Bone disease in HIV infection

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Summary

The advent of highly active anti-retroviral therapy (HAART) has dramatically decreased the rate of AIDS-related mortality and significantly extended the life span of patients with AIDS. A variety of metabolic side effects are associated with these therapies, one of which is metabolic bone disease. The causes of low bone mineral density (BMD) in individuals with HIV infection appear to be multifactorial and likely represent a complex interaction between HIV infection, traditional osteoporosis risk factors, and antiretroviral related factors. This review summarizes the clinical evidence linking HIV-associated osteoporosis to direct infection and antiretroviral therapy use. The purported mechanisms involved in bone loss are also reviewed. Additionally, recommendations regarding the pharmacologic management of HIV/HAART-related osteoporosis are given. In conclusion, we make the point that HIV infection should be considered as a risk factor for bone disease.

KEY WORDS: HIV, antiretroviral therapy, osteopenia/osteoporosis, bone density.

Introduction

Advances in anti-retroviral therapy have resulted in a dramatic decline in mortality for individuals infected with human immunodeficiency virus (HIV). The decrease in mortality in HIV-infected persons initially was the result of improved prophylaxis and treatment of opportunistic infections but was considerably accelerated with the introduction of highly-active antiretroviral therapy (HAART) in the mid- 1990s. In the post-HAART era, opportunistic infections have been replaced by long-term complications of HIV infection itself and of HAART (1).
Long-term HAART is associated with several metabolic and morphological complications, including lipodystrophy, insulin resistance, diabetes, dyslipidemia, osteopenia and osteoporosis (2-4).
Osteoporosis is a disorder characterized by decreased bone density and deterioration of the skeletal microarchitecture, resulting in bone fragility (5). According to the World Health Organization (WHO) criteria osteoporosis is defined as a bone mineral density T-score < -2.5 and osteopenia between -1 and -2.5 SD (6).
Heterogeneous cross-sectional cohort studies, performed over the past ten years, have described a significantly higher prevalence of bone disease in HIV-positive individuals when compared to age-, race- and sex-matched HIV-negative individuals (1, 3, 7-25). The prevalence of reduced BMD in HIV-infected individuals has ranged from 25.7% (21) to 87.5% (8). Moreover, the prevalence of osteopenia in these patients was 22.0% (7) to 67.5% (8), and of osteoporosis from 1% (13) to 26.8% (3). Brown et al. (26) in a meta-analysis of pooled prevalence data from eleven cross-sectional studies performed between 2000 and 2005, which includes a review of the literature from 1993 to 2005, demonstrated an overall prevalence of 67% reduced BMD and 15% osteoporosis in 884 HIV-positive individuals when compared to 654 HIV-negative age and sex-matched controls.
Whereas bone mass is largely genetically determined, certain lifestyle and hormonal factors that are prevalent among HIV infected persons are associated with low peak bone mass and disordered bone metabolism. These include physical inactivity, decreased intake of calcium and vitamin D, cigarette smoking, alcohol use, depression, opiate use and low testosterone levels (27). Actually, the large number of independent disease and lifestyle-related risk factors, and complex HAART combinations used in clinical practice, have generated considerable confusion as to the exact causes and appropriate interventions.
In this review we discuss evidence linking metabolic bone disease to HIV infection and its treatment.

Bone loss intrinsic to HIV-1 infection

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.
Canque et al. (28) in 1995 demonstrated that HIV can infect bone marrow stromal cells. Serrano et al. (29) in the same years showed that HIV infection of preosteoblastic marrow stromal cells could adversely affect their differentiation into osteoblasts. At the present, however, there is insufficient evidence to support this findings (30,31).
In recent years it has become evident that the immune and skeletal systems are interlinked, and consequently changes in the immune system potently affect skeletal metabolism (32, 33).
Recent meta-analysis (1, 33, 34) showed that HIV-infection may have both direct and indirect effects on osteoclasts.
Osteoclast function is influenced by a number of factors modulated during HIV-1 infection, including pro-inflammatory cytokines such as TNF-α, expression of receptor of activated NF-κB ligand

