Increase in bone mineral density and weight in women who switch from TDF/FTC/NNRTI to ABC/3TC/DTG

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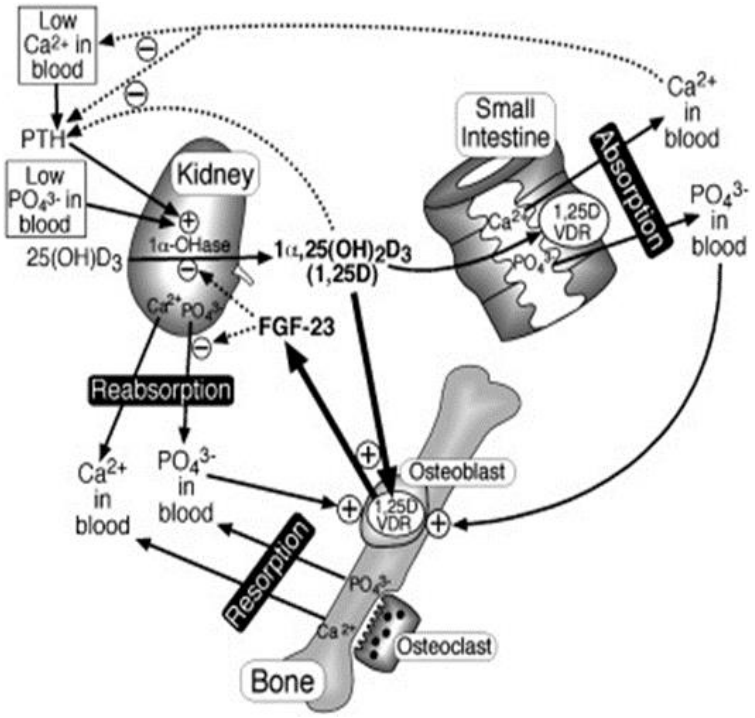
TDF-related bone and kidney complications

- Reduced bone mineral density (BMD)[1,2]
- Increased fracture risk[3,4]

- Reduced estimated glomerular filtration rate (eGFR)
- Chronic kidney disease (CKD)
- Proteinuria
- Severe disease: acute tubular injury, proximal Tubulopathy, Fanconi syndrome[5,6]

