HIV AND BONE MINERAL DENSITY CHANGES A REVIEW OF LITERATURE

Author:
Johnson S.M

Address:
MBBS, MMCP, MWACP. Internal Medicine Department, Jos University Teaching Hospital, Jos.

Correspondence:
Dr. Johnson S.M
Department of Internal Medicine, Jos University Teaching Hospital PMB 2076, Jos.
Email: mafukajohnson@yahoo.co.uk
+2348034819887

ABSTRACT

Background.
Since the beginning of the Human immunodeficiency virus (HIV) epidemic in the early 1990s, more than 60 million people have been infected with the virus and nearly 30 million people have died of Acquired Immune Deficiency syndrome (AIDS) worldwide. The introduction of highly active antiretroviral therapy (HAART) has radically changed the natural history of HIV infection and significantly extended the life-span of patients living with AIDS. The increased mean life-span has given rise to long-term complications of HIV such as metabolic complication, cardiovascular disease and bone mineral density changes. High rates of abnormalities of bone mineralisation have been reported in HIV-infected patients as assessed by the bone mineral density (BMD) using the World Health Organisation (WHO) criteria

Methods:
This is a narrative review of selected literatures following a detailed search of existing literatures and on-line database

Conclusion:
The prevalence of osteoporosis and osteopenia in HIV-infected individuals is more than three times compared with HIV- uninfected individuals.

Key Word*: Osteoporosis, osteopenia, HIV, HAART*

Introduction

Prior to the advent of potent antiretroviral therapy, the most common bone disorders in HIV-infected patients were complications of infections and malignancies. In the current HIV treatment era, with prolongation of survival and the decreased incidence of opportunistic complications, osteopenia and osteoporosis have emerged as the most common bone disorders in this population.[1] HIV mainly replicates in CD4+ T lymphocytes and monocyte/macrophages causing severe immunological impairment. In addition to the immune system, HIV infection affects tissues and organs such as kidney, liver, the central nervous system, heart and bone showing a complex pathogenesis.[2] The advent and widespread use of highly active antiretroviral therapy (HAART) has dramatically changed the course of HIV infection from a fatal infection to a chronic and relatively manageable disease. The high prevalence of bone demineralization among HIV-infected patients has been described in multiple studies.[3-5]

Given the complex metabolic complications of HIV infection and its treatment, the decreased bone mineralization seen in a large percentage of HIV-infected patients is likely the result of heterogeneous causes and interplay of host, viral, and specific antiretroviral factors. Bone is constantly undergoing remodelling in a synchronized balance between resorption and formation, which can become unregulated during HIV infection.[6-7] The major bone lesions detectable in HIV patients are related to bone demineralization (osteopenia/osteoporosis and osteomalacia) and osteonecrosis

The present article reviews the epidemiology, possible pathogenesis, and management of osteopenia and osteoporosis in HIV infection.

Bone Metabolism

Bone is a specialized connective tissue characterized by hardness and plasticity, consisting of cells immersed in a mineralized extracellular matrix. There are three types of cells in mature bone

tissue: osteoblasts, osteocytes, and osteoclasts. Osteoblasts and osteocytes are involved in the deposition of bone matrix. These cells produce collagen type I, which is then calcified. These cells also produce non-collagenous proteins, as well as regulatory factors. The extracellular matrix can be subdivided into organic matrix composed of collagen fibers and ground substance, and inorganic matrix composed mainly of a complex of calcium and phosphate in the form of hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$]. The inorganic portion of the matrix is what gives bone its density, and accounts for approximately 65% of the extracellular matrix. Osteoblasts are located at the surfaces of bone tissue, while osteoclasts are located within the calcified matrix of bones. Both osteoclasts and osteoblasts originate in the marrow. The marrow progenitors of osteoclasts are of the hematopoietic lineage, whereas the progenitors of osteoblasts are of the mesenchymal lineage of the marrow stroma[8]. Osteoblasts, characterized by the ability to secrete bone matrix, and osteoclasts, responsible for bone resorption are involved in bone tissue regulation. Both osteoblasts and osteoclasts act on bone homeostasis through a continuous remodelling process, necessary both to maintain calcium and phosphates homeostasis and to promote body adaptation to external tensional forces. The bone remodelling process begins with the proliferation and activation of osteoclasts on the bone surface and is controlled by systemic hormones such as calcitonin, parathormone, estrogens and local factors, most of them involved in inflammatory responses such as IL-1, IL-6, TNF-α and prostaglandins.[9] Under normal conditions, bone remodelling proceeds in cycles in which osteoclasts adhere to bone and subsequently remove it by acidification and proteolytic digestion. Shortly after the osteoclasts have left the resorption site, osteoblasts invade the area and begin the process of forming new bone by secreting osteoid (a matrix of collagen and other proteins), which is eventually mineralized. After bone formation has ceased, the surface of the bone is covered by lining cells, a distinct type of terminally differentiated osteoblastsBone is continually remodelled throughout life because bones sustain recurring microtrauma. Bone remodelling occurs at discrete sites within the skeleton and proceeds in an orderly fashion. Bone resorption is always followed by bone formation, a phenomenon referred to as coupling. In osteoporosis, this coupling mechanism is thought to be unable to keep up with the constant microtrauma to trabecular bone. In adults, approximately 25% of trabecular bone is resorbed and replaced every year, compared with only 3% of cortical bone. Osteoclasts require weeks to resorb bone, whereas osteoblasts need months to produce new bone. Therefore, any process that increases the rate of bone remodelling results in net bone loss over time.[10]

