Changes in bone mineral density in HIV-positive, virologically suppressed patients switching to lamivudine/dolutegravir dual therapy: preliminary results from clinical practice

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SUMMARY

Bone toxicity is a well-known side effect of several antiviral agents. In a cohort of virologically suppressed HIV-infected patients, we investigated the effects of a lamivudine/dolutegravir dual therapy on bone mineral density (BMD). We observed a significant improvement in lumbar spine BMD as well as T-score after 12 months of observation with concomitant bisphosphonate therapy independently predicting a greater improvement.
These preliminary data show a favorable effect of this 2-drug regimen on bone health.

Keywords: HIV, dolutegravir, lamivudine, bone density, osteoporosis.

INTRODUCTION

Bone toxicity is a growing problem in HIV patients, given the increasing life expectancy; in particular, decrease in bone mineral density (BMD) and higher rate of osteoporosis and pathological fractures have been observed in HIV-infected patients, due to both the direct effect of the systemic inflammation caused by viral activity and to factors related to certain antiviral agents, such as protease inhibitors (PIs) and tenofovir disoproxil fumarate (TDF) [1, 2]. As recent works show, NRTI-sparing, and particularly TDF-sparing, PI-based two-drug regimens, while maintaining virological suppression in treatment-experienced individuals, have also shown an improvement in BMD and a reduction in bone turnover markers; data on integrase inhibitors-based simplification regimens are promising and a recent study by McComsey et al. showed an improvement in BMD and bone turnover bio-markers in patients switching from a TDF-containing regimen to a 2-drug regimen of dolutegravir and rilpivirine [3-5]. Dolutegravir, a second-generation integrase inhibitor, has showed high efficacy in two-drug regimens and clinicians have recently focused on the effectiveness and the favorable tolerability profile of its association with lamivudine. However, while different authors have demonstrated good virological control and an improvement in lipid profile in patients switching to lamivudine plus dolutegravir, studies about the correlation of this regimen with bone toxicity are still lacking [6, 7].

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PATIENTS AND METHODS

We performed a retrospective, observational study, in which we enrolled virologically suppressed (defined as HIV-RNA <50 copies/mL) HIV-positive patients switching to lamivudine plus dolutegravir; patients who discontinued study regimen during the observation period were not included. All participants performed dual-energy x-ray absorptiometry (DEXA) at time of switch and at week 48 of follow-up; areal BMD (g/cm2) was measured at the lumbar spine (L2 - L4) and at the femoral neck and all measurements were performed by the same operator, through a Hologic device (QDR 4500A, Hologic Inc., Bedford MA, USA). Osteoporosis was defined as a value of T-score inferior to -2.5 at any site, osteopenia as a T-score between -1 and -2.49 [8]. Student's t-test was used to compare means at baseline and week 48; we assessed predictors of changes by linear regression. Multivariable models were adjusted for Body Mass Index (BMI), HCV-coinfection and smoking status whether or not significant at univariable analyses. Further adjustment was made for significant parameters ($p<0.05$) at univariable analyses. All patients signed informed consent to allow data recording for an observational clinical study.

RESULTS

Twenty patients were analyzed, prevalently males (16, 80%), with a median age of 55.6 years (interquartile range [IQR] 45.7 to 64.0) and a median of 10.9 years (IQR 4.7 to 16.3) of ART exposure. Ten patients (50%) were active smokers, 3 (15%) had anti-HCV antibodies while nineteen (95%) had taken TDF previously in their life, with a median time of exposure of 4.4 years (IQR 2.1 to 8.6). Full patient characteristics are shown in Table 1. At baseline, seventy-five percent of our population had a pathologic BMD value: 6 patients (30%) had osteoporosis at least at one site, while 9 (45%) were diagnosed with osteopenia. At Week 48 we observed a mean increase in lumbar spine BMD of 4.3% (+0.03 g/cm2, 95% Confidence Interval [CI] 0.01 to 0.05, p=0.001). At multivariate analysis, a greater improvement in spine BMD was independently associated to concomitant use of bisphosphonate (vs no bisphosphonate therapy, mean difference in change +0.04 g/cm2, 95%CI 0.01 to 0.07, p=0.023) whilst we observed a negative relationship with time of TDF exposure (per 1 month longer, -0.001 gr/cm2, 95%CI -0.001 to 0.001, p=0.023), after adjusting for osteopenia or osteoporosis diagnosis at baseline and zenith HIV-RNA value (Table 2a). After 12 months of

Table 1 - Patients' characteristics at baseline (N=20).

