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Bone Density and Fractures in HIV-infected Postmenopausal Women: A Systematic Review

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Abstract

With the development of effective antiretroviral therapy, HIV-infected women are living longer and transitioning through menopause. The purpose of our study was to systematically examine the evidence that menopause is an additional risk predictor for osteoporosis and fractures in HIV-infected women. Electronic databases were searched for studies of low bone density or fractures in HIV-infected postmenopausal women. Studies that met the inclusion criteria ($n = 10$) were appraised using a validated quality assessment tool. The majority of studies were rated as good quality and the remaining were fair. The prevalence of osteoporosis reported in these studies ranged from 7.3% to 84% and 0.7% to 23% in HIV-infected and uninfected postmenopausal women, respectively. In the two qualifying studies, postmenopausal status was not a predictor of fractures in HIV-infected women. Findings suggest that HIV care providers should accurately assess postmenopausal status and modifiable risk factors for osteoporosis in all older HIV-infected women.

Keywords

bone mineral density (BMD); fractures; HIV; menopause

Access to antiretroviral therapy (ART) has increased life expectancy among HIV-infected individuals. By 2020, roughly 70% of all people living with HIV will be ages 50 years and older (Karpiak, 2014). Not only is the aging HIV population at greater risk of developing comorbidities such as osteopenia and osteoporosis, but these conditions may also occur at a younger age (Guaraldi et al., 2011). Accelerated bone loss is a common complication of HIV infection and ART (McComsey et al., 2011). Studies have estimated an osteoporosis prevalence rate of 15% in people living with HIV (Bonjoch et al., 2010; Brown & Qaqish,

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2006), and a 58% higher fracture rate compared to the general population (Shiau, Broun, Arpadi, & Yin, 2013). With the growing prevalence of HIV among people in middle and old age, there is an urgent need to better characterize the impact of HIV on osteoporosis.

From 2007 to 2010, the estimated number of adults ages 50 years or older living with HIV in the United States increased by nearly 47,000, with a growing proportion of women represented in this older group (Centers for Disease Control and Prevention, 2013). HIV-infected women face the additional consequences of estrogen withdrawal and deficiency during meno-pause transition, which give rise to some of the same metabolic alterations as HIV such as insulin resistance, elevated waist circumference, low high-density lipoprotein levels, and bone loss (Adeyemi, Rezai, Bahk, Badri, & Thomas-Gossain, 2008). Accordingly, menopause may accelerate HIV-related bone loss, and in turn, place HIV-infected postmenopausal women at greater risk for osteoporosis and associated fractures. While the National Osteoporosis Foundation (Cosman et al., 2013) added HIV to their list of conditions that cause or contribute to osteoporosis and fractures, the quality of the evidence on bone loss specifically in HIV-infected older women has not been previously examined.

Over the past several years, a number of reviews have been published on menopause-associated metabolic manifestations in HIV-infected women (Imai, Sutton, Mdodo, & Del Rio, 2013; Kojic, Wang, & Cu-Uvin, 2007; Looby, 2012). The evidence on the effect of ART on bone density in HIV-infected women has also been explored (Carvalho, Gelenske, Bandeira, & Albuquerque, 2010). However, to date, the quality of the literature on menopause-associated changes involving bone in HIV-infected women has not been systematically appraised. Therefore, to evaluate the evidence that menopause is an additional risk predictor for accelerated bone pathology in HIV-infected women, we carried out a systematic review of the current literature.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement was used as a guideline (Moher, Liberati, Tetzlaff, & Altman, 2009). The PRISMA Statement consists of a 27-item checklist to ensure a standard method of transparent reporting of systematic reviews and meta-analyses.

Search Strategy

The following electronic databases were thoroughly searched for all studies published through September 2014 on low bone density or fractures in HIV-infected postmenopausal women: Medline, Scopus, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). A combination of the search terms “HIV infections,” “osteoporosis,” “bone density,” and “fractures” were used. The search was limited to English-language peer-reviewed articles, and studies with postmenopausal women. A detailed outline of the search is provided in Table 1. Reference lists of retrieved articles were reviewed to identify additional relevant studies.