Osteoporosis results from bone loss due to age-related changes in bone remodelling as well as extrinsic and intrinsic factors that exaggerate this process. During growth, the skeleton increases in size by linear growth and by apposition of new bone tissue on the outer surfaces of the cortex. This reaches a peak between the ages of 20-30 years but falls thereafter in both sexes. Many factors regulate bone mass in normal individual. Genetic factors are the single most important influence on bone mineral density. Multiple genes are involve and they include vitamin D receptor; type I collagen, the estrogen receptor (ER), interleukin (IL) 6; and insulin-like growth factor (IGF) I]. Nutrition and lifestyle also play an important role in osteoporosis as well as HIV infection

Epidemiology And Pattern Of Bone Mineral Density Disorders

Bone mineral density (BMD) in a patient is related to peak bone mass and subsequently, bone loss. The World Health Organization (WHO) has established the following definitions of osteoporosis based on BMD measurements

Normal - BMD within 1 standard deviation (SD) of the mean bone density for a young adult (T-score at -1 and above)

Low bone mass (osteopenia) - BMD between 1-2.5 SD below the mean for a young adult (T-score between -1 and -2.5)

Osteoporosis - BMD 2.5 SD or more below the normal mean for a young adult (T-score at or below -2.5)

Severe or "established" osteoporosis - BMD 2.5 SD or more below the normal mean for young adult females (T-score at or below -2.5) in a patient who has already experienced 1 or more fractures

The T-score is the bone density compared with the BMD of control subjects who are at their peak BMD. The Z-score reflects a bone density compared with that of patients matched for age and sex.[11]

Osteoporosis is by far the most common metabolic bone disease in the world and is estimated to affect over 200 million people worldwide.[12] An estimated

75 million people in Europe, the United States, and Japan have osteoporosis.[13] One in 3 women older than 50 years will eventually experience osteoporotic fractures, as will 1 in 5 men. By 2050, the worldwide incidence of hip fracture is projected to increase by 240% in women and 310% in men.[14]According to the National Osteoporosis Foundation (NOF), 10 million Americans have osteoporosis. Another 34 million have low bone mass, which leaves them at increased risk for osteoporosis.[15]Osteoporosis is thought rarely to affect blacks[16] and hip fractures are ten times less

Prevalent in these populations. Osteoporotic fractures are also much less prevalent in Afro-Americans in the USA, where the observation is readily explained, based on an approximate 15% higher BMD in this population compared to Caucasians

Osteoporosis(a consequence of reduced BMD) can occur in persons of all races and ethnicities. In general, however, whites (especially of northern European descent) and Asians are at increased risk. Melton et al reported that the prevalence of hip fractures is higher in white populations, regardless of geographic location. Another study indicated that the incidence of hip fractures was lower among African Americans in the United States and South Africa compared to age-matched white populations within the same continent.[17, 18] Risk for osteoporosis increases with age, as BMD declines. Women are at a significantly higher risk for osteoporosis with a female-to-male ratio of 4:1.[15] A study done in Nigeria, also revealed the age related decline in BMD although at a slower rate compared to the Caucasians. [19]

