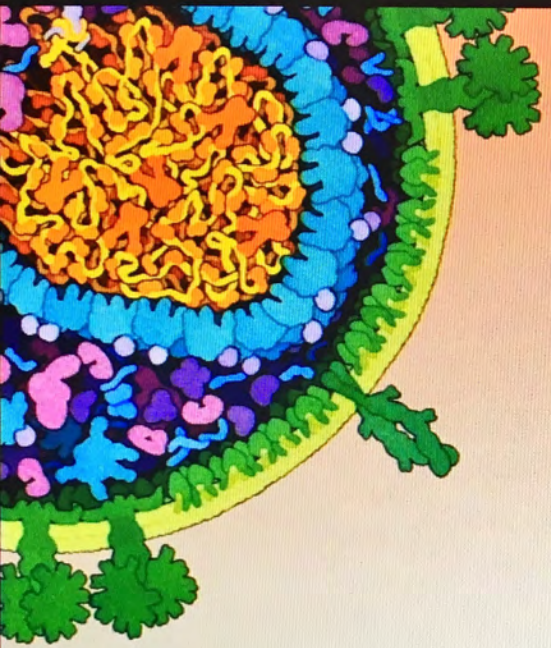

Disclosures:

NOTHING TO DISCLOSE

CYP2B6 Genotype and Weight Gain Differences Between Dolutegravir and Efavirenz

Rulan Griesel, Gary Maartens, Simiso Sokhela, Godspower Akpomiemie, Francois Venter, Michelle Moorhouse, Phumla Sinxadi

CROI
Conference on Retroviruses and Opportunistic Infections

Background

- InSTIs, especially DTG, are associated with more weight gain than other classes of ARVs in PLWH starting ART[1,2]
- Women and people of African ancestry experience more weight gain on ART[1]
- Two RCTs in Africa showed more weight gain with DTG than EFV, especially in women[3,4]

  Treatment emergent obesity at 48 weeks:
  - 12.3% DTG vs 5.4% EFV in NAMSAL[3]
  - 14% TAF/DTG vs 7% TDF/DTG vs 6% TDF/EFV in ADVANCE[4]

[1]Sax P, et al. Clin Infect Dis 2019.
[2]Bourgi K, et al. CROI 2019.
[3]Kouanfack C, et al. NEJM 2019.
[4] Venter WDF, et al. NEJM 2019.

CROI 2020: Live Webcast Schedule

Sunday, March 8, 2020

9:00 AM-12:25 PM ET
12:25 PM-1:40 PM ET
2:00 PM-4:00 PM ET
5:00 PM-7:00 PM ET

Background

- *CYP2B6* loss of function single nucleotide polymorphisms (SNPs) are associated with higher EFV concentrations
- *CYP2B6* slow metaboliser genotypes are common in Africa (~20%)[5]
- *CYP2B6* slow metabolisers gained more weight when switched from EFV to InSTI-based ART,[6] suggesting that higher EFV concentrations impair weight gain
- Potential mechanisms of impaired weight gain on EFV:
  1. Concentration-dependent toxicity to mitochondria & adipocytes[7]
  2. Less limb fat gain vs PIs[8]
  3. Chronic neuropsychiatric toxicity could impair appetite

[5]Barret J, et al. Int J Clin Pharmacol Ther 2002.
[6]Leonard M, et al. CROI 2019.
[7]Moure R, et al. Antiviral Research 2016.
[8]de Waal R, et al. PloS ONE 2013.

Hypothesis

We hypothesised that loss of function SNPs in *CYP2B6*, which increase EFV concentrations, could impair weight gain in PLWH starting EFV-based ART

ADVANCE: *CYP2B6* weight gain sub-study

ADVANCE RCT in ART-naïve in South Africans
3 arms: TDF/FTC/DTG, TAF/FTC/DTG, TDF/FTC/EFV[4]

[4] Venter WDF, et al. NEJM 2019.

