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COMPLICATIONS OF HIV AND ANTIRETROVIRAL THERAPY (G MCCOMSEY, SECTION EDITOR)

Bone Update: Is It Still an Issue Without Tenofovir Disoproxil Fumarate?

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Abstract

Purpose of Review In the era of modern bone-friendly antiretroviral therapy (ART) regimens for people living with HIV (PLWH), this review discusses the research gaps and management concerns that remain for individuals who have already been exposed to ART with negative effects on bone metabolism, especially children and adolescents who have not acquired peak bone mass, and older adults who have additional risk factors for fracture.

Recent Findings Data now support the use of avoidance of TDF and use of bone-friendly regimens that include integrase strand transfer inhibitors in PLWH with increased risk of fracture for either ART initiation or switch.

Summary Despite significant advances in our understanding of ART choice for PLWH with regard to bone health, additional diagnostic tests to determine fracture risk and management strategies beyond ART choice are necessary, especially in vulnerable PLWH populations, such as children and adolescents and older adults.

Keywords Osteoporosis · Bone mineral density · Fracture

Introduction

With effective antiretroviral therapy (ART), healthy aging has become a major focus of HIV management. HIV-associated non-AIDS (HANA) complications and comorbidities, such as cardiovascular disease, cancer, and liver and kidney failure, are more important causes of morbidity in older people living with HIV (PLWH) than opportunistic infections. Osteoporosis and fracture are aging-related comorbidities that have also been shown to be more common in PLWH [1]. The etiology of low bone mineral density (BMD) and bone loss with HIV infection and antiretrovirals is multifactorial. Data from in vitro studies demonstrating the negative effects of HIV-1 proteins on bone cells suggest that HIV may have direct effects on the bone [2–5]. Animal studies and clinical data also suggest that chronic immune activation and upregulation of pro-resorptive inflammatory cytokines may also negatively impact bone mass [6].

Host factors may also contribute to bone loss, such as the higher prevalence of low body weight, HCV co-infection, and smoking among PLWH. However, data from the START study clearly demonstrate that bone loss during ART initiation is far greater than that of HIV infection alone [7•]. Data from multiple studies, mostly with standard nucleoside reverse transcriptase inhibitor (NRTI)-containing regimens, reveal a 2%–4% loss in areal BMD by dual energy x-ray absorptiometry (DXA) at either the lumbar spine or hip within 1–2 years after ART initiation. The lowest BMD is observed at 6 months at the spine or 12 months at the hip, with stabilization and some improvement usually observed 2–3 years after ART initiation, despite remaining on the same regimen.

In particular, tenofovir disoproxil fumarate (TDF) has been reported to be associated with greater bone loss than other NRTIs, such as abacavir, or integrase strand transfer inhibitors

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(INSTIs) when used in combination with other agents for ART initiation [8–10]. TDF utilized in combination with emtricitabine (FTC) for pre-exposure prophylaxis (PrEP) is associated with 1%–2% decrease in BMD [11, 12]. Switching from TDF to abacavir, INSTIs or tenofovir alafenamide fumarate (TAF) results in a 1%–2% improvement in BMD [13–16]. All of these studies suggest that TDF has a distinct negative effect on bone metabolism; however, the exact mechanism is still elusive. TDF use is associated with proximal tubular dysfunction, but development of hypophosphatemia and osteomalacia is rare. Also, bone biopsy data do not reveal a consistent worsening of mineralization with initiation of TDF [17•]. Direct effects of TDF on osteoblasts and osteoclasts have been documented in vitro, but clinical significance is less well defined. Remarkably, a recent study comparing TAF/FTC/bictegravir with abacavir/lamivudine/dolutegravir for ART-initiation demonstrated negligible decreases in BMD at the spine and hip after 96 weeks, with supportive bone turnover marker data [18].

The identification of two first-line regimens that have minimal bone toxicity is a major scientific advance, and it is reasonable to expect that as more people have access to these regimens, long-term complications of osteoporosis and fracture will decrease on an individual basis and for the overall population. However, research gaps and management concerns remain for individuals who have already been exposed to ART with negative effects on bone metabolisms, especially children and adolescents who have not acquired peak bone mass, and older adults who have additional risk factors for bone fragility and falls.

