review

HIV infection, bone metabolism, and fractures

Infecção pelo HIV, o metabolismo ósseo e fraturas

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ABSTRACT

With the advent of high active antiretroviral therapy there was a significant improvement on HIV subjects survival. Thus, bone changes related to HIV became an important aspect of these individuals. HIV affects bone remodeling causing bone fragility. In addition, antiretroviral therapy may also negatively affect bone metabolism. Several studies describe an increased incidence of fractures in these patients when compared with controls without the disease. The European Society of AIDS (EACS), and other societies, have included guidance on management of osteoporosis in HIV-infected patients emphasizing the identification of patients with low bone mass. Supplementation of calcium and vitamin D and the use of alendronate in these individuals should be recommended on a case base. Arq Bras Endocrinol Metab. 2014;58(5):478-83

Keywords
Bone; bone metabolism; HIV; bone fractures

RESUMO

Com o advento da terapia antirretroviral, houve uma melhora considerável na sobrevida dos indivíduos portadores do vírus HIV. Dessa forma, as alterações ósseas referentes ao HIV se tornaram um fator importante no cuidado desses indivíduos. O HIV altera o remodelamento ósseo causando fragilidade óssea. As alterações causadas por esse vírus nos linfócitos T afetam a produção de RANKL e de citocinas pró-inflamatórias levando à osteoclastogênese. Ademais, a terapia antirretroviral também pode afetar negativamente o metabolismo ósseo. Vários estudos descrevem aumento da incidência de fraturas nesses indivíduos quando comparados a controles sem a doença. Diretrizes da Sociedade Europeia de SIDA (EACS) têm orientado o manejo da osteoporose nesses sujeitos, enfatizando a identificação de pacientes com baixa massa óssea. A suplementação de cálcio e vitamina D e o uso de alendronato nesses indivíduos devem ser recomendados caso a caso. Arq Bras Endocrinol Metab. 2014;58(5):478-83

Descritores
Osso; metabolismo ósseo; HIV; fraturas ósseas

INTRODUCTION

With the development of high active antiretroviral therapy life expectancy has improved considerably among HIV infected patients. Now the concern has emerged regarding long-term consequences of both chronic HIV infection itself and related antiretroviral therapies (ART).

One of the organs affected by HIV infection is the bone. Low bone mineral density (BMD) and a decreased bone mass have been reported in HIV-infected patients independently of age and gender (1-3). Although this is well known and characterized, the ultimate reason that leads to that bone loss is still not well understood. Multiple factors appear to be involved, including effects of HIV viral proteins, ART side effects and inflammatory cytokines on bone cells and bone turnover. In addition, the effect of HIV infection on traditional determinants of BMD such as body weight, smoking status or others (4-7) could also play a key role.

DEFINITION AND DIAGNOSIS

Osteoporosis is a global health problem that insidiously deteriorates the microstructure of bone. That deterioration leads to a compromised bone strength, which predisposes the individual to an increased risk of fractures of the hip, spine, forearm, and other skeletal sites. The diagnosis is done in the presence of low-energy traumatic fracture and should be considered when low bone mineral density (BMD) is found. Dual energy X-ray absorptiometry (DEXA) is the gold standard of bone density measurement, at the lumbar spine, and hip. DEXA measurements of BMD are the basis of osteoporosis diagnostic and risk fracture evaluation. Osteoporosis is defined as BMD measurement at the hip or spine ≤ 2.5 standard deviations below the mean BMD for a healthy, young, sex-matched population (T score). Osteopenia is defined as a T score between −1.0 and −2.5 (8).

However, other methods to more accurately estimate fracture risk have been recently developed. One of this methods is the Fracture Risk Assessment tool (FRAX®) (9). FRAX is a computer-based algorithm developed by the WHO. The FRAX score calculates the 10-year probability of a major fracture (hip, clinical spine, humerus or wrist fracture) and the 10-year probability of hip fracture. It takes into account key clinical risk factors in men and women: age, BMI, prior fragility fracture, parental history of hip fracture, current tobacco smoking, long-term oral glucocorticoid use, rheumatoid arthritis, other causes of secondary osteoporosis and alcohol consumption. Femoral neck BMD can be optionally entered to enhance fracture risk prediction.

