New Microbiologica, **38**, 193-199, 2015

Long-term changes in bone mineral density after switching to a protease inhibitor monotherapy in HIV-infected subjects

Eugènia Negredo[1], Anna Bonjoch[1], Jordi Puig[1], Patricia Echeverría[1], Carla Estany[1], José R. Santos[1], José Moltó[1], Nuria Pérez-Álvarez[1], , Arelly Ornelas[2], Bonaventura Clotet[1,3]

[1]Lluita contra la Sida Foundation, Germans Trias i Pujol University Hospital, Badalona, Spain, Universitat Autònoma de Barcelona, Barcelona, Spain;
[2]Statistics and Operations Research Department, Universitat Politècnica de Catalunya, Barcelona, Spain;
[3]Irsicaixa Foundation, Germans Trias i Pujol University Hospital, Badalona, Spain

SUMMARY

Although some clinical trials have studied the impact of treatments on bone mineral density (BMD), scarce data are available about the impact of protease inhibitor (PI) monotherapies on BMD. The aim of this study was to evaluate changes in BMD in patients after one, two, or three years of a PI monotherapy.

This study included 46 HIV-infected patients who switched from a conventional triple antiretroviral strategy to a monotherapy with lopinavir/ritonavir (LPV/r) or darunavir/ritonavir (DRV/r) for one (one-year group, n=16), two (two-year group, n=20), and three (three-year group, n=10) years. BMD was assessed by dual-energy X-ray absorptiometry (DXA).

The median percentage of change in total femur BMD was 0.20% after one, 0.79% after two, and -0.31% after three years. The change in lumbar spine was -0.08%, -0.14%, and 0.50% % after the same years. No significant differences were found when patients were classified regarding the type of PI and whether or not had previously received PI or tenofovir. However, patients who interrupted tenofovir or those who started with DRV/r had a higher BMD increment. Patients who had taken non-nucleoside reverse transcriptase inhibitors previously decreased BMD when started PIs.

Monotherapy treatment with ritonavir-boosted protease inhibitors (both LPV/r and DRV/r) during one, two, or three years leads to the stabilization of BMD in HIV-infected patients with long-term virological suppression. Larger studies are necessary to compare the effect of starting or withdrawing PIs on BMD.

KEY WORDS: HIV, Demineralization, Protease inhibitor, Bone density, Densitometry.

Received November 5, 2014 *Accepted* January 31, 2015

INTRODUCTION

Bone demineralization is a common complication among HIV-infected patients, whose underlying mechanism remains poorly understood (Thomas and Doherty 2003; Paccou *et al.,* 2009). Lower bone mineral density (BMD) rate and higher fracture risk have been reported in both naïve and receiving antiretroviral therapy subjects, compared to non-infected ones (Bruera *et al.,* 2003; Brown and Qaqish 2006). HIV infection has been proposed to participate in the activity of osteogenic cells, alteration of the vitamin D metabolism, and activation of proinflammatory cytokines (Cozzolino *et al.,* 2003; Connolly *et al.,* 2005; Cotter *et al.,* 2008). Antiretroviral therapies also contribute to bone demineralization. (Nolan *et al.,* 2001; Fernandez-Rivera *et al.,* 2003) BMD rate has been reported to decrease during the first months of

Corresponding author
Eugènia Negredo
VIH Unit, Lluita contra la SIDA Foundation
Germans Trias i Pujol Hospital
Carretera de Canyet S/N
08916 Badalona - Barcelona (Spain)
E-mail: enegredo@flsida.org

treatment, and to stabilize thereafter (Brown *et al.,* 2009; Grund *et al.,* 2009; Bolland *et al.,* 2011; Hoy *al.,* 2013) The common first-line regimen tenofovir/emtricitabine has been shown to decrease BMD more dramatically than other regimens, such as abacavir/lamivudine (Gallant *et al.,* 2004; Martin *et al.,* 2009; Stellbrink *et al.,* 2010). Similarly, protease inhibitors (PI) could also play a role in bone loss, although less evidence is available.

