HIV infection and bone changes

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ABSTRACT

The introduction of highly active antiretroviral therapy (HAART) has radically changed the natural history of HIV infection. The significant reduction of plasma viremia accompanied by the arrested immune deterioration following administration of new therapeutic protocols between 1996 and 1999 generated cautious optimism also based on mathematical models claiming the possibility of a complete eradication of HIV infection. Even if the advent of HAART has 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 osteoporosis. Degenerative processes involving the bone compartment are common during the course of HIV-1 infection. Osteopenia and osteoporosis represent a challenge in clinical and therapeutic management. It has yet to be determined whether the cause of this dysfunction is linked to HIV-1-mediated direct and/or indirect effects on osteoblasts/osteoclasts cross-talk regulation. This report analyzes the numerous factors able to favor bone derangement (bone loss and osteopenia/osteoporosis) in HIV-1 infected patients.

Bone and bone changes

Bone is a specialized connective tissue characterized by hardness and plasticity, consisting of cells immersed in a mineralized extracellular matrix. Osteoblasts, characterized by the ability to secrete bone matrix (Harada & Rodan, 2003), and osteoclasts, responsible for bone resorption (Melissa et al., 2004), 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 like calcitonin, parathormone or estrogens, and local factors, most of them involved in inflammatory responses such as IL-1, IL-6, TNF-α and prostaglandins.
Moreover, the OPG/RANKL/RANK triad plays a central role in bone remodelling. In particular, OPG, released by osteoblasts, is a soluble RANKL receptor inhibiting the RANKL/RANK interaction and then the RANKL/RANK-mediated differentiation and activation of osteoclasts (Boyce & Xing, 2007). Remodelling rates of bone tissue can be monitored measuring molecular markers of bone remodelling. In particular, serum osteocalcin and alcaline phosphatase activity reflect bone formation, whereas products of catabolism of the matrix, like cross-linked N-telopeptides of type I collagen (NTx) or C-telopeptides, are indicative of rates of bone resorption (Camozzi et al., 2007).

Osteoporosis represents severe derangement of bone tissue and is considered a skeletal disease characterized by low bone mass and bone microarchitectural deterioration with a major increase in bone fragility and fracture susceptibility.
Clinically osteoporosis is often not disclosed until the occurrence of low-trauma fractures, defined as fragility fractures (Becker, 2006). Fragility fractures mainly involve the vertebral body, distal forearm or hip and have significant effects on patients' quality of life with serious disability and excess mortality in the older subjects. This severe clinical evolution coupled with the high incidence of osteoporosis in the population indicate a central role of this disease in public health.
The progressive bone mass loss is classified by WHO as osteopenia or osteoporosis by dual-energy x-ray absorptiometry (DXA) assay which determines bone mineral density (BMD). DXA results are expressed in terms of T-score, that is the number of standard deviations below or above the mean of BMD of a population matched for race and sex (Cummings et al., 2002). Osteoporosis is characterized by a T-score value lower than -2.5, whereas a T-score between -2.5 and -1 indicates osteopenia and normality is defined as a T-score above -1 (Johnell et al., 2005).

The role of HIV-1 infection

The bone mass loss pathogenesis during HIV infection remains unsettled. Early studies on HIV/osteoblasts interaction to determine whether HIV is able to infect osteoblasts, have yielded controversial results (Mellert *et al.*, 1990; Campbell *et al.*, 1996; Nacher *et al.*, 2001). Several HIV proteins may affect the functionality and maturation of osteoblasts inducing apoptotic stimuli in mesenchymal stem cells, which are precursors of osteoblasts (Wang et al., 2002). In particular HIV-1-gp120 and p55gag can reduce bone alkaline phosphatase activity and calcium deposition by osteoblasts, and Rev and p55gag, but not gp120, affect the differentiation of mesenchymal stem cells toward osteoblastic lineage (Cotter et al., 2007).

In addition we recently demonstrated (Gibellini *et al* 2008) that HIV-1, heat-inactivated HIV-1 and recombinant gp120 trigger apoptosis in primary osteoblasts and HOBIT cells, suggesting that HIV-1 does not infect osteoblasts, and that apoptosis induction is related to gp120/cell membrane interaction, resembling a mechanism similar to that already demonstrated in the derangement of haematopoietic CD34+ progenitor cells (Re et al., 1994, Gibellini et al 2007a,b, De Crignis *et al* 2008).