Males, n (%)	16 (80%)
Age (years), median (IQR)	55.8 (45.7; 64.0)
Risk factors for HIV, n (%) - MSM - Heterosexual - IDUs	 13 (65%) 4 (20%) 3 (15%)
Caucasians, n (%)	19 (95%)
Anti-HCV positive, n (%)	3 (15%)
CDC Stage C, n (%)	6 (30%)
Time since HIV diagnosis (years), median (IQR)	14.0 (6.30; 19.30)
Nadir CD4+ cell count (cells/mm^3), median (IQR)	225.5 (107.0; 272.2)
Zenith viral load (log10 copies/mL), median (IQR)	4.49 (3.99; 5.64)
Time on cART (years), median (IQR)	10.9 (4.7; 16.3)
Previous use of TDF, n (%)	19 (95%)
Months on TDF, median (IQR)	52.5 (25.3; 102.7)
Pre-switch therapy, n (%) - PI-based dual therapy - 2NRTI + NNRTI - 2NRTI + bPI - 2NRTI + INI	 8 (40%) 7 (35%) 3 (15%) 2 (10%)
Reasons for switch to lamivudine/dolutegravir, n (%) - Proactive switch - Dyslipidemia - Bone toxicity - Other toxicity	 5 (25%) 5 (25%) 6 (30%) 4 (20%)
Osteoporosis at any site, n (%)	6 (30%)
Osteopenia at any site, n (%)	9 (45%)
Medications, n (%) - Biphosphonates - Vit. D supplementation	 7 (35%) 9 (45%)
Smokers, n (%)	10 (50%)
Body Mass Index, median (IQR)	24.3 (22.6; 25.7)
Lumbar spine BMD, median (IQR)	0.92 (0.76; 1.07)
Lumbar spine T-score, median (IQR)	-1.50 (-2.77; -0.20)
Lumbar spine Z-score, median (IQR)	-0.95 (-1.70; 0.02)
Femur neck BMD, median (IQR)	0.74 (0.65; 0.87)
Femur neck T-score, median (IQR)	-1.40 (-2.17; -0.45)
Femur neck Z-score, median (IQR)	-0.40 (-1.47; 0.20)

follow-up, we also observed a statistically significant increase in both T-score (+0.28, 95%CI 0.14 to 0.43, p=0.001) and Z-score (+0.29, 95%CI 0.16 to 0.43, p<0.001) at lumbar spine. The increase in T-score was similarly predicted by the use of bisphosphonate (p=0.013) while it was reversely associated with baseline spinal BMD (per 1 g/cm2 more, -0.94 g/cm2, 95%CI -1.85 to -0.03, p=0.021) and zenith HIV-RNA (per 1 log unit more, -0.13 g/cm2, 95%CI -0.20 to -0.05, p=0.004) after adjusting for the presence of osteopenia and osteoporosis at baseline, months of exposure to TDF and baseline Z-score (Table 2b). No predictors of Z-score changes were found. We also registered an improvement of 2.7% in total femur BMD, although not significant (+0.02 g/cm2, p=0.079). At week 48, 4 patients (20%), all of whom presented osteoporosis at baseline, maintained the condition of osteoporosis, while 11 patients (55%) had osteopenia, including 2 patients that were diagnosed with osteoporosis at baseline.

DISCUSSION

To the best of our knowledge, this is the first study evaluating the effects on BMD of a two-drug regimen of lamivudine plus dolutegravir, a regimen that has shown promising results as a switch strategy with its safety profile and good tolerability [9]. Our data show an improvement in bone mineral density at both lumbar spine and femoral neck after 12 months, with a significant change in bone density, T-score and Z-score at the lumbar site. Spine has been discussed to be the

Table 2a - Factors associated to lumbar spine BMD improvement at univariate and multivariate regression analysis.

Variables	*Univariate analysis B (95% CI)*	*p*	*Multivariate analysis B (95% CI)*	*p*
Osteoporosis at baseline (versus negative)	0.041 (0.012; 0.069)	0.007	-0.005 (-0.051; 0.041)	0.818
Osteopenia at baseline (versus negative)	-0.031 (-0.060; -0.020)	0.036	-0.005 (-0.032; 0.022)	0.701
Bisphosphonate use (versus no therapy)	*0.040 (0.012; 0.067)*	*0.007*	*0.038 (0.006; 0.069)*	*0.023*
Time of TDF exposure (per 1 month more)	*-0.001 (-0.001; -0.001)*	*0.011*	*-0.001 (-0.001; -0.001)*	*0.038*
BMI at baseline (per 1 unit more)	-0.001 (-0.007; 0.004)	0.603	0.002 (-0.003; 0.007)	0.420
Smoking habit (versus no smoking)	0.008 (-0.024; 0.039)	0.619	-0.016 (-0.045; 0.013)	0.256
Hepatitis C Ab positive (versus negative)	-0.005 (-0.049; 0.040)	0.828	0.022 (-0.027; 0.072)	0.338
Zenith HIV-RNA (per 1 log unit more)	-0.014 (-0.026; -0.002)	0.023	-0.009 (-0.019; 0.001)	0.067

Table 2b - Factors associated to lumbar spine T-score improvement at univariate and multivariate regression analysis.