Switching the original treatment over time, by reason of failure, toxicity, prevention or simplification, has become a common strategy in the management of HIV (Mocroft *et al.,* 2005; Arribas *et al.,* 2013). In this sense, ritonavir-boosted PI monotherapy, including lopinavir/ritonavir (LPV/r) or darunavir/ritonavir (DRV/r), has demonstrated effective results in patients while reducing nucleoside-related toxicities (lipoatrophy, nephrotoxicity, vitamin D deficiency) and treatment costs (Martin *et al.* 2004; Spire *et al.,* 2008; Fox *et al.,* 2011; Mathis *et al.,* 2011). Although some clinical trials have studied the impact of treatments on BMD, few of them have analyzed the evolution of BMD over two or more years of follow-up (Bonjoch *et al.,* 2010; Cazanave *et al.,* 2010; McComsey *et al.,* 2010; Sharma *et al.,* 2010) and scare data have been published about the role of PI monotherapy on bone mineralization.

The aim of the study was to evaluate changes in BMD by dual-energy X-ray absorptiometry (DXA) in HIV-infected patients after one, two, or three years since the switch from a conventional triple antiretroviral strategy to a ritonavir-boosted PI monotherapy (LPV/r or DRV/r).

Study design and patients

This single-center, longitudinal study included 46 HIV-infected patients of the VIH Unit at the University Hospital Germans Trias i Pujol (Badalona, Spain). The criteria for inclusion in the study were as follows:

1) diagnosed with HIV-1 infection;
2) received PI monotherapy, consisting in LPV/r (Kaletra®, 200 mg/ 50 mg film-coated tablets, twice daily (BID) or DRV/r (Prezista® plus Norvir®, 800/100 mg once daily, QD) for at least one year;
3) received a triple antiretroviral therapy, i.e. nucleoside reverse transcriptase inhibitors (NRTI) or nucleotide reverse transcriptase inhibitors (NtRTI) plus PI or non-nucleoside reverse transcriptase inhibitors (NNRTI), previously to the switch to PI monotherapy;
4) performed a DXA scan close to the date of the switch to the PI monotherapy (from four months before to two months after starting the monotherapy).

The exclusion criteria were as follows:

1) under treatment of osteoporosis/osteopenia (bisphosphonates), or secondary causes of low bone mineralization (testosterone deficit, thyroid disease) during the monotherapy;
2) any change or interruption of the treatment.

All patients gave their informed consent to participate in the study. Procedures were performed in accordance with guidelines established by the Ethics Committee of the hospital.

A DXA scan (Lunar Prodigy, GE Healthcare, Belgium) was performed on the patients when they reached one (one-year group), two (two-year group) or three years (three-year group) after the switch to LPV/r or DRV/r monotherapy.

Objectives and statistical analysis

The main study variable was total femur and lumbar spine (L1–L4) BMD and T scores. The evolution of BMD in total femur and lumbar spine was analyzed comparing the percentage of change in BMD from baseline to one, two, or three years after monotherapy initiation. Additionally, changes in lumbar and total femur T scores were also assessed. Percentages of change were also compared regarding the type of PI used in the monotherapy and whether or not had previously received PI or tenofovir.

According to World Health Organization (WHO), a normal value of BMD is defined when T score >-1 SD, osteopenia when score is between -1 and -2.5 standard deviation (SD), and osteoporosis when value <-2.5 SD (Kanis 1994). Clinical and demographic data were recorded. The numerical variables were expressed as mean SD, or median and interquartile range (IQR) and compared using t-test, Mann-Whitney or Wilcoxon test, depending on the variable distribution. For categorical variables, the number and percentages of patients were giv-

en and compared using the χ^2 or Fisher exact test (as appropriate). Comparisons were made according to characteristics of patients considered of clinical interest. Results were considered significant at p≤0.05 at univariate level. All analyses were performed with SPSS 15 (SPSS, Inc., Chicago, Illinois, USA).