RISK FACTORS FOR BMD

The hallmark of osteoporosis is a reduction in skeletal mass caused by an imbalance between bone resorption and bone formation and this imbalance have been shown to be exaggerated during HIV infection[1,3-5]

Risk factors associated with increased bone loss may be considered as endogenous or exogenous. Endogenous factors include ethnicity, female gender, advancing age and family history of fracture. Exogenous factors include hypogonadism, glucocorticoid treatment, low BMI, previous fracture, smoking, immobilization, excess alcohol and low vitamin D. Other factors contributing to reduced BMD include late menarche, early menopause, and postmenopausal state, drugs like anticonvulsants, thyroid supplements, heparin, chemotherapeutic agents, antiretroviral therapy, oral contraceptive and calcium deficiency

VIROLOGY OF HIV

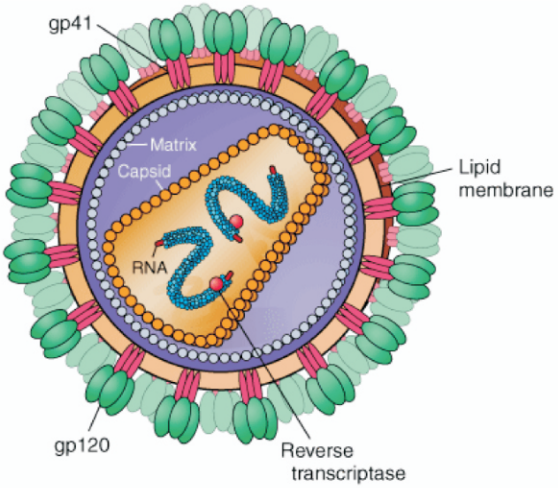

Figure 1: structure of HIV1 virus

The HIV was first isolated in 1983 and was shown to be the cause of AIDS.[20]The two types of HIV (HIV-1and HIV-2) belong to the lentivirus group of the retrovirus family. HIV-1 is widely distributed and accounts for about 95% of all HIV infections worldwide. HIV-2 was isolated in 1986 and it is confined to West Africa, Portugal and countries with historical links to Portugal. In Nigeria, HIV-1 accounts for >95% of the total HIV infections and almost 99% of all AIDS cases.[21] The predominance of HIV-1 can be partly explained by its higher infectivity and transmission efficiency compared to HIV-2.

HIV-1 has genes that encode the structural proteins of the virus: gag encodes the proteins that form the core of the virion (including p24 antigen); pol encodes the enzymes responsible for protease processing of viral proteins, reverse transcription, and integration; and env encodes the envelope glycoproteins. HIV-1 is more complex than other retroviruses, particularly those of the non-primate group, in that it also contains at least six other genes (tat, rev, nef, vif, vpr, and vpu), which code for proteins involved in the modification of the host cell to enhance virus growth and the regulation of viral gene expression. Several of these proteins are thought to play a role in the pathogenesis of HIV disease. The major difference between the genomes of HIV-1 and HIV-2 is the fact that HIV-2 lacks the vpu gene and has a vpx gene not contained in HIV-1.[20]

There are three groups of HIV-1: group M (major), which is responsible for most of the infections in the world; group O (outlier), a relatively rare viral form found originally in Cameroon, Gabon, and France; and group N (new), first identified in a Cameroonian woman with AIDS; only a few cases of the latter have been identified.[20] Group M strains have huge diversity with sub-classification into A-K subtypes. Subtype A is responsible for 80% of HIV cases in West Africa while there is predominance of subtype B in Europe and North America.[30]Recombination of viral material generates an array of circulating recombinant forms (CRF) which increases the genetic diversity seen in HIV-1. The prevalent subtypes in Nigeria are A, G and the CRF A/G[31]; A is predominantly found in the north, G in the south, while the CRF A/G is found in the middle belt zone of the country.[22]

HIV AND THE BONE

THE ROLE OF HIV INFECTION

The mechanism of loss of bone mass in HIV infection is poorly understood.[23] Early studies on HIV/osteoblasts interaction to determine whether HIV is able to infect osteoblasts, have yielded controversial results.[24, 25]