Eligibility Criteria

The titles and abstracts of all studies retrieved in the literature search were reviewed. No time limit was imposed and the last search was performed on September 17, 2014. Studies were eligible for analysis if they included a sample of HIV-infected postmenopausal women, and reported bone mineral density (BMD) or fracture data for HIV-infected postmenopausal women. Studies were included regardless of how postmenopausal was defined (e.g., amenorrhea for 12 consecutive months without confirmational hormone measures). Study selection was limited to BMD data obtained using dual-energy X-ray absorptiometry (DXA). DXA is a validated measure of BMD and meets the requirements of the World Health Organization diagnostic classification of osteopenia and osteoporosis (World Health Organization, 2004). Studies were excluded if they did not report any BMD or fracture data specifically for HIV-infected postmenopausal women.

Data Extraction

The following categories were used for data extraction: authors, year of publication, study design, sample size, number of HIV-infected participants, number of controls (if applicable), and findings. When available, sample characteristics such as age, race/ethnicity, body mass index (BMI), use of hormone replacement therapy (HRT), and ART exposure were also abstracted. Given that bone density and fractures were the outcomes of interest, information on DXA scan body site and fracture type were collected from each study.

Quality Assessment

The methodological quality of each study was assessed using a validated checklist developed by Downs and Black (1998). The checklist consists of 27 items, with a total possible score of 28 for randomized and 25 for nonrandomized health care interventions. The checklist assesses quality across five domains: (a) how well study aims and procedures are reported in the paper, (b) external validity, (c) bias, (d) confounding, and (e) power. With the exception of confounding and power, each item is scored as 0 or 1, with a score of 1 indicating that the quality criterion is satisfied. One of the items on confounding is scored from 0 to 2, indicating the criterion is *not satisfied* (= 0), *partially satisfied* (= 1), or *fully satisfied* (= 2).

As in previously published reviews using the Downs and Black quality assessment tool (Gaynes et al., 2005; Samoocha, Bruinvels, Elbers, Anema, & van der Beek, 2010; Uchida, Pogorzelska-Maziarz, Smith, & Larson, 2013), the checklist was slightly modified for our review given that none of our included articles were interventional studies. Specifically, the item on statistical power was simplified to a score from 0 to 2 (0 = *no power analysis conducted*, 1 = *power analysis conducted for 1 outcome measure*, 2 = *power analysis conducted for 2 or more outcome measures, if applicable*). A quality score was calculated based on the number of quality assessment items satisfied. Items that did not pertain to the study were rated as *not applicable* and were not included in the overall score. Quality assessment scores were grouped into four quality ratings: 18 to 20 (*excellent*), 14 to 17 (*good*), 10 to 13 (*fair*), and less than 10 (*poor*).

Two reviewers (YC, NR) pilot-tested the assessment of methodological quality by independently rating quality scores of two eligible studies and then together determining consensus. As there was no major disagreement in scores, one reviewer (YC) assessed the remaining articles.

Results

Study Selection

The literature search identified 1,093 potentially relevant articles for review. After excluding duplicate records from the electronic databases, 646 titles and abstracts were screened for eligibility. Of these, 618 studies were excluded for two main reasons: postmenopausal women were not included in the sample or the studies did not provide fracture or BMD data. This resulted in the retrieval of 28 articles for full-text review. Upon full-text review, 18 articles were excluded: seven did not include HIV-infected postmenopausal women in the sample, four did not assess BMD or fractures, three studies did not specifically report BMD or fracture data for postmenopausal women, and four articles were duplicate reports. In total, 10 studies were included in our systematic review. Figure 1 provides detailed results of the literature search and study selection process.

The study characteristics of the 10 investigations included in the systematic review are presented in Table 2. Of these, six were conducted in the United States, two in Brazil, and one each in Italy and France. The majority of articles were cross-sectional in design ($n = 6$); the remaining were longitudinal cohort studies ($n = 4$). Eight of the 10 analyses of BMD or fractures compared HIV-infected postmenopausal women with either HIV-infected premenopausal (Cazanave et al., 2008; Jacobson, Spiegelman, Knox, & Wilson, 2008; Yin et al., 2012) or HIV-uninfected postmenopausal women (Anastos et al., 2007; Li Vecchi et al., 2012; Sharma, Cohen, Freeman, Santoro, & Schoenbaum, 2011; Yin et al., 2005; Yin et al., 2010). Comparison groups in the remaining analyses included: HIV-infected pre- and perimenopausal women (Gomes et al., 2014), and HIV-infected men and premenopausal women (Pinto Neto et al., 2011). Five reports described sub-studies of larger investigations, including the Women's Interagency HIV Study (Anastos et al., 2007; Yin et al., 2010), the Menopause Study Cohort (Sharma et al., 2011), the AIDS Clinical Trials Group Longitudinal-Linked Randomized Trial database (Yin et al., 2012), and the Agence National Recherche sur la Sida (ANRS) CO3 Aquitaine Cohort (Cazanave et al., 2008). The primary outcome in three of the studies was incident fractures. Seven studies reported on BMD features.

