Published in final edited form as:
Curr Opin Endocrinol Diabetes. 2006 December 1; 13(6): 497–502. doi:10.1097/MED.0b013e3280109b6c.

Low bone-mineral density in patients with HIV: pathogenesis and clinical significance

Michael T. Yin and **Elizabeth Shane**
Department of Medicine, Division of Infectious Diseases, Columbia University, College of Physicians and Surgeons, New York, New York, USA

Abstract

Purpose of review—Low bone-mineral density is a recently recognized metabolic complication of HIV infection and its treatment. While the clinical impact of low bone-mineral density remains uncertain, the prolongation of survival attributable to more effective antiretroviral therapy has contributed to an aging population of HIV-infected patients who may be prone to developing fragility fractures.

Recent findings—While most of the available data are on young men, recent publications have increased our understanding of the epidemiology of low bone-mineral density and bone loss in HIV-positive women. Most studies suggest that initiation of certain combinations of antiretroviral agents may be associated with moderate bone loss initially, but bone-mineral density usually stabilizes or improves with longer follow-up. Most studies suggest that, despite lower bone-mineral density, fragility fractures are relatively uncommon in HIV-positive patients, perhaps because of their relative youth.

Summary—The pathogenesis of low bone-mineral density in HIV-positive patients is complex and multifactorial, and its clinical impact remains unclear. Further research is needed to clarify the approach to optimal screening and treatment of osteoporosis in the setting of HIV infection.

Keywords

HIV; low bone-mineral density; metabolic complications; osteoporosis

Introduction

Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture [1]. Osteoporosis currently affects 10–12 million people in the United States, and another 28–32 million have low bone mass or osteopenia. Although the vast majority are postmenopausal women and elderly men, osteoporosis may also affect young men and pre-menopausal women, usually in the setting of an underlying disorder or medication exposure that adversely affects the skeleton. In this regard, low bone-mineral density (BMD) is a recently recognized metabolic complication of HIV infection and its treatment. The epidemiology and pathogenesis of HIV-associated bone loss are reviewed here, highlighting recent articles as well as areas of controversy and uncertainty.

Correspondence to Elizabeth Shane, MD, Department of Medicine, Division of Endocrinology, Columbia University Medical Center, 630 West 168th Street, PH8-864, New York, NY 10032, USA, Tel: +1 212 305 6289; fax: +1 212 305 6486; es54@columbia.edu.

Epidemiology of low bone-mineral density and bone loss in HIV-infected individuals

More than 25 cross-sectional studies of BMD in HIV-positive adults have been published. Earlier studies [2–4] were conducted in HIV-positive individuals who were comparatively ill by today's standards and who had one or more known risk factors for osteoporosis, such as wasting, hypogonadism, and intestinal malabsorption. Recent studies have been conducted in healthier individuals, with fewer associated illnesses. While a few of these are multicenter studies that approximate a population sample [5•] (and Anastos and Hessol, presented at the 11th Conference on Retroviruses and Opportunistic Infections; 8–11 February 2004; San Francisco, California, USA), the majority consist of convenience samples from HIV clinics or lipodystrophy cohorts. Data on short-term changes in BMD are now available both from treatment studies with BMD measured before and after initiation of specific antiretroviral (ARV) regimens [6–9] (and Powderly *et al.*, presented at the 12th Conference of Retroviruses and Opportunistic Infections; 22–25 February 2005; Boston, Massachusetts, USA) and from metabolic study cohorts with patients on a variety of ARV regimens [10•,11]. There are no controlled studies investigating the risk of fracture in HIV-positive individuals.

Cross-sectional studies

In ambulatory, HIV-positive men without wasting, BMD at the lumbar spine was marginally (3%) lower in antiretroviral therapy (ART)-naïve men than in age-matched healthy controls [12,13]. In contrast, BMD appeared to be much lower in HIV-positive individuals on ART. Tebas *et al.* [14] reported that lumbar spine BMD was markedly lower in HIV-positive men receiving protease inhibitors in comparison with HIV-positive men not receiving protease inhibitors (either ART naïve or receiving non-protease inhibitor based regimens) and HIV-negative controls. The relative risk for osteoporosis in patients receiving protease inhibitors was 2.19 (95% confidence interval, 1.13–4.23). Subsequent studies have also reported lower BMD in HIV-positive individuals currently on ART [15,16] as compared with those not on ART, but associations between protease inhibitor therapy and lower BMD have not been consistently detected after adjustment for other risk factors [11,16–18].