However, FRAX score does not take into account the presence of HIV-infection nor the use of ART therapies. In a previous study, Calmy and cols. (10) calculated the FRAX score for 153 HIV-infected adults: they evaluated whether the score based on risk factors alone could identify HIV-positive patients with reduced BMD. They did not detect differences in the FRAX score between patients with normal BMD and patients with low BMD; they concluded that the FRAX score does not discriminate between patients with osteopenia and those without osteopenia and thus provides very limited usefulness as a screening tool in the HIV-positive population. In fact, FRAX has not been validated in HIV-infected persons and may underestimate the 10-year risk of fracture in these patients (11).

BONE BIOLOGY

In the processes that lead to HIV-related bone loss a large number of elements that play a role in bone metabolism are implicated. Knowing how these elements are communicated and related becomes of capital importance to understand how bone loss is produced, and finally how bone fracture overcomes in this population.

Bone is a living organ, composed of a cellular part with support and communication cells, the osteocytes, bone forming cells, the osteoblasts, and bone remodeling cells, the osteoclasts. Other components are a non-mineral crystals of collagen and the non-collagen proteins called osteoid, where the mineral matrix with calcium and phosphate in the form of calcium hydroxyapatite is deposited.

During life, bone undergoes processes of longitudinal and radial growth, modeling, and remodeling (12). Bone remodeling begins early in foetal life, and once the skeleton is fully formed in young adults almost all of the metabolic activity is in this form. Remodeling is responsible of maintaining bone competence, as one of its functions is to repair microdamage induced due to the stress of material, besides its role in mobilizing minerals stored in bone to supply physiological needs. The bone remodeling cycle (13) involves a series of highly regulated steps that depend on the interactions of two cell lineages aforementioned: the mesenchymal osteoblastic lineage and the hematopoietic osteoclastic lineage. Abnormalities of bone remodeling can produce a variety of skeletal disorders. When bone resorption becomes higher than bone formation, bone loss and osteopenia/osteoporosis is the consequence. This negative balance of cell cycle is the ultimate mechanism of osteoporosis developing leading to an increased bone fragility, and thus to fragility fractures.

Among different conditions that can produce low bone mass, chronic inflammatory diseases of almost any cause are associated with bone loss. Inflammatory bone loss in periodontal disease and arthritis is probably the combined result of stimulation of resorption and inhibition of formation by cytokines and prostaglandins. Interleukin 1 (IL-1), Interleukin IL-6 (IL-6), and tumor necrosis factor as well as growth factors have been implicated in pathologic responses in the skeleton, particularly in osteoporosis associated with estrogen deficiency, hyperparathyroidism, and Paget disease (14-16). Among these disorders that lead to abnormalities in bone remodeling HIV has emerged as a new cause of bone fragility.

Although osteoporosis is not typically considered to be an immune-mediated disorder, recent data have indicated an overlapping pathway between bone physiology and the biology of inflammation that involves the T-lymphocyte compartment. The role of HIV-specific factors in bone loss and fracture remains unclear. However, HIV itself can produce an inflammatory state that could lead to bone loss through the promotion of osteoclastogenesis and bone resorption due to inflammatory cytokines. T-cells activation are the common element between the immune response to HIV and bone compartment. Activated T-cells affect bone physiology by producing RANKL and pro-inflammatory cytokines, which promote osteoclast activity. As found in both *in vitro* and *in vivo* studies (17), tumor necrosis factor alpha induces the apoptosis of osteoblasts, and interleukin 6 (18) directly induces receptor activator of nuclear factor kappa B ligand (RANKL) expression, an osteoblast-secreted cytokine that promotes osteoclast formation and maduration. In both cases, higher levels of these inflammatory markers are associated with an induced osteoclastogenesis, and, thus, an increased bone resorption. Moreover, high concentrations of HIV RNA have been associated with elevated levels of RANKL, increasing osteoclast presence in bone (19).

