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Impact on bone mineral density after two years of switching to four dolutegravir-based triple or dual regimens

Piscaglia M[1], Gallazzi I[1], Restelli S[1], Baldin GM[2], Paladini L[1], Cossu MV[1], DiGiambenedetto S[2], Rizzardini G[1] and Capetti AF[1]

[1]1st Division of Infectious Diseases, ASST Fatebenefratelli-Sacco, Milano, [2]2nd Division of Infectious Diseases, "Policlinico Universitario Agostino Gemelli" Hospital, Roma

The Doludubone Group

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Background

While several studies describe the impact of protease inhibitors (PIs), tenofovir (TDF, TAF) and raltegravir (RAL) on bone mineral density (BMD), data on dolutegravir (DTG) is limited to the substudy of the SWORD trials [1], on the association of DTG with rilpivirine (RPV) and on a Spanish observation on the switch from PIs [2]. Having retrospectively analysed all the patients who consecutively took at least once DTG from November 2014 to April, 2017 (DOLUTILITY Study), we sook to describe such aspect as well.

Methods

Of the 1039 subjects of the DOLUTILITY study, we selected those who had had a DEXA scan within 6 months prior to switching to DTG and a control 96 weeks ± 4 weeks later with the same HologicTM machine and operator. The DTG plus 3TC cohort, absent in our substudy, comes from a twin cohort from Rome within the ODOACRE study group, of which the DOLUTILITY study is part. Wilcoxon test was used for repeated analyses, and Mann Whitney test for non-parametric analyses.

Results

Only 83 subjects fitted the above specified criteria, and were divided by treatment regimen: 22 patients were on abacavir/lamivudine/dolutegravir (ABC/3TC/DTG), 21 on 3TC plus DTG, 20 on DTG plus boosted darunavir (bDRV) and 20 on DTG plus TFV/FTC (initial 9 – 15 months on tenofovir diisoproxil, TDF, then switched to alafenamide, TAF, plus emtricitabine, FTC). The four groups differed by time from known HIV-1 infection, CDC stage C, time on antiretroviral therapy (ART), HCV coinfection and past use of TDF, with DTG plus bDRV and DTG plus TFV/FTC being the most vulnerable groups. The ABC/3TC/DTG group showed significant improvement at both hip and spine levels, while subjects on DTG plus 3TC benefited only at the spine level, those on DTG plus bDRV beyond the BMD gain at the spine also showed some recovery at the hip level, and finally, despite having switched in the second half period to TAF, the DTG plus TFV/FTC group worsened at both levels. Data are presented in Table 1. The q-fracture and Frax score slightly worsened in all, mainly as an effect of ageing and accumulating comorbidities. The analysis of concordance of radiometric parameters with plasma colecalciperol levels failed to indicate a significant relationship.

Conclusions

Triple and dual regimens based on DTG and excluding TDF lead to significant gains in BMD. Even the simplification of salvage regimens to DTG plus bDRV, though maintaining a PI, yielded some improvement at the spine and hip level.

	DTG/ABC/3TC (N = 22)	DTG + 3TC (N = 21)	DTG + bDRV (N = 20)	DTG + TFV/FTC (N = 20)	p
FEMALE, N (%)	9 (41)	4 (19)	10 (50)	9 (45)	0,22
AGE, AVG (SD)	54 (7,43)	56 (12)	54,8 (6,5)	52,6 (7,37)	0,38
CAUCASIAN, N (%)	22 (100)	21 (100)	17 (85)	19 (95)	0,08
SMOKERS, N (%)	6	11 (52,4)	12 (60)	11 (55)	0,14
HCV COINFECTION, N (%)	4 (18,2)	3 (14,3)	11 (55)	7 (35)	0,018*
CDC C, N (%)	5 (22,7)	6 (28,6)	13 (65)	15 (75)	0,0007*
YEARS FROM DIAGNOSIS, AVG (SD)	17 (8,39)	13,7 (7,6)	20,7 (8,6)	20,1 (5,83)	0,019*
YEARS OF HAART, AVG (SD)	13,45 (5,95)	11,0 (6,7)	17,4 (6,4)	16,1 (5,6)	0,007*
TDF IN THERAPEUTICAL HISTORY, N (%)	18 (81,8)	19 (90,5)	18 (90)	19 (95)	0,57
TDF IN LAST REGIME, N (%)	9 (40,9)	10 (47,6)	17 (85)	19 (95)	0,0002*
BPI IN LAST REGIME, N (%)	13 (59)	10 (47,6)	11 (55)	6 (30)	0,25
BASAL LUMBAR T-SCORE , AVG (SD)	-1,02 (1,15)	-1,43 (1,39)	-1,55 (073)	-1,41 (0,65)	0,38
BASAL VITAMIN D, AVG (SD)	37,7 (13,7)	25,7 (15)	35,5 (19,6)	28,5 (11,3)	0,15