(RANKL) and osteoprotegerin (OPG), vitamin D and calcium metabolism and hormone levels (35, 36).
Under basal physiological conditions, B cells act as critical stabilizers of peak BMD in vivo. This is a consequence of the fact that B cells are a source of OPG. B cell OPG production is further sustained by interactions with T cells, through CD40 ligand (CD40L) costimulation (33, 37, 38). Consequently, during HIV-1 infection, HIV leads to a disruption of T cell to B-cell communication, leading to increased presence of RANKL and diminished OPG production by B cells. The elevated RANKL/OPG ratio is biased in favor of increased osteoclast formation.
Another central cytokine involved in the immuno-skeletal interface is IFN-γ. During HIV infection the cytokine profile favours TNF-α expression and increased viral replication, whilst there is a shift towards a TH2 cytokine balance, with decreased production of IFN-γ (39). The downregulation of IFN- limits availability of a factor which downregulates RANKL (40) and potentially limits the normal cross-talk between RANKL and IFN-γ, resulting in stimulation of osteoclast formation (41).
Yadav et al. (42) have recently reported that the suppressor of cytokine signaling-1 (SOCS-1), a potent inhibitor of IFN-γ signal transduction is significantly elevated in cells derived from individuals with progressive HIV infection. So, the upregulation of SOCS-1 may contribute to elevated osteoclastogenesis by removing the dampening effect of IFN-γ on the differentiation of osteoclast precursors in the context of HIV infection.
Anyway, current data suggest that alterations in the immuno-skeletal interface may be responsible for much of the loss of BMD observed in HIV patients naive to antiretroviral therapy.

Bone loss induced by HAART

Good evidence of reduced BMD in HAART-naïve HIV-infected patients tells us that HAART cannot be the only responsible in the pathogenesis of metabolic bone disease in HIV-infected patients.
Antiretroviral treatment consists of at least three antiretroviral drugs, usually two nucleoside reverse transcriptase inhibitors (NRTI) plus either a protease inhibitor or a non-nucleotide reverse transcriptase inhibitor (NNRTI). Less widely used regimens combine two protease inhibitors or more than three antiretroviral drugs.
HAART has long been suspected of influencing bone turnover independently of the bone loss associated with HIV infection itself (43), although it has been suggested that this effect may be relatively modest in relation to the loss of BMD associated with other established osteoporosis risk factors (14, 22).
Initiation of antiretroviral therapy is associated with a 2%-6% decrease in BMD over the first 48–96 weeks of therapy, a decrease that is similar in magnitude to that sustained during the first 2 years of menopause (44-46).
However, some HAART regimens may be associated with more pronounced bone loss. Brown et al. (26) in a recent meta-analysis of cross-sectional studies, showed that HIV infected patients receiving protease inhibitors had a higher prevalence of osteoporosis compared to those receiving non protease inhibitor regimens. However, with the available studies, the influence of other important factors such as disease severity and prior HAART history, could not be determined and interpretation of studies addressing HAART-associated bone loss have been further confounded by the wide range of antiretroviral regimens utilized in clinical practice, inadequate controlling of traditional osteoporosis risk factors, other disease-related effects, and variability in anatomical sites chosen for BMD analysis.
A high incidence of osteopenia/osteoporosis has been associated with both PI and NRTI use.
PIs are potent inhibitors of cytochrome CYP3A4, which includes inhibition of 1 hydroxylase (47); NRTIs inhibit the enzyme DNA polymerase-γ (48) leading to loss of structure and function of mitochondrial DNA (49).
One of the first studies was conducted by Tebas et al. (43). They measured BMD in HIV infected patients receiving a PI and found that 50% of the patients had osteopenia and 21% had osteoporosis. This incidence is significantly increased compared to patients without therapy or normal controls. Moore et al. (9) confirmed that 71% of HIV infected patients on PI therapy have reduced BMD. Jain et al. (50) compared the effect of various PIs on bone resorption and found that some PIs, but not all, increase bone resorption. Duvivier et al. (51) report that in a randomized clinical trial in which patients received either a non-nucleoside reverse transcriptase inhibitor (NNRTI) and a protease inhibitor, two nucleoside reverse transcriptase inhibitors (NRTIs) with a protease inhibitor, or a combination of one NNRTI with two NRTIs, 48 weeks of treatment revealed an overall combined (average of all treatment groups) significant decline in BMD of -4.1% at lumbar spine and -2.8% at hip. The decrease in BMD at lumbar spine was significantly higher in the protease inhibitor-containing.
Similarly, Carr et al. (7) reported that 3% of 44 HIV-infected patients receiving NRTIs developed osteoporosis and 22% developed osteopenia.
Tsekes et al. (52) determined BMD and whole body fat by dual-energy X ray absorbance (DEXA) of HIV-infected patients on Zidovudine (AZT) and other NRTIs and found significant decreases in both body fat and BMD. Of greatest interest recently, the nucleoside reverse transcriptase inhibitor tenofovir has been strongly associated with an acute decrease in BMD; in a recently presented study, there was more bone loss in patients with HIV suppression who were switched to tenofovir than in those who were switched to abacavir (45, 53).
Not all studies agreed on a negative effect of HAART on bone metabolism.
In 2003 Vescini (16) described a higher prevalence of osteopenia and osteoporosis than was to be expected in age-matched and sex-matched subjects, but he did not find any significance differences among different drug regimens. Dolan et al. (54) showed that change in BMD was associated with CD4 count, weight, follicle-stimulating hormone, bone resorption markers, and baseline BMD, but not with antiretroviral use. Recently, Brown et al. (55) reported that loss of BMD after HAART initiation occurred independently of the antiretroviral regimen. Grund et al. (56) reported that continuous HAART was associated with a decline in BMD and possibly more fractures relative to intermittent HAART, but likewise reported no consistent drug specific association. Furthermore, in the meta-analysis of Paccou et al. (57) conventional risk factors for osteoporotic fractures, including wasting syndrome, hypogonadism, disorders in calcium and phosphate metabolism, and HIV infection per se accounted for bone loss with no evidence of a HAART-related contribution. Yin et al. (58) report that initiation of certain combinations of antiretroviral agents may be associated with moderate bone loss initially, but BMD usually stabilizes or improves with longer follow-up. Similar data were reported by Libois et al. (4) who found that osteopenia and osteoporosis was highly prevalent among HIV infected premenopausal women, but loss of BMD was associated to low BMI and not with antiretroviral therapy, containing PI or not.
Consequently, after more than a decade of investigation no agreement exists as to the direct effects of HAART or their components on bone cells in vivo, or their mechanisms of action on the skeleton. In fact, it's probably that all HAART formulation may be inherently detrimental to the skeleton and that bone loss following HAART may be a recoupling of bone formation and resorption (33). Patient or group differences in rate of remodeling, however, may be due to the differential effects of certain antiretroviral agents, duration of treatment, and stage of immune reconstitution or to differences in nutritional status, hormonal function, and body composition. The effects of individual antiretroviral agents 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.