RESULTS

From a total of 46 HIV-infected patients under standard triple antiretroviral therapy, 16 had switched to monotherapy treatment for one year (one-year group), 20 for two (two-year group), and 10 for three years (three-year group). Demographic and clinical characteristics of patients at baseline are shown in Table 1. Patients were predominantly male (58.7%) with a median age of 43.8 years (IQR, 40.0-48.5); 53% of women and 41% men were older than 50 years. HIV-infection was diagnosed 13.8 years (IQR, 5.4-18.5) from baseline, and patients were receiving antiretroviral therapy for 10.8 years (IQR, 4.2-14.5). Baseline HIV RNA was undetectable (<50 copies/mL) in 95.7% (Table 1). All participants maintained a suppressed plasma viral load during the study,

TABLE 1 - *Demographic and clinical characteristics of patients at baseline grouped according to the duration of the follow-up.*

	One-year group (N=16)	*Two-year group (N=20)*	*Three-year group (N=10)*
Sex Male, n (%)	8 (50.0)	15 (75.0)	4 (40.0)
Age, median (IQR)	44.3 (41.1;47.2)	44.0 (39.3;48.5)	40.2 (37.6;50.9)
HIV risk factors, n (%)			
Injecting drug use	4 (25.0)	1 (5.0)	3 (30.0)
Heterosexual	6 (37.5)	5 (25.0)	3 (30.0)
Homosexual	5 (31.3)	12 (60.0)	4 (40.0)
Bisexual	1 (6.3)	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	2 (10.0)	0 (0.0)
Years since HIV diagnosis, median (IQR)	14.5 (4.6;18.8)	13.8 (9.1;17.1)	11.3 (6.0;20.3)
Years on antiretroviral therapy, median (IQR)	13.0 (3.8;17.7)	11.4 (8.1;14.3)	8.7 (2.36;11.9)
Previous treatment base, n (%)			
Abacavir / Lamivudine	4 (25.0)	6 (30.0)	2 (20.0)
Tenofovir / Emtricitabine	10 (62.5)	8 (40.0)	6 (60.0)
Undetectable HIV RNA (<50 copies/mL), n (%)	15 (93.8)	19 (95.0)	10 (100.0)
Viral load, log copies/mL	1.40 (1.40;1.70)	1.70 (1.50;1.70)	1.70 (1.69;1.70)
CD4 T cells/mL counts, median (IQR)			
Absolute value	537.5 (366.3;713.3)	581.0 (427.3;739.5)	540.5 (501.3;987.8)
Percentage	29.0 (21.5;34.0)	30.5 (21.8;35.8)	38.0 (29.5;45.5)
Nadir	177.5 (103.0;270.5)	233.5 (184.5;285.3)	315.0 (200.0;437.3)
Current Treatment, n (%)			
LPV/r	7 (43.8)	9 (45.0)	5 (50.0)
DRV/r	9 (56.3)	11 (55.0)	5 (50.0)
Bone mineral density (BMD), %			
Normal	25	56.3	18.7
Osteopenia	15	65	20
Osteoporosis	30	40	30
T-score, median (IQR)			
Lumbar spine	-0.9 (-1.6;0.2)	-1.4 (-2.0;-0.5)	-0.7 (-1.4;0.9)
Total femur	-1.1 (-1.4;0.1)	-0.9 (-1.6;-0.5)	-0.6 (-1.2;-0.2)
BMD, median (IQR)			
Lumbar spine	1.1 (1.0;1.2)	(0.9;1.2)	1.1 (1.0;1.3)
Total femur	0.9 (0.9;1.0)	0.9 (0.9;1.0)	0.9 (0.9;1.0)

IQR, interquartile range; LPV/r, lopinavir/ritonavir; DRV/r, darunavir/ritonavir.