Background

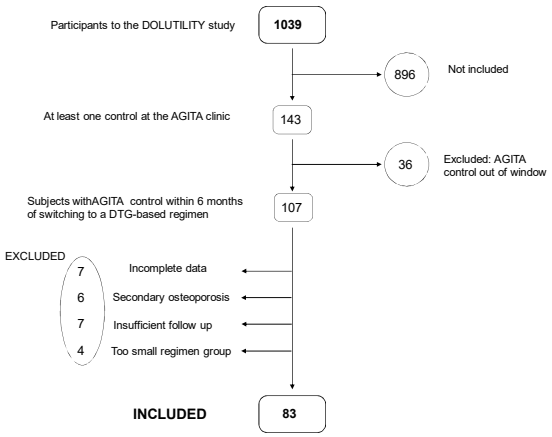
Osteopenia and osteoporosis are conditions that are acquiring greater and greater relevance in cohorts of HIV-infected patients. The mean age of HIV outpatients is progressively increasing and so is the prevalence of osteoporosis, which is currently about 3 greater that that of the general population. Such situation is caused either by the virus' direct action on bone tissue and by the influence of antiretrovirals. In detail, NRTIs reduce BMD by means of mitochondrial toxicity; PIs induce osteoclastic activity; and patricularly TDF has an important impact, acting at the kidney level, hampering phosphate and calcium reabsorption and reducing vitamin D activation. The effect of DTG has not yet been clarified, the only data coming from the SWORD study and by a spanish study.

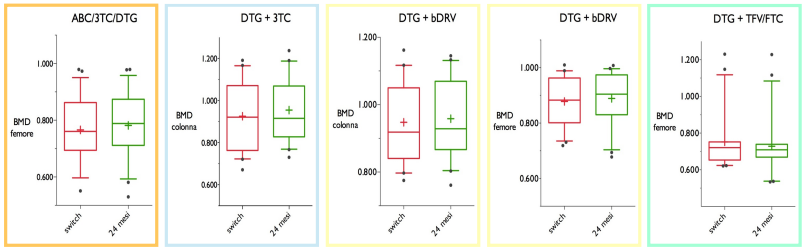
Methods

Subjects taking various DTG-base regimens have been assessed comparing spine and femur BMD at DEXA scan (Hologic™) at baseline and after 24 (+- 6) months. Furthermore, some bone turnover markers (BTM) were assessed as well as the 10-year risk of bone fracture by Frax® and Q-Fracture. Normal variables were compared by t-test for paired data, while non-gaussian variables were compared by the Wilcoxon log rank test.

Results

Of the1039 patients included in the DOLUTILITY study we have selected 143 who had been sent by their physician to a clinic specific for the study of antiretroviral-related toxicities (AGITA), including DEXA scan. Only 107 of these had a baseline evaluation within 6 months of switching to a DTG-based regimen, while additional 24 had other exclusion criteria. The remaining 83 subjects were divided in 4 groups based on their treatment regimen: ABC/3TC/DTG (n = 22), DTG + 3TC (n = 21), DTG + bDRV (n = 20), DTG + TFV/FTC (n = 20; i primi 9-15 mesi con TDF poi switch a TAF).
All groups except DTG + TFV/FTC TDF have shown significant improvement of BMD at least at one site, the bDRV group in both. The group that continued TDF, despite switching to TAF after about one year had worsening results. Comparing BTMs failed to show statistically or clinically significant differences, while the 10-year risk of fracture, increasing in all groups, shows that in some, the increase in the FRAX® score (which takes into account the BMD) is considerably lower than the Q-Fracture score.





+ 2,04%
switch: 0,766 (0,120)
24 months: 0,782 (0,121)
IC: [0,009; 0,022]
p < 0,0001

+ 3,17%
switch: 0,925 (0,161)
24 months: 0,955 (0,149)
IC: [0,014; 0,045]
p < 0,001

+ 1,14%
switch: 0,948 (0,121)
24 months: 0,958 (0,116)
IC: [0,003; 0,018]
p < 0,02

+ 1,26%
switch: 0,878 (0,088)
24 months: 0,889 (0,093)
IC: [0,0009; 0,021]
p < 0,05

- 3,12%
switch: 0,721 [0,086]
24 months: 0,709 [0,05]
median diff: -0,0225
p < 0,05

	ABC/3TC/DTG		DTG + 3TC		DTG + BDRV		DTG + TFV/FTC	
Q-FRACTURE	15,7% (0,8)	+0,4%	15,2% (0,91)	+0,36%	16,2% (0,97)	+0,93%	15,3% (0,8)	+0,53%
FRAX®	15,3% (0,44)	+0,095%	14,6% (0,5)	+0,1%	15,2% (0,55)	+0,48%	14,1% (0,37)	+0,325%

Conclusions

Despite the retrospective design and the small sample size, that limit the quality of evidence of our observations, our data suggest that the combinations containing DTG and excluding TFV improve bones' health in patients in a time frame of 2 years. Prospective randomized trials on larger sample size are needed to quantify the extent of such improvement in a more precise manner. However our data allow us to consider these DTG-based dual regimens as well as the combination of DTG plus abacavir/3TC as reliable options for therapeutic simpification in subject with osteoporotic comorbidity.

References

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