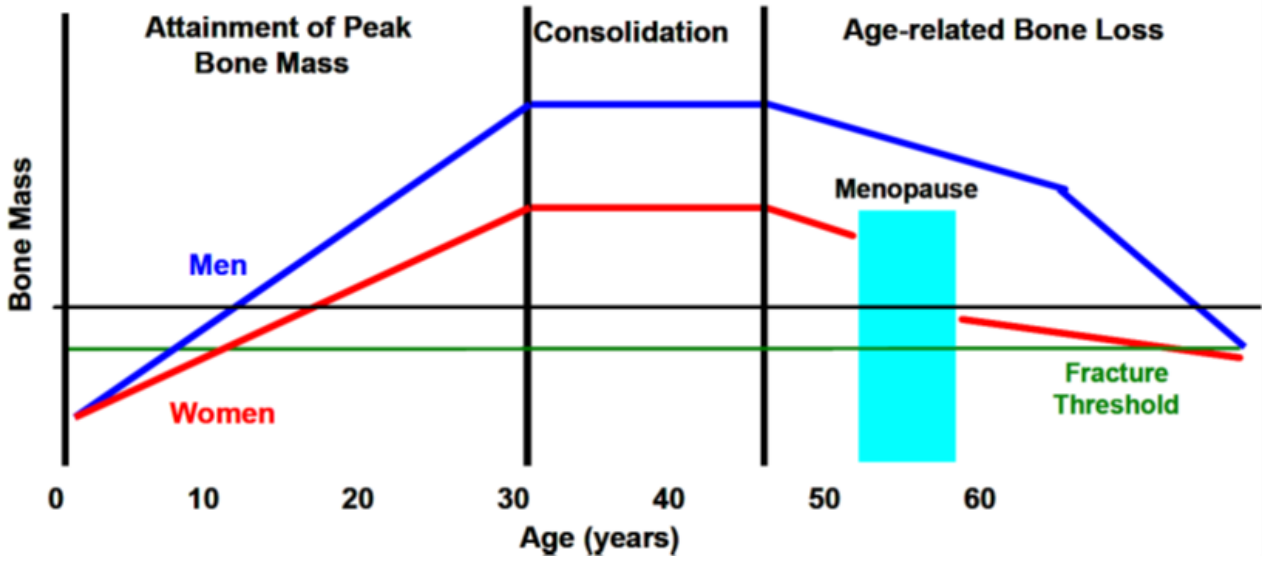


- Adverse effects of tenofovir disoproxil fumarate (TDF) on BMD may occur without changes in renal tubular function[7]

1. Childs K et al. AIDS 2012; 26(3): 253-62
2. McComsey Get al. J Infect Dis 2011; 203 (12): 1791–801
3. Bedimo R et al. AIDS 2012; 26(7): 825-31
4. Borges AH et al. Clin Infect Dis 2017; 64(10): 1413-21
5. Scherzer R et al. AIDS 2012; 26(7): 867-75
6. Hamzah L et al. J Infect 2017; 74(5): 492-500
7. Hamzah L et al. Antivir Ther 2016; 21(4): 287-96

Implications for older women living with HIV

- Older age and female gender associated with reduced BMD[1]
- In women, there is accelerated bone loss post-menopausally[1]



- Older age is a risk factor for CKD and TDF-induced renal injury[2,3]

- HIV infection is associated with increased risk of insulin resistance and metabolic syndrome[4]

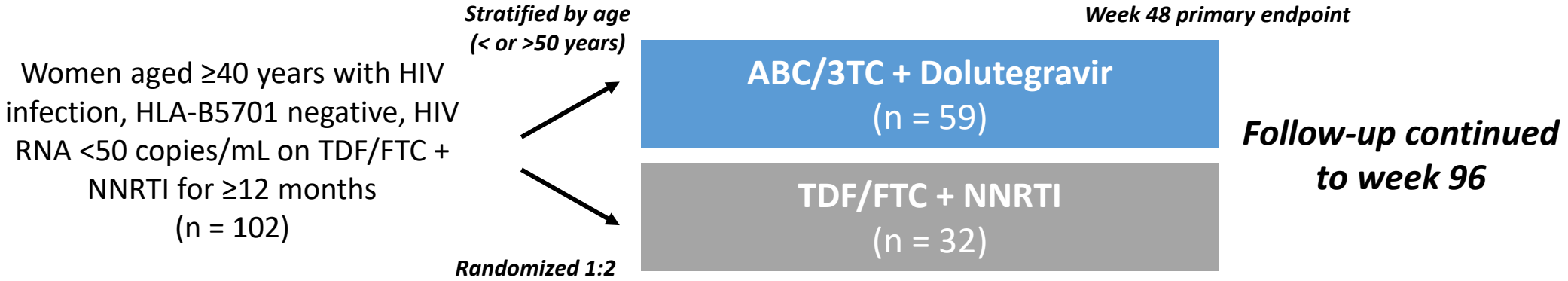
1. Kanis J. Lancet. 2002 Jun 1;359(9321):1929-1936
2. Mocroft A et al. AIDS 2010; 24(11): 1667-1678
3. Hamzah L et al. J Infect 2017; 74 (5): 492–500
4. Willig A et al. Curr HIV/AIDS Rep. 2016 Oct;13(5):289-96

Aims

- In women ≥40 years old, who switched from TDF/FTC/NNRTI to ABC/3TC/DTG, we evaluated the change from baseline to week 48 in:
  - BMD
  - Renal tubular function
- As DTG has been associated with weight gain, we also evaluated change from baseline to week 48 in:
  - Weight
  - Insulin resistance
  - Prevalence of metabolic syndrome

Study design: **B**one **E**valuation in women who **S**witch from **T**DF + 3TC/FTC + NNRTI to **T**riumeq (BESTT)