The etiology of osteoporosis in HIV-infected patients is likely multifactorial, involving traditional risk factors as well as direct effects of chronic HIV infection and antiretroviral therapy. However, to date, most studies in HIV-infected individuals have focused on bone loss rather than fracture risk. Whether the observed reductions in BMD translate into increased fracture risk, particularly in younger individuals, is uncertain. However, there is growing evidence that shows an increased fracture risk among HIV infected patients. We summarize here the essential facts.

HIV AND LOW BONE MASS

Osteoporosis has traditionally affected postmenopausal women. However, some studies have established that osteoporosis is also common amongst HIV-positive men of all ages, as well as in some younger HIV-positive women. Actually, a growing body of evidence indicates that people with HIV are at risk for osteoporosis. Several studies in the past decade have established the association between bone loss and HIV infection.

A first approach to study the role of HIV in bone loss consists of several epidemiological cohort studies (20,21). Many of them have limited sample size, but these studies demonstrated a higher prevalence of low BMD in HIV-infected patients compared to the general population, with osteopenia being present in 40 to 70% of the studied patients. Along these same lines, Cazanave and cols. published that the prevalence of osteopenia in HIV-infected patients was 54.6% in men and 51.1% in women, whereas the prevalence of osteoporosis among this population was 33.7% in men and 8.3% in women (22). A systematic review of cross-sectional studies by Brown and cols. concluded that the probability of osteopenia and osteoporosis would be over 6-fold and almost 4-fold higher in HIV-infected than in uninfected populations respectively (23). In line with these data, in a clinical trial that evaluated BMD before starting ART, the prevalence of osteopenia at the start of ART was in a range of 23 to 28%, clearly higher than that in the general population (24).

Large population-based studies, as the study SUN that included 525 patients with HIV, compared BMD measured by DEXA to uninfected controls in the National Survey of Health and Nutrition Examination U.S. (NHANES). They found that osteoporosis was associated with older age, non-Caucasian ethnic background, lower BMI, unemployment, and time since HIV diagnosis. Nevertheless, since 79% of patients were on ART treatment, it was not possible to draw clear conclusions from this study on the independent contribution of HIV to the loss of bone mass. Other studies (25,26) found the same correlation, but again the data was not useful to disentangle the effects of ART and HIV infection.

ART AND LOW BMD

ART therapy has been associated with low BMD in a number of studies discussed in a meta-analyisis (3). The authors reported a relative risk of 2.5 for osteopenia in patients with ART compared with untreated patients. In fact, other longitudinal studies and clinical trials conducted to date also suggest that ART is associated with low bone mass (24,27).

The analysis of changes in BMD in patients participating in the SMART study, a trial where continuous ART vs intermittent ART were compared, found that 10 out of the total 12 fractures reported amongst study participants, 10 of them appeared in the continuous ART arm. Also, BMD was significantly lower in the continuous ART group when compared to the intermittent ART arm (28).

HIV AND FRACTURES

All this evidence is showing that bone deterioration in HIV is probably the result of the addition of traditional risk factors such as smoking, alcohol use, hypogonadism, low body weight, vitamin D deficiency, and factors directly related to HIV infection (24,29). However, the question in the late 2000's was if that decreased bone mass induced an excess risk of bone fractures. As a result, a number of studies assessed this association.

Several studies have reported fracture rates in HIV cohorts compared to uninfected controls. Initially there was contradictory evidence, and studies in both directions were published: Arnsten and cols. reported no significant increase in risk of fractures in 328 men followed for 2 years (30); Yin and cols. reported no increase in fracture rates in 1,728 women followed for 5 years (31); and, finally, Collin and cols. reported no increase in fractures amongst 1,281 adults taking ART followed for 10 years, compared to the general population of the same age in Europe (32).

