matched population controls, and Young *et al.* [14] used data from NHAMCS-OPDs to obtain bone fracture rates for the general United States population. Of the seven studies that included a control group, four studies reported all incident fractures [11,14,15,23] and six reported incident fragility fractures [11–15,21,22]. However, as we were unable to obtain person-years of observation for fragility fractures from Young *et al.* [14], data from that study were not utilized for the fragility fracture analyses. Thus, four studies were used to perform meta-analysis for all fractures and five for fragility fractures (Fig. 2a,b).

Four of the 13 studies included only or mainly men [12,13,16,23] and one involved women only [11]. Not every study reported sex-specific fracture incidence data. Young *et al.* [14] reported that HIV-infected women aged 25–54 years experienced more fractures at vertebra and femoral neck sites, whereas HIV-positive men aged 25–54 years had more fractures at the wrist and vertebra, than the controls. The age means or medians of the study populations were between 35 and 55 years. Nine studies had a majority identified as 'white' or 'Caucasian' [12,14–17,20,24,25]. In general, the mean and median BMIs of the study participants were similar across the studies. The percentage of HIV-infected individuals on ART varied widely across the studies, from 27 to 100. Although most studies classified those with any ART exposure as ART treated, Bedimo *et al.* [16] applied a minimum exposure time of 1 month.

Fracture incidence

Figure 2a presents estimates of all-fracture IRR in HIV-infected individuals compared with controls. The pooled estimate of the crude IRR for all fracture was 1.58 (95% CI 1.25–2.00). Figure 2b presents estimates of fragility fracture IRR in HIV-infected individuals compared with controls. The pooled estimate of the crude IRR for fragility fracture was 1.35 (95% CI 1.10–1.65). The assessment for heterogeneity was not significant for all fractures ($Q = 6.97$, $P = 0.07$, $I^2 = 57\%$) but was significant for fragility fractures ($Q = 44.58$, $P < 0.00001$, $I^2 = 91\%$). No significant changes in heterogeneity with respect to fragility fracture were noted when the analyses were repeated omitting either the study by Yin *et al.* [11], which included only women and prospectively enrolled HIV-uninfected controls, or the study by Walker-Harris *et al.* [12], which included prospectively enrolled HIV-uninfected controls or both studies (results not shown). Table 3 presents estimates of all-fracture and fragility fracture incidence rate (per 1000 person-years) for HIV-infected individuals. Of note, there was a greater variation in the crude incidence rates of all fractures, which ranged from 0.8 to 30.6 per 1000 person-years, than the crude incidence rates of fragility fractures, which ranged from 1.4 to 7.4 per 1000 person-years.

Predictors of fracture

A summary of significant predictors of all fractures and fragility fractures in multivariable or adjusted analyses for HIV-infected individuals is presented in Table 3. Although predictors varied, several traditional risk factors remained consistent across studies, including older age [11,13–16,25], white race [11,13,15,16,23], low weight or BMI [13,14,16], smoking [11,13,15,16,24], and alcohol or substance abuse [13,14,18], particularly for fragility fractures. Diabetes, liver disease and a comorbidity index were also reported as significant predictors of fracture [11,13–15]. Although not a traditional risk factor, HCV was found to be a significant predictor of

Table 2. Characteristics of studies meeting the inclusion criteria ($n = 13$).