The most important regulative mechanism of osteoclast/osteoblast activity is the OPG/RANKL/RANK system (Boyce & Xing, 2007). RANKL and OPG are yielded by lymphocytes (Chakravarti et al., 2007; Ly et al., 2007) other than osteoblasts, and increased levels of these cytokines are common in diseases characterized by persistent immune activation (Ueland et al., 2001) that can determine bone loss (Clowes et al., 2005, Seminari et al., 2005; Gibellini et al., 2007; Mora et al., 2007). Interestingly, RANKL can be also up-regulated by viral proteins such as gp120 and Vpr (Fakruddin & Laurence, 2004, 2005) suggesting an osteoclastic hyper-activation in the bone compartment with bone homeostasis imbalance. Osteoclasts can also differentiate under the influence of TNF- α, (Breen, 2002) that may play an etiological role in bone loss for TNF- a (Aukrust et al., 1999).

In addition to the direct role of HIV on osteoblast and osteoclast interaction, HIV has been associated with some risk factors for osteoporosis (Tomazic et al., 2007) such as undernutrition and maladsorption pathologies which can influence levels of vitamin D and calcium (Cashman, 2007), or endocrine complications, such as androgen and estrogen deficiency (Madeddu et al., 2004).

In the HIV seronegative population osteopenia and osteoporosis are mostly observed among women (Bonnick, 2006) where bone metabolism is related to hormonal status because of the protective role of estrogens, which mainly consists in down-regulating the production of pro-inflammatory cytokines as IL-1, IL6 and RANKL thereby inhibiting osteoclast differentiation (Sorensen et al., 2006).

The extended course of viral infection and prolonged HAART treatment have 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 if antiretroviral therapy may play an important role in bone loss, a significant decrease of bone density has been observed in HIV positive naïve patients (Loiseau-Peres et al., 2002; Annapoorna et al., 2004; Amorosa & Tebas 2006). Several data demonstrated a correlation between HIV-1 infection and bone loss. A marked decrease in bone turnover and reduced bone formation, more evident in patients with advanced progression of HIV disease (Serrano et al., 1995, Thomas & Doherty, 2003; Bruera et al., 2003; Amiel et al., 2004) and a significant decrease of osteocalcin serum levels and increase in matrix degradation products are reported in HIV-positive individuals (Teichmann et al., 2000).

In addition, the HAART/bone interaction has been studied to determine whether multidrug treatment is involved in BMD decrease (Carr et al., 2001; Bongiovanni et al., 2005; Vescini et al., 2005; Aparicio et al., 2006). Despite a high variability related to specific drug class and treatment duration, HAART seems to have a pivotal role, especially when including a protease inhibitor (PI) (Tebas et al., 2000, Jain & Lenhard, 2002).

Conversely, other reports failed to reveal any influence of HAART on bone condition, finding no differences in BMD reduction between naive and treated patients (Bruera et al., 2003; Dube et al., 2002; Landonio et al., 2004; Amiel et al., 2004). A dual HAART-induced effect has been hypothesized. The drugs initially exacerbate abnormalities in bone homeostasis (Mallon et al., 2003) and then the restoration of some cytokine networks allows the normalization of bone remodelling process. A recent study performed on a large number of HIV-1 infected patients reported a high percentage of osteopenia and osteoporosis suggesting a direct role of HIV in bone mass derangement (Cazanave et al., 2008).

A recent work comparing bone mineral density in 152 HIV-seropositive and 100 healthy women dsclosed a highly significant ($p<0.0001$) decrease in mineralization in HIV subjects, which remained significant also after controlling for race (Dolan et al., 2007). A Canadian Multicentre Study for Osteoporosis reported higher incidences of fractures in HIV patients than in a control group (26.1% vs 17.7%), but failed to find any difference in BMD, suggesting that HIV exerts its influence on bone structure rather than bone mineralization (Prior et al., 2007).

The role of therapy

The true impact of HIV-1 infection and/or HAART therapy in the assessment of bone loss remains largely unsettled (Bongiovanni et al. 2003; Klotsas & Klotsas, 2007; Brown & Qaqish, 2006).