One or more of the following sample characteristics were reported in each study: age, race/ethnicity, BMI, and ART exposure. Two studies reported current or past use of HRT (Yin et al., 2005; Yin et al., 2010). Mean or median ages ranged from 38 to 59 years. Five studies included samples of both men and women (Cazanave et al., 2008; Jacobson et al., 2008; Li Vecchi et al., 2012; Pinto Neto et al., 2011; Yin et al., 2012). Overall, nine studies reported data on race/ethnicity; in four cases, the majority of participants identified as *Black or African American* (Anastos et al., 2007; Jacobson et al., 2008; Sharma et al., 2011; Yin et al., 2010). Participants were mostly overweight across studies (e.g., mean BMI of 25 to 28.5 kg/m²).

The majority of the subjects in each report were on ART, ranging from 61% (Jacobson et al., 2008) to 100% (Yin et al., 2012). In the two studies that reported current or past use of HRT, rates were low: 7% (Yin et al., 2010) and 26% (Yin et al., 2005). While one of the selected investigations purposefully enrolled postmenopausal women with HIV (Yin et al., 2005), the remaining studies included subsets of subjects meeting these criteria. The proportion of subjects meeting these criteria ranged from 5% (20/379) in the study by Jacobson and colleagues (2008) to 15% (45/300) in Pinto Neto and colleagues (2011). Four studies defined postmenopause status as self-reported amenorrhea for at least 12 consecutive months (Anastos et al., 2007; Gomes et al., 2014; Sharma et al., 2011; Yin et al., 2010). One study confirmed postmenopausal status using serum estradiol and follicle-stimulating hormone levels (Yin et al., 2005).

Methodological Quality of Studies

Table 3 summarizes the methodological quality of studies using the checklist by Downs and Black (1998). The mean quality assessment score for included studies was 13.8. None of the studies fulfilled all of the quality criteria. The majority of studies ($n = 6$) were rated *good* and the remainder of studies had *fair* quality. Of the studies with the highest quality scores, two were cohort studies (Sharma et al., 2011; Yin et al., 2010) and one was a cross-sectional investigation (Yin et al., 2005). All studies scored well on the reporting criteria (7 to 9 out of a possible 9).

External validity was limited across studies because the source population was not adequately described and representativeness of the sample could not be determined. As all bone density studies assessed BMD using DXA, a well-established approach for the classification of osteopenia and osteoporosis (World Health Organization, 2004), outcome misclassification bias was low across these studies. In both investigations of fractures, the incidence of fractures was determined by self-report (Yin et al., 2010; Yin et al., 2012). Higher quality studies scored better on the confounding criteria, having sufficiently described sample selection (Sharma et al., 2011; Yin et al., 2005; Yin et al., 2010). Potential confounders examined across studies included: age, BMI, ART use, tobacco use/smoking history, and CD4 count. The most common weakness among studies was the failure to report a power analysis, with only one study having addressed power (Gomes et al., 2014).

Outcomes

Individual study findings are summarized in Table 4. Five studies reported on low BMD or osteoporosis. Two of these investigations reported that the odds of osteoporosis were significantly higher for HIV-infected postmenopausal women compared with uninfected controls. Studies comparing low BMD and osteoporosis in HIV-infected postmenopausal versus premenopausal women also found a greater likelihood of low BMD in postmenopausal women (Cazanave et al., 2008; Gomes et al., 2014). Odds of low BMD were also significantly higher in postmenopausal women with HIV compared to HIV-infected men and premenopausal women (Pinto Neto et al., 2011). The prevalence of osteoporosis reported in these studies ranged from 7.3% to 84% in HIV-infected postmenopausal women (Anastos et al., 2007; Cazanave et al., 2008; Gomes et al., 2014;

Pinto Neto et al., 2011; Yin et al., 2005) and 0.7% to 23% (Anastos et al., 2007; Yin et al., 2005) in uninfected controls.

