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Editorial: Metabolic Bone Disease in Human Immunodeficiency Virus-Infected Children

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Advances in medical management have led to extended survival of HIV-infected children and adults. Skeletal abnormalities, including decreased bone mineral content (BMC) and bone mineral density (BMD), are among the newly recognized morbidities that have emerged in HIV-infected individuals (1–3). However, although decreases in BMC and BMD are well documented, a clear understanding of the natural history and pathogenesis of the decreased bone mass and its effective management has yet to emerge.

In this issue of *JCEM*, Mora *et al.* (4) address several fundamental questions concerning bone mass and metabolism in HIV-infected children. They report decreased BMD, decreased accrual of BMD, and biochemical evidence of increased bone turnover in a cohort of HIV-infected children receiving highly active antiretroviral therapy (HAART). This study is of considerable importance because it is the first longitudinal examination of bone and mineral metabolism in HIV-infected children. Although previous studies of perinatally HIV-infected children have documented decreased BMC and/or BMD, their cross-sectional designs prevented investigators from distinguishing among prior bone loss, ongoing bone loss, or reduced rates of bone accrual during growth as causes for the deficits (1–3). Mora *et al.* (4), using longitudinal measures of BMD, demonstrated a lower annual rate of accrual of whole body, but not lumbar spine, bone mass in HIV-infected children receiving HAART. The reduced accrual of bone mass occurred in the setting of apparently normal statural growth. This is in contrast to previous studies that included children with growth retardation, a pervasive finding in HIV-infected children before the advent of HAART. In addition, Mora *et al.* (4) were able to establish that there were no short-term losses in bone mass over the period of observation. Biochemical markers of bone turnover, both formation and resorption, were elevated at baseline and remained above normal throughout the study despite, or possibly because of, on-going treatment with HAART. Thus, their results also suggest that reduced bone accrual is related to increased bone turnover, extending observations from previous cross-sectional studies (1, 5).

Nonetheless, caution in interpreting these findings is warranted. Although the investigators went to considerable lengths to select a proper comparison group, they did not perform

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longitudinal measures of bone mass and bone turnover markers in the control subjects, rather estimating the rate of change from their cross-sectional data. Thus, we cannot be certain that the HIV-infected children were growing at the same rate as the controls, nor can we be assured of the evolution in bone turnover markers in the controls. The between-groups differences in the baseline bone turnover markers could reflect factors other than HIV or its therapy. For example, increases in growth velocity, experienced by many HIV-infected children when placed on HAART, could account for the group differences in bone turnover markers (6, 7). In addition, this study provides little insight into the pathogenesis of abnormal bone metabolism in HIV-infected children. Because bone mass and bone turnover markers were not measured before administration of antiviral medications, no inferences can be made with respect to the contribution of these medications to the observed abnormalities. Moreover, because data on vitamin D and PTH levels were alluded to but not provided, a potential contribution of vitamin D deficiency to the findings cannot be excluded.

The pathogenesis of bone loss in HIV-infected patients is complex and likely multifactoral involving HIV- and HAART-related factors, as well as other factors known to influence bone metabolism. All of the reports of bone disorders in HIV-infected children and many of those in HIV-infected adults were conducted subsequent to the introduction of potent antiretroviral medications, especially protease inhibitors (PIs), in 1996. However, at least in HIV-infected adults, it is clear that abnormalities in bone and metabolism are not due solely to antiviral medications, because initial reports of skeletal disorders antedated HAART. One of the earliest, a well-controlled study in which transiliac crest bone biopsies were performed after tetracycline labeling in anti-retroviral-naïve adults aged 18–40 yr, revealed markedly decreased bone formation, turnover, and osteoclast number compared with healthy subjects. The decrease in bone formation was more marked among individuals with advanced disease (8). Although several studies published after the advent of effective combination antiviral chemotherapies have observed increased prevalence of osteopenia and osteoporosis, others have found that the bone loss was independent of use of these medications (9, 10) and that osteoporosis was strongly associated with duration of HIV infection and advanced disease (10). Moreover, Lawal *et al.* (11) documented comparable reductions in BMD among HIV-infected subjects studied before HAART(1992–1993) and after HAART (1998–1999).

In addition, some clinical studies suggest that antiviral therapies play a role in the pathogenesis of bone loss in HIV-infected patients. An early HAART-era cross-sectional study by Tebas *et al.* (12) was one of the first to suggest an association between PI use and osteoporosis. In that study, the prevalence of osteopenia and osteoporosis was higher in subjects taking a PI than in those not receiving a PI. In contrast, a longitudinal study by Nolan *et al.* (13) indicated that the association between PI use and BMD may be related to differences in body mass index. Whereas lumbar spine *Z* scores were lower in subjects receiving a PI, the association did not persist after controlling for differences in body mass index by multiple regression analysis (13). Basic studies also support the notion that antiretroviral drugs, particularly PI therapy, alter osteoclast and osteoblast function. However, most cell culture and animal studies suggest that these effects are not drug class specific and vary between members of the same class of drugs. For example, in a recent *ex*

vivo study, cultured osteoclast activity increased in the presence of nelfinavir, indinavir, saquinavir, and ritonavir, but no change was observed with lopinavir and amprenavir (14).