In ambulatory HIV-positive women without wasting, BMD at the lumbar spine and hip were reduced in both treatment-naïve [19] and treatment-experienced women [20,21] (also Anastos and Hessol 2004; and Jacobson *et al.*, presented at the 10th Conference on Retroviruses and Opportunistic Infections; 10–14 February 2003; Boston, Massachusetts, USA) in comparison with age-matched, healthy controls. While differences in BMD were statistically significant, they were also modest (3–6% lower) [5•,20]. In contrast, in a study comparing predominantly ARV-experienced, HIV-positive postmenopausal women with historical controls [21], BMD was considerably lower (9–10%) at the lumbar spine and total hip.

Longitudinal studies

In a retrospective analysis, T sekes *et al.* [8] noted a 3.7% decrease in lumbar spine BMD after 2 years of treatment with only nucleoside reverse transcriptase inhibitors. Similarly, Mallon *et al.* [22] noted an increase in the proportion of patients with low BMD 2 years after beginning protease inhibitor-based ART. Powderly *et al.* (presented at the 12th Conference of Retroviruses and Opportunistic Infections; 22–25 February 2005; Boston, Massachusetts, USA) reported a 2.4–2.8% decrease in total hip BMD after 144 weeks of treatment with either tenofovir/lamivudine/efavirenz or stavudine/lamivudine/efavirenz. Bone loss at the lumbar spine was greater in the group receiving tenofovir as compared with the group receiving stavudine (−2.2% versus −1.0%, P=0.001), but there was no difference in categorical progression from normal BMD to osteoporosis/osteopenia between treatment groups. Additionally, in the tenofovir group, BMD declined during the first 48 weeks after initiation

of ARVs and stabilized thereafter. In contrast, small increases in BMD have been reported in two small series of protease inhibitor-naïve patients initiating indinavir-based [7] and amprenavir-based therapy [9].

Mondy *et al.* [11] reported small but significant increases in BMD at the lumbar spine (2.6%) and hip (2.4%) after 72 weeks of follow-up in 90 predominantly male, HIV-positive individuals receiving mostly protease inhibitor-based regimens. The increase in BMD was associated with increase in CD4 T cells but was not associated with class of ART [11]. A recently published longitudinal study of predominantly premenopausal HIV-positive women [10•] demonstrated that rate of change in BMD did not differ significantly from controls over a 2-year period. Change in BMD was associated with CD4 count, weight, follicle-stimulating hormone, bone resorption markers, and baseline BMD, but not with ARV use [10•].

Fracture studies

Three case series of fragility fractures in HIV-positive patients on ART have been published [23–25]. Although limited, the data do not suggest that the observed reductions in BMD lead to increased fracture rates. Results from a retrospective study of phase III protease inhibitor trials suggest that fracture rates are not higher than expected in HIV-positive participants on treatment (Struble *et al.*, presented at the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy; 16–19 December 2001; Chicago, Illinois, USA). Recently, McComsey *et al.* [25] reported results from an electronic survey of fractures identified by physician recall or Inter-national Classification of Disease-9 coding from nine HIV clinics with cumulative data from 8600 HIV-infected individuals. Fifty-five cases of fracture were identified by this survey, of which only 60% (33/55) were fractures that occurred in the absence of trauma. Fragility fractures may be rare either because reductions in BMD are modest or because most HIV-positive patients are relatively young and are not at increased risk for falls, a major predisposing factor for fracture in the elderly.

Pathogenesis of HIV-associated bone loss

The pathogenesis of excess bone loss associated with HIV is complex and likely multifactorial. Bone loss may result from pathophysiologic interactions within the bone microenvironment between T cells, osteoclasts, and osteoblasts, promoted by elements of both HIV infection and its therapy. Additionally, bone loss may result from nutritional and hormonal changes commonly associated with HIV infection, such as wasting, malnutrition, malabsorption, hypogonadism, and calcium and vitamin D deficiency.

Direct and indirect effects of HIV infection

Infection of bone marrow stromal cells by HIV has been clearly demonstrated [26]. It is thus plausible that HIV infection of preosteoblastic marrow stromal cells could adversely affect their differentiation into osteoblasts [27]. At present, however, there is insufficient evidence to support this finding [28].

