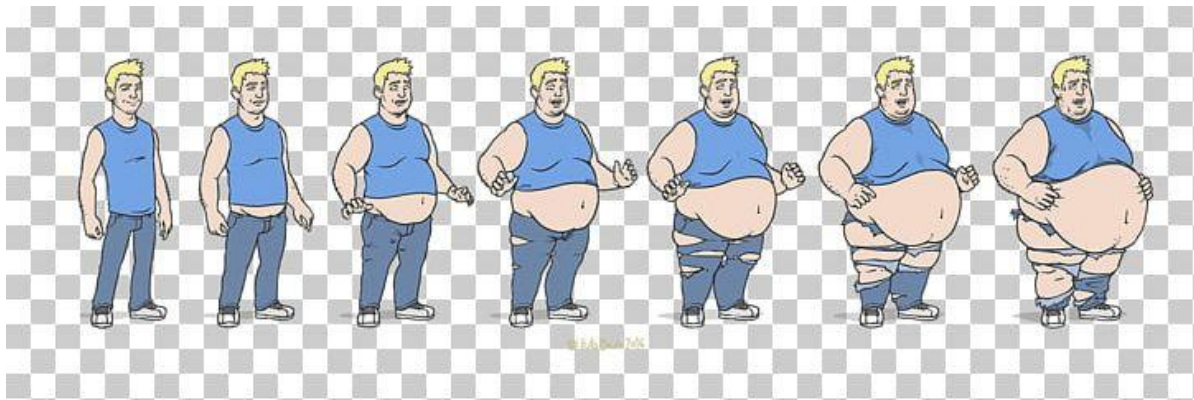


What is known about Weight Gain on INSTI-based regimens?



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What is known about Weight Gain on INSTI-based regimens?

Question

- i have been **on stribild for approx 4 months** and **have gained approx 2.5 stone since starting it**....i had a flat stomach when i started this medication and now i am bloated across my abdomen area.....i am extremely worried as i also have copd.....this bloating is putting alot of pressure on my insides and giving my lungs less room to manouver....i have **went from a 30 waist to 37 waist** and am just eating same as i usually did before starting stribild.....i rekon if i stay on this medication much longer it will kill me.....i have mentioned it to my HIV specialist at last visit and they shrug and seem unconcerned when they should be the opposite...they are afterall supposed to be looking out for me or my health.....what is causing me to grow so fast in such a short period of time?...i was perfectly fine before.

What year was this post made on social media?