The association between osteopenia and PI emerged in several in vitro models and seems to have a different etiology depending on specific molecules (Pan et al., 2004, 2006). Malizia et al. (2007) performed a microarray analysis on osteoblasts demonstrating a transcription increase in several inflammation related genes, such as

MCP-1 and IL-8, after contact with Nelfinavir, Saquinavir or Ritonavir. Similar results (Jain & Lenhard, 2002) were obtained with Nelfinavir, but not Ritonavir and Saquinavir, able to inhibit both osteoblastic differentiation of mesenchymal stem cells, and decrease osteoblast activity.
Bone metabolism alterations can be determined by functional damage to other organs involved in bone homeostasis such as liver (Collier, 2007) or kidney (Moe et al., 2006). Moreover, PIs can impair vitamin D synthesis in vitro, by suppressing the activity of several enzymes involved in its synthesis and catabolism (Cozzolino et al., 2003) inhibiting the osteoblast anabolic activity.
Hence, the control of antiretroviral toxicity and the management of secondary lesions due to both life-long patient treatment and the slower evolution of HIV infection represent a pivotal issue for the clinical and therapeutical approach to HIV positive patients.

Conclusion

Osteopenia and osteoporosis are described in a higher proportion of HIV-infected patients than healthy individuals (Paton et al., 1997; Annapoorna et al., 2004; Glesby, 2003; Amorosa & Tebas, 2006). Although several general mechanisms involved in bone derangement during HIV-1 infection may contribute to decreased bone mineral density in HIV-infected patients, the role of increased levels of pro-inflammatory cytokines associated with HIV infection, and HIV itself, may also contribute directly to accelerated bone loss (Glesby, 2003; Gibellini et al. 2007). Even though a high incidence of osteopenia/osteoporosis has been associated with both protease inhibitor (PI) and nucleoside/nucleotide reverse transcriptase inhibitor (NRTI)-based treatments (Pan et al., 2006), observations on HIV-1 naïve patients suggested a consistent direct pathogenetic role of HIV-1 (Bruera *et al*. 2003; Gibellini et al. 2007) eliciting the derangement of bone homeostasis. Overall, these studies investigating the relationship between HAART, HIV and osteopenia/osteoporosis show the growing clinical importance of bone damage in the course of HIV infection and the need to disclose the pathogenic mechanisms underlying bone derangement. Hence, the management of bone damage in HIV-infected patients represents a major concern to solve in the near future for a useful follow-up of HIV seropositive patients.

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REFERENCES

1. Amiel C., Ostertag A., Slama L., Baudoin C., N'Guyen T, Lajeunie E, Neit-Ngeilh L., Rozenbaum W., De Vernejoul MC. BMD is reduced in HIV-infected men irrespective of treatment. Journal of Bone and Mineral Research 2004,19: 402–409.
2. Amorosa V., Tebas P. Bone disease and HIV Infection. Clinical Infectious Diseases 2006, 42:108–114.
3. Annapoorna N., Rao GV., Reddy NS., Rambabu P., Rao KR. An increased risk of osteoporosis during acquired immunodeficiency syndrome. Int. J. Med. Sci. 2004, 3:152–164.
4. García Aparicio AM., Muñoz Fernández S., González J., Arribas JR., Peña JM., Vázquez JJ., Martínez ME., Coya J., Martín Mola E. Abnormalities in the bone mineral metabolism in HIV-infected patients. Clinical Rheumatology 2006, 25: 537–539.
5. Aukrust P., Haug CJ., Ueland T., Lien E., Muller F., Espevik T., Bollerslev J., Frolan, SS. 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. Journal of Endocrinology and Metabolism 1999, 84:145–150.
6. Becker C. Pathophysiology and Clinical Manifestations of Osteoporosis. Clinical Cornerstone, 2006, 8: 19–27.
7. Bongiovanni M., Chiesa E., Riva A, d' Arminio-Monforte A., Bini T. Avascular necrosis of the femoral head in a HIV-1 infected patient receiving lopinavir/ritonavir. International Journal of Antimicrobial Agents 2003, 22: 630-631
8. Bongiovanni M., Fausto A., Cicconi P., Menicagli L., Melzi S., Ligabo V. E., Cornalba G., Bini T., Sardanelli F., d'Arminio Monforte A. Osteoporosis in HIV-Infected subjects: a combined effect of Highly Active Antiretroviral Therapy and HIV itself? J Acquir Immune Defic Syndr 2005, 40: 503–504.
9. Bonnick SL. Osteoporosis in Men and Women. Clinical Cornerstone 2006, 8: 28–39.
10. Boyce BF., Xing L. Biology of RANK, RANKL and osteoprotegerin. Arthritis Research and Therapy 2007, 9: 405–407.
11. Breen EC. Pro- and anti-inflammatory cytokines in human immunodeficiency virus infection and acquired immunodeficiency syndrome. Pharmacol Ther. 2002, 95:295-304