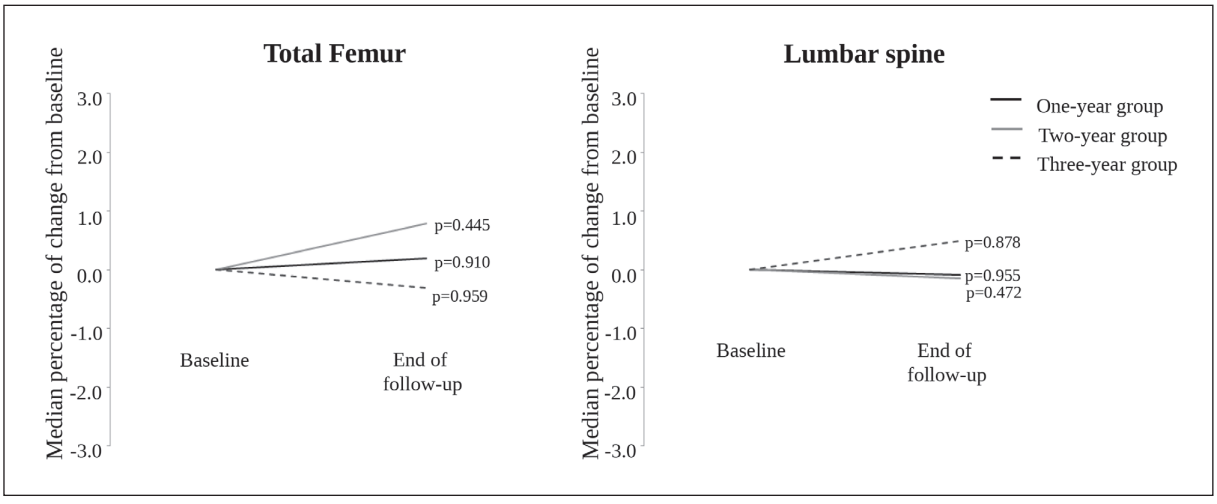

FIGURE 1 - *Median percentage of change from baseline in bone mineral density in total femur and lumbar spine.*

since those who presented a virological failure changed their therapy and were excluded from the study. From the total of HIV-infected patients under standard triple antiretroviral therapy, 45.7% switched to LPV/r and 54.3% to DRV/r monotherapy treatment.

In the one-year group, the median percentage of change was 0.20 (IQR, -2.29 to 2.08, p=0.910) in total femur BMD and -0.08 (IQR, -5.55 to 4.32, p=0.955) in lumbar spine BMD (Figure 1). In the two-year group, the change after this time was 0.79 (IQR, -1.83 to 2.60, p=0.445) in total femur and -0.14 (IQR, -2.95 to 1.07, p=0.472) in L1–L4 spine. Finally, the median percentage of change in the three-year group was -0.31 (IQR, -3.50 to 4.39, p=0.959) in total femur and 0.50 (IQR, -7.54 to 2.71, p=0.878) in lumbar spine.

When considering the previous administration of tenofovir during the triple therapy, no statistically significant intragroup differences were found in the percentage of change in total femur and lumbar spine BMD after one, two, or three years of monotherapy between patients who received tenofovir and those who did not (Table 2). Nevertheless, the percentage of change in total femur was higher for patients who received previously tenofovir in the one-year (0.7%, IQR -4.1-1.6) and two-year groups (1.2%, IQR -1.2-2.6), compared with patients who did not receive tenofovir (-0.3%, IQR -1.4-6.9 for the one-year group, and 0.3%, IQR -3.2–3.4 for the two-year group). By contrast, in the three-year group the change in total femur was more accentuated in those who did not receive tenofovir (0.7%, IQR -1.8-6.2) than who did (-0.6%, IQR -8.4-4.7). In the case of lumbar spine, the percentages of change were higher in the patients who did not received TDF from the two- and three-year treatment groups (Table 2).