Three studies in our review reported on bone loss in HIV infection (Jacobson et al., 2008; Li Vecchi et al., 2012; Sharma et al., 2011). Annual change in BMD was significantly higher for HIV-infected postmenopausal women compared to premenopausal women (Jacobson et al., 2008) and uninfected postmenopausal women (Sharma et al., 2011). Similarly, in a study of HIV-infected men and women, postmenopausal status was correlated with lower DXA T-scores (Li Vecchi et al., 2012).

Of the two studies reporting on fractures, one found that the likelihood of fractures was 1.5 times higher in HIV-infected postmenopausal women compared to uninfected controls (Yin et al., 2010). In the second study, in 614 ART-naïve women, the likelihood of fractures was significantly higher in peri- and postmenopausal women with HIV than the HIV-infected premenopausal comparison group.

Predictors of Low BMD and Fractures

Predictors of low BMD and fractures for the entire sample in each study are presented in Table 4. Several traditional risk factors were independently associated with low BMD: older age (Cazanave et al., 2008; Li Vecchi et al., 2012), lower BMI (Jacobson et al., 2008; Pinto Neto et al., 2011; Sharma et al., 2011), or lowest historical weight (Yin et al., 2005), and corticosteroid use (Jacobson et al., 2008). Behavioral predictors of low BMD included strength training (Jacobson et al., 2008) and substance abuse (Li Vecchi et al., 2012; Sharma et al., 2011). HIV characteristics independently associated with low BMD included: ART with (Anastos et al., 2007) or without (Sharma et al., 2011) a protease inhibitor, time on ART (Jacobson et al., 2008), low nadir CD41 T cell count (Cazanave et al., 2008; Li Vecchi et al., 2012), and higher viral load (Pinto Neto et al., 2011). HIV-hepatitis C virus (HCV) co-infection was associated with low BMD in a single report (Li Vecchi et al., 2012). In six (75%) of the eight BMD studies, postmenopause, or time since menopause, was independently associated with low BMD or bone loss in HIV infection (Anastos et al., 2007; Gomes et al., 2014; Jacobson et al., 2008; Pinto Neto et al., 2011; Sharma et al., 2011; Yin et al., 2005).

Among the fracture studies, older age (Yin et al., 2010), White race (Yin et al., 2010), corticosteroid use (Yin et al., 2012), and current smoking (Yin et al., 2012) were independent predictors of fractures. While HIV characteristics were not independently associated with fractures, both studies found that HIV/HCV co-infection was a predictor of fractures for HIV-infected men and women (Yin et al., 2012; Yin et al., 2010).

Postmenopause was not independently associated with fractures in multivariate models (Yin et al., 2010; Yin et al., 2012).

Discussion

In the general population, BMD screening is recommended for women ages 65 years or older, postmenopausal women of any age, and those in the menopause transition with one or more of the following clinical risk factors for fractures: lower BMI, a prior osteoporotic

fracture, use of glucocorticoids, current smoking, and alcohol intake (Cosman et al., 2013). Similarly, in our review of studies of HIV-infected women, older age (Cazanave et al., 2008; Li Vecchi et al., 2012; Yin et al., 2010), lower BMI (Jacobson et al., 2008; Pinto Neto et al., 2011; Sharma et al., 2011), postmenopausal status (Anastos et al., 2007; Gomes et al., 2014; Jacobson et al., 2008; Pinto Neto et al., 2011; Sharma et al., 2011; Yin et al., 2005), and glucocorticoid use (Jacobson et al., 2008; Yin et al., 2010) were associated with lower BMD. Strength training had a protective effect on bone (Jacobson et al., 2008), which was consistent with evidence from studies of healthy women (Wallace & Ballard, 2002). HIV/HCV co-infection was independently related to fractures in both of the fracture studies (Yin et al., 2010; Yin et al., 2012), a finding previously reported for the general HIV patient population (Lo Re et al., 2012; Maalouf et al., 2013). Studies in this review also confirmed that ART exposure was associated with reduced BMD and osteoporosis (Anastos et al., 2007; Jacobson et al., 2008; Sharma et al., 2011).