These observations raise important issues that limit the interpretation of nearly all clinical studies of bone and mineral metabolism in HIV-infected individuals. In the first place, multiple drugs, typically at least three from two pharmacological classes, are recommended for treatment of HIV because of the risk of inducing virologic resistance. In clinical practice, a single drug is virtually never used and, moreover, there is considerable switching among various drugs to find a regimen that has benefit with the most tolerable side effect profile. There are currently 19 medications from four classes approved and in clinical use for treatment of HIV. Thus, observational studies, especially of children and adolescents in which the pool of study subjects is relatively small, must deal with considerable therapeutic heterogeneity. This is of importance because, as noted previously, although *in vitro* studies indicate that PIs affect bone metabolism, the effects vary by class of drug as well as among drugs within the same class. Thus, the potential for variable effects of antiretroviral drugs on bone metabolism must be considered in the design and interpretation of clinical studies. Short-term studies of the effects of drug exposure on bone metabolism in healthy, and to a limited extent, in HIV-infected volunteers, may provide important drug-specific answers to these questions.

Despite the many inherent difficulties in performing clinical studies in HIV-infected patients, inquiries into the pathogenesis of HIV-associated metabolic bone abnormalities are not entirely lacking, and, in fact, results suggest several potential mechanisms. Early *in vitro* and postmortem tissue studies suggested that bone cells may be infected by HIV (15, 16), leading to the hypothesis that osteoblast dysfunction is a direct consequence of HIV infection. A more recently advanced hypothesis implicates indirect effects of HIV on osteoclasts and osteoblasts, mediated through T-cell activation and increased production of bone-resorbing cytokines. Several cytokines (IL-1, IL-6, and TNF-α) that increase osteoclast activation and that are implicated in the pathogenesis of postmenopausal osteoporosis are elevated in HIV-infected subjects and fall in response to various combinations of antiretroviral drugs (17). It has also been suggested that osteopenia results from lactic acidemia due to nucleoside reverse transcriptase inhibitor-induced mitochondrial toxicity (18). Vitamin D deficiency, as determined by reduced serum levels of 25-hydroxyvitamin D, may also contribute to abnormal bone and mineral metabolism and has been reported in adults with HIV (19). Moreover, several studies performed in adults with HIV reported reduced serum levels of 1,25-dihydroxyvitamin D, whereas serum PTH and calcium were slightly decreased (20, 21). *In vitro* studies indicate 1,25-dihydroxyvitamin D synthesis can be inhibited by certain PIs (22).

Adding to the number of potential mechanisms of bone loss in HIV-infected adults and children are reports suggesting an association between lipodystrophy and reduced BMD. Lipodystrophy is a relatively common syndrome in HIV-infected children and adults that may include atrophy of fat on the face and extremities, accumulation of visceral abdominal fat, dyslipidemia, and insulin resistance. It has been suggested that HIV-associated bone and fat disorders are related and share a common etiology, an attractive concept because osteoblasts and adipocytes share a common cellular progenitor. Mora *et al.* (1) have

previously reported that HAART-treated children with lipodystrophy have lower BMD than those without lipodystrophy (1). Huang *et al.* (23) demonstrated reduced lumbar spine BMD in adult patients with lipodystrophy and reported an inverse relationship between BMD and visceral abdominal fat. Other studies have not detected any association between lipodystrophy and BMD in adults (13, 18) or between lipodystrophy, BMC, and rates of bone accrual in children (24). However, standardization of case definitions for lipodystrophy will be necessary to better evaluate associations between bone and fat metabolism in HIV infection.

Whatever factors are ultimately found to contribute to decreased bone accrual in perinatally HIV-infected children and adolescents, the short- and long-term clinical implications of the findings of Mora *et al.* (4) need to be addressed. In contrast to adults, diagnostic criteria for pediatric osteoporosis or osteopenia have not been established, and the bone density threshold for bone fragility in children has not been defined (25). T scores are not applicable to children and adolescents who have not yet achieved peak bone mass. It is well recognized that two-dimensional measurements of areal BMD by dual-energy x-ray absorptiometry (DXA) can be misleading in growing and maturing children and that age, sex, race, body size, bone size, and stage of pubertal maturation are all important determinants of DXA measurements (26, 27). However, there is no consensus on how to adjust DXA results for these factors, no population-based normative databases, and, thus, no standard approach to the assessment of pediatric bone mass (25). To overcome this, Mora *et al.* (4), like other investigators of pediatric bone disorders, appropriately assembled their own reference group to account for the myriad of variables that affect bone mass and its measurement by DXA and convincingly demonstrated lower values for their pediatric HIV population.

It has been reported that otherwise healthy children with fractures have decreased bone density by DXA compared with control subjects (28, 29), but thus far increased fracture incidence has not been reported in children with HIV infection. Thus, the immediate consequences of decreased BMD for this group are not clear. In contrast, the critical importance of childhood and adolescence for achievement of peak bone mass and the improved survival of individuals with perinatally acquired HIV infection means that the findings of Mora *et al.* (4) may have serious long-term implications for bone health in these patients. Evaluation of measures to improve bone mineral accrual in children and adolescents with HIV infection is an important area of research, especially because bone density has been reported to track during childhood and puberty and to be predictive of adult bone mass (30, 31). Certainly, studies of the effect of optimizing modifiable factors known to enhance bone mass during childhood, such as increasing calcium and vitamin D intake and weight-bearing exercise, are warranted (32, 33). Indeed, the observation by Mora *et al.* (4) of a differential in BMD increases between weight-bearing and nonweight-bearing sites (*i.e.* legs *vs.* arms) suggests that increase in physical activity may be a valuable intervention.

In summary, the findings reported by Mora *et al.* (4) have potentially serious implications for future bone health in individuals with perinatally acquired HIV infection in whom survival into the third decade of life is increasingly common. Evaluation of measures to improve bone mineral accrual in children and adolescents with HIV infection is an important

and timely area of clinical research, even while investigations of the pathogenesis of bone mineral compromise continue.

Abbreviations

BMC	Bone mineral content
BMD	bone mineral density
DXA	dual-energy x-ray absorptiometry
HAART	highly active antiretroviral therapy
PI	protease inhibitor

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