Treatment

With a paucity of data available, a pragmatic approach to managing patients at risk of having reduced BMD or fragility fractures is needed to minimise or reverse validated risk factors for reduced BMD. Because of the high prevalence of low BMD in HIV infection, it is important to focus on factors important to bone health, including adequate nutrition, particularly calcium and vitamin D intake.

The prevalence of low vitamin D levels is 60%–75% in different HIV-infected cohorts (59-62).

Non pharmacologic interventions should be tried in all HIV-infected patients. These include having a minimum of 1200 mg of elemental Ca2+ in the diet, 800 to 1000 IU of vitamin D per day, and regular weight-bearing and muscles strengthening exercises to reduce the risk of falls and fractures (63,64).

All patients with a diagnosed vertebral/hip fracture and/or a DXA score of less than 2.5 at femoral neck/spine should be treated with pharmacologic therapy.

Bisphosphonates are the most commonly prescribed class of antiresorptive agents and typically elicit a 60–70% decrease in markers of bone resorption (65). Over the past few years, data from three randomized trials using alendronate (66-68) have been published, demonstrating the efficacy and tolerability of oral bisphosphonate therapy in HIV-positive patients with low BMD.

In consideration of gastrointestinal side-effects associated to oral bisphosphonates, an alternative could be annual zoledronic acid infusion. It has been shown to be well tolerated and to significantly increase BMD in HIV infected individuals with osteoporosis (69,70).

Conclusion

At the present time, osteopenia and osteoporosis are a frequent finding in HIV-infected patients. At the moment, the etiology of this disease in HIV population is not completely understood. The causes appear to be multifactorial and likely represent a complex interaction between HIV infection, traditional osteoporosis risk factors exacerbated by consequences of chronic HIV infection (eg, poor nutrition and low weight), low vitamin D levels, and HAART-related factors.

Currently, the treatment of HIV-induced bone loss seems to be bisphosphonates in conjunction with vitamin D and calcium supplementation.