Conversely, Prior and cols. reported an increased risk of fractures in a cohort of 137 HIV women, but they did not find differences in BMD (33). Data obtained from population registries or from large cohorts have led to the publication of a series of studies describing a strong association between HIV infection and fractures: Triant and cols. found that the prevalence of fractures was higher in HIV-infected individuals, but the nature of his data did not allow adjustment for differences in risk factors between groups (34); similarly, in a more restricted population, the Male Veterans Cohort, Womack and cols. reported that HIV status was related to fracture incidence, but this association was attenuated after adjustment for co-morbidities (35); more recently a Spanish population-based cohort study including over 1.1 million participants and almost 2,500 HIV-infected patients showed a strong association between HIV infection and hip fracture incidence, with an almost five-fold increased risk in the HIV infected individuals, independent of sex, age, smoking, alcohol drinking, and comorbidities. Similarly, a 75% higher risk of all clinical fractures and a 60% increase in risk of non-hip clinical fractures among patients with a diagnosis of HIV infection was found (36); finally, another nation-wide case-control study in a Nothern-European population found that HIV infection is associated with an almost 3-fold increase in overall fracture risk. In HIV patients with an almost 9-fold higher risk of hip fracture (37).

Independently of the ultimate cause of the observed increased risk of fractures, the latter study described a sharp and early increase in fracture rates in the first few years following HIV infection. This makes a strong case for an early assessment of fracture risk in HIV infected patients, particularly as the HIV population is ageing.

ETIOLOGY OF INCREASED FRACTURED RISK

Apart from the influence of traditional risk factors associated to an increased fracture risk in HIV-infected patients. There are other factors that have influence (Figure 1). It has been hypothesized that inflammatory state promoted by HIV-infection could lead to decreased bone loss. However, it has been in a recent study analyzing BMD an immune activation where Gazzola and cols. found that heightened T-cell activation in HIV-infected patients independently predicts BMD disorders. That could suggest a critical role of immune activation in the pathogenesis of decreased bone mass, even in patients with a full viral response to ART (38).
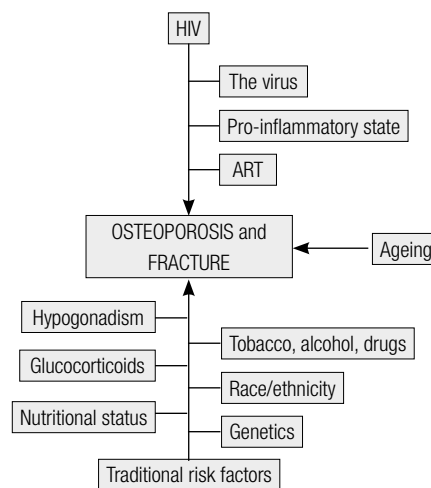
Figure 1. Causes of increased fracture risk in HIV-infected patients

In other studies it has been shown that less than 200CD4 cell/μl (39,40) are associated with increased fragility fracture incidence. Similarly, in the HOPS cohort, nadir CD4 cell count of less than 200 cells/μl was associated with increased all-fracture incidence in a multivariate analysis (41).

In consequence, although there is not a complete explanation for bone loss and fractures in HIV-infected patients, it seems that the chronic inflammatory state due to the HIV infection itself has some responsibility in that condition. However, further studies should be done to confirm that hypothesis.

ART AND FRACTURES

The increased inflammatory status induced by HIV seems not to be enough to justify all the bone loss and excess fracture risk described above. In line with that, several studies have analysed the association between ART exposure and fracture risk. In a number of randomized controlled studies, initiation or switch to ART appears associated with 6-12 months of bone loss, which then stabilizes, specially after two years of treatment (42,43). Hansen and cols. found that ART-exposed patients had a 60% higher risk of fragility fracture than the general population, even after adjusting for comorbidities. Nevertheless, ART use was not associated with an increased risk of non-fragility fractures (44). Other study, by Bedimo and cols. studied retrospectively different ART regimens and their association with fracture risk from 1988 to 2009, and they reported that cumulative exposure to tenofovir was independently predictive of increased risk of osteoporotic fracture (12% higher risk per year of exposure) after controlling for traditional osteoporotic risk factors and concomitant ART. Exposure to abacavir, zidovudine or estavudine or Non-Nucleosid Reverse Transcriptase Inhibitors (NNRTIs) were not significantly associated with increased risk of osteoporotic fracture in neither uni or multivariate models. More importantly, concomitant exposure to both tenofovir and boosted Protease Inhibitors (PI/r) was associated with a greater osteoporotic fracture risk than exposure to either tenofovir without PI/r or PI/r without tenofovir. Among protease inhibitors, only lopinavir/ritonavir was associated with a significantly increased fracture risk (45).