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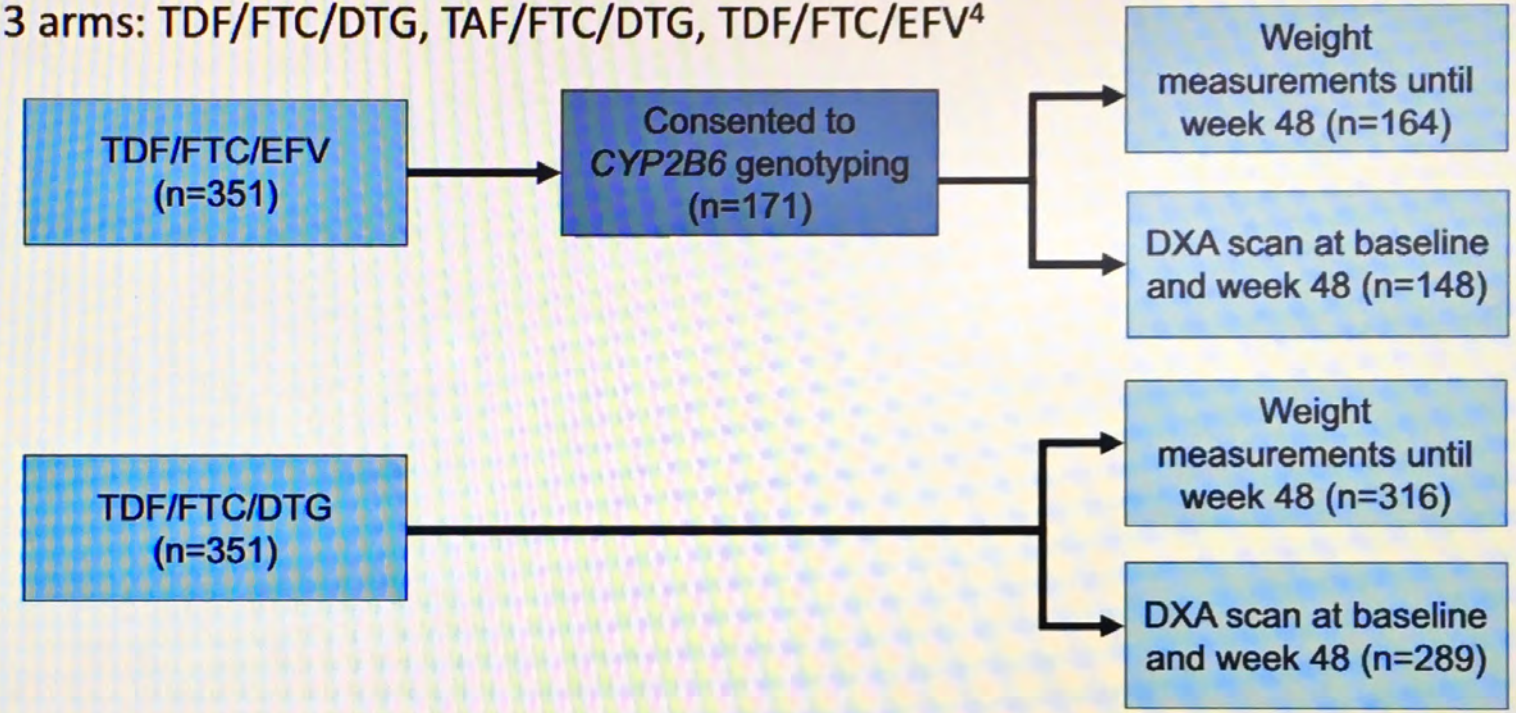


[4] Venter WDF, et al. NEJM 2019.

Methods

- *CYP2B6* genotyping performed:
  - *CYP2B6* 516G→T (rs3745274)
  - *CYP2B6* 983T→C (rs28399499)
  - *CYP2B6* 15582C→T (rs4803419)
- Metaboliser genotype groups for *CYP2B6* SNPs were categorised as extensive, intermediate, or slow
- Weight measured at baseline, weeks 4, 12, 24, 36, and 48
- DXA scan measurements at baseline and week 48

