Bone density, microarchitecture and tissue quality after 1 year of treatment with Tenofovir Disoproxil Fumarate

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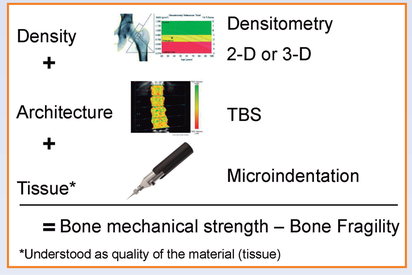
Background

Bone mineral density (BMD) measured by dual-energy x-ray absorptiometry (DXA) is used to assess bone health in HIV patients. DXA measures the amount of mineral, but not other key aspects of bone strength such as bone microarchitecture or bone quality. Besides DXA, other techniques as DXA-3D, Trabecular Bone Score (TBS) and in vivo microindentation directly measure cortical bone, trabecular microarchitecture and mechanical properties of bone at a tissue level, respectively (Fig. 1). TBS and in vivo microindentation has shown a better correlation than DXA with fracture risk. Hence, these techniques allow a more comprehensive assessment of bone health in those situations where BMD is not fully capturing the decrease in bone strength, and thus, the risk of fracture.

Figure 1. Clinical Measurement of Bone Strength



Objectives

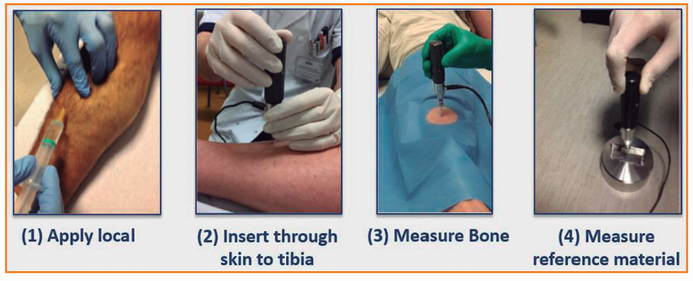
We tested the bone status after 1 year of treatment with Tenofovir Disoproxil Fumarate (TDF) using all 3 techniques.

Methods

Longitudinal study from January 2014 to June 2015; we included 49 HIV naïve patients that were to start antiretroviral treatment (ART). BMD by DXA (DXA-Hologic QDR4500SL) was measured at lumbar spine and the hip. DXA-3D was measured by specific software (Galgo Medical, Barcelona, Spain) on the DXA scans of the hip analyzing the changes in cortical and trabecular bone after 1-year of treatment. 3D-DXA provides a 3D-appearance model of the femoral shape and density onto the DXA projection to obtain a 3D subject-specific model of the femur of the patient and quantify the volumetric BMD (vBMD), bone volume (for trabecular and cortical regions) and cortical thickness distribution. Microindentation test were performed using a handheld Osteoprobe (Active-Life-Scientific, Santa Barbara, CA, US) at the anterior tibial face with a reference-point indenter device. Bone measurements were standardized as percentage of a reference value, expressed as bone material strength index (BMSi) units. The BMSi values correlated with bone tissue quality with better quality with higher values (Fig. 2)

The BMD, BMSi and DXA-3D measurements at baseline and after treatment were compared using paired samples Student's t-test. Multivariable (age, gender and body mass index-adjusted) linear regression models were fitted to study the association between TDF treatment and changes in BMD/TBS/DXA-3D/BMSi.

Figure 2. Bone Microindentation Technique, directly measures bone tissue quality.



Results

Thirty seven HIV patients were included (30 men (81%) and 7 women (19%). Median age at baseline was 38 years (IQR 31.7-44.2). Median time since diagnosis of HIV infection was 1 year (IQR 0-4). All included patients received Darunavir/ritonavir QD as main treatment with TDF + Emtricitavine as backbone. Baseline characteristics of all patients included are shown in table 1.

Changes in DMO (g/cm^2) were: lumbar spine (0.987±0.022 vs 0.953±0.022; p=0.001; -3.4%), total hip (0.936±0.026 vs 0.930±0.025; p=0.56; -0.3%) and femoral neck (0.823±0.021 vs 0.796±0.023; p=0.001; -2.7%) at baseline and after 1 year of TDF treatment respectively. When analyzing DXA-3D a statistically significant decrease of the integral vBMD (-11.9 mg/cm3, -3.0%, p=0.001) and cortical vBMD (-4.0 mg/cm3, -0.4%, p=0.004) was observed at the femoral neck. The cortex at the neck was also significantly thinner after 1-year of treatment (-0.05 mm, -3.2%, p = 0.006) with significantly significant difference for the trabecular vBMD. (Fig. 3)

Changes in bone mineral density and in bone turn-over and inflammatory markers are shown in table 2.

When analysing bone microarchitecture with TBS at spine level a significant reduction of TBS was observed (1.359±0.016 vs 1.322±0.01; p=0.0059; -2.5%).