2013

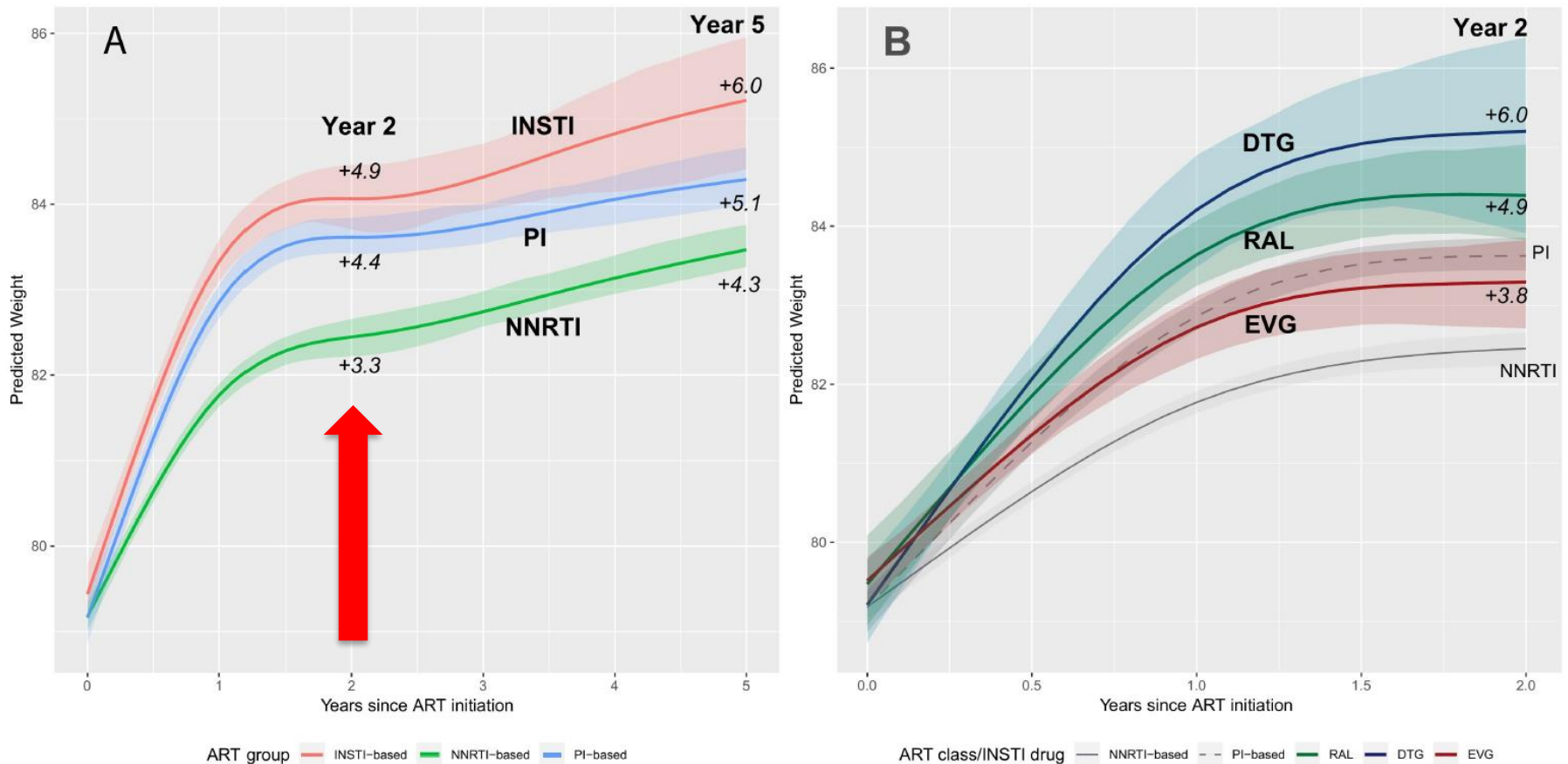


Overview

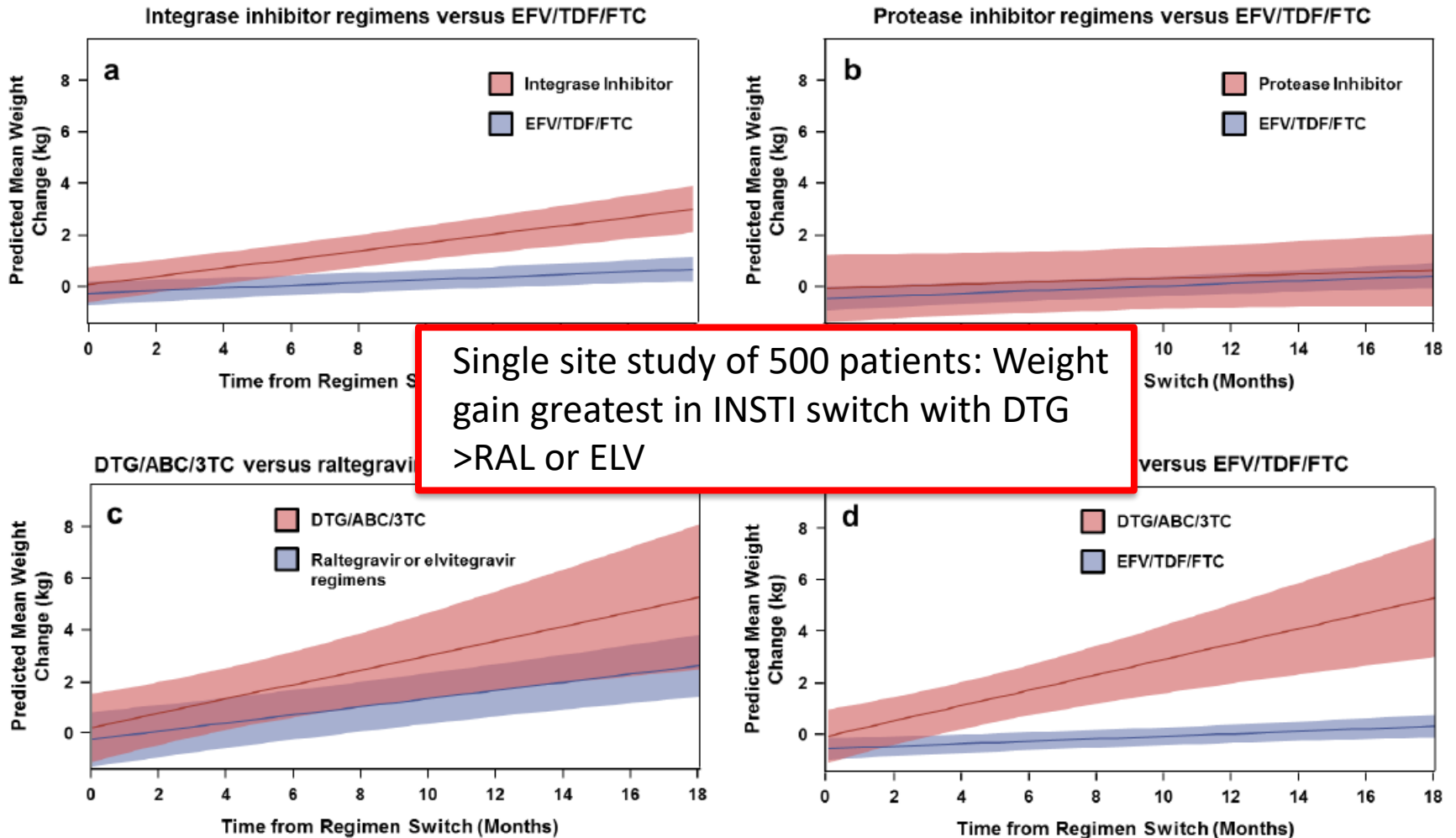
- Are integrase inhibitors associated with greater weight gain than other drugs?
- Who is at greater risk of weight gain on integrase inhibitors?
- Are there differences between integrase inhibitors?
- Are there differences for risk of weight gain between ART naïve PLHIV and those switching regimens?
- Are there differences with companion NRTI drugs?
- What are the long term consequences of weight gain?
- What is the pathogenesis of weight gain with INSTIs?
- Is the weight gain with INSTIs reversible?

CROI 2019: Greater weight gain among treatment-naïve persons starting integrase inhibitors: NA-ACCORD

Predicted weight changes within: (A) 5-years of ART initiation by ART class; (B) 2- years of ART initiation by INSTI drug and ART class



Weight gain in PLHIV switched to INSTI-based regimens from TDF/FTC/EFV



CROI 2019 Weight Gain After Switch to INSTI-Based ART

- Prospective cohort study - weight gain after switch to INSTI-based ART from ACTG A5001, A5322 (N = 691) 2007-2017, virologically suppressed

Adjusted Annual Weight Change,* kg/yr (P Value)	Women		Men		Women		Men		Women ≥ 30 kg/m ² at Switch
	Black	White	Black	White	40 Yrs or Younger	60 Yrs or Older	40 Yrs or Younger	60 Yrs or Older	
2 yrs pre-INSTI	0.4 (.08)	0.6 (.03)	0.4 (.02)	0.4 (< .0001)	1.5 (.01)	-0.2 (.61)	0.8 (.009)	0.1 (.46)	0.2 (.54)
2 yrs post-INSTI	1.3 (< .0001)	2.0 (< .0001)	1.0 (.002)	0.2 (.09)	-1.0 (.17)	1.8 (.0005)	-0.1 (.88)	0.9 (.0008)	1.9 (< .0001)
Post-pre difference	0.9 (.04)	1.4 (.02)	0.6 (.11)	-0.2 (.38)	-2.5 (.02)	2.0 (.008)	-0.9 (.20)	0.8 (.04)	1.7 (.002)

Adjusted for age at switch, sex, race/ethnicity, BL BMI and their interactions, nadir CD4+ cell count, smoking history, diabetes, and % time with HIV-1 RNA < 200 c/mL.

- Annual weight gain increased following switch to INSTI, with **greater increases among women, blacks, and individuals 60 yrs of age or older**
- Increases in weight change per year from pre- to post-INSTI periods statistically significant with:
 - Switch to DTG from PI or NNRTI
 - Switch to EVG from NNRTI
 - Switch to any INSTI + ABC
 - Switch to EVG + TAF

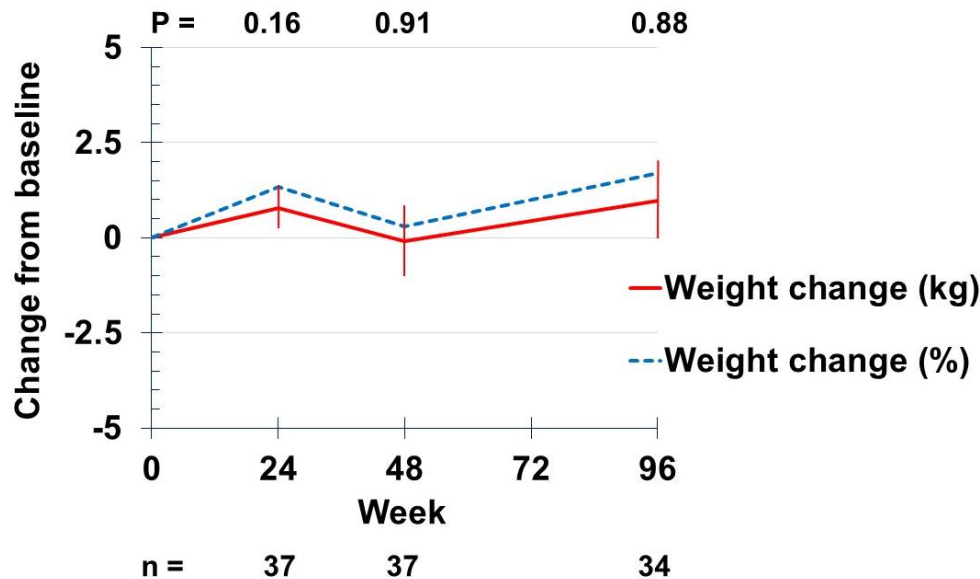
Analysis limited by small sample sizes in subsets

Other studies muddying the waters

- Majority of observational studies did find greater weight gain on initiation or switching to an INSTI-based regimen – magnitude and who was at risk varied
- HIV Outpatient study (switch): non-Hispanic black patients, no prior NRTI
- Bedimo study (naïve): women gained more weight than men on raltegravir and dolutegravir, Black race gained more weight on dolutegravir, entire cohort gained more weight on Elvitegravir than dolutegravir or raltegravir.
- Significantly greater increase in weight and waist circumference for naïve PLHIV randomised to raltegravir versus DRV/r (ACTG A5257) – more pronounced in women, black race