Variables	*Univariate analysis B (95% CI)*	*p*	*Multivariate analysis B (95% CI)*	*p*
Osteoporosis at baseline (versus negative)	0.421 (0.150; 0.691)	0.004	-0.253 (-0.849; 0.343)	0.367
Osteopenia at baseline (versus negative)	-0.309 (-0.593; -0.025)	0.035	-0.202 (-0.509; 0.106)	0.175
Bisphosphonate use (versus no therapy)	*0.418 (0.163; 0.673)*	*0.003*	*0.533 (0.140; 0.926)*	*0.013*
Time of TDF exposure (per 1 month more)	-0.004 (-0.007; -0.001)	0.019	-0.001 (-0.003; 0.001)	0.341
BMI at baseline (per 1 unit more)	-0.014 (-0.067; 0.039)	0.580	-0.019 (-0.070; 0.032)	0.414
Smoking habit (versus no smoking)	0.124 (-0.191; 0.440)	0.417	-0.210 (-0.491; 0.070)	0.120
Hepatitis C Ab positive (versus negative)	-0.054 (-0.494; 0.385)	0.798	0.209 (-0.221; 0.638)	0.288
Zenith HIV-RNA (per 1 log unit more)	*-0.155 (-0.266; -0.043)*	*0.009*	*-0.127 (-0.204; -0.050)*	*0.004*
Baseline lumbar spine BMD (per 1 gr/cm^2 more)	*8.934 (1.627; 16.241)*	*0.043*	*-0.943 (-1.851; -0.035)*	*0.021*
Baseline lumbar spine Z-score (per 1 unit more)	-0.115 (-0.225; -0.005)	0.042	0.228 (-0.035; 0.491)	0.082

primary site of TDF and PIs toxicity regarding BMD decrease, therefore an increase in lumbar spine bone density following the switch to the study regimen is expected, since data from the literature suggest that drug-related bone toxicity is commonly reversible [10, 11]. The modest entity of the improvement observed in hip and lumbar spine BMD is not surprising, since the detrimental effect of certain ART regimens on BMD has been reported to slightly decrease and stabilize after 1 or 2 years [12].

As expected, length of exposure to TDF revealed to be a negative predictor for BMD improvement, while previous use of PIs did not [13]. Also, patients with higher HIV viral load zenith had a lower improvement in BMD, showing that the effect of exposure to a higher viremia and thus to higher rates of inflammation has lasting impact on bone tissue. We observed no correlation between bone density changes and BMI, Vitamin D levels, age or smoking habit in our population, while current use of bisphosphonates predicted a better improvement in bone density; these results are in line with recent works showing that the use of bisphosphonates is superior to TDF-switching in improving BMD and reducing the rate of fractures in HIV-positive adults [14]. Of note, no virological failure occurred during the observation period. Our study presents some limitations including that it is a single-center study with a limited sample size and it lacks a control group. A selection bias is also a possibility since about one third of the patients switched to the study regimen for bone toxicity, so our population may present a higher rate of osteopenia than the general population. Prospective studies, with longer follow-up and a control group are needed to fully generalize our conclusions. Moreover, given the ongoing widespread use of tenofovir-alafenamide fumarate (TAF), a complete study comparing a TAF-based triple-drug combination against this NRTI-reducing regimen may be useful to confirm our findings. Nevertheless, these preliminary data suggest that a two-drug regimen of lamivudine plus dolutegravir has a favorable impact on bone health.

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AC managed patients, collected data and wrote the manuscript. AD managed patients, collected data and helped to draft the manuscript. APL managed patients, performed DEXA scans and collected data. GB and AB contributed participants' data and revised the paper, providing substantial improvement. AD, RG, AE, DM helped in collecting patients' data. SB and FL managed patients. SDG conceived and coordinated the study and critically revised the manuscript. All authors read and approved the final manuscript.

Declarations of interest and source of funding

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