Author	Country	Control group (Y/N)	*N* (Total)	*N* (HIV+)	*N* (Controls)	Sex (% men)	HIV+ Race/ Ethnicity (%)	HIV+ Age (years)	HIV+ BMI (kg/m^2)	HIV+ ART exposure (%)	Fracture classification method	Fracture type
Arnsten *et al.* [23][a]	USA	Y	526	317	209	100	61 B; 12 W; 23 H	54.7, 5 (mean, SD)	15% with BMI ≥30	87 (ever)	Self-report	All
Bedimo *et al.* [16]	USA	N	56 660	56 660		98	With OF: 57 W; Without: 45 W	With OF: 46; Without: 44 (median)	With OF: 49% <20; Without: 33% <20	69 (ever)	ICD codes	Fragility (vertebral, hip, and wrist)
Collin *et al.* [18]	France	N	1281	1281		77	83.1[b]	36.2 (median)	22 (median)	100 (ever)	Self-report	All
Grund *et al.* [20]	USA, Australia, Spain	N	2753 (VS), 2720 (DC)	2753 (VS), 2720 (DC)		73[c]	55.6 W; 29.1 B; 15.3 O[c]	43, 38-50 (median, IQR) [c]	–	95 (ever)	ICD codes	All
Hansen *et al.* [15]	Denmark	Y	31 836	5306	26 530	76	80 W	36.7, 30.5–44.5 (median, IQR)	–	78 (during study period)	ICD codes	All, Fragility (low-energy trauma)
Hasse *et al.* [25]	Switzerland	N	8444	8444		71	66.1 W; 8.4 B; 1.6 H; 2.3 A; 21.5 U[d]	45, 39–51 (median, IQR)	23.5 (median)	94 (ever)	Self-report	All, Fragility (inadequate trauma)
Volk *et al.* [21]	USA	Y	462 656	95 827	366 829	63	27 W; 44 B; 9 H; 20 O	39, 33–46 (median, IQR)	–	100 (ever)	ICD codes	Fragility (hip and vertebral)
Walker Harris *et al.* [12]	USA	Y	5106	–	–	100	70%W	45.2 (mean)	25 (mean)	–	Self-report	Fragility (hip, humerus, forearm, spine)
Womack *et al.* [13]	USA	Y	119 318	40 115	79 203	100	55% B/H	At fracture: 54, 10 (mean, SD)	25 (median)	75 (at any time during follow-up)	ICD codes	Fragility (hip, vertebral, upper arm)
Yin *et al.* [11]	USA	Y	2391	1728	663	0	13.3 W; 56.3 B; 27.2 H; 3.2 O	40.4, 8.8 (mean, SD)	28.5 (mean)	65.6 (at index visit)	Self-report	All, Fragility (fall from standing height or less)
Yin *et al.* [24]	USA	N	4640	4640		83	48 W; 28.7 B; 20.4 H; 1.8 A; 1.2 O	39, 33-45 (median, IQR)	25 (median)	26.5 (ever at index)	Self-report	All, Fragility (spine, hip, and wrist)
Yong *et al.* [17]	Australia	N	2424	2424		89	Cases: 92 W; 3 B; 5 A	Cases: 49.8; Controls: 49.5; (mean)	Cases: 22.5 Controls: 25.2 (mean)	Cases and Controls: 84 (at time of fracture)	ICD codes	All, Fragility (atraumatic or low trauma)
Young *et al.* [14][e]	USA	Y	224 488 004	3004	224 485 000	78	52 W; 33 B; 11.7 H; 3.5 O	40, 36-46 (median, IQR)	24.4 (median)	73 (ever)	Discharge summary or self-report for HIV+ ICD codes for HIV-	All, Fragility (wrist, vertebra, and femoral neck of the nip)

A, Asian; B, black; DC, drug conservation group; H, Hispanic/Latino; IQR, interquartile range; NA, not available; O, Other; OF, osteoporotic fracture; U, unknown; VS, viral suppression group; W, white.
[a]Data presented from Arnsten *et al.* [23] for individuals who had at least one interview following DEXA scan. Characteristics are for the full population ($N = 559$).
[b]Unspecified. 83.1% born in France or England.
[c]Reported in [26].
[d]Reported in [27].
[e]Data presented from Young *et al.* [14] from 2006, characteristics are from all participants followed during 2000–2008.