CONSIDERATIONS ABOUT THE PREVENTION OF OSTEOPOROTIC FRACTURES

The main aim of the treatment of osteoporosis is to reduce the incidence of fractures. It is though not well known, nor established, if pharmacological interventions for low BMD in HIV-infected patients, especially in the younger ones, will reduce their risk of fracture. Actually, due to the increasing awareness of the bone disease related to HIV, the European Society of AIDS (EACS) (46), and other societies, have included guidance on management of osteoporosis in HIV-infected patients and recommendations have also been published. These guidelines suggest identifying those patients at greatest risk of low BMD, measuring BMD in those at risk, and treating osteoporosis where identified (46). Its main recommendations are to follow national guidelines when available; otherwise, bisphosphonate therapy with vitamin D and calcium supplementation should be considered.

Nevertheless, the optimal clinical management of bone health in HIV-infected individuals is not well defined and remains controversial. It will probably be necessary to develop guidelines for screening and treating reversible causes of low bone mineral density and fall risk in HIV patients, and then establish recommendations for the treatment of high-risk patients.

In conclusion, the information currently available suggests that both ART and HIV infection itself favor bone demineralization, subsequently increasing fracture risk. Bone loss is faster in the first two years after initiation of ART and tends to stabilize afterwards. However, given the complex interactions between HIV and ART that leads to low BMD, optimization of ART therapy, and prompt strategies to prevent bone loss may be important. Focus on bone disease as the paradigm of ageing in this population may improve not only long term life-expectancy but also the quality of life of these patients.

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REFERENCES

1. Jacobson DL, Lindsey JC, Gordon CM, Moye J, Hardin DS, Mulligan K, et al. Total body and spinal bone mineral density across Tanner stage in perinatally HIV-infected and uninfected children and youth in PACTG 1045. AIDS. 2010;24(5):687-96.

2. Mulligan K, Harris DR, Emmanuel P, Fielding RA, Worrell C, Kapogiannis BG, et al. Low bone mass in behaviorally HIV-infected young men on antiretroviral therapy: Adolescent Trials Network Study 021B. Clin Infect Dis. 2012;55(3):461-8.

3. Brown TT, Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. AIDS. 2006;20(17):2165-74.

4. Fakruddin JM, Laurence J. HIV-1 Vpr enhances production of receptor of activated NF-kappaB ligand (RANKL) via potentiation of glucocorticoid receptor activity. Arch Virol. 2005;150(1):67-78.

5. 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(2):243-50.

6. Wang MW-H, Wei S, Faccio R, Takeshita S, Tebas P, Powderly WG, et al. The HIV protease inhibitor ritonavir blocks osteoclastogenesis and function by impairing RANKL-induced signaling. J Clin Invest. 2004;114(2):206-13.

7. Bolland MJ, Grey AB, Gamble GD, Reid IR. CLINICAL Review # : low body weight mediates the relationship between HIV infection

and low bone mineral density: a meta-analysis. J Clin Endocrinol Metab. 2007;92(12):4522-8.

8. Watts NB, Lewiecki EM, Miller PD, Baim S. National Osteoporosis Foundation 2008 Clinician's Guide to Prevention and Treatment of Osteoporosis and the World Health Organization Fracture Risk Assessment Tool (FRAX): what they mean to the bone densitometrist and bone technologist. J Clin Densitom. 2008;11(4):473-7.

9. Kanis JA, Oden A, Johansson H, Borgström F, Ström O, McCloskey E. FRAX and its applications to clinical practice. Bone. 2009;44(5):734-43.