Infection with HIV may have both direct and indirect effects on osteoclasts. Chronic HIV infection causes persistent T-cell activation and increased synthesis of proinflammatory, bone-resorbing cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-6 [29,30], systemically and within the bone microenvironment [31–33]. These cytokines both stimulate osteoclast activity and decrease osteoclast apoptosis [34], thereby increasing bone resorption [32,33,35]. Fakruddin and Laurence [36] have shown that exposure of T cells to concentrations of soluble HIV-1 envelope glycoprotein gp120 induced expression of RANKL (receptor activator of nuclear factor-κB ligand). Moreover, exposure of primary human osteoclast precursors to conditioned media from peripheral blood mononuclear cells exposed to gp120

induced the formation of bone-resorbing osteoclasts, an effect that was completely blocked by RANK antibodies and only partly inhibited by TNF-α anti-bodies [36]. These experiments suggest that HIV infection directly stimulates bone resorption via RANKL-dependent mechanisms, which are in part independent of TNF-α.

To date, the only systematic histomorphometric study in HIV-positive patients is a case–control study of tetracycline-labeled transiliac bone biopsies from 22 ARV-naïve patients with advanced disease [27]. Histomorphometric parameters reflecting both bone resorption and bone formation were significantly reduced, especially in subjects with more advanced disease; however, the rate at which newly deposited osteoid was mineralized was not significantly altered [27].

Biochemical markers of bone remodeling measured in serum and urine reflect osteoblast and osteoclast activity at the histologic level and predict rates of bone loss in various adult populations. Serum osteocalcin, bone-specific alkaline phosphatase, and propeptides of type 1 collagen are markers of bone formation. Serum and urinary telopeptides (C-telopeptide [CTX] and N-telo-peptide [NTX]) of type 1 collagen are markers of bone resorption. The few data available before the advent of potent ART [27,37] showed serum osteocalcin concentrations to be markedly suppressed, consistent with the markedly reduced bone formation observed in bone biopsies and correlating with disease severity [27]. Aukrust *et al.* [38] also found that serum osteocalcin decreases and CTX increases with advancing severity of HIV, observations subsequently confirmed in other studies [19,27,39,40]. Divergence of serum osteocalcin and CTX suggest that the usually tightly regulated processes of formation and resorption are disrupted in ARV-naïve patients [38], similar to ‘uncoupled’ bone remodeling in rheumatoid arthritis [41], glucocorticoid excess [42], and myeloma [43].

Effects of antiretroviral therapy

Although several in-vitro studies have attempted to address the differential effect of ARVs, predominantly protease inhibitors, on osteoclasts and osteoblasts, their results are far from conclusive. Using a rat neonatal calvaria assay, Jain and Lenhard [44] reported significant increases in osteoclast activity with the addition of 10-μmol/l concentrations of certain protease inhibitors (nelfinavir, indinavir, saquinavir, and ritonavir) but not others (amprenavir and lopinavir). In contrast, Wang *et al.* [45] observed that ritonavir, but not indinavir, inhibited osteoclast formation and decreased osteoclast pit resorption when co-cultured with bone marrow macrophages stimulated with RANKL and macrophage colony-stimulating factor. The discordant findings may be the result of inherent differences in the in-vitro assays but also may be the result of differences in the concentration of protease inhibitors tested. Fakruddin and Laurence [36] demonstrated that ritonavir (1–5μmol/l), levels consistent with those achieved when used as part of a boosting regimen, increased osteoclastogenesis in human osteoclast precursors, while suprapharmacologic doses of ritonavir (10 and 25μmol/l) were toxic and suppressed osteoclastogenesis. The osteoblast studies are equally difficult to interpret because of differences in experimental models, drug dose, and milieu under which the drugs are administered [44] (and Wang *et al.*, presented at the 24th Meeting of the American Society for Bone and Mineral Research; 20–24 September 2002; San Antonio, Texas, USA).

In aggregate, most studies support the observation of increased bone turnover in HIV-positive patients on ART, characterized by increased concentrations of markers of bone resorption and variable concentrations of formation markers [2,19,46]. Konishi *et al.* [47] also reported that serum levels of RANKL were significantly higher in HIV-positive men on ART than not (241.0 ±236 pg/ml versus 106.7±102, $P<0.05$), correlating inversely with lumbar spine BMD and positively with levels of urinary deoxypyridinoline (a resorption marker). In longitudinal studies of patients on ART, bone formation and resorption markers remain elevated throughout the period of observation [11] (and Vigano *et al.*, presented at the 5th International Workshop

on Adverse Drug Reactions and Lipodystrophy; 8–11 July 2003; Paris, France). Correlation between markers of bone formation and resorption also increased after initiation of ART [38].