Switch from tenofovir DF to raltegravir is not associated with weight gain over 96 weeks

Figure 2: Mean weight change over 96 weeks after switching from TDF to raltegravir



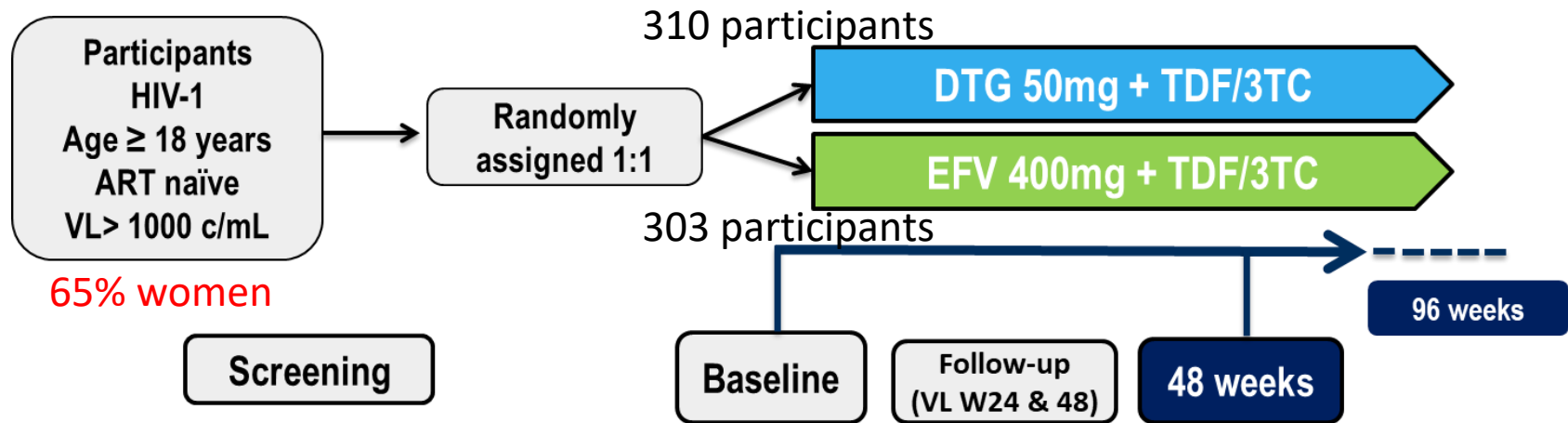
Switching to raltegravir 400mg bd from TDF 300mg daily in virologically-suppressed PLHIV (majority white men) resulted in a BMD increase but no significant weight change

Weight gain may not occur with all INSTIs



NAMSAL: Study design

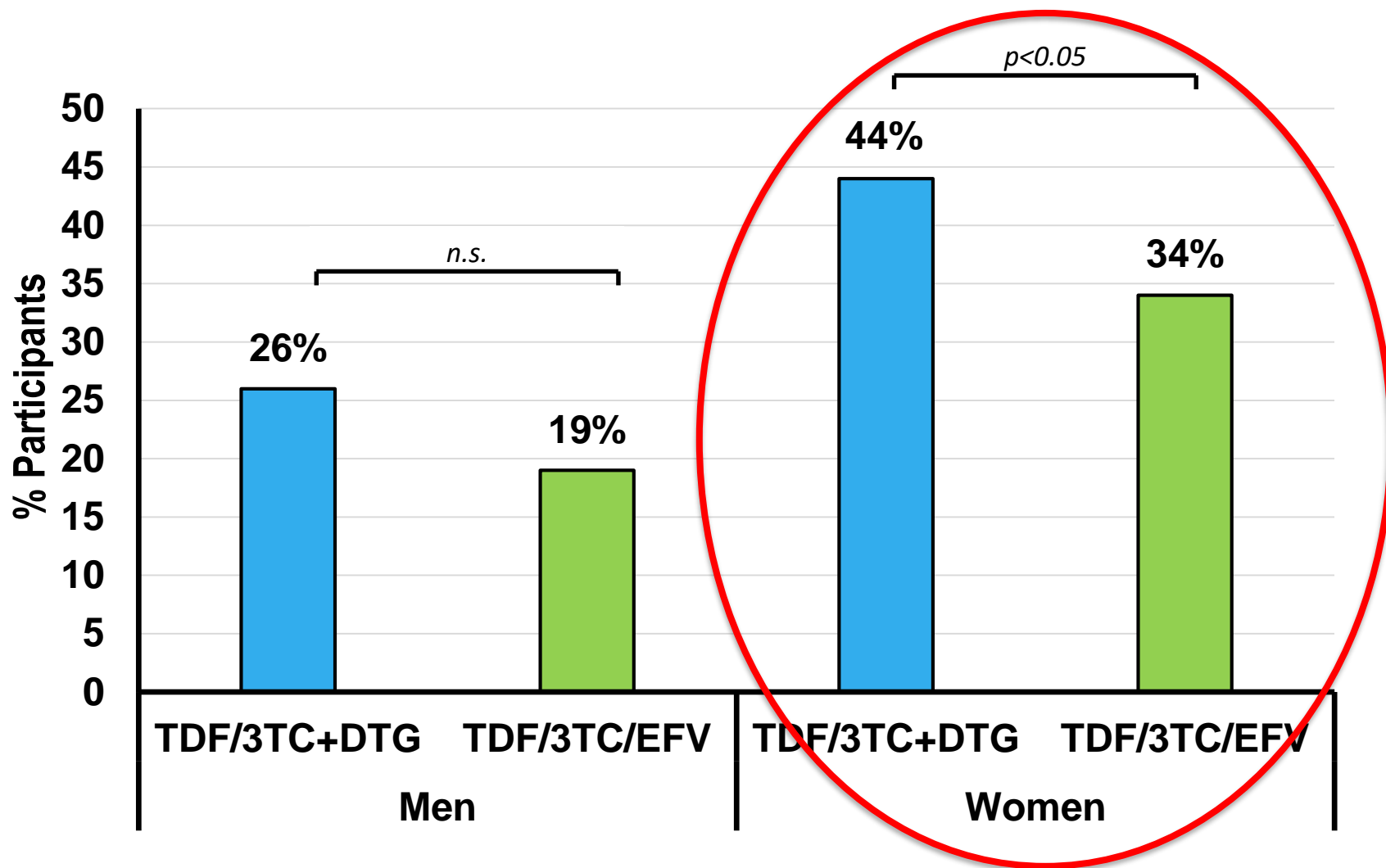
- Phase 3, randomised, open-label trial
- 3 study sites in Cameroon



Mean age – 37 years
Mean BMI - 23

A Cournil *et al.* International Congress on Drug Therapy in HIV Infection 2018. Abstract O342

NAMSAL: $\geq 10\%$ change from baseline weight (Week 48)



Does TAF promote weight increase?