Further longitudinal studies of HIV patients will be needed to clarify the correlation between BMD, HIV and HAART.

References

1. Stone B, Dockrell D, Bowman C et al. HIV and bone disease. Arch Biochem Biophys. 2010;503(1):66-77.
2. Carr A, Samaras K, Burton S et al. A syndrome of peripheral lipodystrophy, hyperlipidemia and insuline resistance in patients receiving HIV protease inhibitors. AIDS 1998; 12:F51-F58.
3. Cazanave C, Dupon M, Lavignolle-Aurillac V et al. Groupe d'Epidémiologie Clinique du SIDA en Aquitaine. Reduced bone mineral density in HIV-infected patients: prevalence and associated factors. AIDS. 2008;22(3):395-402.
4. Libois A, Clumeck N, Kabeya K, et al. Risk factors of osteopenia in HIV-infected women: no role of antiretroviral therapy. Maturitas 2010; 65:51-54.
5. Consensus Development Conference. Diagnosis, prophylaxis, and treatment of osteoporosis. Am J Med. 1993;94:646-50.
6. World Health Organization - Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. WHO technical report series 1994; Geneva, 843:1-129.
7. Carr A, Miller J, Eisman JA et al. Osteopenia in HIV-infected men: association with asymptomatic lactic acidemia and lower weight pre-antiretroviral therapy. AIDS. 2001;15(6):703-9.
8. Knobel H, Guelar A, Vallecillo G et al. Osteopenia in HIV-infected patients: is it the disease or is it the treatment? AIDS. 2001;15(6):807-8.
9. Moore AL, Vashisht A, Sabin CA et al. Reduced bone mineral density in HIV-positive individuals. AIDS. 2001;15(13):1731-3.
10. 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(10):1275-80.
11. Loiseau-Pérès S, Delaunay C, Poupon S et al. Osteopenia in patients infected by the human immunodeficiency virus. A case control study. Joint Bone Spine. 2002;69(5):482-5.
12. Bruera D, Luna N, David DO et al. Decreased bone mineral density in HIV-infected patients is independent of antiretroviral therapy. AIDS. 2003;17(13):1917-23.
13. Fernández-Rivera J, García R, Lozano F et al. Relationship between low bone mineral density and highly active antiretroviral therapy including protease inhibitors in HIV-infected patients. HIV Clin Trials. 2003;4(5):337-46.
14. 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(4):482-90.
15. Teichmann J, Stephan E, Lange U et al. Osteopenia in HIV-infected women prior to highly active antiretroviral therapy. J Infect. 2003;46(4):221-7.
16. Vescini F, Borderi M, Buffa A et al. Bone mass in HIV-infected patients: focus on the role of therapy and sex. J Acquir Immune Defic Syndr. 2003;33(3):405-7.
17. Amiel C, Ostertag A, Slama L et al. BMD is reduced in HIV-infected men irrespective of treatment. J Bone Miner Res. 2004;19(3):402-9.
18. Brown TT, Ruppe MD, Kassner R et al. Reduced bone mineral density in human immunodeficiency virus-infected patients and its association with increased central adiposity and postload hyperglycemia. J Clin Endocrinol Metab. 2004;89(3):1200-6.
19. Dolan SE, Huang JS, Killilea KM et al. Reduced bone density in HIV-infected women. AIDS. 2004;18(3):475-83.
20. Madeddu G, Spanu A, Solinas P et al. Bone mass loss and vitamin D metabolism impairment in HIV patients receiving highly active antiretroviral therapy. Q J Nucl Med Mol Imaging. 2004;48(1):39-48.
21. Konishi M, Takahashi K, Yoshimoto E et al. Association between osteopenia/osteoporosis and the serum RANKL in HIV-infected patients. AIDS. 2005;19(11):1240-1.
22. Yin M, Dobkin J, Brudney K et al. Bone mass and mineral metabolism in HIV+ postmenopausal women. Osteoporos Int. 2005;16(11):1345-52.
23. Fausto A, Bongiovanni M, Cicconi P et al. Potential predictive factors of osteoporosis in HIV-positive subjects. Bone. 2006;38(6):893-7.
24. García Aparicio AM, Muñoz Fernández S, González J et al. Abnormalities in the bone mineral metabolism in HIV-infected patients. Clin Rheumatol. 2006;25(4):537-9.
25. Calmy A, Fux CA, Norris R et al. Low bone mineral density, renal dysfunction, and fracture risk in HIV infection: a cross-sectional study. J Infect Dis. 2009;200(11):1746-54.
26. Brown TT, Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. AIDS. 2006;20(17):2165-74.
27. Arnsten JH, Freeman R, Howard AA et al. Decreased bone mineral density and increased fracture risk in aging men with or at risk for HIV infection. AIDS. 2007;21(5):617-23.
28. Canque B, Marandin A, Rosenzwajg M et al. Susceptibility of human bone marrow stromal cells to human immunodeficiency virus (HIV). Virology. 1995;208(2):779-83.