Methods

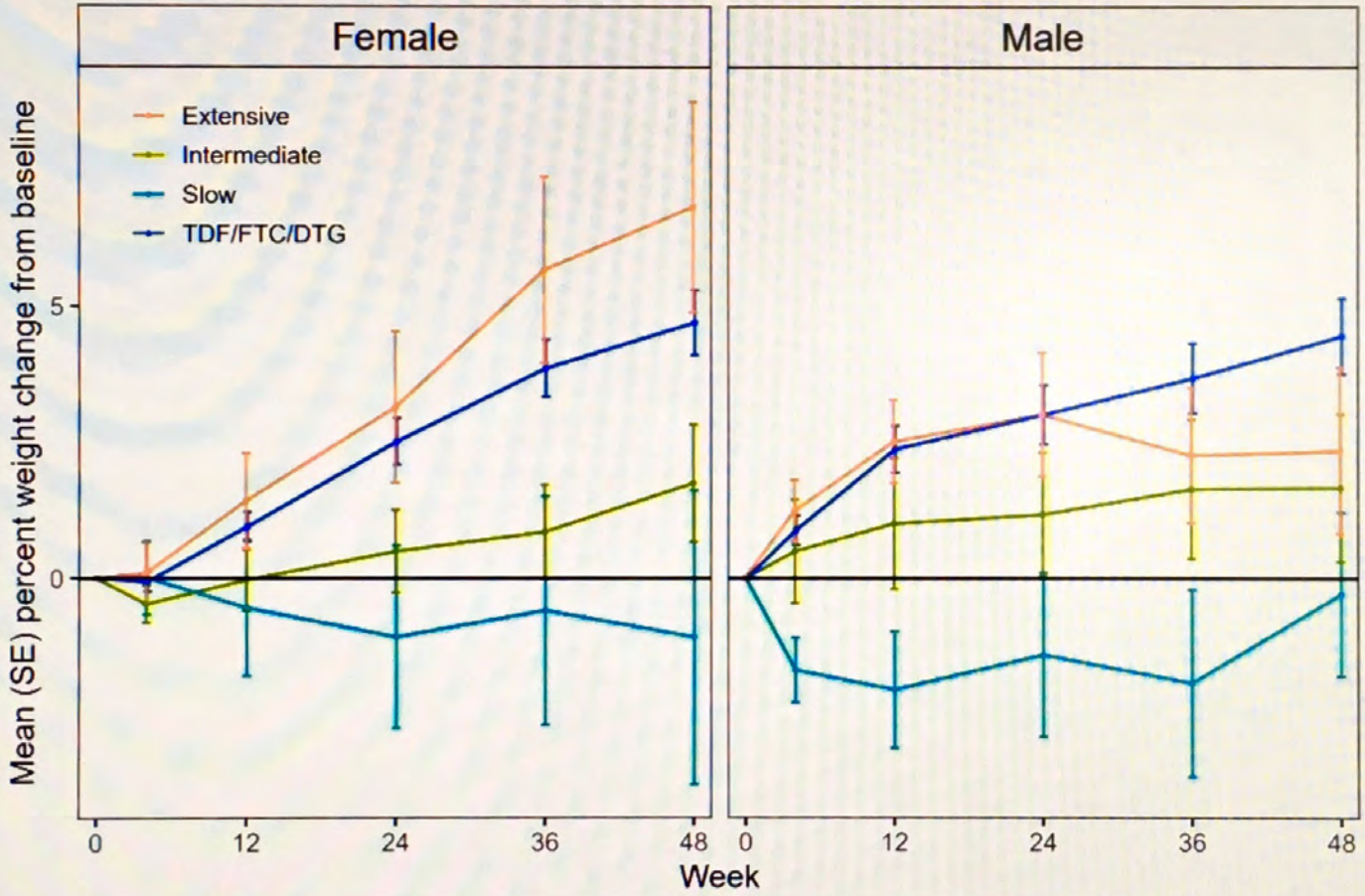
- Outcome variables: percentage change from baseline to week 48 of weight, and of limb and trunk fat
- Kruskal-Wallis followed by Dunn's test with Bonferroni correction for multiple comparisons by *CYP2B6* metaboliser genotype within TDF/FTC/EFV arm and with TDF/FTC/DTG arm
- Univariate and multivariate linear regression for covariates associated with weight change