- 96-week, open-label, phase IV, randomised, controlled, multicentre clinical trial

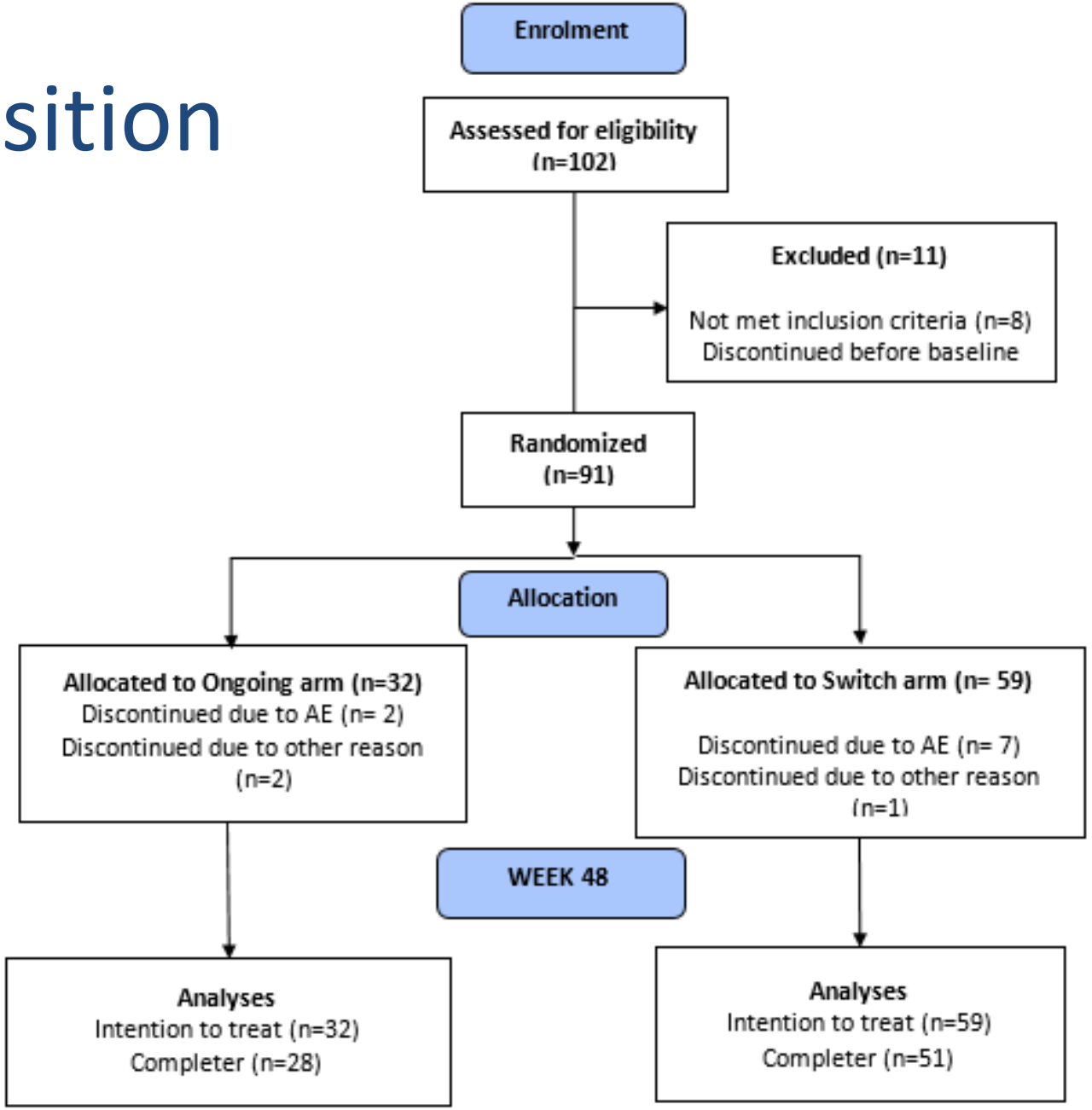


- Procedures at baseline, week 24 and week 48
  - BMD using dual-energy x-ray absorptiometry (DXA) at lumbar spine (L1-L4), non-dominant total hip and femoral neck
  - Bone turnover markers: ALP, CTX, P1NP, vitamin D and PTH
  - Fracture risk: FRAX
  - Renal function: CKD-EPI eGFR, uACR and uPCR
  - Renal tubular function: cystatin C, RBPCR and $FePO_4$
  - Metabolic function: fasting lipids, glucose and insulin
  - Insulin resistance: HOMA-IR, QUICKI and Insulin Resistance index
  - Metabolic syndrome: Adult Treatment Panel diagnostic criteria

Study outcomes and statistical analysis

- **Primary endpoint:** between study-arm change from baseline in total hip BMD at week 48
- **Secondary endpoints:** changes in lumbar spine and femoral neck BMD, PTH, bone turnover and renal biomarkers at week 48
