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Tenofovir replacement in patients with osteoporosis increased sclerostin levels

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BACKGROUND

Tenofovir is one of the antiretroviral drugs involved in accelerated bone mineral density (BMD) loss. However, many patients with osteopenia or osteoporosis are exposed to this drug for many years, and scare data are available about the potential benefit of interrupting tenofovir in case of decreased bone mineral density.

Since the mechanisms underlying these changes in bone density are not fully elucidated, we assessed changes in bone turnover markers and 3 proteins involved in bone regulation in a group of patients who switched tenofovir.

STUDY PATIENTS AND RANDOMIZATION

Inclusion criteria:

- Patients with chronic HIV-1 infection,
- Under a tenofovir-containing regimen,
- Viral suppression,
- Low BMD diagnosed by DXA.

The study was approved by the Institutional Ethics Committee of the coordinating center and the local health authorities (NCT 00795483).

Randomization (1:1)

→ Switch from TDF to abacavir n=26

→ Continue with TDF n=28

Bone markers , RANKL, osteoprotegerin and sclerostin

→ Switch from TDF to abacavir n=20

→ Continue with TDF n=24

DESIGN and OBJECTIVES

We recently published changes in BMD in 54 virologically suppressed patients during a tenofovir-containing regimen and criteria for osteopenia/osteoporosis who were randomized to switch from tenofovir to abacavir (n=26) or to continue with tenofovir (n=28). Forty-eight weeks after switching to abacavir, hip BMD improved by 2.1% (95% CI, –0.6, 4.7) (p=0.043). (JAC 2014,69:3368-71)

Now we present changes from baseline to week 48 in bone markers in 44 of these patients who had stored serum:

- Resorption marker: C-terminal telopeptide of collagen type 1 (CTX),
- Bone formation markers; **osteocalcin** and procollagen type 1 N propeptide (P1NP).

Additionally, we assessed changes in circulating levels of 3 proteins involved in bone regulation:

- **Osteoprotegerin**,
- Receptor activator for nuclear factor K B ligand (RANKL) and
- **Sclerostin**, a selective regulator of bone formation through the Wnt pathway, no previously explored in this population.

Statistical analysis: To compare between study groups, chi-Squared or Fisher and Student t tests were performed according to each variable distribution. Pearson's correlation coefficients were calculated to evaluate the linear relations between the levels of markers (at baseline and week 48, and the difference between them) and baseline PTH and lumbar and femoral BMD.

Table 1. Baseline characteristics of patients

Both groups were well balanced except P1NP, which baseline levels were higher in the abacavir group than in the tenofovir group (p=0.013).

	Abacavir group (n=20)	Tenofovir group (n=24)
Age (years)	48.5 (7.1)	49.3 (8.8)
Gender, male (%)	85	79.2
Body mass index	24.6 (3.0)	22.2 (3.1)
Caucasian (%)	90	83.3
HIV-related data		
HCV coinfection (%)	10	25
Route of HIV transmission (%)		
Men who have sex with men	55	42
Intravenous drug use	15	25
Heterosexual relations	15	21
Cumulative exposure, years		
Protease inhibitor	4.6 (3.3)	5.8 (5.5)
NNRTI	4.0 (3.9)	4.9 (3.6)
Tenofovir	4.5 (2.0)	5.1 (2.8)
Baseline antiretroviral therapy (%)		
Protease inhibitor	30	46
NNRTI	70	54
Nadir CD4 cell count/mm^3	196 (133)	226 (141)
CD4 cell count/mm^3	585 (199)	567 (247)
Biochemical parameters		
25 hydroxyvitamin D, ng/mL	19.7 (7.9)	20.1 (11.4)
PTH, pg/mL	49.6 (25.9)	53.8 (11.3)
TSH, µUI/mL	1.9 (0.7)	1.8 (0.7)
Bone turnover markers		
CTX, ng/mL	0.543 (0.495)	0.424 (0.421)
Osteocalcin, ng/mL	23.72 (22.20)	21.91 (18.00)
P1PN, ng/mL	54.68 (54.52)	38.81 (40.92)
Bone regulators		
Osteoprotegerin, pmol/L	2.47 (2.19)	3.36 (2.84)
Sclerostin, pmol/L	29.53 (27.91)	29.99 (27.18)

All data are expressed as mean (SD) unless otherwise specified. PTH, parathyroid hormone; TSH, thyroid-stimulating hormone; CTX, C-terminal telopeptide of collagen type 1; P1NP, procollagen type 1 N propeptide.

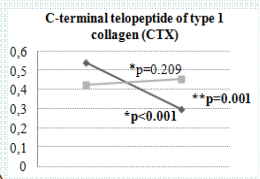
RESULTS

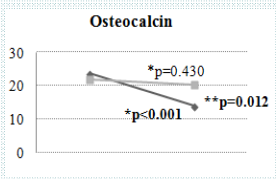
Figure 1. Changes from baseline to week 48 in mean (SD) bone markers (expressed as ng/mL)

*In the tenofovir group:
- CTX, from 0.424 (0.421) to 0.456 (0.435) ng/mL (p=0.209),
- Osteocalcin, from 21.91 (18.00) to 20.45 (20.15) ng/mL (p=0.430),
- P1PN, from 38.81 (40.92) to 39.25 (39.42) ng/mL (p=0.919)).

*In the abacavir group:
- CTX, from 0.543 (0.495) to 0.301 (0.306) ng/mL (p<0.001),
- Osteocalcin, from 23.72 (22.20) to 13.95 (12.40) ng/mL (p<0.001),
- P1PN, from 54.68 (54.52) to 28.65 (27.48) ng/mL (p<0.001).

** Differences between groups at week 48 were significant for all three markers.





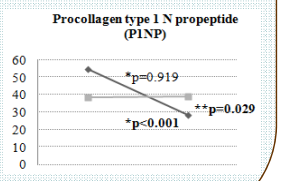


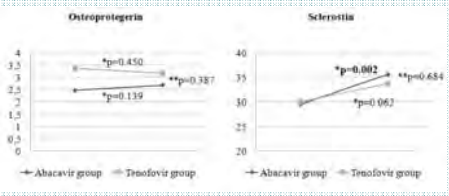
Figure 2. Changes from baseline to week 48 in mean (SD) osteoprotegerin and sclerostin (expressed as pmol/L).

*In the tenofovir group:
- Osteoprotegerin, from 3.36 (2.84) to 3.17 (3.00) pmol/L (p=0.450),
- Sclerostin, from 29.99 (27.18) to 33.71 (31.44) pmol/L (p=0.062).

*In the abacavir group:
- Osteoprotegerin from 2.47 (2.19) to 2.68 (2.50) pmol/L (p=0.139),
- Sclerostin, from 29.53 (27.91) to 35.56 (34.59) pmol/L (p=0.002).

** No significant differences in osteoprotegerin and sclerostin were detected between groups at week 48.

RANKL values were below the limit of detection (< 0.02 pmol/L) in all samples assessed, at baseline and at week 48.



CONCLUSIONS

Switching from tenofovir to abacavir seems to induce a positive effect on bone tissue since resulted in a reduction in markers of bone turnover while hip BMD increased 48 weeks after the switch (Negredo et al, JAC 2014,69:3368-71) . The switching also meant an increased circulating sclerostin levels, a factor that has been associated with better bone properties as density, microarchitecture and strength and decreased risk of fracture.However, a larger study is necessary to find out the possible association between sclerostin levels and BMD in this population.