

PERSPECTIVES

HIV and Low Bone Density: Responsible Party, or Guilty by Association?

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Abstract

Infection with HIV has been associated with low bone mineral density (BMD), and recent guidelines have recommended regular monitoring of BMD every 1-2 years. Preclinical data suggest that HIV can infect bone cells, and alter bone metabolism potentially causing low BMD. A transgenic rat model of HIV exhibited markedly reduced BMD, with increased bone resorption and osteoclastogenesis, attributable in part to dysfunctional B cell-derived RANK signaling. These results are consistent with data from clinical studies of humans with HIV infection, which have reported a high prevalence of low BMD, and suggest that the immune dysfunction characteristic of untreated HIV infection may contribute to the skeletal phenotype. However, HIV-infected patients commonly have classical risk factors for low BMD such as low body weight, cigarette smoking, and excess alcohol use, which may largely account for the observed low BMD. Furthermore, most HIV-infected people in developed/first-world countries receive anti-retroviral therapy, with consequent marked improvements in general health and nutrition. The available clinical evidence suggests that BMD is stable or improves in HIV-infected people receiving long-term combination anti-retroviral therapy (originally termed HAART), and that if fracture risk is increased, it is largely attributable to a higher prevalence of classical risk factors for low BMD and fracture. Consequently, we suggest that management of skeletal health in HIV-infected people be undertaken according to guidelines for the general population. Future research on BMD or fractures and HIV should consider traditional risk factors for low BMD or fracture in HIV-infected cohorts before concentrating on specific HIV-related factors. *IBMS BoneKEy*. 2011 January;8(1):7-15.

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Keywords: HIV; AIDS; Bone mineral density; Osteopenia; Osteoporosis

Background

Treatment for HIV with combinations of antiretroviral agents, originally termed highly active anti-retroviral therapy (HAART), was first introduced in the mid-to-late 1990s and has transformed the management of patients with HIV. Treatment with HAART can cause near-complete suppression of HIV replication that is sustained for many years, and the life-expectancy of patients treated in this way approaches that of uninfected individuals (1). Viewed in this context, for many people HIV is a chronic life-long illness and related co-morbidities assume much greater prominence. One such co-morbidity is low bone mineral density (BMD). In 2000, the first study reporting a link between low BMD and HIV was published (2). Subsequently, numerous

clinical studies and an increasing number of preclinical studies have explored this relationship.

Preclinical Studies

Recently, Vikulina and colleagues reported the skeletal phenotype of HIV transgenic rats (3), which globally express a *gag-pol*-deleted HIV-1 provirus, and develop clinical illnesses and pathological lesions similar to some of those that occur in untreated human HIV infection (29). Compared to controls, these rats had decreased BMD at both trabecular and cortical sites, increased bone resorption assessed by biochemical and histological techniques, but no change in bone formation (3). The authors provide evidence that altered B lymphocyte production of OPG and RANKL contributes

substantially to the dysregulated bone remodeling that drives the observed bone loss. These transgenic rats may be a valuable model for studying BMD in untreated HIV infection in humans because they in part replicate the clinical phenotype of HIV infection, including decreased BMD (4;5), and might provide insights into the mechanism by which bone loss occurs. However, such a model of untreated HIV infection may not be relevant to the majority of HIV-infected individuals in the developed world who are treated with HAART.

The study by Vikulina and colleagues adds to a body of preclinical evidence that both HIV itself, and the individual agents used to treat HIV, have an impact on bone metabolism (reviewed in (6)). HIV can infect osteoblasts, osteoclasts, and mesenchymal stem cells, and can lead to alterations in osteoblastogenesis and osteoclastogenesis both through direct effects and indirectly via alterations in the RANK pathway and in cytokines such as TNF α (6). Agents used to treat HIV may also have direct effects on bone cells, or indirect effects via alterations in the RANK pathway, cytokine production, mitochondrial function, phosphate metabolism and vitamin D metabolism (6). An important feature of the rat model of HIV studied by Vikulina and colleagues was the body weight of the rats: at 11 months of age the transgenic rats weighed 21% less than the controls (7). It is possible that the observed low BMD may be a non-specific effect of low body weight and severe cachexia, and other illnesses related to immunosuppression, rather than a specific effect of HIV. Low body weight is a major determinant of BMD in humans (8), and has also been identified as a key factor in low BMD associated with HIV in clinical studies (4), which raises the question as to whether these specific findings of the effects of HIV or HAART from preclinical studies are relevant to humans with HIV.

