BONE MINERAL DENSITY IMPROVES IN WOMEN WHO SWITCH FROM TDF/FTC/NNRTI TO ABC/3TC/DTG

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BACKGROUND

- TDF is associated with reduced bone mineral density (BMD) and fractures [1-3]; TDF discontinuation is associated with improved BMD [4-6].
- TDF is also associated with reduced estimated glomerular filtration rate (eGFR), chronic kidney disease (CKD), proteinuria, acute tubular injury and proximal tubulopathy/Fanconi syndrome [7, 8].
- While TDF-associated tubular dysfunction & associated phosphaturia may contribute to bone loss [9, 10], adverse effects of TDF on BMD may be observed in without changes in renal tubular function [6].
- The bone effects of TDF are particularly undesirable in older women in view of accelerated bone loss following the menopause.
- We conducted a randomised controlled trial in virologically-suppressed older women living with HIV (WLWH) to examine impact of switch from TDF/FTC/NNRTI to ABC/3TC/DTG on bone & renal function, body weight, insulin resistance & metabolic syndrome.

HYPOTHESIS

- We hypothesized that bone mineral density (BMD) improves in HIV positive women who switch from TDF/FTC/NNRTI to ABC/3TC/DTG.

METHODS

- **B**one **E**valuation in women who **S**witch from **T**DF + 3TC/FTC + NNRTI to **T**riumeq (BESTT) is an ongoing 96-week, open-label, phase IV, randomised, controlled, multicentre clinical trial (EudraCT 2015-005297-37).
- WLWH (HLA-B5701 negative, aged ≥40 years, HIV RNA <50 copies/mL) on TDF/FTC (or TDF/3TC) + NNRTI for ≥12 months were randomized 1:2, stratified by age (< or >50 years), to continue current regimen or switch to ABC/3TC/DTG.
- Post-baseline visits occurred at 4 (switch arm only), 12, 24 and 48 weeks. Aliquots of plasma, serum and urine were snap-frozen and stored at -70°C for biomarker analyses.
- BMD (g/cm2) was assessed by dual energy X-ray absorptiometry [DXA; lumbar spine (L1 – L4), (non-dominant) total hip & femoral neck] at baseline, week 24 and week 48; bone turnover by quantification of alkaline phosphatase (ALP), type I collagen cross-linked C-telopeptide (CTX) and procollagen type 1 N-terminal propeptide (P1NP), renal function by eGFR (Chronic Kidney Disease Epidemiology Collaboration), serum cystatin C, albumin/creatinine ratio (ACR), protein/creatinine ratio (PCR), retinol-binding protein/creatinine ratio, and fractional excretion of phosphate (FE-PO4), 25-hydroxy-vitamin D [25(OH)D], parathyroid hormone (PTH), and insulin at baseline and week 48 in central laboratories.
- The primary outcome was the between study-arm change from baseline in total hip BMD at week 48. Additional prespecified endpoints included changes in lumbar spine and neck of femur BMD, PTH, bone turnover and renal biomarkers through 48 weeks. We conducted a post-hoc analysis of weight and BMI change at 12, 24, 48 weeks.
- We conducted a metabolic sub-study to evaluate changes in insulin resistance from baseline to week 48 in non-diabetic participants; insulin resistance was assessed by Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) [11], Quantitative Insulin Sensitivity Check Index (QUICKI) [12] and Insulin Resistance index [13].
- Analyses were by intention-to-treat, including all randomised patients who received at least one dose of allocated treatment. Linear regression was used to estimate the mean difference in BMD from baseline to week 48 between the two study arms, with adjustment for age, ethnicity, time on TDF, BMD and body mass index (BMI) at baseline. Secondary longitudinal outcomes were analysed using repeated measures mixed effects models with an unstructured variance-covariance matrix to assess mean difference between study arms.