Baseline Characteristics

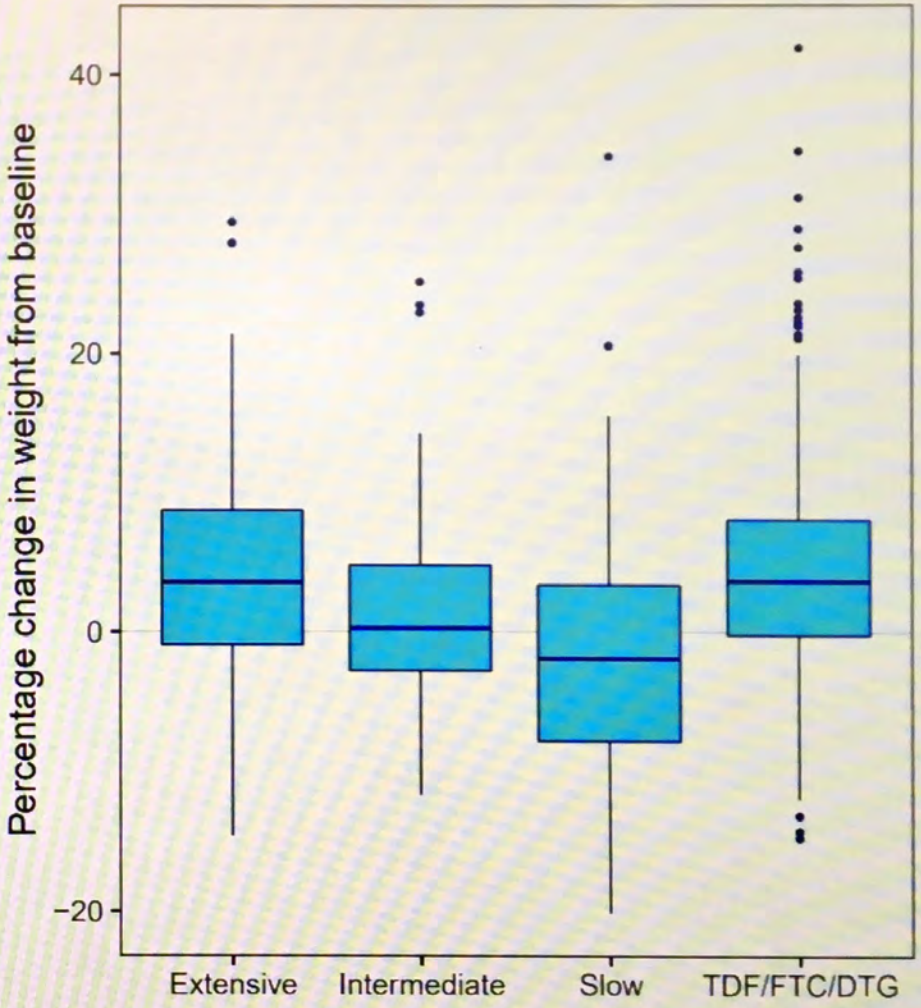
	TDF/FTC/EFV by *CYP2B6* metaboliser genotype			TDF/FTC/DTG (n=351)
	Extensive (n=51)	Intermediate (n=74)	Slow (n=46)	
Age (years), median (IQR)	31 (26-37)	31 (27-36)	32.5 (29-37)	32 (26-37)
Sex (female), n (%)	27 (52.9)	47 (63.5)	23 (50)	208 (59.3)
Race (black), n (%)	51 (100)	74 (100)	46 (100)	351 (100)
BMI (kg/m^2), median (IQR)	21.4 (19.7-25.5)	24.4 (21.4-28.3)	24.1 (20.4-27.5)	22.9 (20.0-26.8)
CD4 count (cells/μL), median (IQR)	290 (181-400)	303 (176-417)	268 (159-384)	275 (163-427)
HIV-1 RNA (log_{10}), median (IQR)	4.4 (3.8-4.8)	4.3 (3.5-5.1)	4.6 (4.0-5.1)	4.4 (3.8-4.9)

No statistically significant differences by group

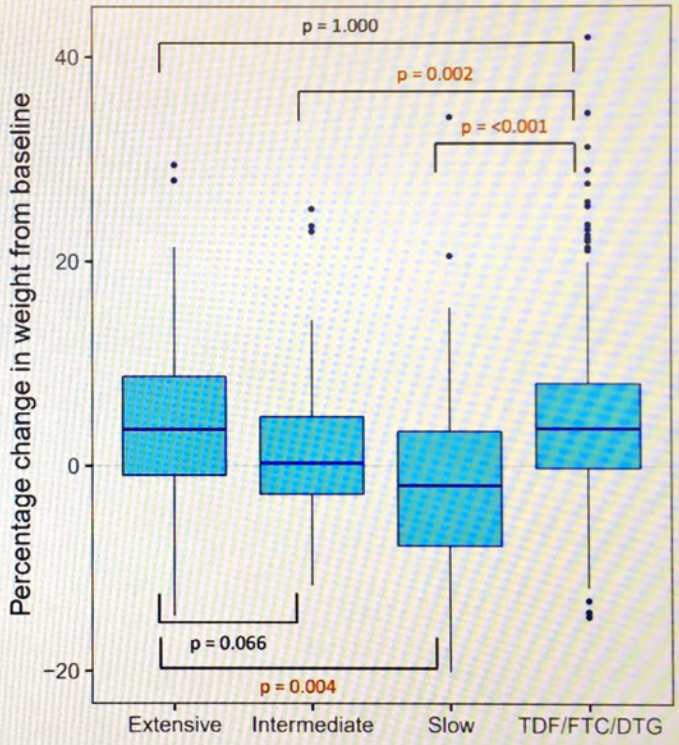
Weight change from baseline by sex & *CYP2B6*