This is the first systematic review to assess the quality of the evidence on low BMD and fractures in HIV-infected postmenopausal women. Our review found moderately strong evidence that HIV-infected postmenopausal women are at heightened risk for osteoporosis, beyond that normally experienced by uninfected women after menopause or HIV-infected premenopausal women. The majority of the studies in our review observed that postmenopausal status, or years since menopause, was independently associated with lower BMD. These findings suggest that the additive effects of HIV infection and menopause may worsen bone loss, perhaps due to an increase in inflammatory markers such as tumor necrosis factor- α (TNF α) and interleukin-6 (IL6). TNF α and IL6 levels have been shown to increase after menopause (Pfeilschifter, Koditz, Pfohl, & Schatz, 2002) and HIV infection (Deeks, 2011). Higher levels of TNF α and IL6 are associated with increased activation and differentiation of osteoclasts, which lead to greater bone resorption (Fouda et al., 2012).

The literature search resulted in only two studies of fractures in HIV-infected postmenopausal women. While these studies found a modest increase in fracture risk for postmenopausal women compared to HIV-uninfected or premenopausal controls, postmenopausal status was not an independent predictor of fractures, despite the higher risk of low BMD. These findings may be attributed to the relatively young age of study participants. Although the incidence of fractures in uninfected individuals increases after age 50 years (Kanis et al., 2001), the mean ages of HIV-infected individuals across fracture studies in this review were 39-40 years (Yin et al., 2012; Yin et al., 2010). At the same time, a recent meta-analysis of 13 studies, conducted primarily in men younger than 50 years of age, found that HIV infection was associated with a modest increase in fractures. To better address the risk of fractures in HIV-infected women, longitudinal studies assessing age, menopause status, and time since menopause will be needed.

Our review identified several gaps in the current research on bone density and fractures in HIV-infected postmenopausal women. First, the literature on postmenopausal women with HIV is limited. Five of the 10 studies in this review were conducted solely in women, with the remaining studies including a large sample of men. Comparison groups varied from uninfected postmenopausal women to HIV-infected premenopausal women and men.

Studies with a larger sample of HIV-infected postmenopausal women would strengthen overall validity of findings in this review.

Next, the majority of studies classified women as postmenopausal based on the exclusive criterion of self-reported amenorrhea for at least 12 consecutive months (Anastos et al., 2007; Gomes et al., 2014; Jacobson et al., 2008; Sharma et al., 2011; Yin et al., 2010). The Stages of Reproductive Aging Workshop (STRAW) defines postmenopause as the cessation of menses for more than 12 consecutive months with confirmational changes in follicle-stimulating hormone, estradiol, and antimüllerian hormone concentrations (Harlow et al., 2012). The importance of reproductive hormone measures was evident in a recent study of low BMD in HIV-infected individuals, where higher levels of estradiol were significantly related to higher BMD measures (El-Maouche, Xu, Cofrancesco, Dobs, & Brown, 2011). Studies have also shown that HIV-infected women experienced prolonged amenorrhea and early menopause more frequently than women in the general population (Cejtin et al., 2006; Prior et al., 2007), indicating the need for more reliable endocrine measures to avoid misclassification of reproductive stage. Thus, the application of the STRAW guidelines for staging menopause may be especially useful in research with middle-aged HIV-infected women.

Another gap in the current literature is the lack of research on emerging risk factors for osteoporosis and fractures in HIV-infected women. Recent studies in otherwise healthy individuals have shown that both depression (Cizza, Primma, Coyle, Gourgiotis, & Csako, 2010) and surgical menopause (Yoshida, Takahashi, Yamatani, Takata, & Kurachi, 2011) were independently associated with lower BMD and fractures. A meta-analysis of 20 studies found that BMD was up to 7.32% lower for individuals of both genders with major or minor depression (Cizza et al., 2010). The sympathetic activation of proinflammatory cytokines in depression, such as IL6 (Anderson et al., 2013), is one potential explanation for the association between bone metabolism and depression. The odds of depressive symptoms are significantly higher for HIV-infected women in early perimenopause (Maki et al., 2012), suggesting its potential role as an important but understudied confound of bone loss in HIV-infected postmenopausal women. One study in our review assessed depression but did not include this variable in its analyses of BMD (Sharma et al., 2011).