10. Calmy A, Fux CA, Norris R, Vallier N, Delhumeau C, Samaras K, 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.

11. McComsey GA, Tebas P, Shane E, Yin MT, Overton ET, Huang JS, et al. Bone disease in HIV infection: a practical review and recommendations for HIV care providers. Clin Infect Dis. 2010;51(8):937-46.

12. Clarke B. Normal bone anatomy and physiology. Clin J Am Soc Nephrol. 2008;3 Suppl 3:S131-9.

13. Jilka RL, Weinstein RS, Bellido T, Parfitt AM, Manolagas SC. Osteoblast programmed cell death (apoptosis): modulation by growth factors and cytokines. J Bone Miner Res. 1998;13(5):793-802.

14. Lorenzo JA. The role of cytokines in the regulation of local bone resorption. Crit Rev Immunol. 1991;11(3-4):195-213.

15. McLeod KJ, Rubin CT, Otter MW, Qin YX. Skeletal cell stresses and bone adaptation. Am J Med Sci. 1998;316(3):176-83.

16. Papanicolaou DA, Wilder RL, Manolagas SC, Chrousos GP. The pathophysiologic roles of interleukin-6 in human disease. Ann Intern Med. 1998;128(2):127-37.

17. Lam J, Takeshita S, Barker JE, Kanagawa O, Ross FP, Teitelbaum SL. TNF-alpha induces osteoclastogenesis by direct stimulation of macrophages exposed to permissive levels of RANK ligand. J Clin Invest. 2000;106(12):1481-8.

18. Hashizume M, Hayakawa N, Mihara M. IL-6 trans-signalling directly induces RANKL on fibroblast-like synovial cells and is involved in RANKL induction by TNF-alpha and IL-17. Rheumatology (Oxford). 2008;47(11):1635-40.

19. Gibellini D, Borderi M, De Crignis E, Cicola R, Vescini F, Caudarella R, et al. RANKL/OPG/TRAIL plasma levels and bone mass loss evaluation in antiretroviral naive HIV-1-positive men. J Med Virol. 2007;79(10):1446-54.

20. Stone B, Dockrell D, Bowman C, McCloskey E. HIV and bone disease. Arch Biochem Biophys. 2010;503(1):66-77.

21. Mallon PWG. HIV and bone mineral density. Curr Opin Infect Dis. 2010;23(1):1-8.

22. Cazanave C, Dupon M, Lavignolle-Aurillac V, Barthe N, Lawson-Ayayi S, Mehsen N, et al. Reduced bone mineral density in HIV-infected patients: prevalence and associated factors. AIDS. 2008;22(3):395-402.

23. Brown TT, Ruppe MD, Kassner R, Kumar P, Kehoe T, Dobs AS, 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.

24. Gallant JE, Staszewski S, Pozniak AL, DeJesus E, Suleiman JMAH, Miller MD, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. JAMA. 2004;292(2):191-201.

25. Knobel H, Guelar A, Vallecillo G, Nogués X, Díez A. Osteopenia in HIV-infected patients: is it the disease or is it the treatment? AIDS. 2001;15(6):807-8.

26. 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(13):1917-23.

27. Brown TT, McComsey GA, King MS, Qaqish RB, Bernstein BM, da Silva BA. Loss of bone mineral density after antiretroviral therapy initiation, independent of antiretroviral regimen. J Acquir Immune Defic Syndr. 2009;51(5):554-61.

28. Grund B, Peng G, Gibert CL, Hoy JF, Isaksson RL, Shlay JC, et al. Continuous antiretroviral therapy decreases bone mineral density. AIDS. 2009;23(12):1519-29.

29. Tebas P, Powderly WG, Claxton S, Marin D, Tantisiriwat W, Teitelbaum SL, et al. Accelerated bone mineral loss in HIV-infected patients receiving potent antiretroviral therapy. AIDS. 2000;14(4):F63-7.

30. Arnsten JH, Freeman R, Howard AA, Floris-Moore M, Lo Y, Klein RS. Decreased bone mineral density and increased fracture risk in aging men with or at risk for HIV infection. AIDS. 2007;21(5):617-23.