Several HIV proteins may affect the functionality and maturation of osteoblasts by inducing apoptotic stimuli in mesenchymal stem cells, which are precursors of osteoblasts. In particular, HIV-1-gp120 and p55gag can reduce bone alkaline phosphatase activity and calcium deposition by osteoblasts, and Rev and p55gag affect the differentiation of mesenchymal stem cells toward osteoblastic lineage. In addition it has been shown that HIV-1 triggers apoptosis in primary osteoblast.[26, 27]

The most important regulatory mechanism of osteoclast/osteoblast activity is the OPG/RANKL/RANK system.[28] RANKL and OPG are produced by lymphocytes[29] other than osteoblasts, and increased levels of these cytokines are common in diseases characterized by persistent immune activation[30] that can determine bone loss.[26,31,] Interestingly, RANKL can be also up-regulated by viral proteins such as gp120 and Vpr[32, 33] suggesting an osteoclastic hyper-activation in the bone compartment with bone homeostasis imbalance.

In addition to the direct role of HIV on osteoblast and osteoclast interaction, HIV has been associated with some risk factors for osteoporosis[34] such as under nutrition and malabsorption pathologies which can influence levels of vitamin D and calcium or endocrine complications, such as androgen and estrogen deficiency.[35]

The extended course of viral infection and prolonged HAART treatment has displayed several degenerative aspects of HIV-related disease regarding different cell lineages. In particular, HIV infection per se and HAART therapy can directly affect the homeostasis of bone tissue. Even though it has been shown that antiretroviral therapy may play an important role in bone loss, a significant decrease of bone density has been observed in HIV positive HAART naïve patients .[1,4, 36] A marked decrease in bone turnover and reduced bone formation is more evident in patients with advanced HIV disease [37-38] and a significant decrease of osteocalcin serum levels and increase in matrix degradation products are reported in HIV-positive individuals.[39]

A recent study performed on a large number of HIV-1 infected patients reported a high percentage of osteopenia and osteoporosis (53.7% and 26.8%) suggesting a direct role of HIV in bone mass derangement.[40] A recent work comparing bone mineral density in 152 HIV-seropositive and 100 healthy women disclosed a highly significant ($p<0.0001$) decrease in mineralization in HIV subjects, which remained significant also after controlling for race.[41] A Canadian Multicentre Study for Osteoporosis reported higher incidences of fractures in HIV patients than in a control group (26.1% vs 17.7%)[42].

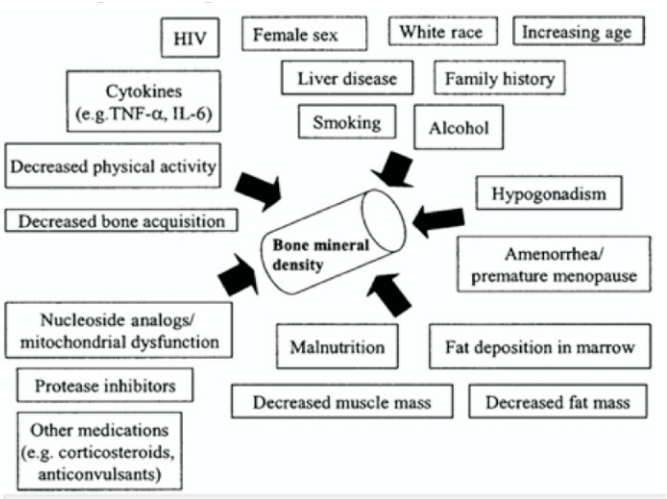

Figure 2: Factors that may contribute to decreased bone mineral density in HIV infected patients

THE ROLE OF HAART

The true impact of HIV-1 infection and/or HAART therapy in the development of BMD abnormalities remains largely unconfirmed[43]. The association between osteopenia and PIs emerged in several in-vitro models and seems to have a different etiology depending on specific molecules[44,45]. Antiretrovirals like tenofovir, ritonavir and the NRTI have been implicated in bone mineral density changes in HIV infected patients[11,44-49].

In addition, the HAART/bone interaction has been studied to determine whether multidrug treatment is involved in BMD decrease.[50-51] Despite a high variability related to specific drug class and treatment duration, HAART seems to have a pivotal role, especially when it includes a protease inhibitor (PI) .[3,52] Conversely, other reports failed to reveal any influence of HAART on bone condition, finding no differences in BMD reduction between naive and treated patient.[37,53] A dual HAART-induced effect has been hypothesized. The drugs initially exacerbate abnormalities in bone homeostasis[54] and then the restoration of some cytokine networks allows the normalization of bone remodelling process.