Regarding the previous use of PI, no significant differences were found in any group between patients who were receiving a PI-based triple therapy and those who received a NNRTI-based regimen (Table 2). However, BMD basically decreased in patients who received an NNRTI-based treatment and started a PI monotherapy compared with those who already were receiving a PI.

Finally, when considering the PI used in monotherapy, no significant differences were found in total femur and lumbar spine BMD after the monotherapy between patients who received DRV/r or LPV/r (Table 2), although patients receiving DRV/r achieved higher values of change in total femur and lumbar spine in the groups of one and two years of treatment.

Total femur and lumbar spine (L1-L4) T scores at different times of follow-up are shown in Table 3. No significant differences were found in total femur and lumbar spine T scores between baseline and one, two or three years of treatment, respectively in each group.

TABLE 2 - *Median percentage of change in bone mineral density from baseline in the three study groups of patients classified regarding the type of protease inhibitor used and whether or not had previously received protease inhibitors or tenofovir.*

	Total Femur		*Lumbar Spine*	
	median (IQR) change	*p-value between subgroups*	*median (IQR) change*	*p-value between subgroups*
One-year group (N=16)				
Regarding the current PI				
DRV/r arm, n=7	0.4 (-4.0;2.3)	p=0.791	1.2 (-5.9;6.2)	p=0.427
LPV/r arm, n=9	0.0 (-1.9;2.3)		-0.2 (-5.4;2.6)	
Regarding previous ARV				
NNRTI, n=5	-2.7 (-6.8;1.8)	p=0.157	-3.1 (-6.2;3.4)	p=0.462
PI, n=11	0.9 (-0.6;2.3)		1.2 (-4.3;4.6)	
Regarding previous TDF				
Not, n=6	-0.3 (-1.4;6.9)	p=0.828	-1.6 (-29.5;7.1)	p=0.664
Yes, n=10	0.7 (-4.1;1.6)		0.6 (-4.7;4.2)	
Two-year group (N=20)				
Regarding the current PI				
DRV/r arm, n=9	0.9* (-0.1;3.8)	p=0.271	0.5 (-3.2;3.2)	p=0.732
LPV/r arm, n=11	-1.6 (-3.9;2.8)		-0.3 (-2.9;0.7)	
Regarding previous ARV				
NNRTI, n=4	-1.7 (-4.9;1.2)	p=0.156	-1.1 (-3.7;2.6)	p=0.925
PI, n=16	0.9 (-0.3;3.6)		-0.1 (-2.7;1.1)	
Regarding previous TDF				
Not, n=12	0.3 (-3.2;3.4)	p=0.758	0.0 (-3.8;3.2)	p=0.817
Yes, n=8	1.2 (-1.2;2.6)		-0.9 (-2.7;0.8)	
Three-year group (N=10)				
Regarding the current PI				
DRV/r arm, n=5	-1.4 (-1.9;8.0)	p=0.465	2.3 (-3.2;7.3)	p=0.117
LPV/r arm, n=5	0.7 (-8.9;3.1)		-2.1 (-12.5;1.2)	
Regarding previous ARV				
NNRTI, n=1	-9.8 (-9.8;-9.8)	p=0.117	-10.6 (-10.6;-10.6)	p=0.223
PI, n=9	0.7 (-1.9;5.4)		0.9 (-4.3;3.1)	
Regarding previous TDF				
Not, n=4	0.7 (-1.8;6.2)	p=0.670	2.6 (-4.6;9.7)	p=0.136
Yes, n=6	-0.6 (-8.4;4.7)		-0.9 (-11.5;1.3)	

IQR, interquartile range; PI, protease inhibitor; ARV, antiretroviral therapy; NNRTI, Non-nucleoside reverse transcriptase inhibitor; TDF, tenofovir. No differences were seen between subgroups (p-values are specified). Intragroup changes in every subgroup were not statistically significant except indicated (*p=0.036).