12. Brown TT., Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. AIDS 2006a., 20: 2165–2174.
13. Brown TT, Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. AIDS 2006b, 20: 2165–2174.
14. Bruera D., Luna N., David DO., Bergoglio LM., Zamudio J. Decreased bone mineral density in HIV-infected patients is independent of antiretroviral therapy. AIDS 2003, 17:1917–1923.
15. Camozzi V., Tossi A., Simoni E., Pagani F., Francucci CM., Moro L. Role of biochemical markers of bone remodelling in clinical practice. J Endocrinol Invest 2007, 30:13–17.
16. Campbell DG., Stephenson AJ., Li P., Oakeshott RD. Human Immunodeficiency Virus infection of human bone derived cells. Clinical Orthopaedics and Related Research 1996, 331:291–299.
17. Carr A., Miller J., Eisman JA., Cooper DA. Osteopenia in HIV infected men: association with asymptomatic lactic acidemia and lower weight pre-antiretroviral therapy. Clinical Orthopaedics and Related Research, 2001, 15:703–709.
18. Cashman KD. Diet, Nutrition and bone health. The Journal of Nutrition, 2007, 137: 2507S–2512S.
19. Cazanave C., Dupon M., Lavignolle-Aurillac V., Barthe N., Lawson-Ayayi S., Mehsen N., Mercie P., Morlat, P., Thiebaut R., Dabis, F. Groupe d'Epidémiologie Clinique du SIDA en Aquitaine. Reduced bone mineral density in HIV infected patients: prevalence and associated factors. AIDS 2008, 22 : 395–402.
20. Chakravarti A., Marceu AA., Flamand L., Poubelle PE. Normal human primary CD4+ T lymphocytes synthesize and release functional osteoprotegerin in vitro. Laboratory investigation 2007, 78: 48251–48258.
21. Clowes JA., Riggs BL., Khosla S. The role of the immune system in the pathophysiology of osteoporosis. Immunological Reviews, 2005, 208: 207–227.
22. Collier J. Bone Disorders in Chronic Liver. Hepatology 2007, 46: 1271–1278.
23. Cotter EJ., Malizia AP., Chew N., Powderly W. G., Doran PP. HIV proteins regulate bone markers secretion and transcription factor activity in cultured human osteoblasts with consequent potential implications for osteoblast function and development. AIDS Research and Human Retrovirus 2007, 23:1521–1529.
24. Cozzolino M., Vidal M., Arcidiacono MV., Tebas P., E.Yarasheski K., Dusso AS. HIV protease inhibitors impair vitamin D bioactivation to 1,25- dihydroxyvitamin D. AIDS 2003, 17: 513–520.
25. Cummings SR., Bates D., Black DM. Clinical use of bone densitometry. JAMA 2002, 288:1889–1898.
26. De Crignis E, Cimatti L, Borderi M, Gibellini D, Re MC. Bone alterations during HIV infection. New Microbiol. 2008, 31:155-64
27. 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, 45:161–168.
28. Dube MP., Qian D., Edmonson-Melancon HE., Sattler FR., Goodwin D., Martinez C., Williams V., Buchanan TA., Johnson D.. Prospective, intensive study of metabolic changes associated with 48 weeks of amprenavir based antiretroviral therapy. Clinical Infectious diseases 2002, 35: 475–481.
29. 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: 538–545.
30. 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: 67–78.
31. Gibellini D, Vitone F, Buzzi M, Schiavone P, De Crignis E, Cicola R, Conte R, Ponti C, Re MC. HIV-1 negatively affects the survival/maturation of cord blood CD34(+) hematopoietic progenitor cells differentiated towards megakaryocytic lineage by HIV-1 gp120/CD4 membrane interaction. J Cell Physiol. 2007, 210:315-24
32. Gibellini D., Borderi M., De Crignis E., Cicola R., Vescini F., Caudarella R., Chiodo F., Re MC. RANKL/OPG/TRAIL plasma levels and bone mass loss evaluation in antiretroviral naive HIV-1-positive men. J Med Virol 2007, 79:1446–1454.
33. Gibellini D, De Crignis E, Ponti C, Cimatti L, Borderi M, Tschon M, Giardino R, Re MC. HIV-1 triggers apoptosis in primary osteoblasts and HOBIT cells through TNFalpha activation. J Med Virol. 2008, 80:1507-14
34. Gkrania-Klotsas E., Klotsas AE. HIV and HIV treatment: effects on fats, glucose and lipids. British Medical Bullettin, 2007, 84:49–68.
35. Glesby MJ. Bone disorders in human immunodeficiency virus infection. Clinical Infectious Diseases 2003, 37: S91–S95.
36. Harada SI., Rodan GA. Control of osteoblast function and regulation of bone mass. Nature 2003, 423: 349–355.
37. Jain RG., Lenhard JM. Select HIV protease inhibitors alter bone and fat metabolism ex vivo. The Journal of Biological Chemistry 2002, 277: 19247–19250.
38. Johnell O., Kanis JA., Oden A., Johansson H., Delmas C. De Laetand P., Eisman J. A., Fujiwara S., Kroger H., Mellstrom D., Meunier PJ., Melton LJ., ONeil T., Pols H., Reeve J., Silman A., Tenenhouse A. Predictive value of BMD for hip and other fractures. Journal of Bone and Mineral Research, 2005, 20: 1185–1194.
39. Landonio S., Quirino T., Bonfanti P., Gabris A., Boccassini L., Gulisano C., Vulpio L., Ricci E., Carrabba M., Vigevani GM. Osteopenia and osteoporosis in HIV+ patients, untreated or receiving HAART. Biomedicine and Pharmacotherapy 2004, 58, 505–508.
40. Li Y, Toraldo G, Li A, Yang X, Zhang H, Qian WP, Weitzmann MN. B cells and T cells are critical for the preservation of bone homeostasis and attainment of peak bone mass in vivo. Blood 2007, 109:3839-48.