- Post-hoc analysis of weight change at 12, 24, 48 weeks and changes in insulin resistance from baseline to week 48 in non-diabetic participants (n = 53)
- Intention-to-treat analysis
- Not powered to assess virological efficacy

Subject disposition



Baseline characteristics

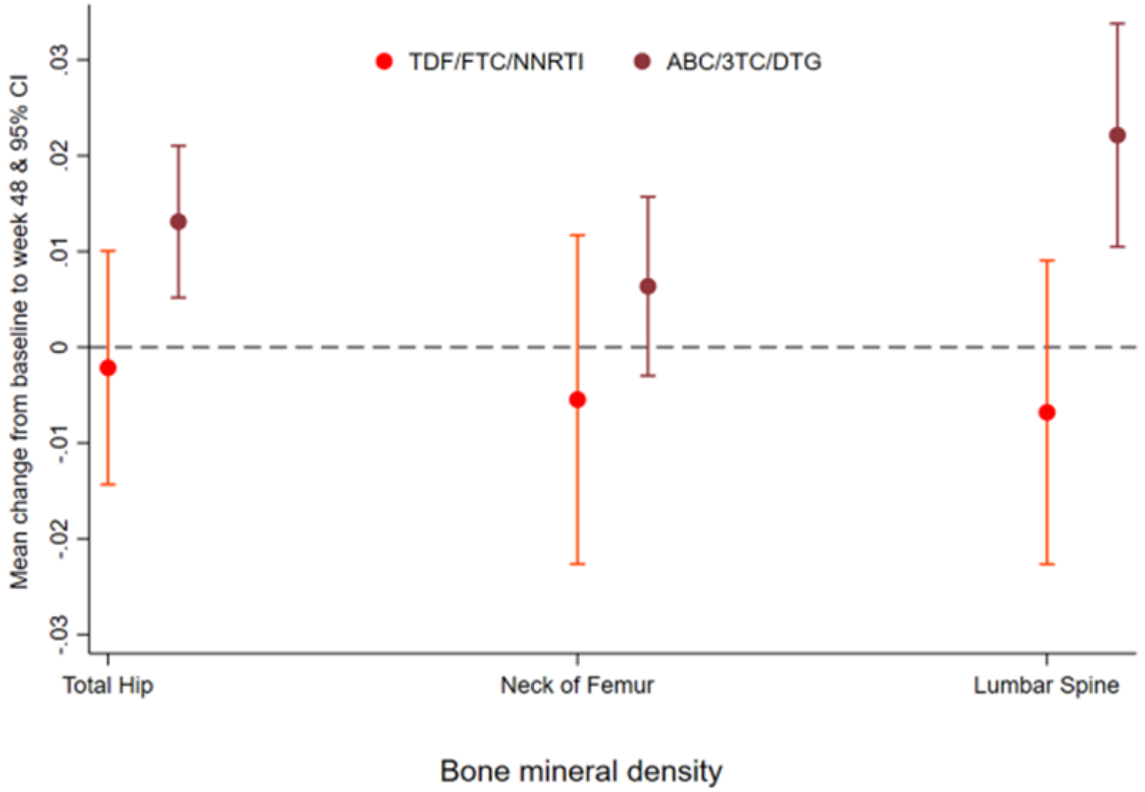
		TDF/FTC/NNRTI (n=32)	ABC/3TC/DTG (n=59)
Age, years	mean (SD)	49.5 (6.0)	50.9 (7.0)
Black ethnicity	n (%)	27 (84.4)	51 (86.4)
Post-menopausal	n (%)*	14 (50.0)	26 (52.0)
Time since HIV diagnosis, years	mean (SD)	11.7 (5.2)	13.9 (6.6)
Prior AIDS	n (%)	5 (15.6)	10 (17.0)
CD4 current, cells/mm^3	median (IQR)	579 (510, 712)	612 (454, 807)
CD4 nadir, cells/mm^3	median (IQR)	161 (88, 290)	195 (129, 323)
Time on TDF, years	mean (SD)	7.3 (3.1)	8.7 (3.4)
Weight, kg	mean (SD)	86.3 (16.2)	77.4 (17.0)
Body mass index, kg/m^2	mean (SD)	32.7 (7.0)	29.0 (5.8)
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)
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