Taken together, these findings suggest that in ARV-naïve and ARV-experienced HIV-positive patients, bone formation may be depressed and bone resorption increased in association with expression of proinflammatory cytokines. After initiation of ART, there is a recoupling of bone formation and resorption, but the rate of bone remodeling remains increased. Patient or group differences in rate of remodeling, however, may be due to the differential effects of certain ARVs, duration of treatment, and stage of immune reconstitution or to differences in nutritional status, hormonal function, and body composition. The effects of individual ARVs are difficult to ascertain since most patients are treated with combination therapy and have experienced multiple regimens, and most studies have lacked the power to detect BMD change between different treatment groups.

Anthropomorphic and hormonal factors associated with HIV infection

Low body weight as defined by low body mass index [4,11] (and Dolan *et al.*, 2003), lowest body weight [4,11] (and Dolan *et al.*), pre-ART weight [16], low fat mass [11,48] (and Dolan *et al.*), low lean body mass [4,49] (and Dolan *et al.* 2003), or significant weight loss [11] is associated with low BMD in most studies.

Disturbances of calcium homeostasis and the vitamin D–parathyroid hormone (PTH) endocrine system have been frequently but not consistently reported in association with advanced HIV infection. Impaired PTH secretion and PTH resistance resulting in mild hypocalcemia have been reported in several small studies [50–54], but not others [4,17,55] (and Dolan *et al.* 2003). Markedly decreased serum $1,25(OH)_2D$ has also been reported, particularly in patients with advanced disease [19,38,39,56] (and Dolan *et al.* 2003) and may be the result of decreased 1α-hydroxylase activity [50,56,57]. In addition, conversion of 25-OHD to $1,25(OH)_2D$, which is controlled by cytochrome P450 mixed-function oxygenases, is inhibited by certain protease inhibitors *in vitro* [58]. Most studies have been quite small, and given the complexity of the situation, independent effects of PTH and vitamin D abnormalities are difficult to ascertain.

Gonadal hormone deficiency is indisputably linked to bone loss in otherwise healthy men and women. Both gonadal and adrenal hormones decline in men concomitant with progression of HIV infection [59,60]. Few studies, however, have evaluated associations between gonadal hormones concentrations and BMD [61]. Amenorrhea or oligomenorrhea are common in HIV-positive women [62,63] and both estrogen and testosterone levels are strongly associated with BMD in HIV-positive women [4]. Estrogen could attenuate effects of HIV-associated bone loss by downregulating both the expression of bone-resorbing cytokines by activated T cells [64,65] and expression of RANKL by bone marrow cells [66], as well as by upregulating gene expression and synthesis of osteoprotegerin [67].

Treatment

Owing to the unclear clinical significance of low BMD in an HIV-positive patient and perhaps to the unfamiliarity of many HIV providers with the evaluation and treatment of osteoporosis, very few patients with HIV-associated osteoporosis receive adequate treatment. One noteworthy finding from the fracture survey reported by McComsey *et al.* [25] was that diagnostic tests for correctable secondary causes of fracture were performed on only 20–27% of patients with prevalent fractures, and treatment for secondary prevention including calcium supplementation was initiated in only 35% of cases.

Over the past few years, data from three randomized trials using alendronate [68,69•,70] have been published, demonstrating the efficacy and tolerability of oral bisphosphonate therapy in HIV-positive patients with low BMD. There have been no controlled studies examining the efficacy and safety of other formulations of bisphosphonates. The concept of using intravenous bisphosphonates, such as ibandronate, to treat osteoporosis in HIV-positive patients may be extremely attractive, as these agents may have significant gastrointestinal symptoms, high pill burden, and challenging dosing regimens. Data are limited on the effects of calcium and vitamin D supplementation, and nonexistent on effects of hormone replacement therapy, selective estrogen receptor modulators, calcitonin, or teriparatide on osteoporosis in HIV-positive patients. There is no reason to expect, however, that these agents would not be effective.