41. Loiseau-Peres S., Delaunay C., Lespessailles E., Ballouche N., Arsac P., Benhamou CL. Osteopenia in patients infected by the human immunodeficiency virus. A case control study. Clinical Infectious Diseases, 2002, 69, 482–485.
42. Madeddu G., Spanu A., Solinas P., Calia G. M., Lovigu C., Chessa F., Mannazzu M., Falchi A., Mura MS., Madeddu G. Bone mass loss and vitamin D metabolism impairment in HIV patients receiving highly active antiretroviral therapy. J Nucl Med Mol Imaging 2004, 48: 39–48.
43. Malizia AP., Cotter E., Chew N., Powderly WG., Doran PP. HIV protease inhibitors selectively induce gene expression alterations associated with reduced calcium deposition in primary human osteoblasts. AIDS Res Hum Retroviruses 2007, 23, 243–250.
44. Mallon PWG., Miller J., Cooper DA., Carr A. Prospective evaluation of the effects of antiretroviral therapy on body composition in HIV-1-infected men starting therapy. AIDS 2003, 17: 971–979.
45. Melissa L., Knothe T., Adamson JR., Tami AE., Bauer TW. The osteocyte. The International Journal of Biochemistry and Cell Biology 2004, 36: 1–8.
46. Mellert W., Kleinschmidt A., Schmidt J., Festl H., Emler S., Roth WK., Erfle V. Infection of human fibroblasts and osteoblast-like cells with HIV-1. AIDS 1990, 6: 527–535.
47. Moe S., Drueke T., Cunningham J., Goodman W., Martin K., Olgaard K., Ott S., Sprague S., Lameire N., Eknoyan G. Definition, evaluation and classification of renal osteodystrophy: a positive statement from kidney disease: improving global outcomes. Kidney International 2006, 69: 1945–1953.
48. Mora S., Zamproni I., Cafarelli L., Giacomet V., Erba P., Zuccotti G., Vigano, A. Alterations in circulating osteoimmune factors may be responsible for high bone resorption rate in HIV- infected children and adolescents. AIDS 2007, 21: 1129–1135.
49. Nacher M., Serrano S., Gonzalez A., Hernandez A., Marinoso ML., Vilella R., Hinarejos P., Diez A., Aubia, J. Osteoblasts in HIV-infected patients: HIV-1 infection and cell function. AIDS 2001, 15, 2239–2243.
50. Pan G., Wu X., McKenna MA., Feng X., Nagy TR., McDonald JM. (2004). AZT enhances osteoclastogenesis and bone loss. Osteoporosis Int, 20: 608–620.
51. Pan G., Kilby M, McDonald JM. Modulation of osteoclastogenesis induced by nucleoside reverse transcriptase inhibitors. AIDS Res Hum Retroviruses 2006, 22: 1131–1141.
52. Prior J., Burdge D., Maan E., Milner R., Hankins C., Klein M., Walmsley S. Fragility fractures and bone mineral density in HIV positive women: a case control population-based study. Osteoporosis Int 2007, 18:1345–1353.