Retrospective analysis of a German cohort - mean increase in body weight of 2.3 kg after switching from TDF to TAF¹

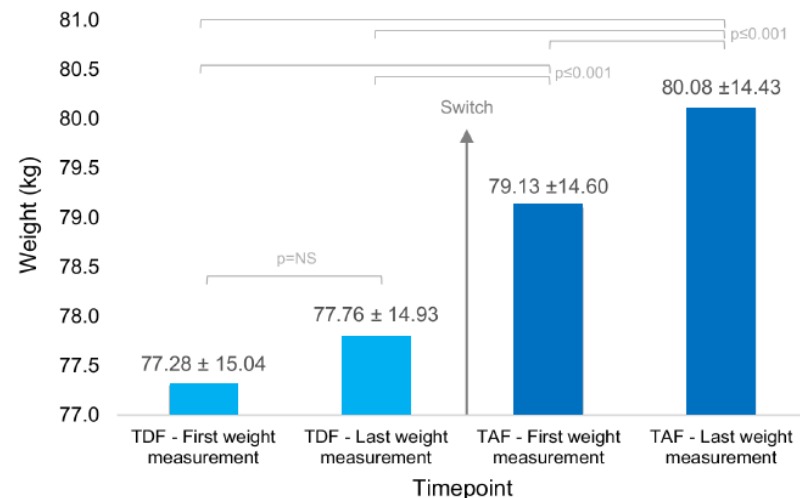
241 treatment-experienced adults treated with TDF or TAF from 2015-2017

- N=129 switched TDF to TAF
- N=112 remained on TDF (control)

Third agent switches in the 129 also occurred:

- 13 NNRTI → INSTI
- 7 PI → INSTI
- Weight change with TDF → TAF switch significant in these 21, but lower (78.8 kg at first TAF measurement and 79.8 kg at second TAF measurement)

Retrospective, single-site analysis of 129 patients switched from a TDF- to a TAF-containing regimen



Weight increased after TDF → TAF switch

- Last TDF to first TAF measurement: 77.8 to 79.1 kg ($p < 0.001$)
- First TAF to last TAF measurement: 79.1 to 80.1 kg ($p < 0.001$)

1. Gomez M et al. Infection 2018;

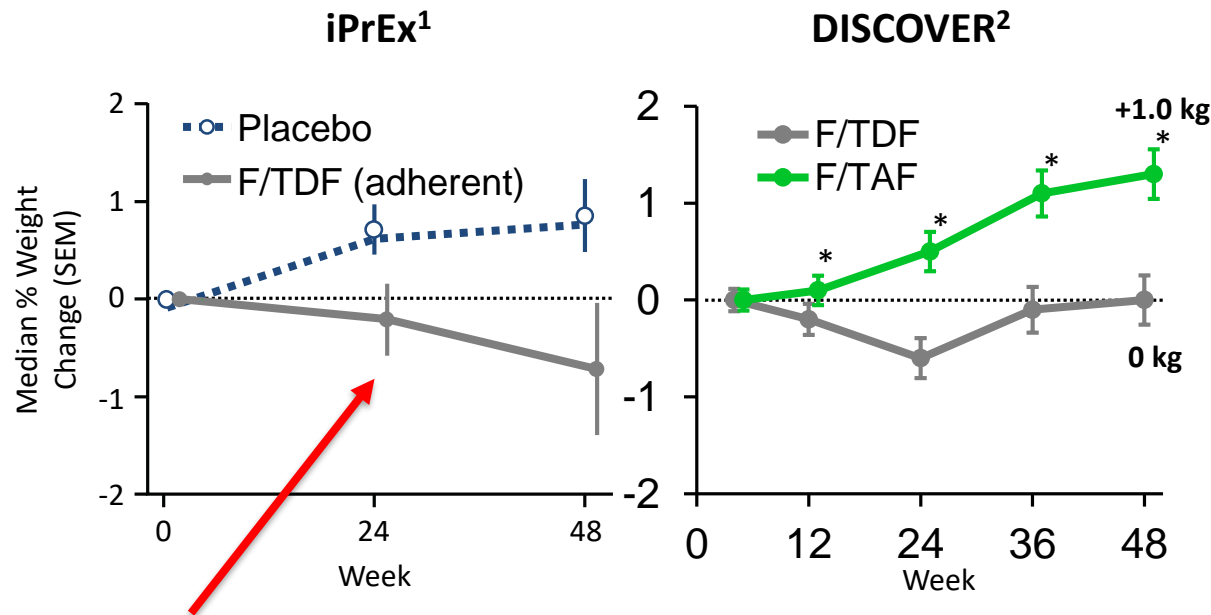
Does TAF promote weight increase?

Randomised Controlled Trials in Naive PLHIV:

Study	ARV agents	Weight gain
AMBER ²	Darunavir/cobi/FTC/TAF (48 weeks)	1.8 kg
	Darunavir/cobi/FTC/TDF (48 weeks)	0.8 kg
Bictegravir 1489 ³	Bictegravir/FTC/TAF (96 weeks)	3.6 (IQR 0-8.5) kg
	Dolutegravir/3TC/ABC (96 weeks)	2.4 (IQR -0.4-5.8) kg
Bictegravir 1490 ⁴	Bictegravir/FTC/TAF (96 weeks)	3.5 (IQR 0.1-8.2) kg
	Dolutegravir/FTC/TAF (96 weeks)	3.9 (IQR 0.8-7.4) kg

2. Eron JJ et al. AIDS 2018; 3. Wohl DA et al. Lancet HIV 2019; 4. Stellbrink et al. Lancet HIV 2019

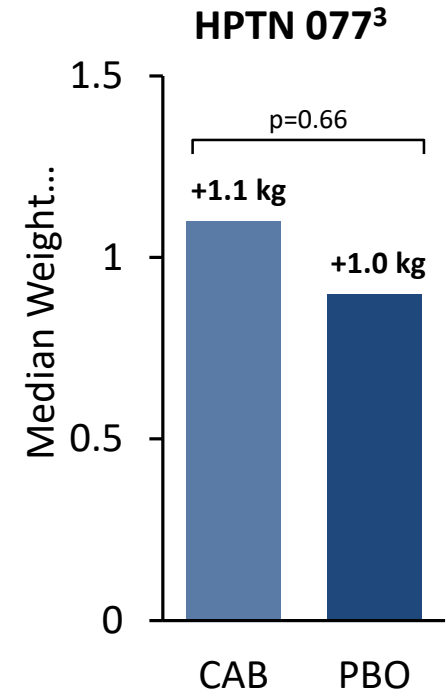
Weight Gain in PrEP Trials HIV negative individuals



Week 24 Diff -0.8% (95%CI -1.5 to -0.1%)