Concerns for Children with Perinatally Acquired HIV

The scale-up of ART has dramatically improved survival for children living with perinatally acquired HIV. However, even in the era of ART, children experience a range of early comorbidities due to HIV and/or ART. Low bone mass has been reported in children, adolescents, and young adults with perinatally acquired HIV in many countries around the world, including the USA [19], South Africa [20, 21], Zimbabwe [22], Brazil [23], and Thailand [24]. Decreased bone mass accrual in childhood is a concern as the pubertal years are a critical period for bone mass acquisition and obtaining peak bone mass at the end of skeletal maturation. Low peak bone mass is an important predictor of osteoporotic fracture risk adulthood [25–28]. Newer bone-friendly ART options such as TAF are not widely available for young children in resource-limited settings. Children in many low- and middle-income countries continue to receive TDF or will have had prior exposure to TDF. A study of the effect of TDF on bone metabolism and bone mass in Thai and Indonesian adolescents with perinatally acquired HIV found elevated parathyroid hormone (PTH) and bone turnover dysregulation but no reduction in bone mass [29]. However, in children and adolescents where bone acquisition is ongoing, the negative impact of ART may not manifest in short-term BMD loss but rather inadequate increase in bone mineral content (BMC) or BMD, and ultimately in decreased peak bone mass, which is much more difficult to define. Additionally, the negative effects of HIV on somatic growth and neurodevelopment and of environmental factors such as malnutrition and chronic infections, especially in sub-Saharan Africa, can also contribute to poor bone health outcomes over the lifespan. Bone-friendly drugs, therefore, are unlikely to completely resolve bone issues in perinatal HIV.

Concerns for Youth Who Acquired HIV in Adolescence

In addition, those who acquire HIV during adolescence or early adult life also experience bone mass reductions or loss as well as a number of bone architectural abnormalities and reduced bone strength. Several studies point to sub-optimal peak bone mass acquisition. Mulligan et al. observed low bone mass in a study of young men with recently acquired HIV infection [30]. This study (ATN 021B) evaluated bone outcomes in 199 young men who recently acquired HIV. The participants were between the ages of 14–25 years, living in the USA and Puerto Rico, and included those who were ART-naive ($N = 105$), on a non-nucleoside reverse-transcriptase inhibitor (NNRTI)-containing regimen ($N = 52$) or on a protease inhibitor (PI)-containing regimen ($N = 42$) [30]. Median time since HIV diagnosis ranged from 1.3 years in the ART-naive group to 2.2 years in the PI group. Those on ART (NNRTI or PI-based regimens) had lower total body BMC Z-scores and lower total hip BMD Z-scores than uninfected controls. The PI group had significantly lower total body BMD Z-scores than both the NNRTI group and uninfected controls. These findings are similar to reports among adults who acquired HIV later in life and have experienced longer durations of disease and exposures to ART. Another study of young men ages 20–25 years evaluated an average of 2.5 years after HIV diagnosis also observed decreases in bone mass indices by high-resolution peripheral quantitative computed tomography (HR-pQCT), including volumetric BMD and abnormalities in bone microarchitecture [31]. Deficiencies in plate-related parameters by individual trabeculae segmentation (ITS) analyses and an estimated 14%–17% reduction in bone stiffness by finite element analysis were detected in comparison to uninfected controls [31].

Concerns for Children Exposed to HIV but Negative

Given that TDF is widely used in pregnancy, especially in resource-limited settings, there have been concerns about the effects of in utero TDF exposure on growth and bone health in infants. Data on the effects of fetal TDF exposure on growth

and bone development are limited, but most show no effect [32–36]. In a study of 464 pregnant women initiating TDF-containing regimens in South Africa and their infants, no association between duration of TDF exposure in utero was found with early linear growth [32]. A study of in utero TDF exposure and fetal long bone growth found no association between duration of in utero TDF exposure per 1-week increment and change in femur length Z-scores or change in humerus length Z-scores [33]. However, long-term follow-up is still needed.

Concerns for Youth Who Are Exposed to TDF

Given the effects of TDF on BMD, there are concerns that prolonged exposure to TDF and FTC for prevention of HIV through pre-exposure prophylaxis (PrEP) at young ages, prior to skeletal maturation and achievement of peak bone mass, may result in alterations in bone homeostasis, decreased bone mass accrual, lower bone strength, and possible increase long term fracture risk. TDF-containing regimens used for PrEP were recently approved for adolescents > 35 kg and have been evaluated in a number of clinical trials involving both men and women [37]. In a randomized trial of TDF and FTC use in 498 HIV-seronegative men who have sex with men (MSM) and transgender women conducted in the USA, Thailand, South Africa, Peru, and Brazil, in which greater than half were less than 25 years old, BMD decreased modestly but statistically significantly by 24 weeks in the spine and hip in those randomized to FTC/TDF PrEP [11]. Changes in BMD by week 24 correlated inversely with intracellular tenofovir diphosphate (TFV-DP) levels, implicating either a direct or indirect role for TDF in bone loss. Discontinuation of treatment resulted in a reversal of bone loss, although not completely.