Change in BMD

Switching to ABC/3TC/DTG resulted in significant improvements in non-dominant total hip and lumbar spine BMD



	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		
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**
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**

Data are expressed as means (95%CI); BMD was adjusted for age, BMI at baseline, ethnicity, time on TDF, NNRTI (efavirenz vs. other) and BMD at baseline. Abbreviations: BMD=bone mineral density; TDF = tenofovir disoproxil fumarate; FTC = emtricitabine; NNRTI = non-nucleoside reverse transcriptase inhibitor; ABC = abacavir; 3TC = lamivudine; DTG = dolutegravir

Change in bone biomarkers

	Unadjusted Coefficients (95% CI)	P-value	Adjusted Coefficients (95% CI)	P-value
25(OH) vitamin D, nmol/L	-	-		
Parathyroid hormone, ng/L	-2.48 (-7.10, 2.14)	0.293	-	-
Alkaline phosphatase, IU/L	**-14.79 (-19.75, -9.82)**	**<0.001**	**-15.7 (-19.6, -11.7)**	**<0.001**
CTX, µg/L	**-0.12 (-0.19, -0.05)**	**0.001**	**-0.07 (-0.13, -0.02)**	**0.004**
P1NP, µg/L	-5.71 (-11.66, 0.23)	0.060	-	-

Change in BMD (over the three time points) was the dependent variable in the mixed effect model; these models were adjusted for age, BMI at baseline, ethnicity, time on TDF, non-nucleoside reverse transcriptase inhibitor (efavirenz vs. other) and BMD at baseline; all secondary outcomes were also modelled as change and adjusted for age, ethnicity; BMI at baseline, time on TDF and NNRTI (efavirenz vs. other) and their baseline score. Abbreviations: ABC = abacavir; 3TC = lamivudine; DTG = dolutegravir; CTX = type I collagen cross-linked C-telopeptide; P1NP = procollagen type 1 N-terminal propeptide;

Switching to ABC/3TC/DTG resulted in significant decreases in alkaline phosphatase and CTX but not other markers of bone turnover

Change in renal biomarkers

	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		
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

Data are expressed as mean (95%CI); all secondary outcomes were adjusted for age, ethnicity; BMI at baseline, time on TDF and baseline measurements except BMI (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; eGFR = estimated glomerular filtration rate

- Switching to ABC/3TC/DTG resulted in significant improvement in total proteinuria but not other renal tubular markers
- In the switch arm, creatinine increased and eGFR-creatinine decreased, consistent with known effect of DTG on tubular secretion of creatinine