HIGHLIGHTS

- **We observed small but significant increases in total hip and lumbar spine bone mineral density in women who switched from TDF/FTC/NNRTI to ABC/3TC/DTG.**
- **These changes in BMD occurred in the absence of changes in specific markers of bone turnover or renal tubular function.**
- **Modest weight gain in the ABC/3TC/DTG arm was not associated with worsening insulin resistance.**

Table 2

	Baseline		Week 48		Adjusted difference between study arms (baseline to week 48)	P-value
	TDF/FTC/NNRTI	ABC/3TC/DTG	TDF/FTC/NNRTI	ABC/3TC/DTG		
Bone mineral density						
Total hip, g/cm²	1.03 (0.98, 1.08)	0.96 (0.92, 0.99)	1.03 (0.98, 1.08)	0.97 (0.94, 1.00)	**0.01 (0.002, 0.03)**	**0.027**
Neck of femur, g/cm²	0.90 (0.85, 0.96)	0.87 (0.83, 0.90)	0.90 (0.84, 0.95)	0.88 (0.84, 0.91)	0.02 (-0.003, 0.03)	0.093
Lumbar spine, g/cm²	1.07 (1.02, 1.12)	1.03 (0.99, 1.07)	1.06 (1.02, 1.11)	1.05 (1.01, 1.10)	**0.03 (0.01, 0.05)**	**0.002**
Bone biomarkers						
25(OH) vitamin D, nmol/L	40.8 (33.1, 48.4)	49.0 (42.9, 55.1)	37.8 (31.4, 44.2)	47.2 (41.3, 53.1)	3.7 (-2.5, 9.9)	0.235
Parathyroid hormone, ng/L	34.7 (29.3, 40.2)	32.5 (27.3, 37.7)	35.6 (29.9, 41.2)	30.5 (26.6, 34.4)	-3.8 (-9.9, 2.4)	0.230
Alkaline phosphatase, IU/L	89.9 (79.8, 100.0)	93.2 (84.7, 101.8)	88.1 (77.9, 98.3)	73.0 (67.0, 78.9)	**-17.8 (-25.9, -9.6)**	**<0.001**
CTX, µg/L	0.44 (0.36, 0.51)	0.53 (0.45, 0.62)	0.42 (0.34, 0.50)	0.37 (0.32, 0.42)	-0.06 (-0.15, 0.03)	0.217
P1NP, µg/L	61.6 (54.6, 68.7)	68.7 (62.1, 75.3)	59.4 (51.6, 67.1)	58.4 (52.4, 64.5)	-1.8 (-10.9, 7.2)	0.691
Renal biomarkers						
Creatinine, µmol/L	67.7 (64.0, 71.4)	67.8 (65.4, 70.3)	71.4 (67.4,75.3)	78.1 (75.2,81.0)	**6.7 (2.7, 10.7)**	**0.001**
eGFR (creatinine), mL/min/1.73m²	103.5 (97.1, 109.9)	102.1 (98.1, 106.2)	97.7 (91.3, 104.0)	87.8 (83.8, 91.8)	**-8.8 (-14.5, -3.2)**	**0.003**
Cystatin C, mg/L	0.81 (0.74, 0.88)	0.80 (0.76, 0.85)	0.83 (0.77, 0.89)	0.82 (0.78, 0.86)	-0.01 (-0.04, 0.03)	0.624
eGFR (cystatin C), mL/min/1.73m²	101.8 (91.2, 112.4)	99.8 (93.1, 106.4)	98.1 (88.5, 107.7)	96.5 (91.1, 102.0)	0.4 (-4.4, 5.1)	0.881
Albumin/creatinine ratio, mg/mmol	1.78 (0.61,2.95)	1.94 (0.79,3.10)	1.32 (0.69,1.96)	0.91 (0.58,1.24)	-0.54 (-1.25, 0.16)	0.131
Protein/creatinine ratio, mg/mmol	10.74 (7.12,14.35)	10.22 (8.05,12.38)	9.42 (6.95,11.89)	6.69 (5.56,7.82)	**-0.03 (-0.06, -0.01)**	**0.003**
Retinol-binding protein/creatinine ratio, µg/mmol	2.76 (0.97,4.54)	2.31 (1.50,3.12)	2.28 (0.63,3.93)	1.29 (0.68,1.89)	-0.79 (-1.92, 0.34)	0.168
Fractional excretion of phosphate, %	0.10 (0.07, 0.12)	0.10 (0.08, 0.11)	0.09 (0.07, 0.11)	0.09 (0.07, 0.10)	-0.003 (-0.03, 0.02)	0.792
Weight and body mass index (post-hoc analyses)						
Weight	86.3 (79.7, 93.0)	77.4 (72.7, 82.1)	86.3 (79.5, 93.0)	79.2 (74.7, 83.8)	**1.81 (0.03,3.59)**	**0.046**
Body mass index	32.7 (30.2, 35.1)	29.0 (27.5, 30.5)	32.8 (30.2, 35.4)	31.1 (27.6, 34.7)	1.50 (-2.73, 5.73)	0.481