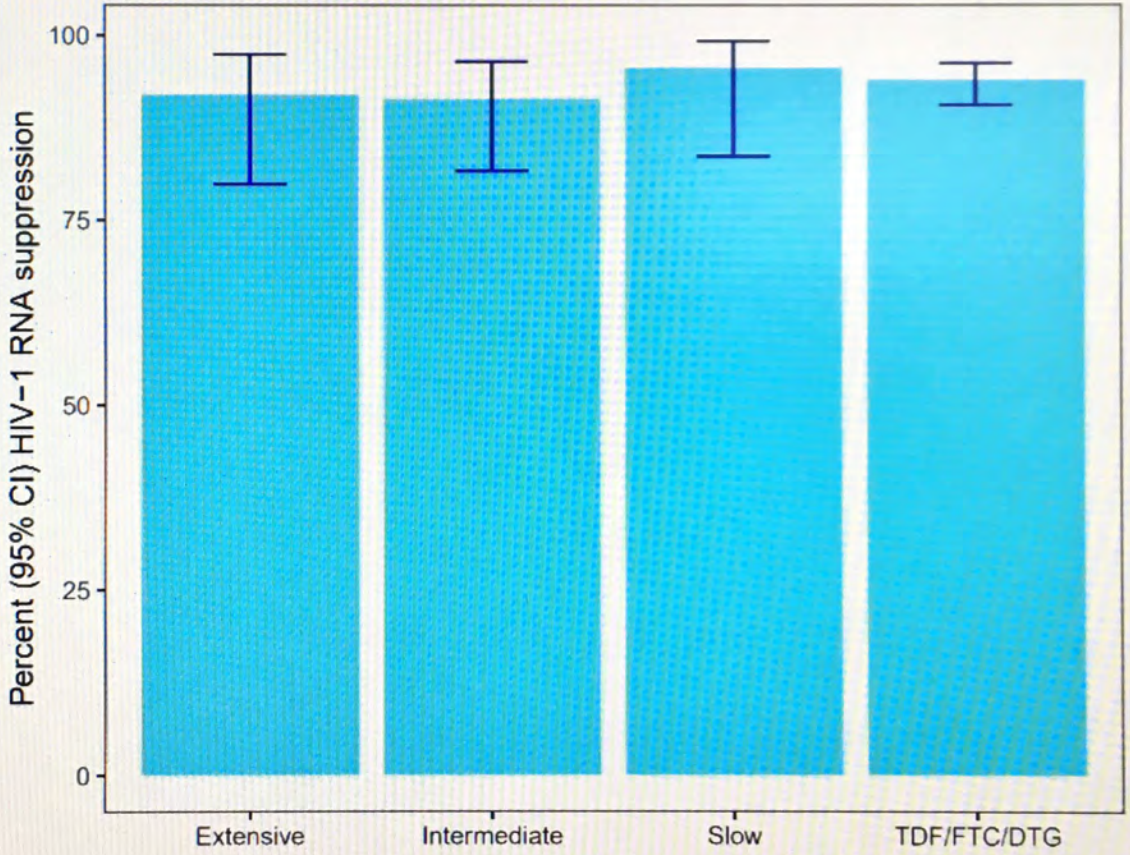
Weight change from baseline to week 48



Weight change from baseline to week 48

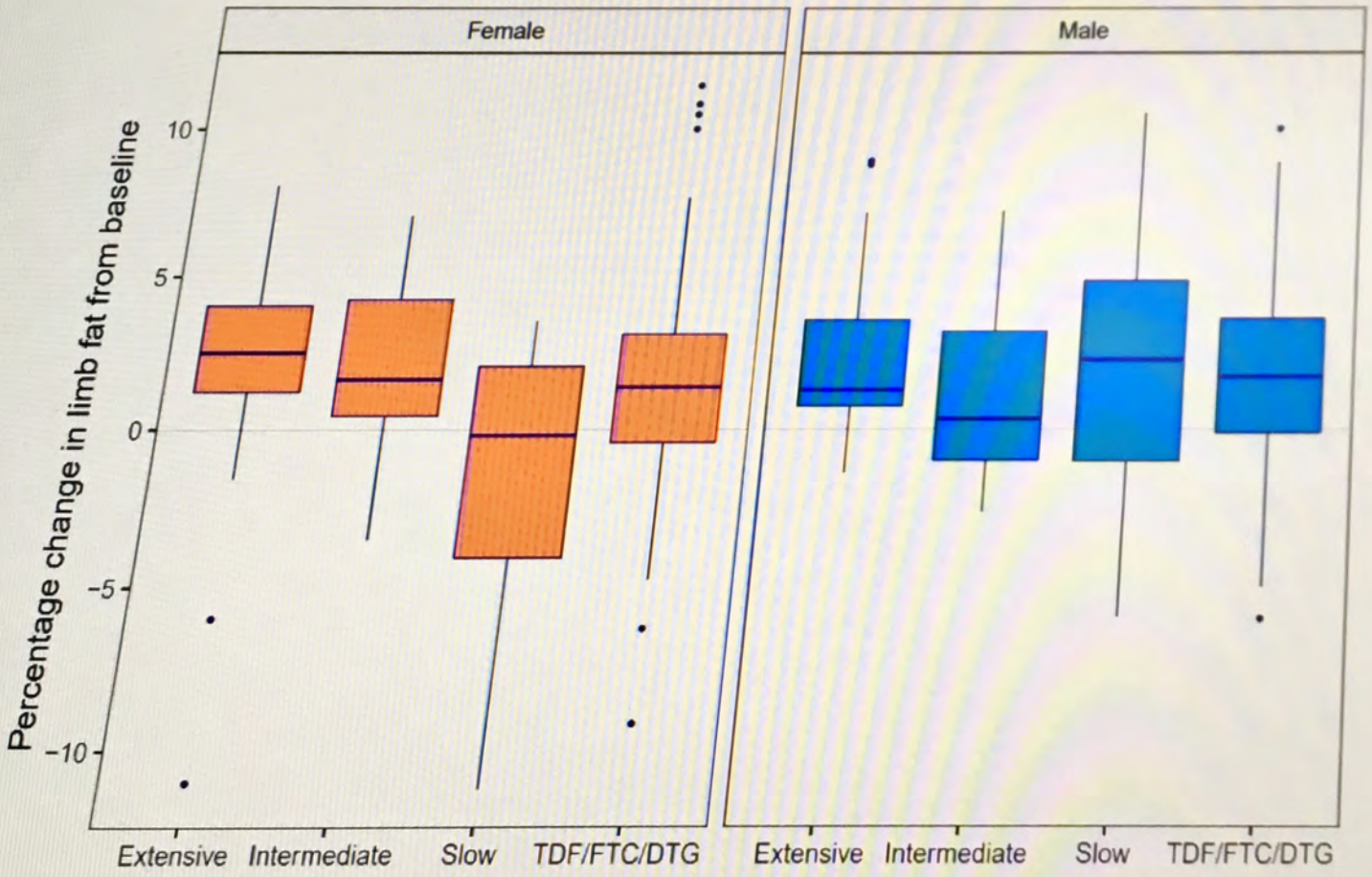


HIV-1 RNA suppression (<50 copies/mL) at week 48

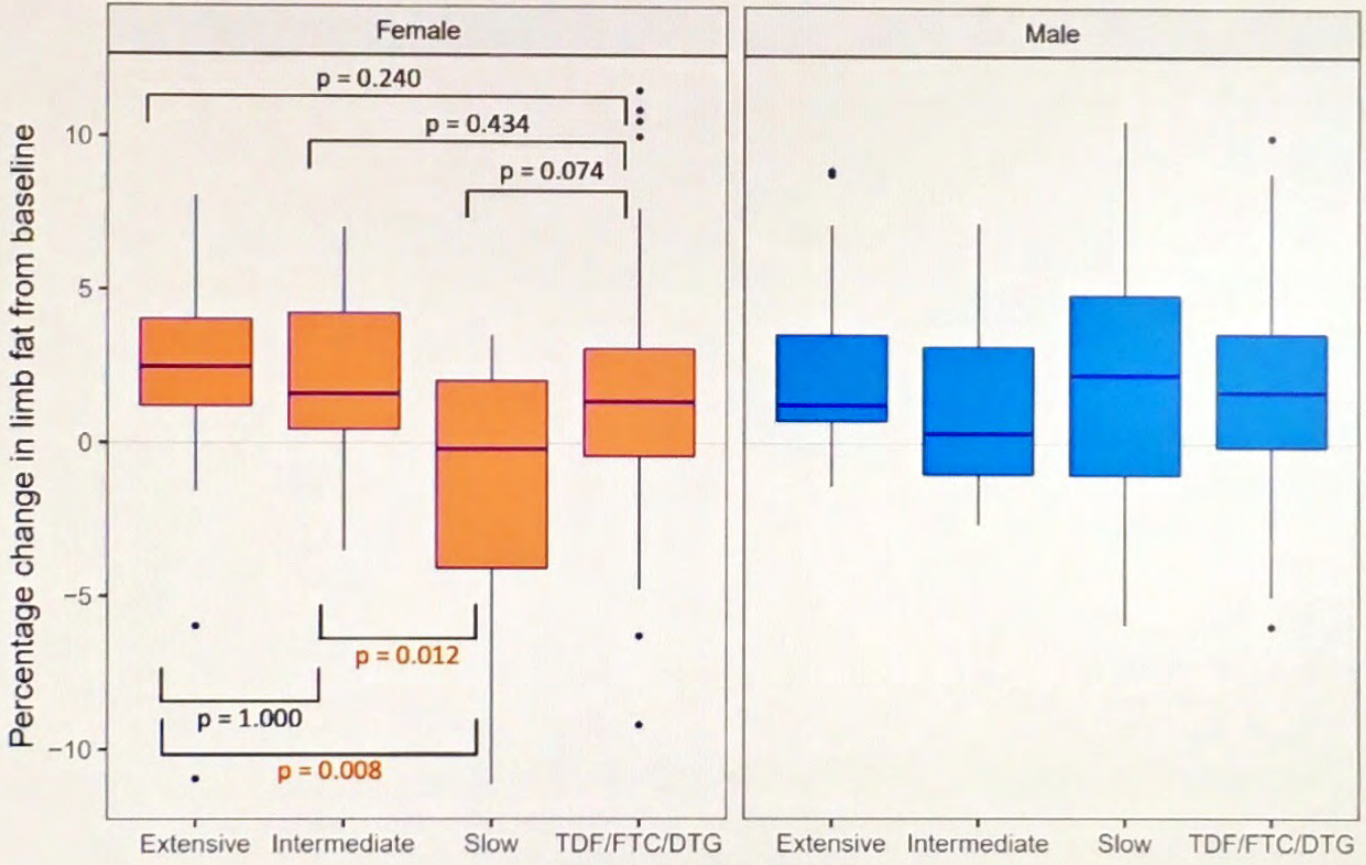


Fisher's exact test: p = 0.750

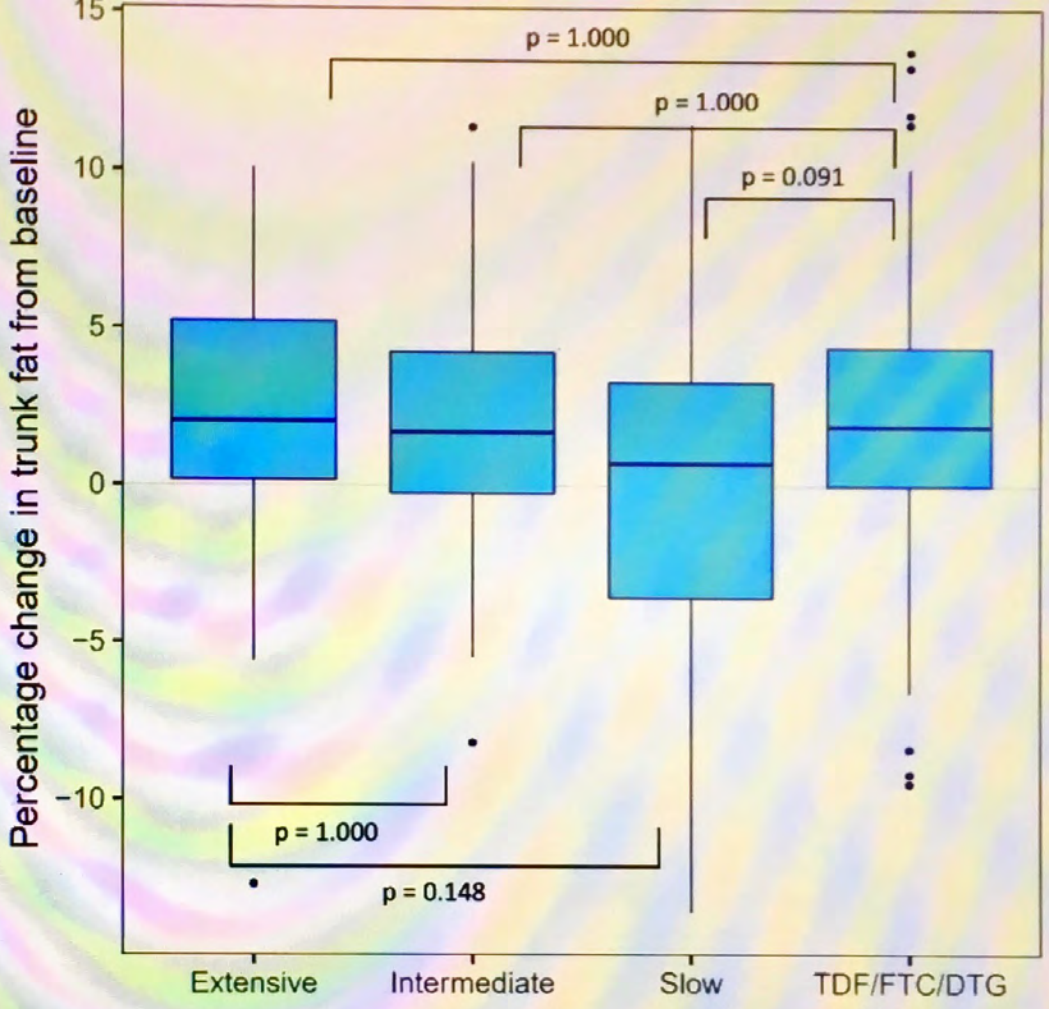
Change in limb fat from baseline to week 48 by sex



Change in limb fat from baseline to week 48 by sex



Trunk fat change from baseline to week 48



Linear regression: weight change from baseline to week 48 (n=480)

Variable	Multivariate associations	
