

Osteoporosis in postmenopausal women living with HIV

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ABSTRACT

The widespread availability of effective antiretroviral therapy (ART) has transformed HIV from a life-limiting condition to one that is chronic with near-normal life expectancy. HIV is associated with an increased risk of osteopenia and osteoporosis, with people living with HIV (PLHIV) potentially experiencing these conditions at a younger age than their HIV-negative counterparts. The mechanisms driving bone disease in HIV are complex and include: an increased prevalence of traditional risk factors; other comorbid conditions; and HIV-associated factors such as viral effects, systemic inflammation, and ART-related factors.

One third of PLHIV in the United Kingdom are female, with increasing numbers of women living with HIV (WLHIV) reaching menopausal age. Oestrogen decline in the context of an elevated background risk of poor bone health results in WLHIV being at greater risk of osteoporosis than women without HIV. European HIV guidelines therefore recommend routine screening of postmenopausal WLHIV using FRAX® for clinical risk factors with/without bone mineral density scanning.

Data support the use of calcium and vitamin D supplementation, and bisphosphonates in the treatment of osteoporosis in PLHIV. Additionally, some patients with confirmed osteoporosis may benefit from a switch to an ART agent with a better bone safety profile. However, there remains a notable paucity of data on HIV and menopause, including the impact of hormone replacement therapy on the bone health of WLHIV.

In conclusion, it is important that clinicians are aware that postmenopausal WLHIV are a group at particular risk of bone disease, requiring proactive screening and advice about preventative measures.

Keywords:

HIV; women; osteoporosis; menopause

1. Introduction

1.1 Why focus on bone health in women living with HIV

The advent of effective antiretroviral therapy (ART) has transformed HIV from a life-limiting illness to a chronic condition with normal life expectancy for those achieving virological suppression [1]. This has led to a shift in the age distribution of those living with HIV both in the United Kingdom (UK) and globally, with increasing numbers of people ageing with HIV.

Approximately half of the 37 million people living with HIV (PLHIV) globally are women (www.unaids.org, accessed 25 September 2016). Specifically looking at the UK, women represent a third of all those living with HIV [2]. In 2014, nearly 9000 women of potentially menopausal age (between 45 and 56 years) attended for HIV-related care in the UK, a six-fold increase over a 10-year period (Z Yin, Public Health England, personal communication). A recently-published review article highlights a possible association between HIV-infection and both earlier age at menopause, and increased prevalence and severity of menopausal symptoms in the literature, although the authors conclude that there is a paucity of data on menopause in this population [3].

One important metabolic consequence of the menopause in women is the reduction in bone mineral density (BMD), and the attendant risk of osteoporosis. For WLHIV this is of particular concern as HIV-infection itself is associated with an increased risk of osteopenia and osteoporosis [4], and fractures when compared to the general population [5]. Oestrogen-depletion is therefore likely to have an additive effect to the already elevated background risk of bone disease in this patient group.

In this mini-review we discuss the mechanisms underlying bone disease in PLHIV, before summarising the literature on bone disease specifically in postmenopausal WLHIV and concluding with recommendations for screening and management of osteoporosis in HIV-positive women.

2. HIV and bone disease

2.1 The impact of HIV on bone health

The mechanisms by which HIV is associated with poor bone health are complex and not fully understood, involving an increased prevalence of some of the traditional risk factors for osteoporosis, other comorbidities, and HIV-associated factors including viral effects, systemic inflammation and ART-related factors (Figure 1).

Chronic inflammation and persistently elevated cytokines, such as tumor necrosis factor (TNF α) and interleukins (Il-1 and Il-6), activate proteins including receptor activator of nuclear factor kappa-B ligand (RANKL), which in turn lead to osteoclast activation and bone resorption [6]. Laboratory studies have shown that systemic inflammation persists after initiation of ART, even after effective suppression of viral replication, and that this is associated with bone turnover markers [6]. Some studies suggest that people living with HIV who are ART-naïve have lower

BMD than age-matched controls [7]. This may be due to direct toxic effects of HIV viral proteins including gp120 and p55gag on osteoblast function [8], in addition to the chronic inflammatory effects of HIV.

The results of case-control and longitudinal studies consistently demonstrate a negative impact of ART on BMD [9]. Almost independent of the regimen, initiation of ART among treatment-naïve patients is associated with a loss of BMD at the spine and hip ranging between 2 and 6%, with stabilisation of bone loss thereafter [9]. The mechanisms underlying accelerated bone loss in the early stages of ART treatment remain poorly understood. Studies including bone turnover markers suggest uncoupling of bone resorption and formation, perhaps caused by direct drug effects on bone cells or bone-cell signalling [9]. Furthermore, specific antiretroviral agents affect vitamin D metabolism and may increase vitamin D deficiency [10]. Finally, immune reconstitution after initiation of ART, as measured by CD4 + cell recovery, has been found to be associated with markers of bone resorption [11].