Data are expressed as mean (95%CI) except weight & body mass index [expressed as median (inter-quartile range)]; BMD was adjusted for age, BMI at baseline, ethnicity, time on TDF, non-nucleoside reverse transcriptase inhibitor (efavirenz vs. other) and BMD at baseline; all other secondary outcomes were adjusted for age, ethnicity; BMI at baseline, time on TDF and baseline measurements except weight (where weight at baseline was used instead of BMI baseline). Abbreviations: TDF = tenofovir disoproxil fumarate; FTC = emtricitabine; NNRTI = non-nucleoside reverse transcriptase inhibitor; ABC = abacavir; 3TC = lamivudine; DTG = dolutegravir; CTX = type I collagen cross-linked C-telopeptide; P1NP = procollagen type 1 N-terminal propeptide; eGFR = estimated glomerular filtration rate

Table 3: Results from the metabolic sub-study

		Baseline		Week 48		Mean difference between arms (baseline to week 48)	P-value
		TDF/FTC/NNRTI (n=19)	ABC/3TC/DTG (n=34)	TDF/FTC/NNRTI (n=19)	ABC/3TC/DTG (n=34)		
Weight	kilogram	85.0 [17.9]	76.8 [17.1]	85.4 [18.1]	79.7 [16.9]	1.38 [-0.87, 3.63]	0.22
Waist circumference	centimetre	99.6 [10.4]	92.8 [15.1]	100.1 [11.0]	93.2 [20.5]	0.27 [-5.35, 5.88]	0.93
Systolic blood pressure	mm Hg	123.3 [14.9]	122.9 [20.3]	122.2 [28.3]	125.7 [16.9]	7.87 [-6.97, 22.7]	0.29
Diastolic blood pressure	mm Hg	78.4 [8.2]	78.5 [13.4]	80.7 [9.8]	78.9 [10.8]	-3.00 [-7.62, 1.61]	0.18
HDL-cholesterol	mmol/L	1.6 [0.4]	1.7 [0.4]	1.7 [0.4]	1.8 [0.5]	0.03 [-0.21, 0.27]	0.27
Triglycerides	mmol/L	0.9 [0.8, 1.4]	0.8 [0.7, 1.2]	1.0 [0.8, 1.3]	1.8 [0.7, 1.2]	0.03 [-0.11, 0.18]	0.66
Glucose	mg/dL	89.1 [7.5]	85.1 [8.9]	87.0 [9.5]	88.2 [10.7]	3.56 [-1.94, 9.07]	0.20
Insulin	µU/mL	6.6 [4.2, 9.1]	5.7 [3.0, 9.6]	10.4 [4.9, 16.1]	6.4 [4.0, 9.3]	**-3.23 [-6.20, -0.27]**	**0.033**
HOMA-IR		1.6 [0.9, 2.2]	1.2 [0.6, 2.1]	2.3 [1.1, 3.5]	1.9 [0.8, 2.2]	-0.29 [-0.90, 0.32]	0.35
QUICKI index		0.2 [0.0]	0.2 [0.0]	0.2 [0.0]	0.2 [0.0]	0.002 [-0.005, 0.01]	0.46
Insulin Resistance index		7.9 [7.4, 9.0]	8.4 [7.0, 11.0]	7.0 [6.0, 9.1]	8.7 [6.7, 10.2]	0.56 [-0.24, 1.36]	0.16