	Estimate (95% CI)	p-value
Age (per 5 years)	-0.011 (-0.505 to 0.482)	0.964
Sex		
Female	Referent group	
Male	-1.236 (-2.700 to 0.228)	0.098
Baseline CD4 count (per 50 cells/μL)	-0.233 (-0.397 to -0.068)	0.006
Baseline HIV-1 RNA (per 1 $\log_{10}$)	2.251 (1.289 to 3.214)	<0.001
ARV category		
TDF/FTC/DTG arm	Referent group	
TDF/FTC/EFV arm		
***CYP2B6* extensive metaboliser**	-0.023 (-2.468 to 2.421)	0.985
***CYP2B6* intermediate metaboliser**	-2.893 (-4.725 to -1.061)	0.002
***CYP2B6* slow metaboliser**	-5.751 (-8.861 to -2.641)	<0.001

Covariates explored: age, sex, baseline BMI, CD4 count, HIV-1 RNA, HIV-1 RNA suppression (<50 copies/mL) at week 48, and treatment emergent nausea/vomiting and neuropsychiatric adverse events

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Covariates explored: age, sex, baseline BMI, CD4 count, HIV-1 RNA, HIV-1 RNA suppression (<50 copies/mL) at week 48, and treatment emergent nausea/vomiting and neuropsychiatric adverse events

Conclusions

- Weight gain was less in *CYP2B6* intermediate and slow metabolisers, but was similar between extensive metabolisers in the EFV arm and the DTG arm
- Female *CYP2B6* slow metabolisers gained less limb fat than extensive and intermediate metabolisers
- *CYP2B6* metaboliser genotype, baseline HIV-1 RNA and CD4 count were independent predictors of weight change
- Our findings suggest that weight differences between EFV and DTG are driven by impaired weight gain in PLWH with loss of function *CYP2B6* SNPs
- Limitations: post hoc analysis; EFV concentrations not measured

Acknowledgements

wellcome centre infectious diseases research in africa

Ezintsha/Wits RHI - ADVANCE trial
Study participants

Donors
- USAID
- Unitaid
- SA MRC

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