29. Serrano S., Marinoso M.L., Soriano J.C. Bone remodelling in human immunodeficiency virus-1-infection patients. A histomorphometric study. Bone. 1995;16, 185-191.
30. Montserrat Nacher, Sergi Serrano, Alicia Gonzalez et al. Osteoblasts in HIV-infected Patients: HIV-1 Infection and Cell Function. AIDS. 15 (2001), no. 17, 2239-2243.
31. Gibellini D, De Crignis E, Ponti C, et al. HIV-1 triggers apoptosis in primary osteoblasts and HOBIT cells through TNFalpha activation. J Med Virol. 2008; 80:1507-1514.
32. Weitzmann MN, Pacifici R. Estrogen deficiency and bone loss: an inflammatory tale. J Clin Invest 2006; 116:1186-1194.
33. Ofotokun I, Weitzmann MN. HIV-1 infection and antiretroviral therapies: risk factors for osteoporosis and bone fracture. Curr Opin Endocrinol Diabetes Obes.2010;17(6):523-9.
34. Yin MT, Shane E. Low bone-mineral density in patients with HIV: pathogenesis and clinical significance. Curr Opin Endocrinol Diabetes. 2006;13(6):497-502.
35. Amorosa V, Tebas P. Bone disease and HIV infection. Clin Infect Dis. 2006;42(1):108-14.
36. Pan G, Kilby M, McDonald JM. Modulation of osteoclastogenesis induced by nucleoside reverse transcriptase inhibitors. AIDS Res Hum Retroviruses. 2006;22(11):1131-41.
37. Yun TJ, Chaudhary PM, Shu GL, et al. OPG/FDCR-1, a TNF receptor family member, is expressed in lymphoid cells and is up-regulated by ligating CD40. J Immunol. 1998; 161:6113-6121.
38. Li Y, Toraldo G, Li A, et al. B cells and T cells are critical for the preservation of bone homeostasis and attainment of peak bone mass in vivo. Blood. 2007; 109:3839-3848.
39. Clerici M, Shearer GM. A TH1-->TH2 switch is a critical step in the etiology of HIV infection. Immunol Today. 1993;14(3):107-11.
40. Takayanagi H, Ogasawara K, Hida S et al. T-cell-mediated regulation of osteoclastogenesis by signalling cross-talk between RANKL and IFN-gamma. Nature. 2000;408(6812):600-5.
41. Wei S, Kitaura H, Zhou P et al. IL-1 mediates TNF-induced osteoclastogenesis. J Clin Invest. 2005;115(2):282-90.
42. Yadav A, Fitzgerald P, Sajadi MM, et al. Increased expression of suppressor of cytokine signaling-1 (SOCS-1): a mechanism for dysregulated T helper-1 responses in HIV-1 disease. Virology. 2009; 385:126-133.
43. Tebas P, Powderly WG, Claxton S, et al. Accelerated bone mineral loss in HIV-infected patients receiving potent antiretroviral therapy. AIDS. 2000; 14:F63-67.
44. 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.
45. Gallant JE, Staszewski S, Pozniak AL, et al. Efficacy and safety of tenofovir DF vs. stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. J Am Med Assoc. 2004; 292:191-201.
46. Yin MT, McMahon DJ, Ferris DC, et al. Low bone mass and high bone turnover in postmenopausal human immunodeficiency virus-infected women. J Clin Endocrinol Metab. 2010; 95:620-629.
47. Von Moltke LL, Greenblatt DJ, Grassi JM, et al.: Protease inhibitors as inhibitors of human cytochromes P450: high risk associated with ritonavir. J Clin Pharmacol. 1998, 38:106-111.
48. Martin JL, Brown CE, Matthews-Davis N et al. Effects of antiviral nucleoside analogs on human DNA polymerases and mitochondrial DNA synthesis. Antimicrob Agents Chemother. 1994; 38:2743-2749.
49. Lewis W, Dalakas MC. Mitochondrial toxicity of antiviral drugs. Nat Med 1995, 1:417-422.
50. Jain RG, Lenhard JM. Select HIV protease inhibitors alter bone and fat metabolism ex vivo. J. Biol. Chem. 2002;277:19247-19250.