Similarly, the role of hysterectomy as a contributing risk factor to elevated bone loss in HIV-infected postmenopausal women remains understudied. In healthy women, serum bone turnover markers rapidly increase after bilateral oophorectomy (Bahar et al., 2011). Women with HIV are more likely than uninfected women to require a hysterectomy, most often due to a higher prevalence of cervical neoplasia (Massad et al., 2007). Although information on hysterectomy was collected at baseline in several of the reports reviewed here, none of these studies included surgical menopause in their analyses of bone loss predictors (Anastos et al., 2007; Jacobson et al., 2008; Yin et al., 2012; Yin et al., 2010).

Our systematic review highlights areas for strengthening design and methods in future research of reduced BMD and fractures in HIV-infected postmenopausal women. Going forward, studies should plan for an adequate sample size of postmenopausal women, sufficient to determine the potential additive effects of menopause and HIV infection on

bone. Serial endocrine biomarkers should be incorporated into study designs to confirm menopause status, as well as confirmatory records of surgical procedures to avoid the misclassification of postmenopausal women. Finally, given the well-established influence of depression on bone in uninfected individuals, and the high rates of depression in HIV-infected patients, mental health status should also be adjusted for when calculating bone loss and fracture risk in HIV-infected postmenopausal women.

This review has several limitations. Included studies were restricted to English-language articles published in peer-reviewed journals. Only studies that assessed BMD by DXA were included, so it is possible that other less rigorous studies were missed. Given the significant heterogeneity, a meta-analysis was not conducted.

Conclusions

Although there is sufficient evidence to support menopause as an important predictor of bone loss and low BMD in HIV-infected postmenopausal women, there is still inadequate evidence to suggest a role in fracture rates at this time. Future studies that follow women across the menopause transition, using confirmatory endocrine biomarkers, are needed to gain a better understanding of the impact of menopause on HIV disease progression and bone loss. Longer-than-usual follow-up of HIV-infected women may be necessary to determine risk for fractures in this population, given their earlier age of menopause and age at which fractures commonly occur. In addition, a greater understanding of the effect of reproductive hormones on HIV-associated non-AIDS conditions, such as low BMD, is important to prevent and treat these conditions more effectively in the growing population of older women with HIV (High et al., 2012). Findings in our review are relevant to health care providers with an HIV-infected patient population because they highlight the need to accurately assess postmenopausal status and modifiable risk factors for osteoporosis in all older HIV-infected women.

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Key Considerations

- With the development of antiretroviral therapy, HIV-infected women are living longer and transitioning through menopause. The current state of the evidence suggests that HIV-infected postmenopausal women are at greater risk of bone loss compared to HIV-infected premenopausal women and HIV-uninfected postmenopausal women.
- The evidence on fractures in HIV-infected postmenopausal women is limited. However, studies have found a modest increase in fracture risk for postmenopausal women compared to HIV-uninfected or premenopausal controls.
- The quality of the evidence of bone mineral density and fractures in HIV-infected postmenopausal women is *fair to good*, suggesting the need for HIV care providers to more accurately assess postmenopausal status and modifiable risk factors for osteoporosis in all older HIV-infected women.

Figure 1.

Flow diagram of the study selection process. *Note.* CINAHL = Cumulative Index to Nursing and Allied Health Literature; BMD = bone mineral density. ^aInclusion criteria: (a) peer-reviewed English-language articles; (b) includes a sample of HIV-infected postmenopausal women; (c) reports BMD or fracture incidence data for HIV-infected postmenopausal women; and (d) BMD data obtained using dual-energy X-ray absorptiometry.

Table 1

Databases and Search Terms Used in the Search Strategy

Database	Years	Search Terms
Medline	Up to September 2014	Exp "HIV infections" (MeSH Terms) AND exp "Bone density" (MeSH Terms) OR exp "Fractures, Bone" (MeSH Terms) OR exp "Osteoporosis, Postmenopausal" (MeSH Terms)
Scopus	Up to September 2014	Bone density OR Osteoporosis OR Fractures AND HIV infections
CINAHL	Up to September 2014	Bone density (MW) OR Osteoporosis (MW) OR Fractures (MW) AND HIV infections (MW)

Note. Exp = exploded; MeSH = Medical Subject Heading; CI-NAHL = Cumulative Index to Nursing and Allied Health Literature; MW = Word in Subject Heading.

