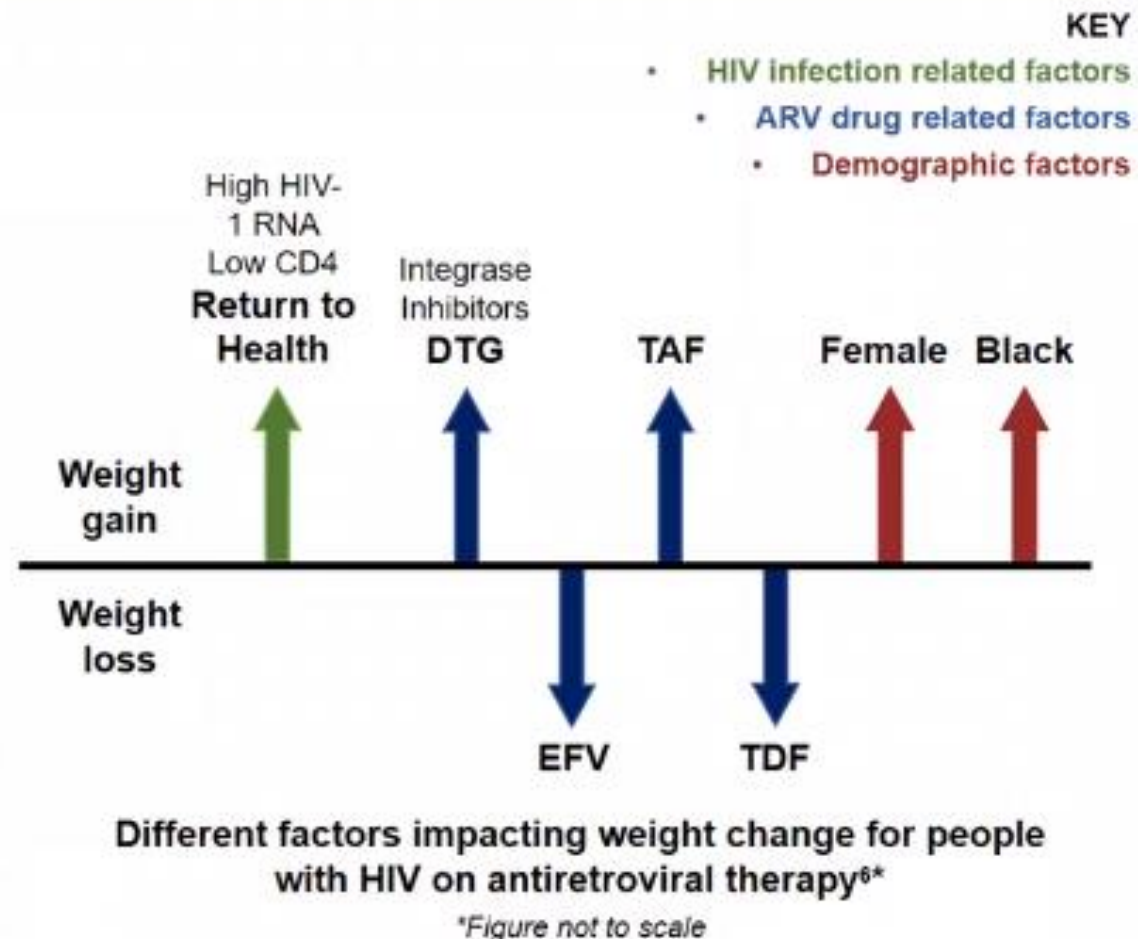# Background

Background

- TDF/XTC/DTG is the recommended first-line regimen for HIV in WHO guidelines[1]. TAF is recommended as first-line therapy in EACS and DHHS guidelines[2,3]

- DTG has been associated with significant weight gain. This is higher if DTG is combined with TAF in black women[4]

- In the ADVANCE trial, more participants developed obesity on TAF/FTC+DTG vs TDF/FTC+DTG and TDF/FTC/EFV to week 96[5]

- Overweight and obesity are associated with elevated risk of cardiovascular disease (CVD) and type 2 diabetes mellitus (T2D)

Study Objective

- This analysis aimed to quantify the 10-year predicted risk of CVD and diabetes for ADVANCE participants using standard risk algorithms