51. Duvivier C, Kolta S, Assoumou L, et al. Greater decrease in bone mineral density with protease inhibitor regimens compared with non-nucleoside reverse transcriptase inhibitor regimens in HIV-1 infected naive patients. AIDS. 2009; 27:817-824.
52. 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.
53. Cooper DA, Bloch M, Humphries A, et al. Simplification with fixed-dose tenofovir-emtricitaine or abacavir-lamivudine in adults with suppressed HIV repliation (The Steal Study): A randomized, open-label, 96-week, non-inferiority trial [abstract 576]. In Program and abstracts of the 16th Conference on Retroviruses and Opportunistic Infections 8-11 February 2009, Montreal, Canada.
54. Dolan SE, Kanter JR, Grinspoon S. Longitudinal analysis of bone density in HIV-infected women. J Clin Endocrinol Metab. 2006;91:2938-2945.
55. Brown TT, McComsey GA, King MS, et al. Loss of bone mineral density after antiretroviral therapy initiation, independent of antiretroviral regimen. J Acquir Immune Defic Syndr. 2009; 51:554-561.
56. Grund B, Peng G, Gibert CL, et al. Continuous antiretroviral therapy decreases bone mineral density. AIDS. 2009; 23:1519-1529.
57. Paccou J, Viget N, Legrout-Gerot I, et al. Bone loss in patients with HIV infection. Joint Bone Spine 2009; 76:637-641.
58. Yin MT, Lu D, Cremers S, et al. Short-term bone loss in HIV-infected premenopausal women. J Acquir Immune Defic Syndr. 2010; 53:202-208.
59. Guaraldi G, Orlando G, Squillace N, et al. Prevalence of secondary causes of osteoporosis among HIV-infected individuals. In: Program and abstracts of the 8th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, San Francisco, CA, 24-26 September 2006.
60. Stephensen CB, Marquis GS, Kruzich LA et al. Vitamin D status in adolescents and young adults with HIV infection. Am J Clin Nutr. 2006; 83(5):1135-1141.
61. Rodriguez M, Daniels B, Gunawardene S et al. High frequency of vitamin D deficiency in ambulatory HIV-Positive patients. AIDS Res Hum Retroviruses. 2009; 25(1):9-14.
62. McComsey GA, Tebas P, Shane E et al. Bone disease in HIV infection: a practical review and recommendations for HIV care providers. Clin Infect Dis. 2010;51(8):937-46.
63. National Osteoporosis Foundation: The Clinician's Guide to Prevention and Treatment of Osteoporosis. Available at http://www.nof.org/professionals/pdfs/NOF_ClinicianGuide2009_v7. pdf. Accessed August 2010.
64. Arora S, Agrawal M, Sun L et al. HIV and bone loss. Curr Osteoporos Rep. 2010;8(4):219-26.
65. Epstein S. Update of current therapeutic options for the treatment of postmenopausal osteoporosis. Clin Ther 2006; 28:151-173.
66. Guaraldi G, Orlando G, Madeddu G, et al. Alendronate reduces bone resorption in HIV-associated osteopenia/osteoporosis. HIV Clin Trials 2004;5:269-277.
67. 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.
68. Negredo E, Martinez-Lopez E, Paredes R, et al. Reversal of HIV-1 associated osteopenia with onceweekly alendronate. AIDS. 2005;19:243-245.
69. Bolland MJ, Grey AB, Horne AM, et al. Annual zoledronate increases bone density in highly active antiretroviral therapy-treated human immunodeficiency virus-infected men: a randomized controlled trial. J Clin Endocrinol Metab. 2007; 92:1283-1288.
70. Huang J, Meixner L, Fernandez S et al. A double-blinded, randomized controlled trial of zoledronate therapy for HIV-associated osteopenia and osteoporosis. AIDS. 2009; 23:51-57.