Conclusion

Low BMD is relatively common among HIV-positive patients and may be due to direct and indirect effects of HIV infection. The contribution of ART is uncertain. Although certain ARVs exhibit profound effects on bone cells *in vitro*, clinical studies suggest that initiation of certain combinations of ARVs may be associated with moderate bone loss initially, but BMD usually stabilizes or improves with longer follow-up. As the majority of HIV-positive patients are young, fragility fractures are not commonly encountered. As the availability of effective ART permits the population of HIV-positive patients to age, screening, diagnosis, and treatment of osteoporosis to prevent fragility fractures will become more important. At present, routine BMD screening of HIV-positive individuals is not warranted. Measurement of BMD should be considered, however, for HIV-positive individuals with known risk factors such as menopause, premenopausal amenorrhea, age greater than 65 years, history of fracture as an adult, low body weight (<127 lb), current smoking, or use of oral corticosteroids for more than 3 months. Further research is needed to clarify the approach to optimal screening and treatment of osteoporosis in the setting of HIV infection.

Acknowledgments

This work is supported in part by NIH 5K23AI059884-03 (MTY) and R01AI065200-02 (ES).

Abbreviations

ART	antiretroviral therapy
ARV	antiretroviral
BMD	bone-mineral density
CTX	C-telopeptide
PTH	parathyroid hormone
RANKL	receptor activator of nuclear factor-κB ligand
TNF-α	tumor necrosis factor-α

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

• • of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 543).

1. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy; JAMA. 2001. p. 785-795.
2. Fairfield WP, Finkelstein JS, Klibanski A, et al. Osteopenia in eugonadal men with acquired immune deficiency syndrome wasting syndrome. J Clin Endocrinol Metab 2001;86:2020–2026. [PubMed: 11344201]
3. Fairfield WP, Treat M, Rosenthal DI, et al. Effects of testosterone and exercise on muscle leanness in eugonadal men with AIDS wasting. J Appl Physiol 2001;90:2166–2171. [PubMed: 11356779]
4. Huang JS, Wilkie SJ, Sullivan MP, et al. Reduced bone density in androgen-deficient women with acquired immune deficiency syndrome wasting. J Clin Endocrinol Metab 2001;86:3533–3539. [PubMed: 11502775]
5. Arnsten JH, Freeman R, Howard AA, et al. HIV infection and bone mineral density in middle-aged women. Clin Infect Dis 2006;42:1014–1020. [PubMed: 16511769] A large cross-sectional study of BMD in HIV-infected women with well matched controls
6. McComsey GA, Ward DJ, Hessenthaler SM, et al. Improvement in lipoatrophy associated with highly active antiretroviral therapy in human immunodeficiency virus-infected patients switched from stavudine to abacavir or zidovudine: the results of the TARHEEL study. Clin Infect Dis 2004;38:263–270. [PubMed: 14699460]
7. Nolan D, Upton R, McKinnon E, et al. Stable or increasing bone mineral density in HIV-infected patients treated with nelfinavir or indinavir. AIDS 2001;15:1275–1280. [PubMed: 11426072]
8. Tsekes G, Chrysos G, Douskas G, et al. Body composition changes in protease inhibitor-naive HIV-infected patients treated with two nucleoside reverse transcriptase inhibitors. HIV Med 2002;3:85–90. [PubMed: 12010354]
9. Dube MP, Qian D, Edmondson-Melancon H, et al. Prospective, intensive study of metabolic changes associated with 48 weeks of amprenavir-based antiretroviral therapy. Clin Infect Dis 2002;35:475–481. [PubMed: 12145733]
10. Dolan SE, Kanter JR, Grinspoon S. Longitudinal analysis of bone density in HIV-infected women. J Clin Endocrinol Metab 2006;91:2938–2945. [Epub ahead of print]. [PubMed: 16735489] The only published longitudinal study of BMD in HIV-infected women.
11. Mondy K, Yarasheski K, Powderly WG, et al. Longitudinal evolution of bone mineral density and bone markers in human immunodeficiency virus-infected individuals. Clin Infect Dis 2003;36:482–490. [PubMed: 12567307]
12. Hernandez Quero J, Ortego Centeno N, Munoz-Torres M, et al. Alterations in bone turnover in HIV-positive patients. Infection 1993;21:220–222. [PubMed: 7901171]
13. Paton NI, Macallan DC, Griffin GE, et al. Bone mineral density in patients with human immunodeficiency virus infection. Calcif Tissue Int 1997;61:30–32. [PubMed: 9192508]
14. Tebas P, Powderly WG, Claxton S, et al. Accelerated bone mineral loss in HIV-infected patients receiving potent antiretroviral therapy. AIDS 2000;14:F63–F67. [see comments]. [PubMed: 10770534]
15. McDermott AY, Shevitz A, Knox T, et al. Effect of highly active antiretroviral therapy on fat, lean, and bone mass in HIV-seropositive men and women. Am J Clin Nutr 2001;74:679–686. [PubMed: 11684538]
16. Carr A, Miller J, Eisman JA, et al. Osteopenia in HIV-infected men: association with asymptomatic lactic acidemia and lower weight preantiretroviral therapy. AIDS 2001;15:703–709. [PubMed: 11371684]
17. Brown T, Ruppe M, Kassner R, et al. Reduced bone mineral density in HIV infected patients and its association with increased central adiposity and postload hyperglycemia. J Clin Endocrinol Metab 2004;89:1200–1206. [PubMed: 15001610]
18. Moore AL, Vashisht A, Sabin CA, et al. Reduced bone mineral density in HIV-positive individuals. AIDS 2001;15:1731–1733. [PubMed: 11546951]
19. Teichmann J, Stephan E, Lange U, et al. Osteopenia in HIV-infected women prior to highly active antiretroviral therapy. J Infect 2003;46:221–227. [PubMed: 12799147]