KEY
- HIV infection related factors
- ARV drug related factors
- Demographic factors

High HIV-1 RNA Low CD4
Return to Health

Integrase Inhibitors
DTG

TAF

Female   Black

Weight gain

Weight loss

EFV   TDF

Different factors impacting weight change for people with HIV on antiretroviral therapy[6]*

*Figure not to scale

[1]World Health Organisation. Update of recommendations on first- and second-line antiretroviral regimens. 2019. [2]Panel on Antiretroviral Guidelines for adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. 2019. [3]European AIDS Clinical Society. Guidelines. 2019. [5]Sax PE et al. 2019. doi:10.1093/cid/ciz999. [6]Venter W et al. 2020. doi.org/10.1016/S2352-3018(20)30241-1. [4]Adapted from Hill et al. 2019.

Methods

ADVANCE trial design (2017 – 2022)

Inclusion criteria: Treatment-naïve, HIV-1 RNA level > 500 copies/mL, no TB or pregnancy, no baseline genotyping

1053 Participants
- TAF/FTC+DTG n = 351
- TDF/FTC+DTG n = 351
- TDF/FTC/EFV n = 351
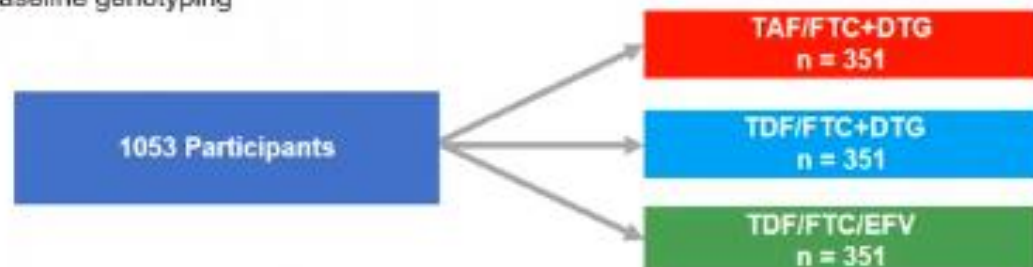
Study visits: Baseline, Weeks 4, 12, 24, 36, 48, 60, 72, 84, 96 then every 24 weeks to Week 192
Sample characteristics: 99% black, 56% female, 62% South African

Risk prediction analysis

Week 144 weight + Week 144 laboratory factors* → Predicted 10-year risk of CVD & T2D

- Body weight and laboratory measures from Week 144 were used to calculate the 10-year risk of CVD and T2D using the **QRISK**[1], **Framingham**[2] (non-laboratory) and **QDiabetes**[3] risk algorithms
- Participants ≥30 years old at baseline included in analysis
- *Most recent laboratory measure since Week 96 used when Week 144 measure was unavailable

10-year risk of developing:

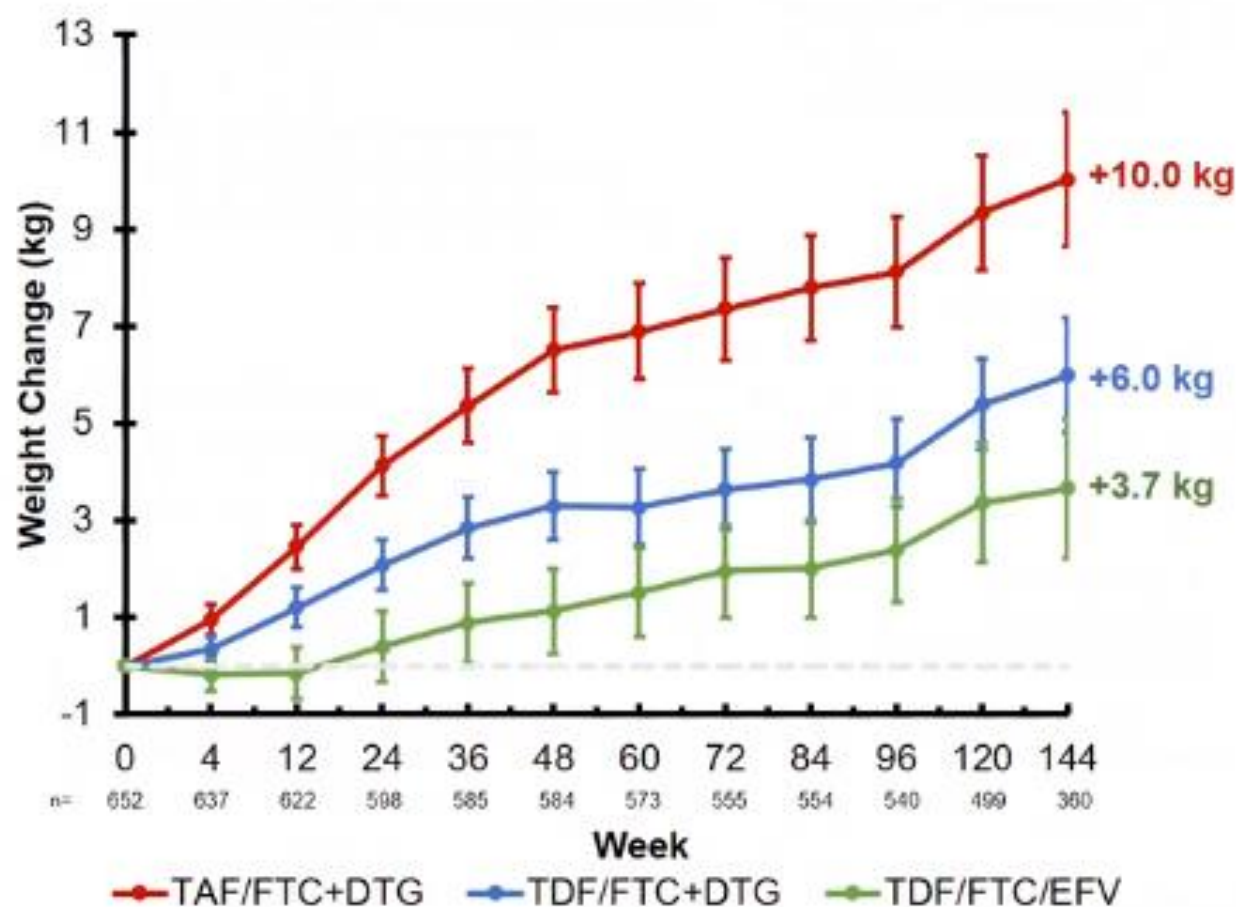| Risk equation Variables	QRISK3-2018 (Heart attack or stroke)	Framingham (non-laboratory) (Atherosclerotic CVD)	QDiabetes-2018 (Type II diabetes)
Age (validated population)	✓ (25-84)	✓ (≥30)	✓ (25-84)
Gender	✓	✓	✓
Smoking status	✓	✓	✓
Ethnicity	✓	✗	✓
Personal history of CVD	✓	✗	✓
Family history of CVD (X)	✓	✗	✗
Family history of diabetes (X)	✗	✗	✓
Treatment for hypertension	✓	✓	✓
Prescribed steroids	✓	✗	✓
Prescribed statins	✗	✗	✓
Cholesterol ratio (total cholesterol / HDL)	✓	✗	✗
Fasting blood glucose (mmol/L)	✗	✗	✓
Haemoglobin A1C (X)	✗	✗	✓
Systolic blood pressure (mmHg)	✓	✓	✓
Body mass index (kg/m²)	✓	✓	✓
Other	*	✗	*