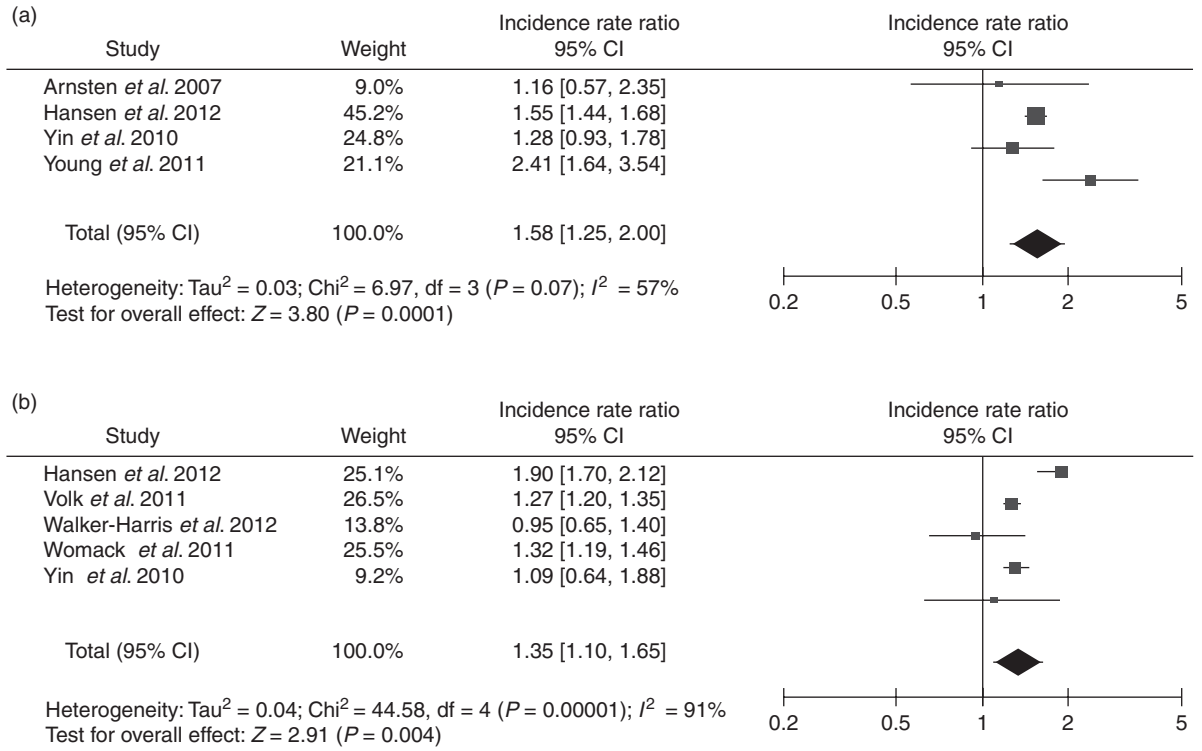

Fig. 2. A meta-analysis of crude incidence rate ratios for all fractures and fragility fractures in HIV-infected compared with controls. (a) All fractures. (b) Fragility fractures. CI, confidence interval.

fracture in many studies [14–16,18,21,22]. Use of corticosteroids was also found to be a significant predictor of fracture in three studies [13,17,24], although only one study found proton pump inhibitors to be associated with fractures [13]. As for HIV-specific variables, several studies found an association between low $CD4^+$ cell count and fracture risk [14,17,25]. Few studies reported an independent effect of ART types or exposure on fractures. Bedimo *et al.* [16] found that tenofovir and ritonavir-boosted protease inhibitors were associated with an increased risk of osteoporotic fractures, adjusted for traditional risk factors among those who entered the cohort in the HAART era (1996–2009).

Discussion

We found that HIV-infected individuals have a modestly increased risk for all fractures and fragility fractures compared with uninfected individuals or the general population. The test for statistical heterogeneity was not significant for the pooled estimate of all fractures; therefore, the IRR for all fractures appears to be a valid estimate. The test for heterogeneity, however, was significant for the pooled risk estimate for fragility fracture, and therefore, this IRR should be interpreted with caution. It should be noted that the overall incidence rate of fracture among HIV-infected individuals varied widely across studies, possibly due to the differences in demographics of the study populations.