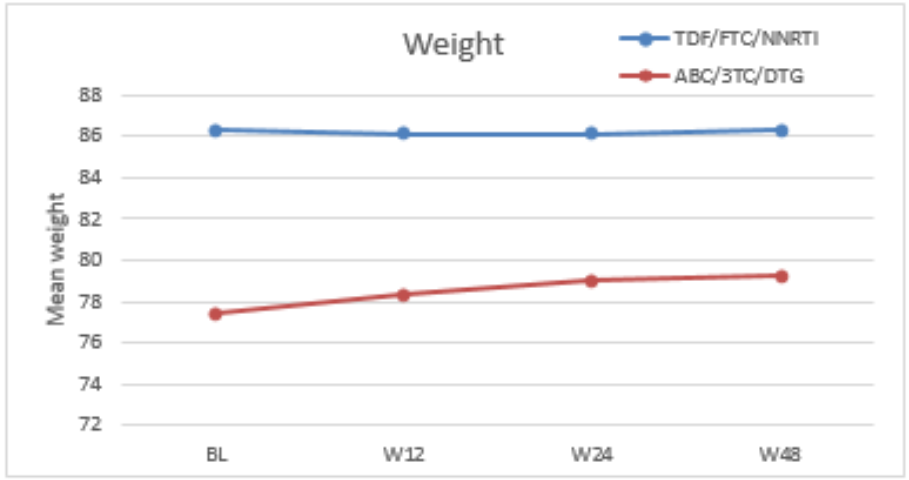
Change in weight and BMI

- Switching to ABC/3TC/DTG resulted in a significant 1.8 kg increase in body weight but in BMI
- β coefficient [95% CI] of the mean difference between arms: 1.81 [0.03,3.59], p=0.046

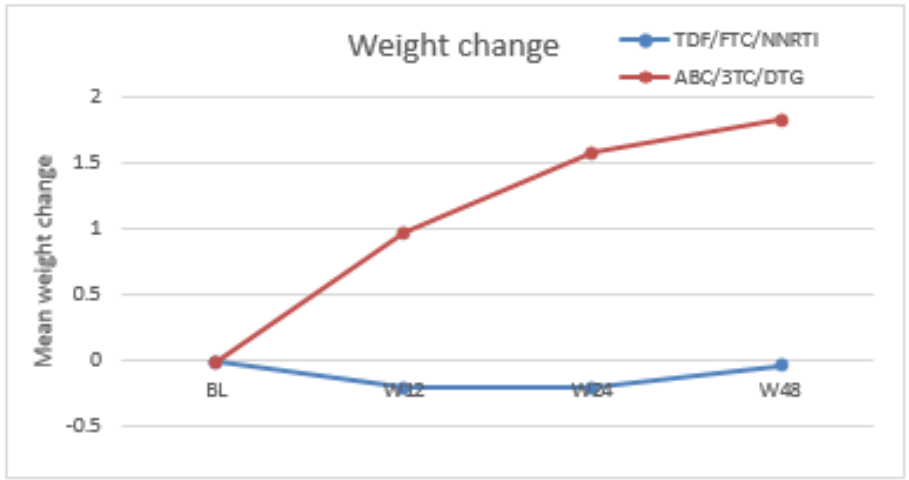
	Baseline		Week 48	
	TDF/FTC/NNRTI	**ABC/3TC/DTG**	**TDF/FTC/NNRTI**	**ABC/3TC/DTG**
Weight	86.3 (79.7, 93.0)	77.4 (72.7, 82.1)	86.3 (79.5, 93.0)	79.2 (74.7, 83.8)

Data are expressed as mean (95%CI); all secondary outcomes were adjusted for age, ethnicity; BMI at baseline, time on TDF and baseline measurements except BMI (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; BMI = body mass index

A Mean weight (kilograms; n=91) for each visit (TDF/FTC/NNRTI, n=32; ABC/3TC/DTG, n=59)



B Mean weight change (kilograms)