Clinical Studies

Cross-sectional studies

Numerous cross-sectional studies of HIV-infected individuals have reported low BMD.

In a meta-analysis of 11 cross-sectional studies, 67% of 884 HIV-infected patients had reduced BMD, defined as a BMD T score < -1 at the lumbar spine, total hip, femoral neck, distal radius or total body, a 6.4-fold increase compared to uninfected controls (5). Of note, the mean age of patients was approximately 40 years. There is little clinical relevance of a BMD T score < -1 for young individuals, as 16% of the population of this age will have a BMD T score < -1 at a single site, and an even higher proportion when the lowest measurement from 5 different sites is used to define low BMD. In the meta-analysis, the number of individuals with BMD below the normal range for age (*i.e.* Z score < -2) was not reported, but HIV-infected individuals were 3.7-fold more likely to have a BMD T score < -2.5 (5). We carried out a subsequent meta-analysis of 10 HIV-infected cohorts with age- and gender-matched cohorts with data available on body weight (4). When compared to controls, HIV cohorts had lower BMD by 4.7% at the spine, 4.4% at the total hip, 7.0% at the femoral neck, and 5.5% at the total body (4). It seems clear that HIV-infected individuals have lower BMD than controls, despite the issues regarding use and interpretation of BMD T scores in the first meta-analysis.

Many studies have attempted to determine the cause of the low BMD, with initial focus upon HIV and HAART as putative causes. Results from these studies have been conflicting. For example, in the first report of low BMD in HIV (2), low BMD was restricted to individuals taking HAART regimens that included a protease inhibitor, whereas individuals taking HAART without a protease inhibitor had BMD similar to that of controls, suggesting that low BMD was a side-effect of protease inhibitors. However, in a later, larger study that reported low BMD with HIV, there was no relationship between type or duration of HAART, suggesting that HIV itself might be the cause (9). In our cross-sectional study of HIV-infected men compared with healthy age-, race- and gender-matched controls, we found no difference between groups in BMD at the spine or total body, with a small decrease in BMD in the HIV group at the total hip (10).

Importantly, the HIV group was 6.3 kg lighter than the control group, and after adjusting for this difference, there were no differences in BMD between the groups at any site (10). We therefore asked whether previous reports of low BMD might have been confounded by a failure to consider body weight differences between groups. We meta-analyzed all available studies that reported body weight and BMD in an HIV cohort with an age- and gender-comparable control group (4). BMD was 4.4-7% lower in the HIV groups than the controls. However, the HIV cohorts were on average 5 kg lighter than the controls, and after taking this into account, the differences in BMD between groups ranged from 2-3%. Thus, controlling for low body weight largely explains the low BMD observed in cross-sectional studies of HIV cohorts.

Low body weight in HIV-infected individuals is likely to be multifactorial. The majority of participants included in these cross-sectional studies were men who have sex with men (MSM) or current or previous intravenous drug users. MSM have been reported to have lower body weight (11) and to be more concerned with body shape and appearance (12) than heterosexual men. Intravenous drug users also have higher rates of low body weight than non-users (13). In addition, HIV seroconversion (14;15) and advancing untreated HIV infection lead to loss of body weight (16), but even with effective HAART treatment, loss of body weight is a common symptom (16). In chronic untreated HIV infection, the cause of the loss of body weight appears to be multifactorial and includes poor nutritional state, chronic illness and recurrent infections, malabsorption, chronic diarrhea, and wasting syndromes (17). MSM also have higher rates of cigarette smoking than heterosexual men (18), and intravenous drug users have higher rates of smoking than non-users (13). Both body weight and cigarette smoking are important determinants of BMD (8;19). Thus, individuals at risk of HIV infection have significant risk factors for low BMD, and the low BMD observed in HIV could be substantially due to these factors. A recent cross-sectional study supports this