Variables marked with (X) were not available from the ADVANCE database.
*Other variables included in QRISK: standard deviation of at least two recent SBP readings (mmHg), erectile dysfunction, atypical antipsychotic medication, history of severe mental, systemic lupus erythematosus, rheumatoid arthritis, migraines, atrial fibrillation, stage 3-5 chronic kidney disease. *Other variables included in QDiabetes: atypical antipsychotic medication, severe mental illness, gestational diabetes and polycystic ovary syndrome.
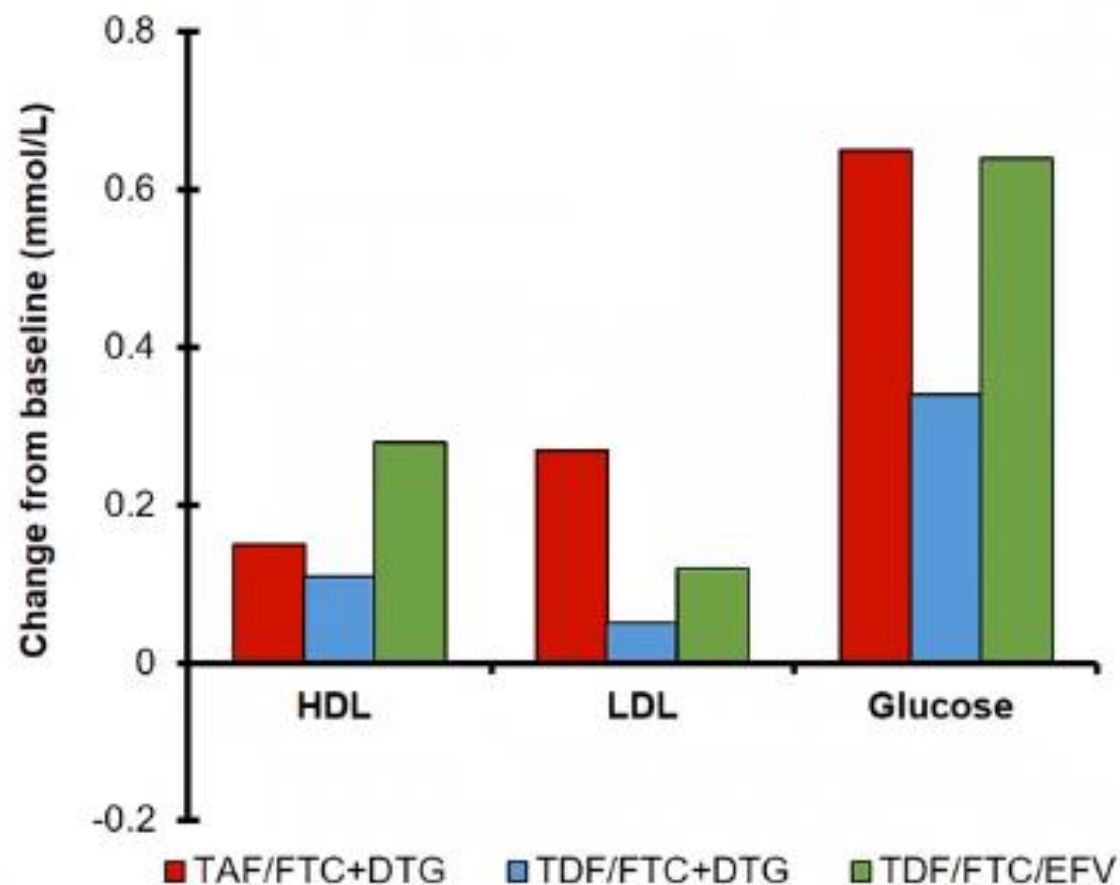
[1] Hippisley-Cox et al. 2017. doi:10.1136/bmj.j2099. [2] D'Agostino et al. 2008. doi:10.1161/CIRCULATIONAHA.107.699579. [3] Hippisley-Cox et al. 2017 doi:10.1136/bmj.j5019

Results (1/2)

Weight gain to week 144, participants ≥ 30 years*

Weight Change (kg)

+10.0 kg
+6.0 kg
+3.7 kg

Week	0	4	12	24	36	48	60	72	84	96	120	144
n=	652	637	622	598	585	584	573	555	554	540	499	360

Week

●—TAF/FTC+DTG ●—TDF/FTC+DTG ●—TDF/FTC/EFV

Changes in lab parameters to week 144, participants ≥ 30 years**

Change from baseline (mmol/L)

HDL   LDL   Glucose

■ TAF/FTC+DTG ■ TDF/FTC+DTG ■ TDF/FTC/EFV

*Refer to the supplementary handout to see the breakdown by gender of weight gain to week 144 in ADVANCE; **Lab parameters included in risk equations using participants' last available measure between Week 96 and Week 144

Results (2/2)