Of the four studies that reported IRRs of all fractures, those with mainly white individuals reported a risk increase, whereas the two that did not reach significance had a majority of black participants [11,14,15,23]. With respect to fragility fracture, Lo Re *et al.* [21,22] and Womack *et al.* [13] found an increased risk in primarily minority cohorts; the largest risk, however, was reported by Hansen *et al.* [15] in which 80% of the individuals were white. Non-black race is a well known risk factor for osteoporosis. Our analysis suggests that race modifies the relationship between HIV infection and fracture and may explain some of the heterogeneity found in our analysis.

Review of the adjusted analyses of each study revealed that a number of traditional risk factors are importantly associated with fractures among individuals with HIV, including smoking [11,13,15], use of corticosteroids [17] or proton pump inhibitors [13], alcohol or substance abuse [14,18], low weight or BMI [13], and comorbidities such as diabetes and liver disease [13–15]. BMI may be of particular importance, as a meta-analysis conducted by Bolland *et al.* [8] found that lower body weight mediated the effect of HIV status on low BMD; however, reporting of weight or BMI in available fracture studies was

Table 3. Crude incidence rates of all fractures and fragility fractures and significant predictors of all fractures and fragility fractures (in adjusted analyses) in HIV-infected individuals.

(a) All fractures ($n = 9$)

Author	All-fracture crude incidence rate (95% CI) per 1000 person-years	Significant predictors of all fractures[a]
Arnsten *et al.* [23]	30.6 (19.0–46.8)	Nonblack race, low bone mineral density
Collin *et al.* [18]	3.3 (2.0–4.6)	Excessive alcohol use, HCV coinfection
Grund *et al.* [20]	0.8 (0.5–1.41)	N/A
Hansen *et al.* [15]	21.0 (19.8–22.2)	HCV coinfection[b]
Hasse *et al.* [25]	7.1 (6.1–8.3)	Older age
Yin *et al.* [11]	18.1 (15.4–21.3)	White race, older age, smoking, history of AIDS-defining illness, cumulative NNRTI use
Yin *et al.* [24]	4.0 (3.3–4.8)	Smoking, HCV coinfection, bisphosphonate use, corticosteroid use
Yong *et al.* [17]	5.3 (4.3–6.5)	N/A
Young *et al.* [14]	8.7 (5.9–12.7)	Substance abuse, HCV coinfection, older age, nadir CD4 cell count <200 cells/μl, diabetes

(b) Fragility fractures ($n = 10$)

Author	Fragility fracture crude incidence rate (95% CI) per 1000 person-years	Significant predictors of fragility fractures[a]
Bedimo *et al.* [16]	3.1 (2.9–3.3)	White race, older age, tobacco use, BMI <20 kg/m^2, HCV coinfection, tenofovir/ritonavir-boosted PI use in HAART era
Hansen *et al.* [15]	7.4 (6.7–8.2)	White race, older age, smoking, medium or high comorbidity score
Hasse *et al.* [25]	1.9 (1.7–2.2)	Older age, low CD4 count
Volk *et al.* [21]	4.2 (4.0–4.5) – HIV only 6.6 (6.3–7.0) – HIV/HCV	HCV coinfection[b]
Walker-Harris *et al.* [12]	1.4 (1.0–1.8)	Age[b]
Womack *et al.* [13]	2.5 (2.3–2.7)	White race, older age, smoking, low BMI, alcohol abuse, liver disease, corticosteroid use, proton pump inhibitor use, PI use
Yin *et al.* [11]	5.8 (4.3–7.7)	N/A
Yin *et al.* [24]	1.0 (0.7–1.5)	N/A
Yong *et al.* [17]	4.1 (3.2–5.2)	Index CD4 cell count <200 cells/μl, corticosteroid use, antiepileptic medications
Young *et al.* [14]	N/A	Older age, HCV coinfection, BMI <18.5 kg/m^2

HCV, hepatitis C virus; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.
[a]Significant factors in multivariate models.
[b]Significant factor in stratified analysis.

inconsistent and therefore, could not be evaluated in an adjusted analysis. Low body weight may not only increase risk of fracture by leading to decreased BMD but may also be associated with increased prevalence of the frailty phenotype at earlier ages and predisposition to falls. Although early frailty has been previously documented in HIV-infected men [28,29], current data on fall rates in HIV-infected individuals are limited and is an important area for future research.