Bone metabolism alterations can be determined by functional damage to other organs involved in bone homeostasis such as liver [55] or kidney[56] Moreover, PIs can impair vitamin D synthesis in vitro, by suppressing the activity of several enzymes involved in its synthesis and catabolism[57] inhibiting osteoblasts anabolic activity. Hence, the control of antiretroviral toxicity and the management of secondary lesions due to life-long patient treatment and the slower evolution of HIV infection represent a pivotal issue for the clinical and therapeutic approach to HIV positive patients.

MANAGEMENT

No data are yet available to guide the clinical management or prevention of osteopenia/osteoporosis in HIV-infected patients. It is reasonable to recommend weight-bearing exercise, decreased alcohol consumption, smoking cessation, and the treatment of reversible factors summarized in figure 2. Vitamin D and calcium supplementation may also be appropriate. The role of estrogen, selective estrogen receptor modulators is uncertain, and some of these treatment approaches are presently under study. Bisphosphonates have been shown to be a safe, convenient, and effective option for treatment of osteopenia or osteoporosis in HIV-infected individuals on HAART.[58] Retrospective data have suggested that anabolic steroids and growth hormone, when given for HIV-associated wasting or lipodystrophy, respectively, do not significantly affect BMD. [59] A possible future direction in the treatment of osteoporosis may be the use of the anti-RANKL monoclonal antibody (denosumab).

Conclusion

Bone derangement is a major clinical complication in the course of HIV infection. The advent of HAART has led to a longer life expectancy and therefore HIV/HAART-related bone disease is destined to increase, enhancing the physiological age-related bone loss. The number of HIV patients with bone disease and silent fractures can be expected to increase dramatically in the next few years because these patients also have two other potentially worsening factors: HIV itself and antiretroviral therapy. Hence, antiretroviral therapy must be accompanied by the clinical management of HIV/HAART-related bone disease to reduce the risk of osteoporosis and fractures in these patients.

REFERENCES

1. Glesby MJ. Bone disorders in human immunodeficiency virus infection. *Clin Infect Dis. 2003; 37: 91-95*
2. Levy JA. HIV pathogenesis: 25 years of progress and persistent challenges. AIDS 2009; 23:147160.
3. Tebas P, Powderly WG, Claxton S, et al. Accelerated bone mineral loss in HIV-infected patients receiving potent antiretroviral therapy. AIDS2000; 14:63-7.
4. Moore AL, Vashisht A, Sabin CA, et al. Reduced bone mineral density in HIV-positive individuals. AIDS 2001; 15:1731-3.
5. Landonio S, Quirino T, Bonfanti P, et al. Osteopenia and osteoporosis in HIV+ patients, untreated or receiving HAART. Biomed Pharmacother 2004; 58:505-8.
6. Mondy K, Yarasheski K, Powderly WG, et al. Longitudinal evolution of bone mineral density and bone markers in HIV-infected individuals. Clin Infect Dis 2003;36:482-90
7. Aukrust P, Haug C, Ueland T, et al. Decreased bone formative and enhanced resorptive markers in human immunodeficiency virus infection: indication of normalization of the bone-remodelling process during highly active antiretroviral therapy. J Clin Endocrinol Metab 1999; 84:145-50.