Metabolic parameters in non-diabetic patients

		TDF/FTC/NNRTI (n=19)		ABC/3TC/DTG (n=34)		Mean difference [95% CI] between arms (baseline to week 48)	P-value
		Baseline	Week 48	Baseline	Week 48		
Weight, kg	Mean [SD]	85.0 [17.9]	85.4 [18.1]	76.8 [17.1]	79.7 [16.9]	1.38 [-0.87, 3.63]	0.22
Waist circumference, cm	Mean [SD]	99.6 [10.4]	100.1 [11.0]	92.8 [15.1]	93.2 [20.5]	0.27 [-5.35, 5.88]	0.93
Systolic blood pressure, mm Hg	Mean [SD]	123.3 [14.9]	122.2 [28.3]	122.9 [20.3]	125.7 [16.9]	7.87 [-6.97, 22.7]	0.29
Diastolic blood pressure, mm Hg	Mean [SD]	78.4 [8.2]	80.7 [9.8]	78.5 [13.4]	78.9 [10.8]	-3.00 [-7.62, 1.61]	0.18
HDL-cholesterol , mmol/L	Mean [SD]	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	Median [IQR]	0.9 [0.8, 1.4]	1.0 [0.8, 1.3]	0.8 [0.7, 1.2]	1.8 [0.7, 1.2]	0.03 [-0.11, 0.18]	0.66
Glucose, mg/dL	Mean [SD]	89.1 [7.5]	87.0 [9.5]	85.1 [8.9]	88.2 [10.7]	3.56 [-1.94, 9.07]	0.20
Insulin, µU/mL	Median [IQR]	6.6 [4.2, 9.1]	10.4 [4.9, 16.1]	5.7 [3.0, 9.6]	6.4 [4.0, 9.3]	**-3.23 [-6.20, -0.27]**	**0.033**
HOMA-IR	Median [IQR]	1.6 [0.9, 2.2]	2.3 [1.1, 3.5]	1.2 [0.6, 2.1]	1.9 [0.8, 2.2]	-0.29 [-0.90, 0.32]	0.35
QUICKI index	Mean [SD]	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	Median [IQR]	7.9 [7.4, 9.0]	7.0 [6.0, 9.1]	8.4 [7.0, 11.0]	8.7 [6.7, 10.2]	0.56 [-0.24, 1.36]	0.16

Data are for non-diabetic participants with fasting samples: N=19 in the TDF/FTC/NNRTI arm and N=34 in the ABC/3TC/DTG arm. Abbreviations: TDF = tenofovir disoproxil fumarate; FTC = emtricitabine; NNRTI = non-nucleoside reverse transcriptase inhibitor; ABC = abacavir; 3TC = lamivudine; DTG = dolutegravir; HOMA-IR = Homeostatic Model Assessment of Insulin Resistance, QUICKI = Quantitative Insulin Sensitivity Check Index; Insulin Resistance index

Switching to ABC/3TC/DTG resulted in significant decrease in insulin concentrations but no change in insulin resistance

Adverse events

- Twelve participants discontinued prior to week 48:
  - TDF/FTC/NNRTI arm: 4
  - ABC/3TC/DTG arm: 8
- Treatment-limiting adverse events
  - TDF/FTC/NNRTI arm: 1 (3.1%, acute kidney injury)
  - ABC/3TC/DTG arm: 9 (15.3%, neuropsychiatric n=5, including suicidal intent in 2, hypersensitivity n=2, other n=2)
- One person in each arm discontinued due to osteoporosis requiring bisphosphonates
- No participants developed virological failure

Limitations

- Large proportion of discontinuations in the study arm led to loss of power
- Peri-menopausal state may have impacted on ART-attributable changes in BMD and bone turnover
- Switching both NRTI backbone and 3rd agent made it difficult to analyse the effects of each strategy
- Some women attended non-fasting, excluding them from insulin resistance and metabolic syndrome analyses
- Results may not be generalizable to other study populations

Summary

- BMD improved in women who switched from TDF/FTC/NNRTI to ABC/3TC/DTG, with greatest increase occurring in lumbar spine BMD

- Improvement in BMD occurred in the absence of changes in specific markers of renal tubular function

- Although women in the ABC/3TC/DTG arm gained an average of 1.8kg of weight, this was not associated with insulin resistance or metabolic syndrome

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