TDF and quantitative ultrasound bone density in African patients on second line ART

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Introduction

Several reports indicated that HIV-1 infected people have lower bone mineral density (BMD) than general population, independently of traditional osteoporosis risk factors. Currently, Tenofovir Disoproxil Fumarate (TDF) is the most widely used antiretroviral because of its efficacy on both HIV and hepatitis B infections, and its favorable resistance profile, safety and availability as a coformulation with other antiretroviral drugs in once-daily pills. However, some reports indicated that TDF-including regimens were associated with greater loss of BMD than other regimens.

Objective

The aim was to identify factors associated with BMD and to assess the impact of TDF-including regimens on BMD evolution, in African patients starting a second line antiretroviral treatment (ART) and included in METABODY / ANRS 12250 (Cameroon, Burkina Faso, Sénégal).

Methods

Study design – METABODY / ANRS 12250 is an observational longitudinal study nested in the 2LADY / ANRS 12169 trial (ClinicalTrial.gov n° NCT00928187) [1].

Population – HIV-1-positive adults failing standard first line ART from Yaoundé, Cameroun; Bobo Dioulasso, Burkina Faso and Dakar, Sénégal.

2LADY intervention - 2LADY is a multicenter randomized, open-label, phase III trial that compared efficacy and safety of three second line combinations in Africa. Patients were randomized to receive either TDF/FTC + LPVr, ABC + ddI + LPVr or TDF/FTC + DRVr.

Procedures - BMD was assessed by calcaneum quantitative ultrasound (QUS) (*Achilles GE Healthcare*) at baseline and every 24 weeks. QUS parameters include broadband ultrasound attenuation (BUA), a measure of the frequency-dependent attenuation of ultrasound, and speed of sound (SOS), reflecting the transmission velocity of ultrasound passing through soft tissue and bone tissue. At each visit, biological and clinical data were collected; 3 BMD repeated measurements were realized for each patient and the average of the two closest measures was used for the analysis. Stiffness index (SI = 0,67xBUA + 0,28xSOS – 420) [2] was used to evaluate BMD.

Low BMD was defined according to International Society for Clinical Densitometry recommendations using QUS reference data from Nigeria (SI T-score < -1 in post-menopausal women and men age 50 and older; SI Z-score ≤ -2 in women prior to menopause and men younger than age 50).

Analysis - Mixed linear models with random effects were used to determine associated factors during the follow-up.

Ethics - Written informed consent was obtained from all patients. Study protocol was approved by the appropriate ethic committees and regulatory authorities and were conducted in accordance with the Declaration of Helsinski and Good Clinical Practices.

References

1. Ciaffi L et al. Efficacy and safety of three second-line antiretroviral regimens in HIV-infected patients in Africa. AIDS 2015, 29:1473–1481.
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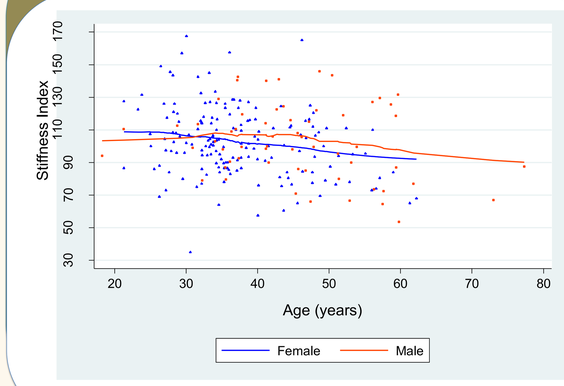
Results