8. Stavros CM, Robert LJ. Bone Marrow, Cytokines, and Bone Remodelling Emerging Insights into the Pathophysiology of Osteoporosis. N Engl J Med 1995;332:305-311
9. Maria Carla Re, Elisa De Crignis, Laura Cimatti et al. HIV infection and bone changes. In: HAART and correlated pathologies ~2008
10. Raisz LG. Pathogenesis of osteoporosis: concepts, conflicts, and prospects. *J Clin Invest*. Dec 2005; 115:3318-3325.
11. Fauci AS, Lane HC. Osteoporosis. In: Harrison's Principles of Internal Medicine, 18th edition. New York: The McGraw-Hill companies 2008:2397-2408
12. Kanis JA, McCloskey EV, Johansson H, et al. A reference standard for the description of osteoporosis. *Bone* Mar 2008;42:467-475
13. Cooper C, Campion G, Melton LJ. Hip fractures in the elderly: a world-wide projection. *Osteoporos Int*. Nov 1992; 2:285-289.
14. Consensus development statement.Who are candidates for prevention and treatment for osteoporosis? *Osteoporos Int*. 1997;7:1-6
15. Gullberg B, Johnell O, Kanis JA. World-wide projections for hip fracture. *Osteoporos Int*. 1997;7:407-413
16. Solomon L. Bone density in ageing Caucasian and African populations. Lancet 1979; 2:1326-1330.
17. Aloia JF, Vaswani A, Yeh JK, et al. Risk for osteoporosis in black women. *Calcif Tissue Int*. Dec 1996; 59:415-423.
18. Melton LJ, Sampson JM, Morrey BF, et al. Epidemiologic features of pelvic fractures. *Clin Orthop Relat Res*. Mar-Apr 1981; 43-47.
19. VanderJagt DJ, Damiani LA, Goodman TM, et al. Assessment of the skeletal health of healthy Nigerian men and women using quantitative ultrasound. Bone 2004; 35: 387394.
20. Fauci AS, Lane HC. Human immunodeficiency virus disease:AIDS and related disorders. In: Harrison's Principles of Internal Medicine, 17th edition. New York: The McGraw-Hill companies 2008:1137-1204
21. Meloni ST, Ojesina A, Olaleye DO. The molecular epidemiology of HIV: in: Adeyi O, Kanki PJ, Odutolu O, Idoko JA (eds). AIDS in Nigeria. Boston: Harvard center for population and development studies 2006:67-93
22. Peters M, Esu-Williams E. Predominance of subtype A and G HIV type-1 in Nigeria with geographical differences in their distribution. AIDS Research and Human Retrovirus 2000; 16: 315-325.
23. Jacobson D, Spiegelman D, Knox TK, et al. Evolution and predictors of change in total bone mineral density over time in HIV-infected men and women in the nutrition for healthy living study. J Acquir Immune Defic Syndr 2008; 49: 298-308.
24. Campbell DG, Stephenson AJ, Li P, et al. Human Immunodeficiency Virus infection of human bone derived cells. Clinical Orthopaedics and Related Research 1996; 331:291299
25. Nacher M, Serrano S, Gonzalez A, et al. Osteoblasts in HIV-infected patients: HIV-1 infection and cell function. AIDS 2001; 15:22392243.
26. Gibellini D., Borderi M., De Crignis E., et al. RANKL/OPG/TRAIL plasma levels and bone mass loss evaluation in antiretroviral naive HIV-1-positive men. J Med Virol 2007; 79:14461454
27. 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
28. Boyce BF, Xing L. Biology of RANK, RANKL and osteoprotegerin. Arthritis Research and Therapy 2007; 9:405407.
29. Chakravarti A, Marceu AA, Flamand L, et al. Normal human primary CD4+ T lymphocytes synthesize and release functional osteoprotegerin in vitro. Laboratory investigation 2007; 78: 4825148258.
30. Ueland T, Bollerslev J, Godang K, et al. Increased serum osteoprotegerin in disorders characterized by persistent immune activation or glucocorticoid excess - possible role in bone homeostasis. European Journal of Endocrinology 2001; 145: 685690.
31. Clowes JA, Riggs BL, Khosla S. The role of the immune system in the pathophysiology of osteoporosis. Immunological Reviews 2005; 208:207227.
32. Fakruddin JM, Laurence J. Interactions among human immunodeficiency virus