20. Dolan SE, Huang JS, Killilea KM, et al. Reduced bone density in HIV-infected women. AIDS 2004;18:475–483. [PubMed: 15090800]
21. Yin M, Dobkin J, Brudney K, et al. Bone mass and mineral metabolism in HIV+postmenopausal women. Osteoporos Int 2005;16:1345–1352. [PubMed: 15754081]
22. Mallon PW, Miller J, Cooper DA, et al. Prospective evaluation of the effects of antiretroviral therapy on body composition in HIV-1-infected men starting therapy. AIDS 2003;17:971–979. [PubMed: 12700446]
23. Guaraldi G, Ventura P, Albuzza M, et al. Pathological fractures in AIDS patients with osteopenia and osteoporosis induced by antiretroviral therapy. AIDS 2001;15:137–138. [PubMed: 11192861]
24. Stephens EA, Das R, Madge S, et al. Symptomatic osteoporosis in two young HIV-positive African women. AIDS 1999;13:2605–2606. [PubMed: 10630537]
25. McComsey GA, Huang JS, Woolley IJ, et al. Fragility fractures in HIV-infected patients: need for better understanding of diagnosis and management. J Int Assoc Physicians AIDS Care (Chic Ill) 2004;3:86–91. [PubMed: 15573712]
26. Canque B, Marandin A, Rosenzwajg M, et al. Susceptibility of human bone marrow stromal cells to human immunodeficiency virus (HIV). Virology 1995;208:779–783. [PubMed: 7747451]
27. Serrano S, Marinoso ML, Soriano JC, et al. Bone remodelling in human immunodeficiency virus-1-infected patients: a histomorphometric study. Bone 1995;16:185–191. [PubMed: 7756046]
28. Toneguzzi S, Lisignoli G, Monaco MC, et al. Osteoblastic cell lines are not susceptible to HIV infection. Boll Soc Ital Biol Sper 1995;71:275–279. [PubMed: 8962698]
29. Lahdevirta J, Maury CP, Teppo AM, et al. Elevated levels of circulating cachectin/tumor necrosis factor in patients with acquired immunodeficiency syndrome. Am J Med 1988;85:289–291. [PubMed: 3414726]
30. Breen EC, Rezai AR, Nakajima K, et al. Infection with HIV is associated with elevated IL-6 levels and production. J Immunol 1990;144:480–484. [PubMed: 2295799]
31. Manolagas SC, Jilka RL. Bone marrow, cytokines, and bone remodeling: emerging insights into the pathophysiology of osteoporosis. N Engl J Med 1995;332:305–311. [PubMed: 7816067]
32. Alsina M, Guise TA, Roodman GD. Cytokine regulation of bone cell differentiation. Vitam Horm 1996;52:63–98. [PubMed: 8909157]
33. Roodman GD. Role of cytokines in the regulation of bone resorption. Calcif Tissue Int 1993;53:S94–S98. [PubMed: 8275387]
34. Armstrong AP, Tometsko ME, Glaccum M, et al. A RANK/TRAF6-dependent signal transduction pathway is essential for osteoclast cytoskeletal organization and resorptive function. J Biol Chem 2002;277:44347–44356. [PubMed: 12185073]
35. Manolagas SC, Bellido T, Jilka RL. New insights into the cellular, biochemical, and molecular basis of postmenopausal and senile osteoporosis: roles of IL-6 and gp130. Int J Immunopharmacol 1995;17:109–116. [PubMed: 7657404]
36. Fakruddin JM, Laurence J. HIV envelope gp 120-mediated regulation of osteoclastogenesis via RANKL secretion and its modulation by certain HIV protease inhibitors through interferon-gamma/RANKL cross-talk. J Biol Chem 2003;278:48251–48258. [PubMed: 12975380]
37. Mellert W, Kleinschmidt A, Schmidt J, et al. Infection of human fibroblasts and osteoblast-like cells with HIV-1. AIDS 1990;4:527–535. [PubMed: 2201317]
38. Aukrust P, Haug CJ, Ueland T, et al. Decreased bone formative and enhanced resorptive markers in human immunodeficiency virus infection: indication of normalization of the bone-remodeling process during highly active antiretroviral therapy. J Clin Endocrinol Metab 1999;84:145–150. [PubMed: 9920075]
39. Teichmann J, Stephan E, Discher T, et al. Changes in calciotropic hormones and biochemical markers of bone metabolism in patients with human immunodeficiency virus infection. Metab Clin Exp 2000;49:1134–1139. [PubMed: 11016893]
40. McNurlan MA, Garlick PJ, Frost RA, et al. Albumin synthesis and bone collagen formation in human immunodeficiency virus-positive subjects: differential effects of growth hormone administration. J Clin Endocrinol Metab 1998;83:3050–3055. [PubMed: 9745402]