hypothesis. 33 men (mean age 38 years) had a BMD measurement approximately 1 month after HIV diagnosis, and within a few months of infection (20). BMD was lower than expected at the spine and femoral neck, and 51% had a BMD T score < -1 at the spine or hip. The mean BMI was 22.7 kg/m² and 55% were smokers. It is doubtful that such a short duration of HIV infection/treatment could account for the low BMD, which seems most likely to be related to traditional risk factors for low BMD – especially low body weight and smoking.

Longitudinal studies

More than 20 longitudinal studies of BMD in HIV-infected cohorts have been carried out, although most studies are of short duration (1-2 years), included small numbers of participants, and few have included a comparable uninfected control group. A distinct pattern of results has emerged. Most studies in which the majority of the cohort is already established on HAART report stable or increasing BMD over time (21-24). In contrast, studies of cohorts initiating HAART report substantial short-term bone loss (2-4% at 1 year) (25-30) that stabilizes over time (26;31).

A number of studies have compared the effect of different HAART regimens on BMD changes over time. Two studies have suggested that initiation of HAART regimens containing tenofovir might lead to greater short-term bone loss by about 1-1.5% at 1 year compared to other regimens (26;30), although these differences subsequently diminished or stabilized (26;31). Tenofovir has also been rarely associated with urinary phosphate wasting leading to hypophosphatemia and osteomalacia (32), although this adverse effect was not reported in clinical trials (26;31). Other studies have compared groups randomized to different HAART regimens (27-29), or switched from one regimen to another (33), but the results are inconsistent and no agent(s) to date has been consistently associated with greater bone loss. One study assessed the effect of continuous HAART compared with intermittent CD4 count-guided therapy (34). Continuous

treatment was associated with 1-1.5% decreases in BMD relative to intermittent treatment, and the authors concluded that HAART causes accelerated bone loss. This conclusion should be viewed with caution. Participants were not blinded to study treatment, there was a high dropout rate that was different between the groups, and the study was terminated early after the intermittent treatment strategy was found to cause greater mortality. The progressive loss of BMD observed in the continuous treatment group of 0.5-1.0%/year has not been consistently observed in other cohorts established on HAART and suggests that individuals with normal BMD or no accelerated bone loss were more likely to be lost to follow-up, exaggerating the estimate of bone loss. In the setting of large changes in lean mass or fat mass, theoretical concerns have been raised about the accuracy of BMD measurements using dual-energy x-ray absorptiometry (DXA). However, there are no consistent clinical data confirming these concerns. This issue may be of relevance to HIV-infected people with lipodystrophy, but the accuracy of DXA measurements of BMD has not been studied in such individuals.

The discrepant results from the longitudinal studies of cohorts established on HAART and those initiating HAART seem hard to reconcile at first glance. If HIV infection causes accelerated bone loss, why should bone loss increase when effective treatment is started? If treatment with HAART causes bone loss, why should there be a short period of substantial accelerated bone loss followed by equally impressive increases in BMD? One possible explanation is the temporal changes of body weight that occur with HIV: in untreated HIV infection, there is progressive loss of body weight, with steady regain of this lost weight following initiation of HAART. In our cohort, the average weight loss prior to initiation of HAART was 4 kg over about 6-12 months, the lowest body weight occurred on average 9 months *after* HAART was started, and thereafter there was a progressive increase in body weight at a rate of about 1 kg/year for the first 4 years of HAART treatment (10;22). Since weight is a major determinant of BMD and

changes in weight are positively correlated with changes in BMD in various populations (8;35;36), the temporal changes in body weight are likely to lead to substantial changes in BMD. Thus, with untreated HIV infection ongoing weight loss will lead to accelerated bone loss. After initiation of HAART, weight stabilizes and then increases, which will in turn lead to stabilization of bone loss and then increases in BMD. This hypothesis suggests that the early bone loss seen in cohorts initiating HAART is, at least in part, related to previous weight loss during untreated HIV infection, while the stability/increases in BMD in cohorts established on HAART is due to immune reconstitution, improved nutritional status and weight gain resulting from effective treatment.