The role of HIV-specific factors in bone loss and fracture also remains unclear. Lower $CD4^+$ cell counts before ART initiation have been reported to be a predictor of both bone loss after ART initiation and increases in bone turnover [30]. Low current $CD4^+$ cell counts (<200 cells/μl) in studies by Yong *et al.* [17] and Hasse *et al.* [25] were associated with increased fragility fracture incidence in multivariate analyses. Similarly, nadir $CD4^+$ cell count of less than 200 cells/μl in the study by Young *et al.* [14] was associated with increased all-fracture incidence in multivariate analysis. However, pretreatment $CD4^+$ cell count was not associated with fracture incidence in the longitudinal follow-up of participants enrolled in randomized clinical trials of ART initiation [24], and nadir or current $CD4^+$ cell count was not predictive of fractures in other studies [13,15].

Several studies analysed the association between ART exposure and fracture risk. Hansen *et al.* [15] found that ART-exposed patients had a higher risk of fragility fracture than the general population that remained significant after adjusting for the comorbidity index (IRR = 1.6; 95% CI 1.36–1.87), but ART exposure was not associated with an increased risk of nonfragility fracture. In a larger database of HIV-infected individuals, when analyses were restricted to those entering the cohort in the era of potent ART, Bedimo *et al.* [16] found that exposure to either tenofovir or protease inhibitors was associated with an increased incidence of osteoporotic fracture. Most other studies failed to find an association between ART and fracture incidence; however, this may be partly due to insufficient sample size and differences in the classification of antiretroviral regimens used across the studies.

Interestingly, HCV was consistently identified as an independent risk factor for both fragility and nonfragility incident fractures [14–16,18,21,22]. The increased risk of fracture is approximately 1.5–2 times greater in HIV/HCV coinfected than HIV monoinfected individuals [15,16,21,22]. One study [31] found that BMD was lower in HIV/HCV coinfected than HIV monoinfected women, but not in men. A recent study found that DXA-derived hip geometry measures (buckling ratio and centroid position) differed between HIV/HCV coinfected men and uninfected controls, suggesting that fracture risk in HIV/HCV coinfected individuals may be due to compromised bone strength as well as lower bone density [32]. Although the mechanisms are not well understood, HIV/HCV coinfection appears to have a negative effect on bone strength and fracture risk. The relationship between HIV/HCV coinfection and fracture risk warrants further study.

Our study has a number of limitations. We cannot exclude the possibility of publication bias, though we attempted to minimize this by reviewing abstracts from major scientific meetings. We were also unable to evaluate funnel plots due to the small number of published studies that met our criteria for inclusion. As mentioned, there was a considerable diversity across the studies in terms of study populations and how fractures were determined, thus introducing heterogeneity into our pooled analyses. The accuracy and reliability of the methods used to distinguish fragility from nonfragility fractures is also unknown, allowing for potential misclassification bias. In addition, we were not able to perform analyses on adjusted estimates of incidence rate for important factors such as age, race, sex, weight, antiretroviral exposure and $CD4^+$ cell count, as these data were not available in most studies and those that conducted adjusted analyses included different variables.

This systematic review and meta-analysis suggests that HIV infection and/or ART are associated with modest increases in fracture risk with a pooled IRR of 1.58 (95% CI 1.25–2.00) for all fracture. Our results show the importance of including fracture outcomes in prospective studies that provide individual patient level data in order to establish the attributable risk of HIV infection and/or ART on fracture, as well as the contribution of other risk factors, including age, sex, race, weight and smoking. Validation of fracture prediction algorithms, such as FRAX [33], for HIV-infected individuals remains an important area of research. Although at present the overall increase in risk of fracture is modest, this can be expected to increase in the future as the HIV-infected population continues to age, and studies of risk reduction interventions are warranted.

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E.C.B. and S.S. undertook searches, extracted data and contacted authors for additional data. S.S. performed the statistical analysis. All authors played a role in writing, editing and approving the text as submitted to AIDS.

Conflicts of interest

M.T.Y. has served as a consultant for Gilead and Abbott.

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