P=0.02

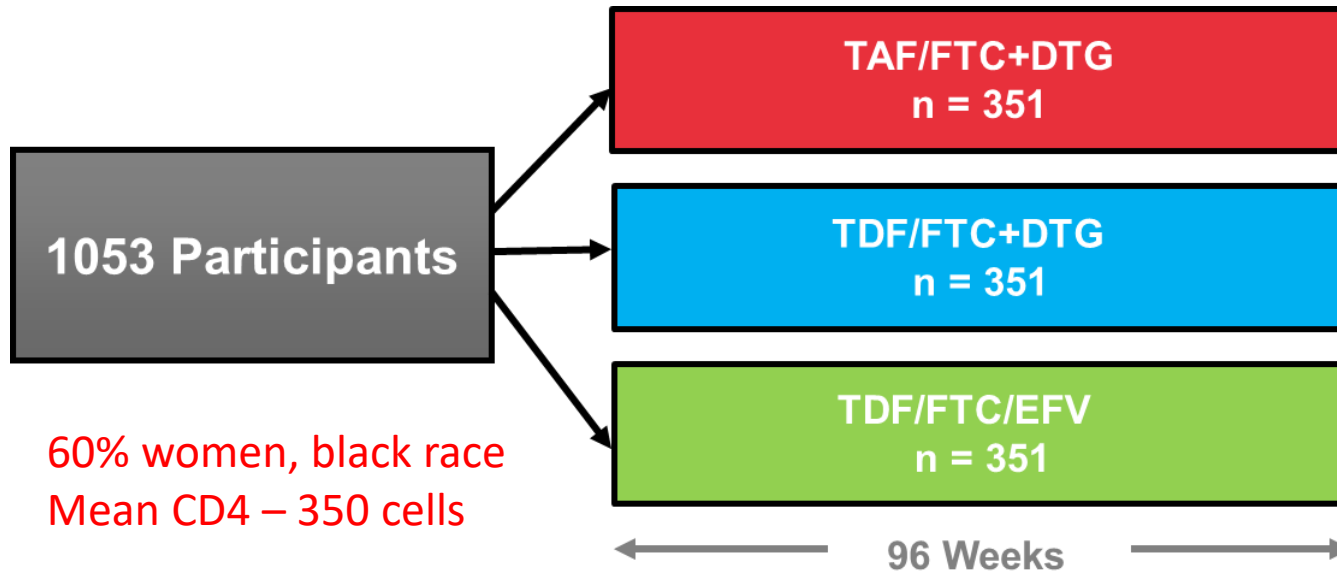
NOT driven by nausea



1. Adapted from Glidden DV, et al. Clin Infect Dis 2018;67:411-9, 2. . 3. Landovitz RJ, et al. Clin Infect Dis 2019 May 24.

ADVANCE: Study design

- **Inclusion criteria:** treatment-naïve, HIV-1 RNA level ≥ 500 copies/mL



- Open-label, 96-week study in Johannesburg, South Africa

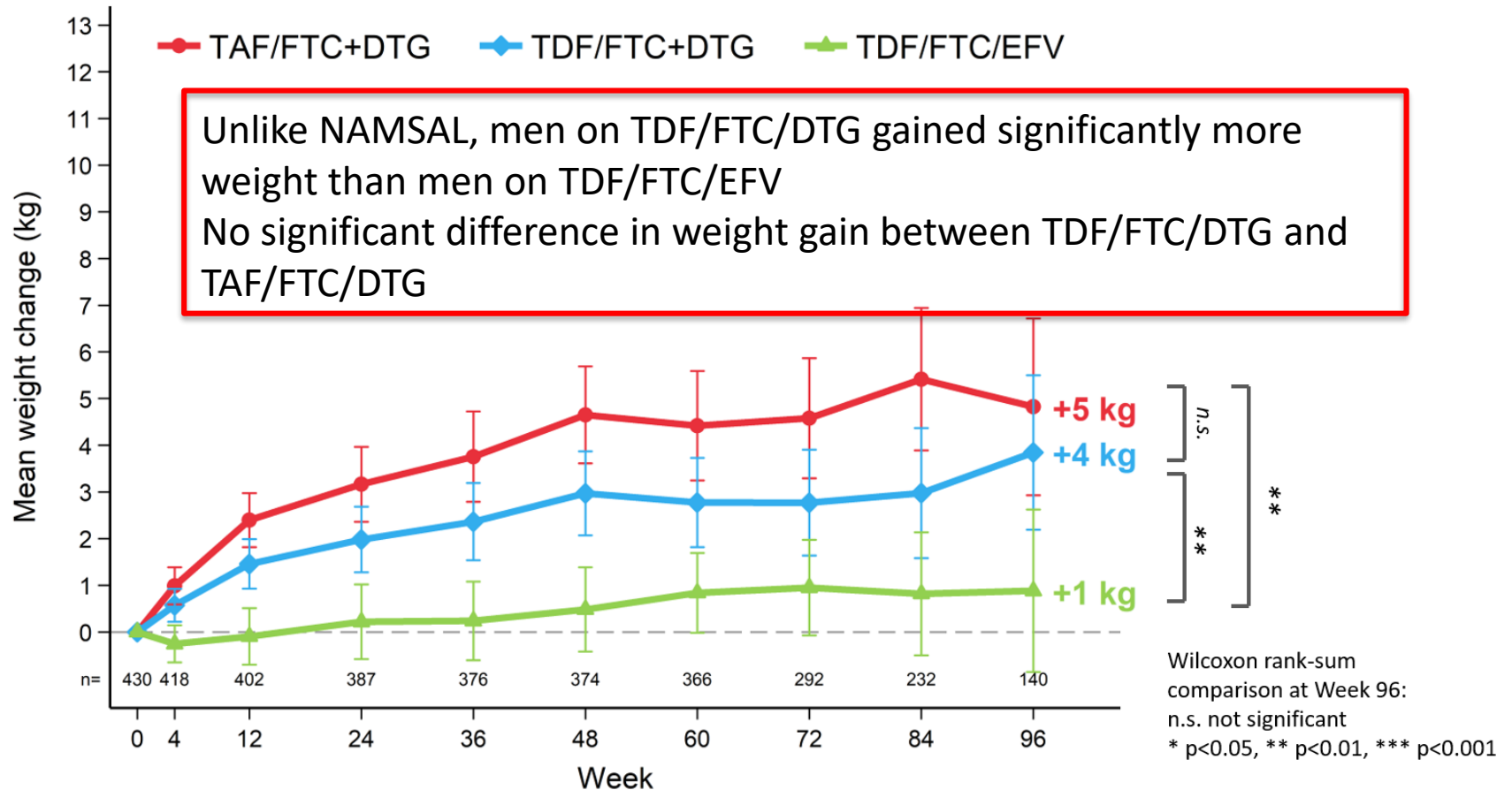
Venter et al, NEJM 2019

ADVANCE: Baseline characteristics

Characteristic	TAF/FTC+DTG (n=351)	TDF/FTC+DTG (n=351)	TDF/FTC/EFV (n=351)
Weight, mean (kg)			
Male	67.9	67.1	67.3
Female	68.8	69.5	70.2
BMI, mean (kg/m²)			
Male	21.7	21.6	21.8
Female	25.6	26.1	26.1
Categories of BMI, n (%)			
Underweight (< 18.5)	42 (12)	35 (10)	37 (11)
Normal (18.5-25)	177 (51)	190 (54)	193 (55)
Overweight (25-30)	96 (27)	78 (22)	77 (22)
Obese (> 30)	35 (10)	48 (14)	44 (13)