In a clinical trial of 101 younger MSM (15–22 years, median age 20 years) in the USA, statistically significant changes from baseline were observed at both 24 and 48 weeks in lumbar spine, total hip, and total body BMD z scores [12]. Participants with the greatest TDF exposure experienced the greatest declines in femoral neck total hip BMD. Of interest, changes in BMD indices in this study were related to increased PTH and decreased fibroblast growth factor (FGF)-23 levels and not to change in creatinine, phosphate, or renal tubular reabsorption of phosphate.

While there are fewer studies specifically addressing the question of impact on bone development with TDF and FTC exposure among women prior to completion of skeletal maturation, adverse effects of TDF and FTC on BMD in otherwise healthy young women taking PrEP have been documented. In a randomized clinical trial involving 575 women in Zimbabwe and Uganda with a median age of 29 years, significant decreases from baseline to 48 weeks of 1.4% in lumbar spine and 0.9% in total hip BMD were noted in women deemed adherent to TDF/FTC as measured by plasma levels compared to those in the placebo arm [38]. In adults, losses in BMD due to TDF/FTC PrEP are largely reversible with discontinuation of PrEP [38, 39]. However a recent study of young MSM in the USA found that the youngest age group (15–19 years) experienced greater decline in both whole body and lumbar spine BMD compared to older men ages 20–22 years, and that both whole body and lumbar spine BMD remained below baseline even 48 weeks after discontinuation of TDF/FTC, suggesting an elevated vulnerability to the adverse drug effects during late adolescence [40].

Concerns for Older Adults with HIV

Data from antiretroviral switch studies are limited to DXA and bone turnover marker evaluations. None of the studies examined bone structure using high-resolution computed tomography scans or direct measures of bone strength using biopsies or tissue analysis. There are also no clinical data to indicate whether switching off of TDF or other ART combination with negative bone effects will decrease fracture risk over time. This is of particular concern for older individuals who may already have osteoporosis and be at risk of fracture because of bone fragility or have additional fall risks. In this situation, switching to an INSTI-based regimen with either TAF or abacavir may not be enough and consideration for bone-specific agents such as bisphosphonates may also be necessary. Screening DXAs are helpful, and have been recommended for all PLWH over age 50 given the higher risk of fracture but in practice are performed infrequently. Similarly, although bisphosphonates have been studied and shown to be effective in prevention of bone loss with antiretroviral therapy [41, 42] or treatment of low bone density/osteoporosis in PLWH [43], there are no clear guidelines on when they should be used. Some experts advocate for switching to a bone friendly regimen first and monitoring for improvement in BMD by DXA after 1–2 years and delaying initiation of bisphosphonates, given potential risks of long-term bisphosphonate use. This strategy would appear to be safe in situations where patients have no fracture history or evidence of fracture, and the 10-year absolute risk of fracture when calculating with FRAX plus femoral neck BMD data is below treatment threshold (< 20% risk of major osteoporotic fracture and < 3% risk of hip fracture). Identification of additional biomarkers or other imaging modalities that can further risk stratify and determine which patients would benefit from initiation of bisphosphonates [41] would be an important scientific advance.

Conclusions

Significant advances in our understanding of the effect of HIV and antiretrovirals on bone mass and fracture risk during the

lifespan has improved our ability to individualize treatment for PLWH to mitigate aging-related complications such as osteoporosis and fracture. Data now support the avoidance of TDF and use of bone-friendly regimens such as TAF/FTC/bictegravir or abacavir/3TC/dolutegravir in PLWH with fracture risks. However, TDF will continue to be utilized as part of combination regimens for HIV therapy and for PrEP and hepatitis B virus (HBV) therapy globally. Certain vulnerable populations, such as children and young adults with HIV from perinatal or behavioral acquisition and older PLWH, are likely to remain at higher risk of fracture despite optimization of ART. Therefore, additional research to define nutritional and lifestyle modifications as well as better biomarkers for risk stratification for fracture risk in this population are needed.

Compliance with Ethical Standards

Conflict of Interest The authors have no disclosures to declare.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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