Data are expressed as mean [SD] except triglycerides, insulin, HOMA-IR and Insulin Resistance Index [expressed as median (inter-quartile range

RESULTS

91 women were enrolled, with the following characteristics:

Table 1

		TDF/FTC/NNRTI (n=32)	ABC/3TC/DTG (n=59)
Age, years	Mean (SD)	49.5 (6.0)	50.9 (7.0)
Black ethnicity	n (%)	27 (84.4)	51 (86.4)
Weight, kg	Mean (SD)	86.3 (16.2)	77.4 (17.0)
Body Mass Index, kg/m²	Mean (SD)	32.7 (7.0)	29.0 (5.8)
Post-menopausal	[n (%)] *	14 (50.0)	26 (52.0)
Diabetes mellitus	n (%)	1 (3.1)	3 (5.1)
Hypertension	n (%)	8 (25.0)	13 (22.0)
Current smoker	n (%)	3 (9.4)	4 (9.8)
Time since HIV diagnosis, years	Mean (SD)	11.7 (5.2)	13.9 (6.6)
Prior AIDS	n (%)	5 (15.6)	10 (17.0)
CD4 current, cells/mm³	Median (IQR)	579 (510, 712)	612 (454, 807)
CD4 nadir, cells/mm³	Median (IQR)	161 (88, 290)	195 (129, 323)
Time on TDF, years	Mean (SD)	7.3 (3.1)	8.7 (3.4)
Taking vitamin D supplements	n (%)	7 (21.9)	13 (22.0)
FRAX: major osteoporotic fracture	Median (IQR)	3.1 (2.5, 5.1)	3.2 (2.6, 5.5)
FRAX: hip fracture	Median (IQR)	0.2 (0.1, 0.4)	0.2 (0.1, 0.6)

Abbreviations: TDF = tenofovir disoproxil fumarate; FTC = emtricitabine; NNRTI = non-nucleoside reverse transcriptase inhibitor; ABC = abacavir; 3TC = lamivudine; DTG = dolutegravir; SD = standard deviation; IQR = inter-quartile range; FRAX = risk of fracture (over 10 years)
* menopausal status could be determined for 78 participants; ** Viral load missing N=2 and <200 N=2

Table 2 (all participants):
Switching to ABC/3TC/DTG resulted in significant improvements in:
- Total hip and lumbar spine BMD, ALP (but not other markers of bone turnover) and total proteinuria (but not other markers tubular function)

We also observed:
- Changes in creatinine/eGFR consistent with the known effects of DTG on creatinine secretion, and an increase in body weight in the ABC/3TC/DTG arm

Table 3 (exploratory analyses in 53 participants):
- Switching to ABC/3TC/DTG resulted in significant reductions in plasma insulin concentration; we observed no change in insulin resistance

CONCLUSIONS

- BMD improved in women who switched from TDF/FTC/DTG to ABC/3TC/DTG, with the greatest increase in lumbar spine BMD.
- While the switch strategy resulted in reductions in total proteinuria, specific markers of renal tubular function were unaffected, suggesting that the effects of TDF discontinuation on bone were not explained by reversal of renal tubular dysfunction or phosphaturia.
- We observed modest weight gain in the ABC/3TC/DTG arm, with no change in those who continued TDF-containing ART; we found no evidence that the switch strategy was associated with worsening insulin resistance.

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