41. Garnero P, Jouvenne P, Buchs N, et al. Uncoupling of bone metabolism in rheumatoid arthritis patients with or without joint destruction: assessment with serum type I collagen breakdown products. Bone 1999;24:381–385. [PubMed: 10221550]
42. Canalis E. Mechanisms of glucocorticoid-induced osteoporosis. Curr Opin Rheumatol 2003;15:454–457. [PubMed: 12819474]
43. Callander NS, Roodman GD. Myeloma bone disease. Semin Hematol 2001;38:276–285. [PubMed: 11486316]
44. Jain RG, Lenhard JM. Select HIV protease inhibitors alter bone and fat metabolism ex vivo. J Biol Chem 2002;277:19247–19250. [PubMed: 11937496]
45. Wang MWH, Wei S, Faccio R, et al. The HIV protease inhibitor ritonavir blocks osteoclastogenesis and function by impairing RANKL-induced signaling. J Clin Invest 2004;114:206–213. [PubMed: 15254587]
46. Zamboni G, Antoniazzi F, Bertoldo F, et al. Altered bone metabolism in children infected with human immunodeficiency virus. Acta Paediatr 2003;92:12–16. [PubMed: 12650292]
47. Konishi M, Takahashi K, Yoshimoto E, et al. Association between osteopenia/osteoporosis and the serum RANKL in HIV-infected patients. AIDS 2005;19:1240–1241. [PubMed: 15990584]
48. Rosenthall L, Falutz J. Bone mineral changes in AIDS associated lipodystrophy. J Bone Miner Res 2003;18:278. [abstract]. [PubMed: 12568405]
49. Gold J, Pocock N, Li Y, et al. Bone mineral density abnormalities in patients with HIV infection. J Acquir Immune Defic Syndr 2002;30:131–132. [PubMed: 12048375]
50. Kuhne CA, Heufelder AE, Hofbauer LC. Bone and mineral metabolism in human immunodeficiency virus infection. J Bone Miner Res 2001;16:2–9. [PubMed: 11149485]
51. Welch K, Finkbeiner W, Alpers CE, et al. Autopsy findings in the acquired immune deficiency syndrome. JAMA 1984;252:1152–1159. [PubMed: 6471338]
52. Hellman P, Albert J, Gidlund M, et al. Impaired parathyroid hormone release in human immunodeficiency virus infection. AIDS Res Hum Retroviruses 1994;10:391–394. [PubMed: 7915122]
53. Palestine AG, Polis MA, De Smet MD, et al. A randomized, controlled trial of foscarnet in the treatment of cytomegalovirus retinitis in patients with AIDS. Ann Intern Med 1991;115:665–673. [comment]. [PubMed: 1656826]
54. Wharton JM, Coleman DL, Wofsy CB, et al. Trimethoprim-sulfamethoxazole or pentamidine for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome: a prospective randomized trial. Ann Intern Med 1986;105:37–44. [PubMed: 3521428]
55. Bruera D, Luna N, David DO, et al. Decreased bone mineral density in HIV-infected patients is independent of antiretroviral therapy. AIDS 2003;17:1917–1923. [PubMed: 12960824]
56. Haug CJ, Aukrust P, Haug E, et al. Severe deficiency of 1,25-dihydroxyvitamin D3 in human immunodeficiency virus infection: association with immunological hyperactivity and only minor changes in calcium homeostasis. J Clin Endocrinol Metab 1998;83:3832–3838. [PubMed: 9814454]
57. Kuehn EW, Anders HJ, Bogner JR, et al. Hypocalcaemia in HIV infection and AIDS. J Intern Med 1999;245:69–73. [PubMed: 10095819]
58. Cozzolino M, Vidal M, Arcidiacono MV, et al. HIV-protease inhibitors impair vitamin D bioactivation to 1,25-dihydroxyvitamin D. AIDS 2003;17:513–520. [PubMed: 12598771]
59. Honour JW, Schneider MA, Miller RF. Low adrenal androgens in men with HIV infection and the acquired immunodeficiency syndrome. Horm Res 1995;44:35–39. [PubMed: 7649525]
60. Christeff N, Gharakhanian S, Thobie N, et al. Evidence for changes in adrenal and testicular steroids during HIV infection. J Acquir Immune Defic Syndr 1992;5:841–846. [PubMed: 1387684]
61. Huang JS, Rietschel P, Hadigan CM, et al. Increased abdominal visceral fat is associated with reduced bone density in HIV-infected men with lipodystrophy. AIDS 2001;15:975–982. [PubMed: 11399979]
62. Clark RA, Mulligan K, Stamenovic E, et al. Frequency of anovulation and early menopause among women enrolled in selected adult AIDS Clinical Trials Group studies. J Infect Dis 2001;184:1325–1327. [PubMed: 11679923]