Table 2

Characteristics of Studies Included in the Review ($n = 10$)

Study (Year)	Study Design	N (Total)	N (HIV+ PoM)	N (Comparison)	Age (Years)	Race/Ethnicity (%)	BMI (kg/m ²)	% ART Exposure
Anastos et al. (2007)	Cross-sectional	426	73	10 (HIV+/PoM)	42.8 (Mean)	61.3 B; 19.7 W; 19 L/H	28.0 (Mean)	72.3
Cazanave et al. (2008) ^a	Cross-sectional	492	31	102 (HIV+/PrM)	41.0 (Median)	—	38.8% with BMI < 20	93.1
Gomes et al. (2014)	Cross-sectional	273	111	162 (HIV+/PrM and PeriM)	47.7 (Mean)	60.1 NW	48.3% with BMI < 25	92
Pinto Neto et al. (2011) ^a	Cross-sectional	300	45	255 (HIV+/PrM and HIV+ men)	—	70.7 W	41.1% with BMI > 25	88.3
Yin et al. (2005)	Cross-sectional	217	31	186 (HIV+/PoM)	56 (Mean)	26 AA; 74 L/H	26 (Mean)	90.3
Jacobson et al. (2008) ^a	Longitudinal cohort	379	20	76 (HIV+/PrM)	43 (Median)	51 AA; 34.4 W; 14.6 O	29.2% with BMI < 30	60.6
Li Vecchi et al. (2012) ^a	Cross-sectional	188	18	26 (HIV+/PoM)	47 (Mean)	100 C	31.2% with BMI < 25	93
Sharma et al. (2011)	Longitudinal cohort	620	46	41 (HIV+/PoM)	45 (Mean)	57.6 B; 5.7 W; 31.4 L/H; 5.3 O	28.2 (Mean)	87.8
Yin et al. (2010)	Longitudinal cohort	2,391	338	74 (HIV+/PoM)	40.4 (Mean)	56.3 B; 13.3 W; 27.2 L/H; 3.2 O	28.5 (Mean)	65.6
Yin et al. (2012) ^a	Longitudinal cohort	4,640	185 (PoM or PeriM)	477 HIV+/PrM	39 (Mean)	28.7 B; 48 W; 20.4 L/H; 1.8 A; 1.2 O	25 (Mean)	99.7

Note. A = Asian; AA = African American; ART = antiretroviral therapy; B = Black; BMD = bone mineral density; BMI = body mass index; C = Caucasian; FN = femoral neck; L/H = Latino/Hispanic; HRT = hormone replacement therapy; LS = lumbar spine; NW = Non-white; O = Other; PeriM = perimenopausal; PoM = postmenopausal; PrM = premenopausal; W = White.

^aStudy sample included men and women.

Table 3

Methodological Quality of Studies Included in the Review

Author (Year)	Reporting ^a	External Validity ^b	Bias ^c	Confounding ^d	Power ^e	Quality Score	Rating
Anastos et al. (2007)	8	1	3	2	0	14	Good
Cazanave et al. (2008)	8	1	3	1	0	13	Fair
Gomes et al. (2014)	8	0	3	1	2	12	Fair
Pinto Neto et al. (2011)	8	1	3	2	0	14	Good
Yin et al. (2005)	8	1	3	3	0	15	Good
Jacobson et al. (2008) ^a	7	0	4	1	0	12	Fair
Li Vecchi et al. (2012) ^a	7	0	3	1	0	11	Fair
Sharma et al. (2011)	8	1	4	3	0	16	Good
Yin et al. (2010)	9	1	4	3	0	17	Good
Yin et al. (2012)	7	1	4	2	0	14	Good

Note. Methodological quality was assessed using a checklist by Downs and Black (1998). Each criterion was scored from 0 to 1 (0 = *no*, 1 = *yes*, n/a = not applicable), with the exception of confounding and power, which were scored from 0 to 2. Ratings were as follows: excellent (18-20), good (14-17) fair (10-13), poor (<10).

^aReporting: how well study aims and procedures are reported in the paper.