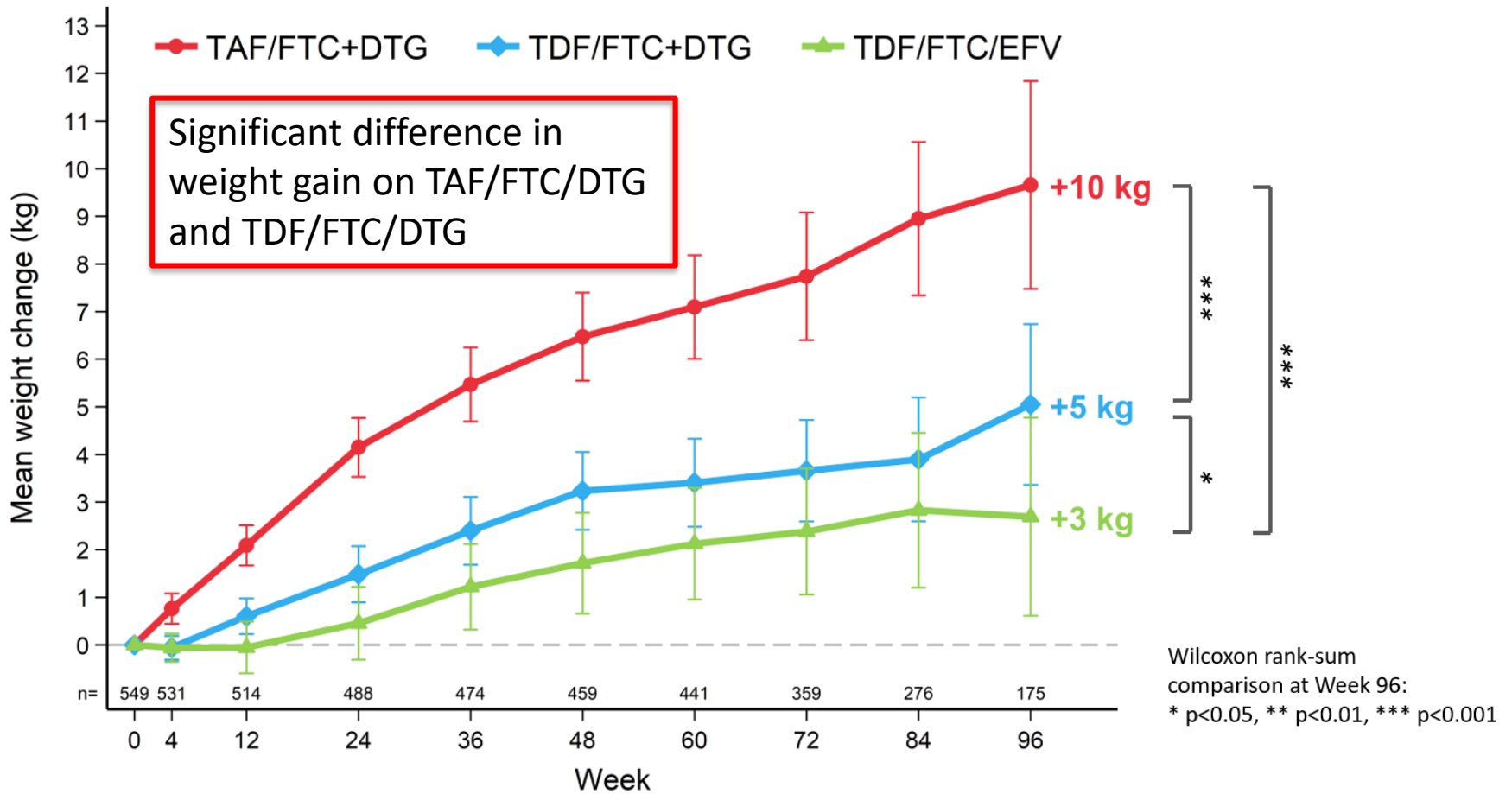
Venter et al, NEJM 2019

ADVANCE: Mean change in weight (kg) to Week 96: Men



Venter et al, NEJM 2019

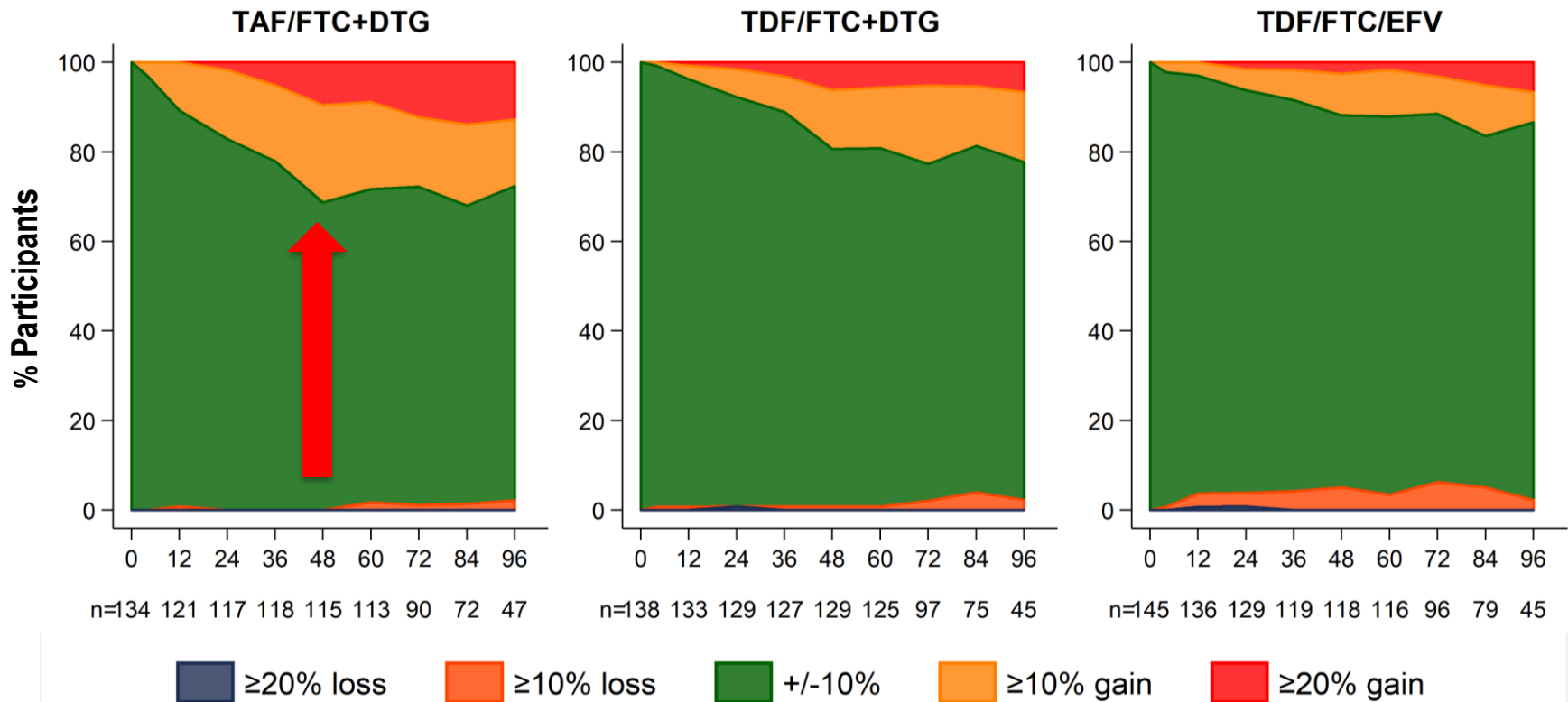
ADVANCE: Mean change in weight (kg) to Week 96: Women