On the other side, when studying the other component of bone strength, bone tissue quality with microindentation, the BMSi was significantly higher (85.5±1.1 vs 88.5±1.2; p=0.03; +3.8%), showing better bone material properties after 1 year of treatment with TDF. (Fig. 4)

Table 1. Characteristics of study population

	HIV naïve patients
N	37
Age	38 (9)*
Male (n, %)	30 (81)
Weight (kg)	69.1 (11.6)
BMI (kg/m^2)	23.6 (2.4)
Smoking (n, %)	
Never	17 (45.7)
Former	3 (8.5)
Current	17 (45.8)
Cigarettes (pack-year)	12.8 (14.2)
Alcohol (>20g/d)	0
Family History of Fracture (n, %)	4 (11)
Prevalent Spine Fractures (n, %)	0
Years since HIV diagnosis	2.8 (3.3)
nadir CD4 count (per ml)	378 (255)
Viral load at baseline (log$_{10}$)	4.5 (0.9)
Ever met AIDS criteria (%)	3 (23)

** Results are shown as mean (SD), unless indicated otherwise*

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Figure 4

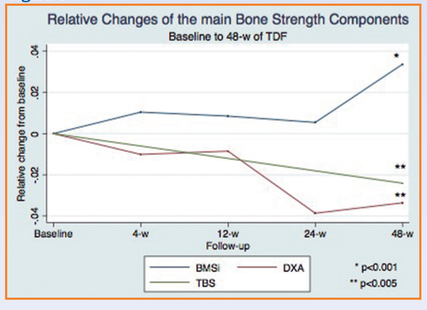

Figure 3. A. Statistically significant differences (p<0.05, paired samples t-test) in cortical thicknessbetween baseline and follow-up in mm (left) and as a percentage (right). B. Microindentation on tibia for assessment of bone quality, comparative box-plot after 6 months and 1 year of follow-up of TDF. C.TBS results and comparative after 1 year of follow up of TDF treatment

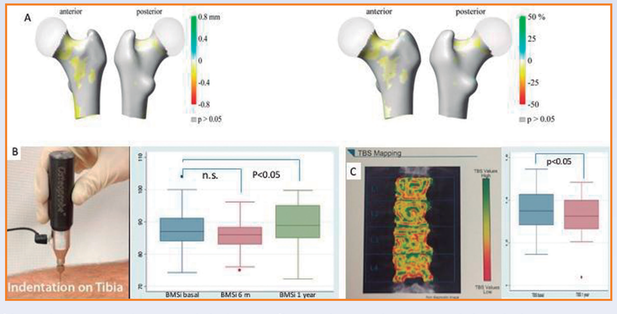

Table 2. Differences in Bone mineral density, and markers of bone turnover, calcium metabolism, inflammation and pro-coagulation between baseline and 48-weeks of TDF treatment

	Baseline		48-weeks		difference	p-value
Bone Mineral Density						
Femoral Neck BMD (g/cm^2)	0.823	(0.021)	0.796	(0.02)	-0.027(-0.04–0.01)	**0.001**
Femoral Neck T-score	-0.71	(0.16)	-0.87	(0.15)	-0.16(-0.28–0.04)	**0.018**
Lumbar Spine BMD (g/cm^2)	0.987	(0.022)	0.953	(0.022)	-0.034(-0.05 -0.18)	**0.001**
Lumbar Spine T-score	-0.839	(0.219)	-1103	(0.207)	-0.264(-0.46–0.05)	**0.013**
Bone Turnover						
Amino pro-peptide of Type 1 collagen (ng/ml)	52.61	(3.91)	78.61	(5.37)	26.1(17.57-34.42)	**0.000**
Bone Alkaline Phosphatase (µg/ml)	13.60	(0.89)	18.81	(1.02)	5.21(3.4-7.1)	**0.000**
C-telopeptide (ng/ml)	0.278	(0.02)	0.411	(0.02)	0.133(0.07-0.19-)	**0.001**
Calcium Metabolism						
Parathormone pg/ml	33.4	(3.9)	47.1	(4.2)	13.61(3.76-23.45)	**0.008**
25-OH Vitamin D (ng/ml)	20.3	(1.96)	26.7	(3.15)	6.37(1.31-11.4)	**0.015**
Calcium (mg/dl)	9.3	(0.06)	9.5	(0.5)	-0.13(-0.04-0.32)	0.135
Phosphorus (mg/dl)	3.1	(0.08)	3.1	(0.9)	0.12(-0.05-0.301)	0.132
Inflamation and Coagulation						
High Sensitivity C-Reactive Protein (mg/dl)	0.45	(0.101)	0.13	(0.02)	-0.31(-0.09—0.53)	**0.006**
Erythrocyte Sedimentation Rate, (mm/h)	22.8	(3.5)	9.8	(1.4)	-13(-19.8- -6.1)	**0.000**
D-Dimer, (ng/ml)	240.3	(48.1)	138.5	(22.6)	-101.8(-180- -23)	**0.013**
Fibrinogen, (mg/dl),	374.6	(18.4)	347.5	(14.6)	-27.1(-70.3-16.1)	**0.037**
Beta-2 microglobulin, (mg/l)	2.3	(0.19)	1.73	(0.07)	-0.65(-1.03- -0.26)	**0.002**

** Results are shown as mean (SD), unless indicated otherwise*

Conclusion

Besides persistent significant decrease in BMD a decrease in trabecular microarchitecture at spine and hip level was observed after 1 year of TDF therapy with TBS and DXA-3D respectively. However, tissue quality significantly improved after 1 year of treatment, suggesting a recovery of bone material properties following the control of the infection despite the significant reduction of BMD. These three techniques provide additional and necessary information to DXA about bone health in treated HIV patients, and due to its convenience and feasibility they could be routinely apply to assess bone in clinical practice.