31. Yin MT, Shi Q, Hoover DR, Anastos K, Sharma A, Young M, et al. Fracture incidence in HIV-infected women: results from the Women's Interagency HIV Study. AIDS. 2010;24(17):2679-86.

32. Collin F, Duval X, Le Moing V, Piroth L, Al Kaied F, Massip P, et al. Ten-year incidence and risk factors of bone fractures in a cohort of treated HIV1-infected adults. AIDS. 2009;23(8):1021-4.

33. Prior J, Burdge D, Maan E, Milner R, Hankins C, Klein M, et al. Fragility fractures and bone mineral density in HIV positive women: a case-control population-based study. Osteoporos Int. 2007;18(10):1345-53.

34. Triant VA, Brown TT, Lee H, Grinspoon SK. Fracture prevalence among human immunodeficiency virus (HIV)-infected versus non-HIV-infected patients in a large U.S. healthcare system. J Clin Endocrinol Metab. 2008;93(9):3499-504.

35. Womack JA, Goulet JL, Gibert C, Brandt C, Chang CC, Gulanski B, et al. Increased risk of fragility fractures among HIV infected compared to uninfected male veterans. PLoS One. 2011;6(2):e17217.

36. Güerri-Fernandez R, Vestergaard P, Carbonell C, Knobel H, Avilés FF, Castro AS, et al. HIV infection is strongly associated with hip fracture risk, independently of age, gender, and comorbidities: a population-based cohort study. J Bone Miner Res. 2013;28(6):1259-63.

37. Prieto-Alhambra D, Güerri-Fernández R, De Vries F, Lalmohamed A, Bazelier M, Starup-Linde J, et al. HIV infection and its association with an excess risk of clinical fractures and: a nationwide case-control study. J Acquir Immune Defic Syndr. 2014;66(1):90-5.

38. Gazzola L, Bellistri GM, Tincati C, Ierardi V, Savoldi A, del Dole A, et al. Association between peripheral T-lymphocyte activation and impaired bone mineral density in HIV-infected patients. J Transl Med. 2013;11:51.

39. Yong MK, Elliott JH, Woolley IJ, Hoy JF. Low CD4 count is associated with an increased risk of fragility fracture in HIV-infected patients. J Acquir Immune Defic Syndr. 2011;57(3):205-10.

40. Hasse B, Ledergerber B, Furrer H, Battegay M, Hirschel B, Cavassini M, et al. Morbidity and aging in HIV-infected persons: the Swiss HIV cohort study. Clin Infect Dis. 2011;53(11):1130-9.

41. Young B, Dao CN, Buchacz K, Baker R, Brooks JT. Increased rates of bone fracture among HIV-infected persons in the HIV Outpatient Study (HOPS) compared with the US general population, 2000-2006. Clin Infect Dis. 2011;52(8):1061-8.

42. Martin A, Bloch M, Amin J, Baker D, Cooper DA, Emery S, et al. Simplification of antiretroviral therapy with tenofovir-emtricitabine or abacavir-Lamivudine: a randomized, 96-week trial. Clin Infect Dis. 2009;49(10):1591-601.

43. McComsey GA, Kitch D, Daar ES, Tierney C, Jahed NC, Tebas P, et al. Bone mineral density and fractures in antiretroviral-naive persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: Aids Clinical Trials Group A5224s, a substudy of ACTG. J Infect Dis. 2011;203(12):1791-801.

44. Hansen A-BE, Gerstoft J, Kronborg G, Larsen CS, Pedersen C, Pedersen G, et al. Incidence of low and high-energy fractures in persons with and without HIV infection: a Danish population-based cohort study. AIDS. 2012;26(3):285-93.

45. Bedimo R, Maalouf NM, Zhang S, Drechsler H, Tebas P. Osteoporotic fracture risk associated with cumulative exposure to tenofovir and other antiretroviral agents. AIDS. 2012;26(7):825-31.

46. EACS guidelines v.7.0 [Internet]. [cited 2014 Feb 28]. Available from: http://www.eacsociety.org/Portals/0/Guidelines_Online_131014.pdf