53. Re MC, Furlini G, Zauli G, La Placa M. Human immunodeficiency virus type 1 (HIV-1) and human hematopoietic progenitor cells.Arch Virol. 1994:137:1-23.
54. Seminari E., Castagna A., Soldarini A., Galli L., Fusetti G., Dorigatti F., Hasson H., Danise A., Guffanti M., Lazzarin A., Rubinacci A. Osteoprotegerin and bone turnover markers in heavily pretreated HIV-infected patients. HIV Medicine 2005, 6: 145–150.
55. Serrano S, Mariñoso ML, Soriano JC, Rubiés-Prat J, Aubia J, Coll J, Bosch J, Del Rio L, Vila J, Goday A, Nacher, M. Bone Remodelling in Human Immunodeficiency Virus-1-Infected Patients. A Histomorphometric Study. Bone 1995, 16: 185–191.
56. Sorensen MG., Henriksen K., Dzigiel MH., Tanko LB., Karsdal MA. Estrogen directly attenuates human osteoclastogenesis, but has no effect on resorption by mature osteoclasts. Clinical Infectious Diseases 2006, 25: 475–483.
57. Tebas P., Powderly W. G., Claxton S., Marin D., Tantisiriwat W., Teitelbaum S. L., Yarasheski KE. Accelerated bone mineral loss in HIV-infected patients receiving potent antiretroviral therapy. Metabolism, 2000, 14: F63–F67.
58. Teichmann J., Stephan E., Discher T., Lange U., Federlin K., Stracke H., Friese G., Lohmeyer J., Bretzel R. G. Changes in calciotropic hormones and biochemical markers of bone metabolism in patients with Human Immunodeficiency Virus infection. Metabolism 2000, 9: 1134–1139.
59. Thomas J., Doherty SM. HIV-infection: a risk factor for osteoporosis. Journal of Acquired Immune Syndrome 2003, 33: 281-291.
60. Tomazic J., Ul K., Volcansek G., Gorensek S., Pfeifer M., Karner P., Prezelj J., Vidmar G., Vidmar L. Prevalence and risk factors for osteopenia/osteoporosis in an HIV-infected male population. Wien Klin Wochenschr 2007, 119, 639–646.
61. Ueland T., Bollerslev J., Godang K., Muller F., Froland SS., Aukrust P. Increased serum osteoprotegerin in disorders characterized by persistent immune activation or glucocorticoid excess - possible role in bone homeostasis. European Journal of Endocrinology 2001, 145: 685–690.
62. Vescini F., Borderi M., Buffa A., Sinicropi G., Tampellini L., Chiodo F., Caudarella R. Bone Mass in HIV-Infected Patients: Focus on the Role of Therapy and Sex. J Acquir Immune Defic Syndr 2005, 33, 405–407.
63. Wang L., Mondal D., Russa VF, Agrawal KC. Suppression of clonogenic potential of human bone marrow mesenchymal stem cells by HIV type 1: putative role of HIV type 1 tat protein and inflammatory cytokines. Metabolism 2002, 18: 917–931.
64. in the HIV positive population, second on the difference between the patients treated with HAART or not, and lastly on the difference between the patients treated with PI or not.
65. In 2003 Bruera[2] addressed the changes in bone