Fracture rates in HIV populations

Several studies have reported fracture rates in HIV cohorts compared to uninfected controls. Arnsten and colleagues reported no significant increase in risk of fractures in 328 men (mean age 55 years) followed for 2 years (37). Prior and colleagues reported an increased risk of lifetime fragility fractures in a cohort of 137 women (mean age 38 years), but did not report whether these fractures occurred before or after HIV diagnosis, and the increase was not statistically significant after adjustment for differences between the groups (38). Yin and colleagues reported no increase in fracture rates in 1,728 women (mean age 40 years) followed for 5 years (39). Collin and colleagues reported no increase in the rate of fractures in 1,281 adults (median age 36 years) taking HAART followed for 10 years, compared to the general population of the same age in Europe (40). In that study, the majority of fractures were due to trauma, and 1 in 5 fractures were associated with alcohol excess.

Other investigators have assessed fracture rates using registries to form large cohorts. Triant and colleagues compared fracture prevalence by HIV status in > 2 million individuals who had at least 1 in-patient or out-patient assessment over a 12-year period (41). Fracture prevalence was higher

in HIV-infected individuals, but the design of the study did not allow adjustment for differences in risk factors between groups, the mode of fracture was not reported, and the timing of fractures in relation to diagnosis of HIV was not reported. Womack and colleagues reported that HIV status was not related to fracture incidence in > 100,000 male veterans after adjustment for co-morbidities (42).

In summary, there is currently no clear evidence of increased fragility fractures in HIV after taking into account established risk factors for fracture. The relationship between BMD and fracture risk in HIV has not yet been reported. Most HIV-infected individuals are young, and the majority of fractures such individuals experience are not osteoporotic/fragility fractures related to low BMD, but are more likely to be related to trauma. Any increase in risk of fractures in HIV is plausibly the result of an increased prevalence of risk factors such as low body weight, smoking, and alcohol use.

A Unifying Hypothesis

Individuals at risk of HIV infection have lower BMD than their peers because of increased frequency of risk factors for low BMD such as cigarette smoking, alcohol use and low body weight. Infection with HIV leads to loss in body weight that in turn leads to decreases in BMD. Initiation of HAART leads to stabilization and then increases in body weight. The initiation of HAART is associated with initial losses in BMD, in part related to previous weight loss associated with untreated HIV infection. There may be some contribution to this early bone loss from specific components of HAART, however, these effects are small and do not persist. The initial loss in BMD is followed by a longer period of stabilization and increases in BMD related to immune reconstitution, improved nutritional status and increasing body weight. HIV-infected individuals may be at increased risk of fractures because of an increased prevalence of classical risk factors for fracture.

Conclusions and Recommendations for Monitoring BMD

Adequately treated HIV infection does not appear to have a substantial impact on bone density or fracture rates. Thus, for the majority of people with HIV, who are adequately treated with anti-retroviral therapy and well-nourished, low BMD should not be a concern. Recommendations for lifelong monitoring of BMD every 1-2 years during antiretroviral therapy (6;43) are difficult to justify. Instead, decisions about investigating and treating low BMD in HIV-infected patients should be made using guidelines available for the general population (44;45), with particular focus on addressing modifiable risk factors for low BMD or fractures such as alcohol use, cigarette smoking, and low body weight. Effective antiretroviral treatment and avoidance of undernutrition remain the two most important factors in optimizing skeletal health in HIV-infected individuals. Future research on BMD or fractures and HIV should address the impact of traditional risk factors for low BMD or fracture in HIV-infected cohorts, before concentrating on specific HIV-related factors.

Conflict of interest: None reported.

Peer Review: This article has been peer-reviewed.

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