Summary of risk score changes from baseline to week 144

Risk Equation		Arm 1 (TAF/FTC+DTG)		Arm 2 (TDF/FTC+DTG)		Arm 3 (TDF/FTC/EFV)		P-value Arm 1 vs Arm 3	P-value Arm 1 vs Arm 2	P-value Arm 2 vs Arm 3
		n	Median (Q1, Q3)	n	Median (Q1, Q3)	n	Median (Q1, Q3)			
Framingham (CVD)	Baseline	216	2.63 (1.63, 4.57)	218	2.70 (1.70, 5.42)	215	2.64 (1.60, 4.35)			
	Change to week 144	139	+1.37 (0.56, 2.77)	133	+1.02 (0.38, 2.05)	125	+0.96 (0.46, 2.33)	0.034	0.038	0.982
QRISK (CVD)	Baseline	216	0.60 (0.30, 1.00)	218	0.50 (0.30, 1.10)	215	0.50 (0.30, 1.00)			
	Change to week 144	131	+0.36 (0.14, 0.80)	139	+0.25 (0.10, 0.65)	116	+0.2 (0.10, 0.60)	0.016	0.113	0.377
QDiabetes (T2D)	Baseline	213	0.30 (0.10, 0.70)	210	0.30 (0.10, 1.00)	211	0.30 (0.10, 0.90)			
	Change to week 144	129	+1.50 (0.5, 3.5)	131	+0.80 (0.3, 2.6)	114	+1.25 (0.4, 3.4)	0.674	0.024	0.048

Risk score given as median change (Q1, Q3) in score from baseline. Risk score gives 10-year risk (%) of developing an incident CVD or T2D event. P-values were derived from Mann-Whitney U tests comparing two different treatment groups. All participants ≥30 years old at baseline. The supplementary handout gives risk equation predictions by gender.

> **1 additional heart attack or stroke** over 10 years per 1000 people treated with TAF/FTC+DTG vs TDF/FTC+EFV (p=0.016, *QRISK*)
>
> **7 additional diabetes cases** over 10 years per 1000 people treated with TAF/FTC+DTG vs TDF/FTC+DTG (p=0.024, *QDiabetes*)

*Refer to the supplementary handout to see the results breakdown by gender

Key Messages

- Treatment-emergent weight gain, particularly on TAF/FTC+DTG, increased ADVANCE participants' predicted 10-year risk of developing CVD and T2D

  ➢ Pooled analyses and trials with longer follow up, as well as a predictive risk equation validated in a HIV-positive population in sub-Saharan Africa, are needed to explore this effect further

- Mass use of TAF/FTC+DTG across sub-Saharan Africa could lead to an increase in additional cases of diabetes and myocardial infarction/stroke over the next 10 years

  ➢ Clinicians prescribing these newer antiretrovirals should monitor participants' weight changes and offer guidance on weight management such as dietary advice

  ➢ We need nuanced approaches to HIV medicine and policy that identify and respect differences in biology resulting from gender and race

PREDICTED 10-YEAR RISKS OF CARDIOVASCULAR DISEASE AND DIABETES IN THE ADVANCE TRIAL: Supplementary Handout
Presenting author: Laura Hindley MPH, School of Public Health, Imperial College London, United Kingdom

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Appendix 1A, 1B: Summary of weight gain from baseline to week 144. Men and women ≥30 years old at baseline.