2.2 What do we know about bone disease in postmenopausal women living with HIV?

A recent systematic review by Cortes et al. reports a widely varying prevalence of osteoporosis in postmenopausal WLHIV, ranging from 7 to 84% [12]. This contrasts with an estimated prevalence of between 0.7 and 23% in HIV-negative comparison groups. The authors identified several studies demonstrating an increased risk of osteoporosis and accelerated bone loss in postmenopausal WLHIV, compared to men living with HIV, premenopausal WLHIV, and female HIV-uninfected age-matched controls [12]. They also report a modest increase in fractures in this group. Risk factors for osteoporosis and/or fractures in postmenopausal WLHIV include low body mass index, corticosteroid use, Caucasian ethnicity, smoking and substance misuse [12]. Some HIV-related risk factors have been identified such as prior AIDS-defining illness, uncontrolled HIV infection, and use of ART, although data are conflicting on the effects of specific agents [12]. It is important to note that the overwhelming majority of studies on bone disease in postmenopausal WLHIV originate in North America, and may therefore not be applicable to a UK setting where women are less likely to have advanced HIV infection, or to report substance misuse or smoking.

3. Management

3.1 Assessment of fracture risk in people living with HIV

The European AIDS Clinical Society has produced guidance on screening PLHIV for bone disease, recommending that all postmenopausal women be screened for osteoporosis (Figure 2). Clinical risk factor screening should be undertaken for all postmenopausal women using FRAX[®]. Bone mineral density measurement using DXA should be ‘considered’ according to the National Osteoporosis Guideline Group (NOGG) recommendations (automatically generated after calculation of the FRAX score). However, there is evidence that FRAX under-estimates absolute fracture risk in PLHIV [13]. In practice most clinicians tick the “secondary causes of osteoporosis” box in the FRAX algorithm, although this has not been demonstrated to mitigate the under-estimation completely.

3.2 Assessing bone health and managing HIV-associated osteoporosis

For women, menopausal status (assessed primarily through menstrual history) should be recorded, as well as their lifetime history of clinical gonadal function (including age at menarche, number of pregnancies, duration of breast-feeding, duration of prolonged amenorrhoea). Women with premature ovarian insufficiency and those with menopause-associated vasomotor symptoms may be advised to consider hormone replacement therapy (HRT) as per national guidelines [14]. HRT is likely to have a protective effect on bone density, however data on the use of HRT specifically in WLHIV are lacking.

As with all patients, lifestyle advice is recommended, particularly around smoking cessation, safe alcohol consumption, and the importance of diet (especially dietary calcium intake) and physical activity levels. An assessment of falls risk is also important, given that both ART and the virus itself are associated with peripheral neuropathy.

To date, there has been insufficient evidence to recommend 'safer' ART regimens for bone health unless in the clinical presentation of overt phosphate deficiency/Fanconi syndrome associated with TDF. However, very recent evidence suggests that switching patients who are on the antiretroviral agent tenofovir disoproxil fumarate to the newer agent tenofovir alafenamide improves bone density in the short term, although longitudinal data on the clinical impact of this are lacking [15].

There are some data on treating osteoporosis in PLHIV with calcium and vitamin D, testosterone, and bisphosphonates, although none of these studies use fracture as the clinical endpoint [16]. Alendronate and intravenous zoledronate have been shown to effectively increase bone mass in PLHIV, and are recommended with calcium and vitamin D supplementation if dietary calcium intake is inadequate and/or there is evidence of vitamin D insufficiency. In patients starting ART for the first time, there is evidence that calcium and vitamin D supplementation attenuates bone loss [17].

4. Conclusions

Advances in the treatment of HIV have resulted in increasing numbers of WLHIV reaching menopausal age. Clinicians should be aware that postmenopausal WLHIV are at particularly risk of osteoporosis as a result of the additive effects of oestrogen-depletion and the virus itself. Guidelines recommend routine screening of postmenopausal WLHIV with FRAX, although this may still underestimate fracture risk in this population. Management strategies primarily comprise lifestyle modification, calcium and vitamin D supplementation, and bisphosphonates, as in the HIV-negative population. Close liaison between rheumatologists and HIV physicians is key in managing bone disease in this patient group.

5. Practice points

- WLHIV are at increased risk of osteoporosis, particularly if they are postmenopausal.
- Risk factors for osteoporosis and/or fractures in postmenopausal WLHIV include traditional risk factors (e.g. low body mass index, corticosteroid use, smoking and substance misuse) and HIV-related factors (e.g. prior AIDS-defining illness, uncontrolled HIV infection, and use of antiretroviral therapy).
- Postmenopausal WLHIV should be screened using FRAX, with HIV entered as a “secondary cause of osteoporosis”, although this may still underestimate risk.
- There are conflicting data on the role of specific antiretroviral agents and loss of bone mineral density.
- The new antiretroviral agent tenofovir alafenamide may have a better bone safety profile, however data on long-term clinical impact are currently lacking. Any changes to antiretroviral therapy should be made under the guidance of an HIV physician.
- Treatment of osteoporosis in HIV does not differ from treatment in the HIV-negative population, with lifestyle modification, calcium and vitamin D supplementation, and bisphosphonates all playing an important role.

6. Research agenda

Important areas for future research include:

- Prospective longitudinal studies of bone density and fractures in women living with HIV in Europe.
- Studies of the impact of HRT on bone density and fracture rates in postmenopausal WLHIV.
- Longitudinal data on the clinical impact of tenofovir alafenimide in terms of fracture risk in WLHIV.
- The role of other interventions, such as strength training programmes, on the bone health of postmenopausal WLHIV.

Conflicts of interest:

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Figure 1: Summary of the mechanisms by which HIV impacts adversely on bone health

Figure 2: European Guidelines on screening for bone disease in people living with HIV (adapted from European AIDS Clinical Society Guidelines Version 8.0, 2015)