63. Grinspoon S, Corcoran C, Miller K, et al. Body composition and endocrine function in women with acquired immunodeficiency syndrome wasting. J Clin Endocrinol Metab 1997;82:1332–1337. [erratum appears in J Clin Endocrinol Metab 1997, 82:3360]. [PubMed: 9141512]

64. Manolagas SC. Role of cytokines in bone resorption. Bone 1995;17(2 Suppl):63S–67S. [PubMed: 8579900]

65. Pacifici R. Estrogen, cytokines, and pathogenesis of postmenopausal osteoporosis. J Bone Miner Res 1996;11:1043–1051. [PubMed: 8854239]

66. Eghbali-Fatourechi G, Khosla S, Sanyal A, et al. Role of RANK ligand in mediating increased bone resorption in early postmenopausal women. J Clin Invest 2003;111:1221–1230. [PubMed: 12697741]

67. Hofbauer LC, Khosla S, Dunstan CR, et al. Estrogen stimulates gene expression and protein production of osteoprotegerin in human osteoblastic cells. Endocrinology 1999;140:4367–4370. [PubMed: 10465311]

68. Guaraldi G, Orlando G, Madeddu G, et al. Alendronate reduces bone resorption in HIV-associated osteopenia/osteoporosis. HIV Clin Trials 2004;5:269–277. [PubMed: 15562367]

69. Mondy K, Powderly WG, Claxton SA, et al. Alendronate, vitamin D, and calcium for the treatment of osteopenia/osteoporosis associated with HIV infection. J Acquir Immune Defic Syndr 2005;38:426–431. [PubMed: 15764959] A controlled study demonstrating short-term increase in BMD and tolerability of alendronate in HIV-infected individuals.

70. Negredo E, Martinez-Lopez E, Paredes R, et al. Reversal of HIV-1 associated osteopenia with once-weekly alendronate. AIDS 2005;19:243–245.