1A. Weight gain, women ≥ 30 years

1B. Weight gain, men ≥ 30 years
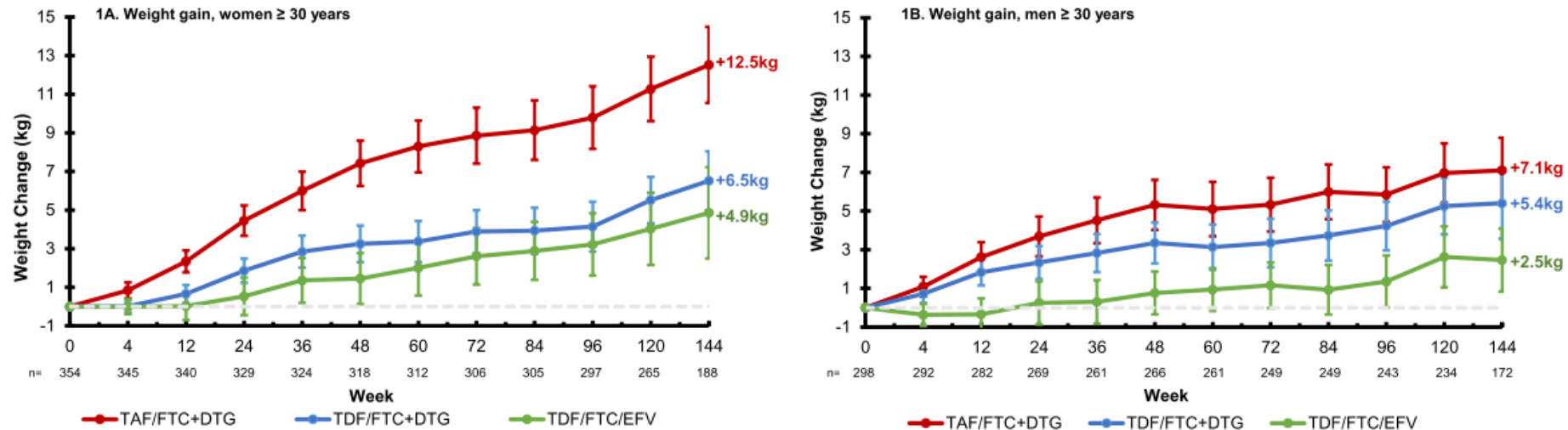
Appendix 2: Summary of risk score changes from baseline to week 144. Men and women ≥30 years old at baseline.

	Equation		Arm 1 (TAF/FTC+DTG)		Arm 2 (TDF/FTC+DTG)		Arm 3 (TDF/FTC/EFV)		P-value Arm 1 vs Arm 3	P-value Arm 1 vs Arm 2	P-value Arm 2 vs Arm 3
			n	Median (Q1, Q3)	n	Median (Q1, Q3)	n	Median (Q1, Q3)			
Framingham (CVD)	Females	Baseline	119	1.88 (1.36,2.81)	117	1.97 (1.18,3.50)	116	1.94 (1.19,3.12)			
		Change to week 144	73	+0.96 (0.46,1.69)	66	+0.75 (0.30,1.44)	65	+0.64 (0.28,1.26)	0.14	0.15	0.95
	Males	Baseline	97	3.99 (2.78,5.82)	101	3.99 (2.58,6.61)	99	3.57 (2.36,6.08)			
		Change to week 144	66	+2.06 (1.03,4.79)	67	+1.63 (0.60,3.63)	60	+1.51 (0.68,2.98)	0.05	0.06	0.92
QRISK (CVD)	Females	Baseline	120	0.40 (0.20,0.80)	117	0.40 (0.20,0.80)	116	0.40 (0.20,0.80)			
		Change to week 144	72	+0.20 (0.10,0.51)	69	+0.19 (0.06,0.40)	63	+ 0.18 (0.05,0.40)	0.08	0.09	0.98
	Males	Baseline	96	0.70 (0.50,1.25)	101	0.70 (0.30,1.40)	99	0.60 (0.30,1.50)			
		Change to week 144	59	+0.52 (0.24,1.29)	70	+0.38 (0.16,1.20)	53	+0.30 (0.12,0.85)	0.05	0.26	0.31
Qdiabetes (T2D)	Females	Baseline	120	0.30 (0.10,0.65)	111	0.30 (0.10,1.10)	116	0.30 (0.10,0.80)			
		Change to week 144	72	+1.70 (0.5, 3.6)	63	+0.80 (0.3, 3.0)	62	+1.15 (0.4, 2.6)	0.39	0.22	0.59
	Males	Baseline	92	0.40 (0.20,0.70)	99	0.30 (0.10,1.00)	95	0.30 (0.10,1.00)			
		Change to week 144	57	+1.40 (0.5, 3.5)	68	+0.70 (0.25, 2.45)	52	+1.35 (0.45, 3.60)	0.79	0.05	0.02

Risk score given as median change (Q1, Q3) in score from baseline. Risk score gives 10-year risk (%) of developing an incident CVD or T2D event. P-values were derived from Mann-Whitney U tests comparing two different treatment groups