(HIV)-1, interferon- and receptor of activated NF-kB ligand (RANKL): implications for HIV pathogenesis. Clin Exp Immunol 2004; 137:538545.
33. Fakruddin JM, Laurence J. HIV-1 Vpr enhances production of receptor of activated NF-kB ligand (RANKL) via potentiation of glucocorticoid receptor activity. Arch Virol 2005; 150: 6778.
34. Tomazic J, Ul K, Volcansek G, et al. Prevalence and risk factors for osteopenia/osteoporosis in an HIV-infected male population. Wien Klin Wochenschr 2007; 119: 639646.
35. Madeddu G, Spanu A, Solinas P, et al. Bone mass loss and vitamin D metabolism impairment in HIV patients receiving highly active antiretroviral therapy. J Nucl Med Mol Imaging 2004; 48: 3948.
36. Annapoorna N, Rao GV, Reddy NS, et al. An increased risk of osteoporosis during acquired immunodeficiency syndrome. Int. J. Med. Sci. 2004; 3:152164
37. Bruera D, Luna N, David DO, et al. Decreased bone mineral density in HIV-infected patients is independent of antiretroviral therapy. AIDS 2003; 17:19171923.
38. Amorosa V, Tebas P. Bone disease and HIV Infection. Clin Infect Dis 2006; 42:108114.
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. Metabolism 2000; 9: 11341139.
40. Cazanave C, Dupon M, Lavignolle-Aurillac V, et al. Groupe d'Epidemiologie Clinique du SIDA en Aquitaine. Reduced bone mineral density in HIV infected patients: prevalence and associated factors. AIDS 2008; 22:395402.
41. Dolan SE, Carpenter S, Grinspoon S. Effects of weight, body composition, and testosterone on bone mineral density in HIV-infected women. Journal of Acquired Immune Deficiency Syndrome 2007; 45:161168.
42. Prior J, Burdge D, Maan E, et al. Fragility fractures and bone mineral density in HIV positive women: a case control population-based study. Osteoporosis Int 2007; 18:13451353.
43. Brown TT, Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. AIDS 2006; 20:2165-2174
44. Pan G, Wu X, McKenna MA, et al. AZT enhances osteoclastogenesis and bone loss. Osteoporosis Int, 20: 608620.
45. Pan G, Kilby M, McDonald JM. Modulation of osteoclastogenesis induced by nucleoside reverse transcriptase inhibitors.AIDS Res Hum Retroviruses 2006;22:11311141
46. Jacobson D, Huang J, Shevitz A, et al. Duration of ART and change in bone mineral density over time [Abstract 825]. In: Program and Abstracts of the 12th Conference on Retroviruses and Opportunistic Infections (Boston). Alexandria, VA: Foundation for Retrovirology and Human Health, 2005
47. Jacobson D, Huang J, Shevitz A, et al. Duration of ART and change in bone mineral density over time [Abstract 825]. In: Program and Abstracts of the 12th Conference on Retroviruses and Opportunistic Infections (Boston). Alexandria, VA: Foundation for Retrovirology and Human Health; 2005.
48. Hazra R, Gafni R, Maldarelli F, et al. Safety, tolerability, and clinical responses to tenofovir DF in combination with other antiretrovirals in heavily treatment-experienced HIV-infected children: data through 48 weeks [Abstract 928] Program and Abstracts of the 11th Conference on Retroviruses and Opportunistic Infections (San Francisco). Alexandria, VA: Foundation for Retrovirology and Human Health; 2004.
49. Wang MW, 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.
50. Bongiovanni M, Fausto A, Cicconi P, et al. Osteoporosis in HIV-Infected subjects: a combined effect of Highly Active Antiretroviral Therapy and HIV itself? J Acquir Immune Defic Syndr 2005; 40:503504.
51. 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 2005; 33:405407.

52. Jain RG, Lenhard JM. Select HIV protease inhibitors alter bone and fat metabolism ex vivo. The Journal of Biological Chemistry 2002; 277: 1924719250.
53. Landonio S, Quirino T, Bonfanti P, et al. Osteopenia and osteoporosis in HIV+ patients, untreated or receiving HAART. Biomedicine and Pharmacotherapy 2004; 58: 505508.
54. Mallon PWG, 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: 971979.
55. Collier J. Bone Disorders in Chronic Liver. Hepatology 2007; 46: 12711278.
56. Moe S, Drueke T, Cunningham J, et al. Definition, evaluation and classification of renal osteodystrophy: a positive statement from kidney disease: improving global outcomes. Kidney International 2006; 69: 19451953.
57. Cozzolino M, Vidal M, Arcidiacono MV, et al. HIV protease inhibitors impair vitamin D bioactivation to 1,25- dihydroxyvitamin D. AIDS 2003; 17: 513520.
58. Mondy K, Powderly, WG, Claxton SA, et al. Alendronate, Vitamin D, and Calcium for the Treatment of Osteopenia/Osteoporosis Associated With HIV Infection.JAIDS 2005; 38: 426-431
59. Lawal A, Engelson E, Wang J, et al. Effect of growth hormone on osteopenia in HIV+ patients [abstract 635]. In: Program and abstracts of the 8th Conference on Retroviruses and Opportunistic Infections (Chicago). Alexandria, VA: Foundation for Retrovirology and Human Health; 2001. p. 235.