DISCUSSION

A tendency for bone demineralization has been widely described in HIV patients initiating antiretroviral treatments,(Sharma *et al.,* 2010) although prospective trials evaluating long-term effects on BMD are scarce (Bolland *et al.,* 2011; Bolland *et al.,* 2012). Simplification therapy from triple to mono antiretroviral regimens has proved antiviral efficacy while reducing toxicity (Martin *et al.,* 2004; Spire *et al.,*. 2008; Fox *et al.,* 2011; Mathis *et al.,* 2011). However, no data have been published on its long-term impact on BMD. Results from our study indicate that the switch to a ritonavir-boosted PI monotherapy (both LPV/r and DRV/r) leads to stabilization of the BMD. The switch to monotherapy just meant a change between 1.0 and -1.0% in BMD in all study groups compared to baseline; the greater improvement was seen in total femur BMD after two years of monotherapy (0.79%). Although with limitations, this stabilization might be considered a clinically relevant outcome because BMD is expected to decrease with age, mainly after three years (Mazess 1982; Bonnick 2004; Parkinson and Fazzalari 2013). The lack of a control group maintaining triple antiretroviral therapy prevents check the

evolution of BMD over the same periods of time and compare with monotherapy.

Since tenofovir-containing regimens have been mostly related to increased rates of bone demineralization (Gallant *et al.,* 2004; Martin *et al.,* 2009; Stellbrink *et al.,* 2010), the stabilization of bone loss achieved in our patients might have been induced by the withdrawal of tenofovir. In fact, a greater increase in BMD was seen in general one and two years, but not three years, after starting monotherapy in the subgroup of patients who interrupted tenofovir, compared with those who had not receive this drug. However, no significant differences were found between patients who received tenofovir from those who did not. The low number of patients does not allow differences to be disclosed.

Although controversial, bone turnover and bone loss in patients under PI regimens seem to be more significant than under NNRTIs (Duvivier *et al.,* 2009). This means that a possible negative effect of PI on bone mineralization might avoid finding a greater improvement of BMD after the nucleoside interruption. In our study, no statistically significant differences were found between patients previously receiving a PI-based regimen and those on a NNRTI-based combination. Nonetheless, a more evident decrease of BMD was seen among those patients who switched from a NNRTI regimen to a PI monotherapy, suggesting the negative effect of PI on BMD already published (Duvivier *et al.,* 2009). The reason for the lack of differences is probably, again, the small number of patients in each group.

Finally, overall, only patients receiving DRV/r showed discrete increments of BMD, statistically significant in femur after 2 years, while those on LPV/r did not.

Once again, this result may not be considered conclusive because no statistically differences were seen between groups possibly due to be a small cohort of subjects. Further studies involving large number of patients are needed to confirm these results, not only about the impact of withdrawing tenofovir but also the effect of starting a PI. However, despite limitations, data emerged from this study adds further information about effects of PI monotherapies on bone metabolism beyond two years of follow-up.

Other limitation of the study is the lack of information on smoking habits or of exercise, as well as the levels of vitamin D, due to the retrospective nature of the study".

In conclusion, the monotherapy treatment with ritonavir-boosted protease inhibitor (both LPV/r and DRV/r) during one, two, or three years leads to the stabilization of BMD in HIV-infected patients with long-term virological suppression. However, prospective comparative studies are necessary to define the exact role of protease inhibitors on BMD.

ACKNOWLEDGMENTS

Conflicts of interest: AB has received fees from VIIV, Jansen Cilag, Abbott, and Roche; PE has received personal fees from VIIV, Jansen Cilag, and Abbott; EN and BC have received personal fees from VIIV, Merck, Jansen Cilag, Abbott, Roche, and Boehringer Ingelheim. The remaining authors report no competing interests. No financial support was received for this study.