Venter et al, NEJM 2019

ADVANCE: Percentage change in weight over time: Men

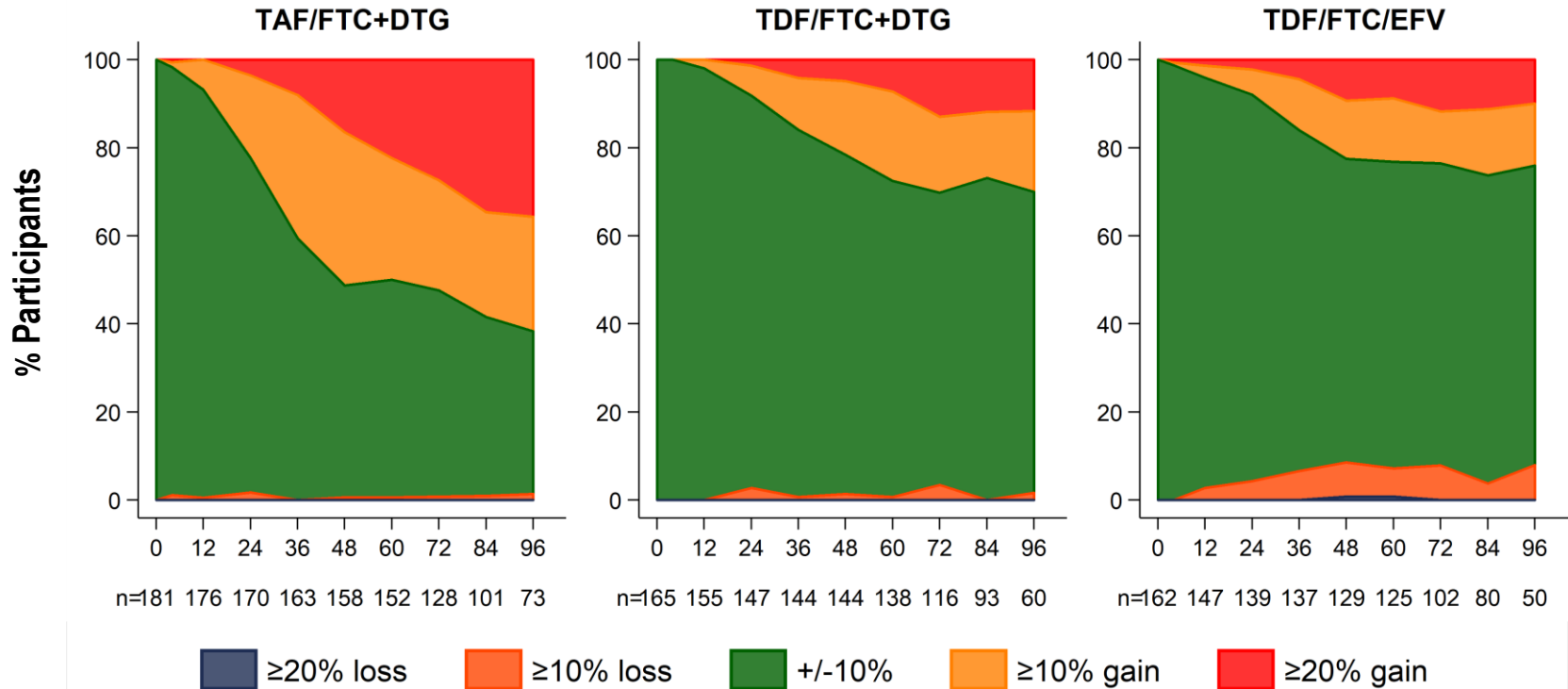
Majority of weight gain occurs by 48 weeks in men, then appears to stabilize



Hill et al, IAS 2019

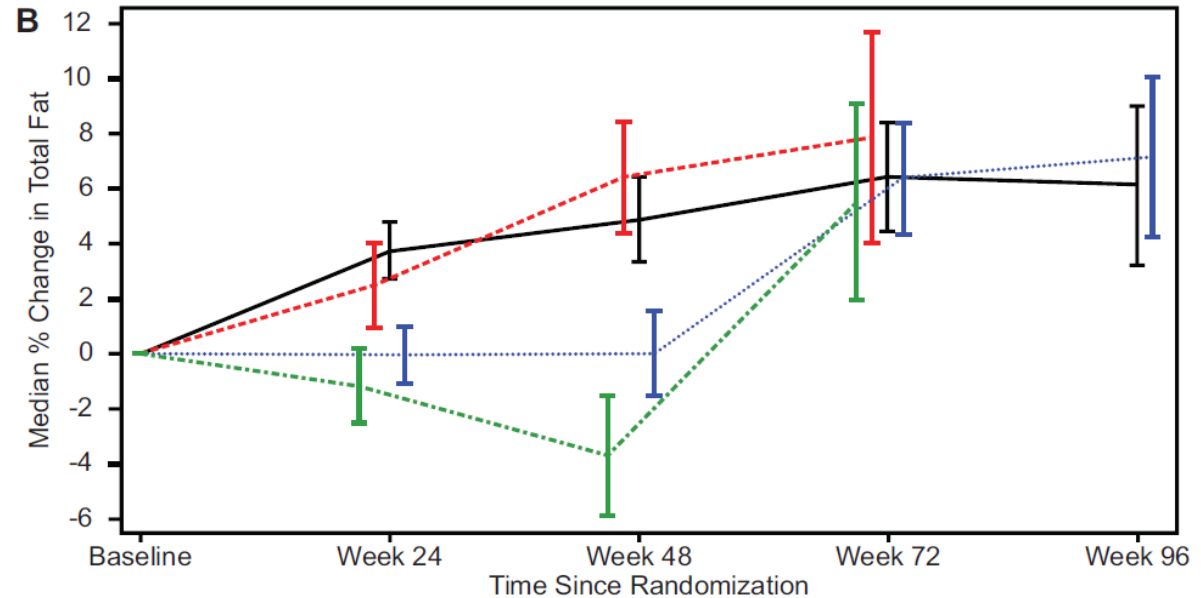
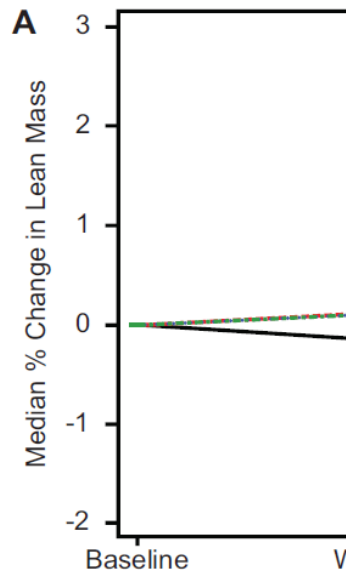
ADVANCE: Percentage change in weight over time: women

Increases in body weight on TAF/FTC+DTG are progressive and do not plateau to 96 weeks in women