^bExternal validity: generalizability to study findings to the population from which the study subjects were derived.

^cBias: examines biases in measurement of the intervention and the outcome.

^dConfounding: assesses selection bias and comparability of groups.

^ePower: whether a power analysis was conducted.

Table 4**Individual Study Findings of Postmenopausal Status and Low BMD or Fractures in HIV Infection**

Author	Outcome Variable	Findings (95% CI)	Significant Predictors in Multivariate Models
OR/PR of low BMD or osteoporosis			
Anastos et al. (2007)	Low BMD (T-score < -1.0) and osteoporosis (T-score < -2.5) at LS or FN in HIV+ PoM versus HIV+ PrM	OR low BMD: 3.2 (1.6 to 6.2) OR osteoporosis: 4.8 (1.2 to 18.9)	ART-naïve, HIV on ART with PI, postmenopause
Cazanave et al. (2008)	Low BMD (T-score < -1.0) at LS or FN in HIV+ PoM versus HIV+ PrM	OR low BMD: 1.2 (0.54 to 2.7) ^b OR osteoporosis: 7.1 (1.9 to 26.4) ^b	Older age, nadir CD4 cell count
Gomes et al. (2014) ^d	Low BMD (T-score < -1.0) at LS and FN in HIV+ PoM versus HIV+ PrM or perimenopausal	PR low BMD LS: 23.3 (7.3 to 74.2) PR low BMD FN: 56.7 (7.9 to 409.4)	Postmenopause
Pinto Neto et al. (2011) ^d	Odds of low BMD (T-score < -1.0) at LS, FN, or total hip in HIV+/PoM versus HIV+ men and women not PoM	OR: 13.4 (2.5 to 71.1)	Male, lower BMI, postmenopause, undetectable viral load
Yin et al. (2005) ^c	Osteoporosis (T-score < -2.5) at LS, FN, and non-dominant radius in HIV+ PoM versus HIV- PoM	OR osteoporosis: 2.4 (1.1 to 5.3) ^b	Years since menopause, lowest historical weight
Change in BMD			
Jacobson et al. (2008)	Annual percent change in total body BMD in HIV+ PoM versus HIV+ PrM	PoM: -1.0 (-1.7 to -0.34) ^a PrM: 0.12 (-0.16 to 0.41) ^a	Postmenopause, low albumin (mg/dL), lower BMI, no strength training, prednisone/hydrocortisone use, time on ART (d4T, ddi, tenofovir, saquinavir)
Li Vecchi et al. (2012)	Correlation between postmenopause and BMD T-score at LS and FN	Correlation coefficient LS = -0.17 ^a Correlation coefficient FN = -0.17 ^a	HIV/HCV co-infection, older age, low yogurt intake, nadir CD4, drug addiction
Sharma et al. (2011)	Annual change in BMD (g/cm ²) at LS, FN, and total hip associated with PoM in HIV+	LS: -0.010 (-0.019 to -0.001) FN: -0.007 (-0.014 to 0.000) TH: -0.016 (-0.024 to -0.008)	Postmenopause, methadone use, baseline BMD, lower BMI, no protease inhibitor use
HR of fractures			
Yin et al. (2010)	Self-reported fragility and nonfragility fractures in HIV+ PoM versus HIV- PoM	HR: 1.5 (1.1 to 2.2) ^a	Older age, white race, HIV/HCV co-infection, higher serum creatinine
Yin et al. (2012) ^d	Self-reported fragility and nonfragility fractures in HIV+ PoM and perimenopausal versus HIV+ PrM	HR: 5.8 (1.4 to 23.3) ^a	Bisphosphonate use, HIV/HCV co-infection, current smoking, glucocorticoid use

Note. ART = antiretroviral therapy; BMD = bone mineral density; BMI = body mass index; FN = femoral neck; HCV = hepatitis C virus; HIV+ = HIV-infected; HIV- = HIV uninfected; HR = hazard ratio; LS = lumbar spine; OR = odds ratio; PoM = postmenopausal; PeriM = perimenopausal; PrM = premenopausal; PR = prevalence ratio.

^aUnadjusted model.

^bCalculated by reviewer (YC) from information available in article.

^cStudy population limited to postmenopausal women.

^dStudy population limited to HIV-infected ART-naïve women.