REFERENCES

Arribas J.R., Doroana M., Turner D., Vandekerckhove L. and Streinu-Cercel A. (2013). Boosted protease inhibitor monotherapy in HIV-infected adults: outputs from a pan-European expert panel meeting. *AIDS Res. Ther.* **10**, 3.

Bolland M.J., Grey A., Horne A.M., Briggs S.E., Thomas M.G., et al. (2012). Stable bone mineral density over 6 years in HIV-infected men treated with highly active antiretroviral therapy (HAART). *Clin. Endocrinol.* (Oxf). **76**, 643-648.

Bolland M.J., Wang T.K., Grey A., Gamble G.D., Reid I.R. (2011). Stable bone density in HAART-treated individuals with HIV: a meta-analysis. *J. Clin. Endocrinol. Metab.* **96**, 2721-2731.

Bonjoch A., Figueras M., Estany C., Perez-Alvarez N., Rosales J., et al. (2010). High prevalence of and progression to low bone mineral density in HIV-infected patients: a longitudinal cohort study. *Aids.* **24**, 2827-2833.

Bonnick S. (2004). The effect of Age, Disease, Procedures, and Drugs on bone density. In: . Bone densitometry in clinical practice. *Human Press*. 127-128.

Brown T.T., McComsey G.A., King M.S., Qaqis R.B, Bernstein B.M., et al. (2009). Loss of bone mineral density after antiretroviral therapy initiation, independent of antiretroviral regimen. *J. Acquir. Immune Defic. Syndr.* **51**, 554-561.

Brown T.T., Qaqish R.B. (2006). Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. *Aids.* **20**, 2165-2174.

Bruera D, Luna N., David D.O., Bergoglio L.M., Zamu-

dio J. (2003). Decreased bone mineral density in HIV-infected patients is independent of antiretroviral therapy. *Aids*. **17**, 1917-1923.

Cazanave C., Lawson-Ayayi S., Barthe N., Uwamaliya-Nziyumvira B., Kpozehouen A., et al. (2010). Changes in bone mineral density: 2-years of follow up of the ANRS CO3 Aquitaine Cohort. 17th Conference on Retroviruses and Opportunistic Infections, San Francisco.

Connolly N.C., Riddler S.A. and Rinald C.R. (2005). Proinflammatory cytokines in HIV disease-a review and rationale for new therapeutic approaches. *AIDS Rev*. **7**, 168-180.

Cotter E.J., Ip H.S., Powderly W.G., Doran P.P. (2008). Mechanism of HIV protein induced modulation of mesenchymal stem cell osteogenic differentiation. *BMC Musculoskelet Disord*. **9**, 33.

Cozzolino M., Vidal M., Arcidiacono M.V., Tebas P., Yarasheski K.E., et al. (2003). HIV-protease inhibitors impair vitamin D bioactivation to 1,25-dihydroxyvitamin D. *Aids*. **17**, 513-520.

Duvivier C., Kolta S., Assoumou L., Ghosn J., Rozenberg S., et al. (2009). Greater decrease in bone mineral density with protease inhibitor regimens compared with nonnucleoside reverse transcriptase inhibitor regimens in HIV-1 infected naive patients. *Aids*. **23**, 817-824.

Fernandez-Rivera J., Garcia R., Lozano F., Macias J., Garcia-Garcia J.A., et al. (2003). Relationship between low bone mineral density and highly active antiretroviral therapy including protease inhibitors in HIV-infected patients. *HIV Clin. Trials*. **4**, 337-346.

Fox J., Peters B., Prakash M., Arribas J., Hill A., et al. (2011). Improvement in vitamin D deficiency following antiretroviral regime change: Results from the MONET trial. *AIDS Res. Hum. Retroviruses*. **27**, 29-34.

Gallant J.E., Staszewski S., Pozniak A.L., DeJesus E., Suleiman J.M., et al. (2004). Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. *JAMA*. **292**, 191-201.

Grund B., Peng G., Gibert C.L., Hoy J.F., Isaksson R.L., et al. (2009). Continuous antiretroviral therapy decreases bone mineral density. *Aids*. **23**, 1519-1529.