Table 1. Baseline characteristics

		Total N = 228
Study site, n(%)	Burkina Faso	51 (22.4)
	Sénégal	19 (8.3)
	Cameroun	158 (69.3)
Female, n (%)		168 (73.7)
Mean age, years (SD)		39.6 (9.9)
Mean BMI, kg/m² (SD)		24.5 (4.4)
Mean vitamin D, ng/ml (SD)*		35.3 (11.9)
Mean parathormon, pg/ml (SD)*		44.0 (17.6)
Menopause, n(%)**		25 (14.9)
Antigen HBs positive, n(%)		17 (7.5)
Symptomatic for HIV, n(%)		21 (9.2)
Viral load ≥ 100 000 copies/ml, n(%)		63 (27.6)
Mean CD4, cells/µl (SD)		219 (139)
CD4 count <200 cells/µl, n(%)		115 (50.4)
Mean antiretroviral treatment duration, months (SD)		54.8 (24.3)
Mean bone mineral density, SI (SD)		102.5 (21.6)

* 4 missing data; ** for female only
SD, standard deviation; **BMI**, body mass index; **SI**, Stiffness Index

Figure 1. Baseline BMD distribution by age and sex



Out of 273 patients included in the METABODY sub-study, 45 subjects without baseline BMD measurement were not included in the analysis.

Baseline BMD description and its associated factors (table 1 & figure 1)
At baseline, 27 subjects (12%) had low BMD; the proportion being much higher among subjects aged ≥ 50 years (44% versus 6% for age < 50 years). Independent factors associated with baseline BMD were sex (β=-10.8 [-18.1,-3.5] for women), age (β=-0.9 [-1.2,-0.5] per year), body mass index (BMI) (β=+0.8 [-0.1,1.5] per unit of BMI) and study site (β=+12.8 [6.5,19.1] for Cameroun).

Figure 2. Mean BMD evolution by treatment groups

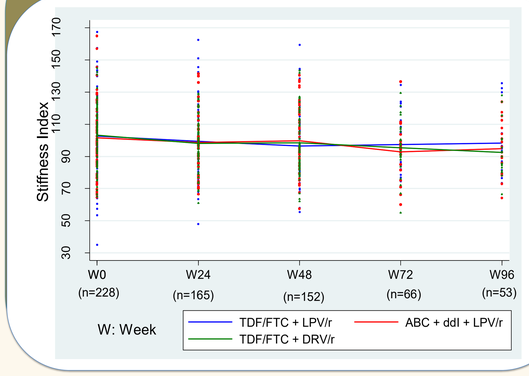


Table 2. BMD associated factors in African patients during the first 96 weeks follow-up on a second line antiretroviral treatment

		Multivariable β	95% CI	P
Follow-up (/24 weeks)		**-0.9**	[-1.4,-0.4]	**0.001**
Age (per ten years)		**-6.8**	[-9.4,-4.1]	**<0.001**
Female		**-9.6**	[-15.5,-8.8]	**0.001**
Baseline BMI		**0.8**	[0.3,1.4]	**0.004**
Physical activity		-1.0	[-2.5,0.6]	0.23
Duration of first line ART (months)	< 36	Ref.	---	
	[36-72[	6.4	[0.6,12.2]	0,07
	≥ 72	2.5	[-4.4,9.3]	
Year of inclusion (2011 vs 2012)		2.3	[-2.6,7.2]	0.35
Cameroun		**10.9**	[5.7,16.1]	**<0.001**
TDF exposure		1.7	[-4.1,7.4]	0.57
LPV exposure		1.6	[-4.0,7.2]	0.57

BMI, Body mass index; **ART**, antiretroviral treatment

Evolution of BMD over time and associated factors (figure 2 & table 2)
After 96 weeks of second line therapy, a reduction of 7.3% of mean stiffness index was observed, compared to baseline. The factors associated with BMD during the follow-up were similar to those found at baseline. Neither treatment arm, nor TDF exposure was associated with loss of BMD over time.

Conclusions

BMD decreases after second line ART initiation in African patients independently of TDF exposition. Factors associated with BMD were age, sex, baseline BMI, study site and time of follow up. Our results do not suggest the need for systematic bone loss screening in HIV infected people in Africa. Screening procedures applied for the general population can be used.

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