Hoy J., Grund B., Roediger M., Ensrud K.E., Brar I., et al. (2013). Interruption or deferral of antiretroviral therapy reduces markers of bone turnover compared with continuous therapy: The SMART body composition substudy. *J. Bone Miner. Res*. **28**, 1264-1274.

Kanis J.A. (1994). Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. WHO Study Group. *Osteoporos. Int*. **4**, 368-381.

Martin A., Bloch M., Amin J., Baker D., Cooper D.A., et al. (2009). Simplification of antiretroviral therapy with tenofovir-emtricitabine or abacavir-Lamivudine: a randomized, 96-week trial. *Clin. Infect. Dis*. **49**, 1591-1601.

Martin A., Smith D.E., Carr A., Ringland C., Amin J., et al. (2004). Reversibility of lipoatrophy in HIV-infected patients 2 years after switching from a thymidine analogue to abacavir: the MITOX Extension Study. *Aids*. **18**, 1029-1036.

Mathis S., Khanlari B., Pulido F., Schechter M., Negredo E., et al. (2011). Effectiveness of protease inhibitor monotherapy versus combination antiretroviral maintenance therapy: a meta-analysis. *PLoS One*. **6**, e22003.

Mazess R.B. (1982). On aging bone loss. *Clin. Orthop. Relat. Res*. **165**, 239-252.

McComsey G., D. Kitch, E. Daar, C. Tierney, N. Jahed, et al. (2010). Bone and Limb Fat Outcomes of ACTG A5224s, a Substudy of ACTG A5202: A Prospective, Randomized, Partially Blinded Phase III Trial of ABC/3TC or TDF/FTC with EFV or ATV/r for Initial Treatment of HIV-1 Infection. 17TH Conference on Retroviruses and Opportunistic Infections, San Francisco.

Mocroft A., Phillips A.N., Soriano V., Rockstroh J., Blaxhult A., et al. (2005). Reasons for stopping antiretrovirals used in an initial highly active antiretroviral regimen: increased incidence of stopping due to toxicity or patient/physician choice in patients with hepatitis C coinfection. *AIDS Res. Hum. Retroviruses*. **21**, 743-752.

Nolan D., Upton R., McKinnon E., John M., James I., et al. (2001). Stable or increasing bone mineral density in HIV-infected patients treated with nelfinavir or indinavir. *Aids*. **15**, 1275-1280.

Paccou J., Viget N., Legrout-Gerot I., Yazdanpanah Y., Cortet B. (2009). Bone loss in patients with HIV infection. *Joint Bone Spine*. **76**, 637-641.

Parkinson I.H., Fazzalari N.L. (2013). Characterisation of Trabecular Bone Structure. Skeletal Aging and Osteoporosis. *Biomechanics and Mechanobiology*. M.J. Silva. New York, Springer. 31-46.

Sharma A., Flom P., Weedon J. and Klein R. (2010). Longitudinal analysis of bone mineral density in aging men with or at risk for HIV. 17TH Conference on Retroviruses and Opportunistic Infections.

Spire B., Marcellin F., Cohen-Codar I., Flandre P., Boue F., et al. (2008). Effect of lopinavir/ritonavir monotherapy on quality of life and self-reported symptoms among antiretroviral-naive patients: results of the MONARK trial. *Antivir. Ther*. **13**, 591-599.

Stellbrink H.J., Orkin C., Arribas J.R., Compston J., Gerstoft J., et al. (2010). Comparison of changes in bone density and turnover with abacavir-lamivudine versus tenofovir-emtricitabine in HIV-infected adults: 48-week results from the ASSERT study. *Clin. Infect. Dis*. **51**, 963-972.

Thomas J., Doherty S.M. (2003). HIV infection--a risk factor for osteoporosis. *J. Acquir. Immune Defic. Syndr*. **33**, 281-291.