Hill et al, IAS 2019

Changes in lean mass and fat in HIV negative young men on TDF versus placebo



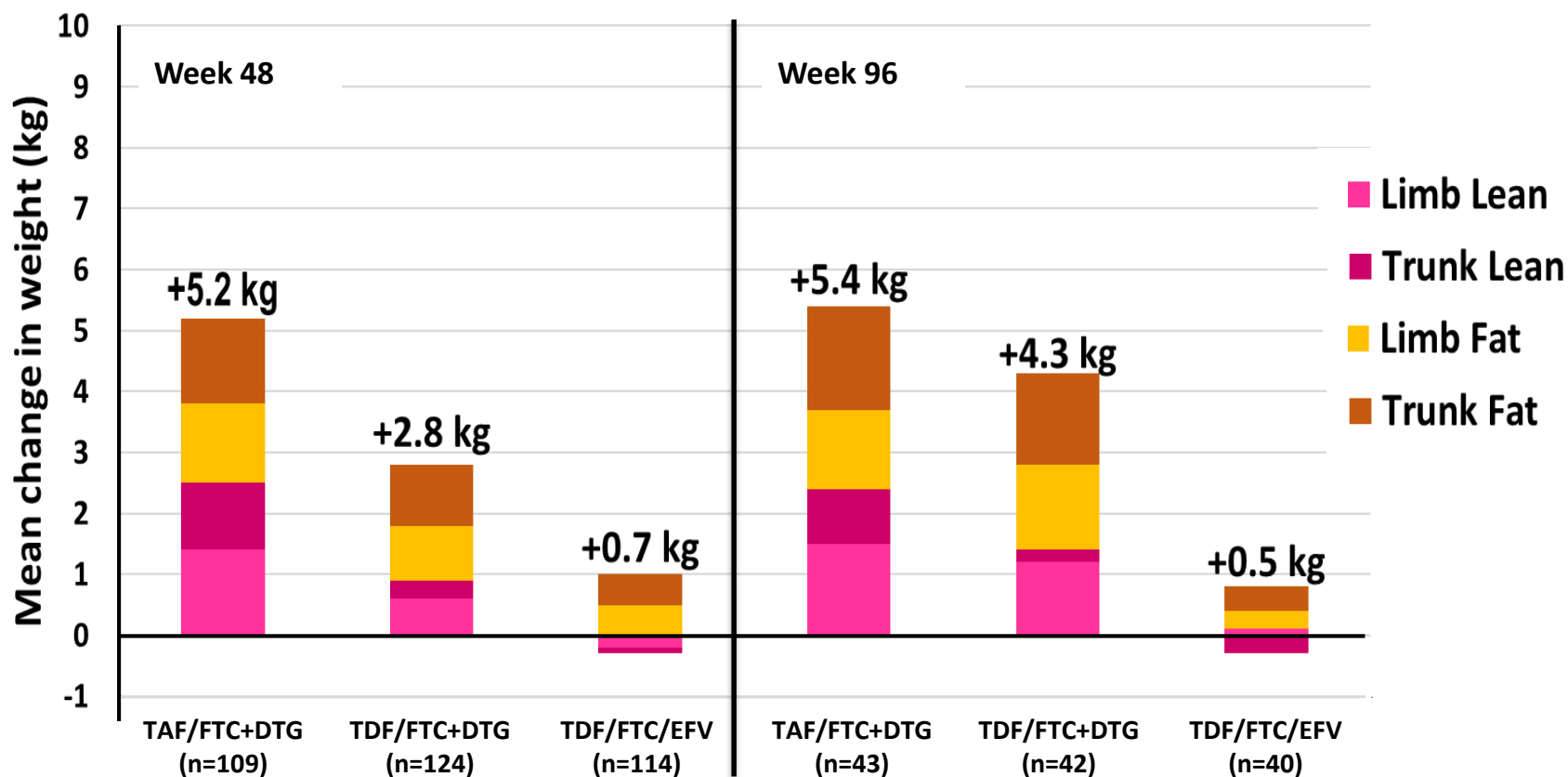
Number of Scans	
Placebo	—
TDF/FTC
Plasma BLQ	-----
Plasma Detect	-----

Number of Scans	Week 24	Week 48	Week 72	Week 96
Placebo	211	168	112	56
TDF/FTC	210	166	108	55
Plasma BLQ	86	80	34	
Plasma Detect	116	70	39	

Increase in body weight accounted for by increase in total fat

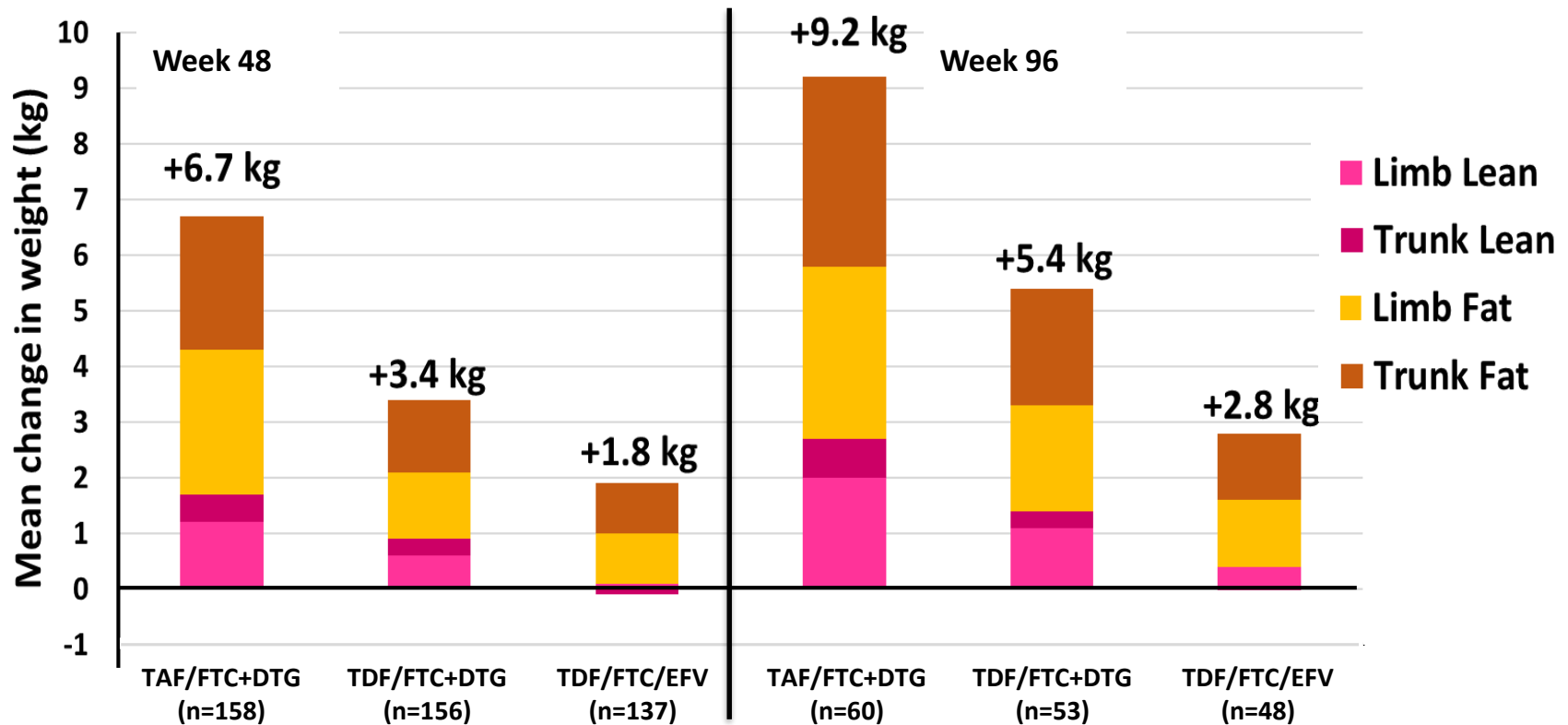
Glidden et al, Clin Infect Dis 2018

ADVANCE: Changes in body composition: men



Hill et al, IAS 2019

ADVANCE: Changes in body composition: women



Hill et al, IAS 2019

What are the potential consequences of Weight Gain?

- Weight gain with INSTIs (general fat gain – both subcutaneous and central) not the same as lipodystrophy (peripheral lipoatrophy and visceral fat accumulation)
- Concerns raised about type 2 diabetes, hypertension, cardiovascular risks
- VACS study¹ showed weight gain of 2.25 kg after ART initiation increased risk of diabetes by 14%
- D:A:D cohort² revealed every unit of increased BMI raised risk of diabetes by 13%
- In those with normal BMI pre-cART, 20% increase in relative risk of CVD per increased 1 kg /m²

Summary: Weight gain with Contemporary ART regimens

- Are integrase inhibitors associated with greater weight gain? **Yes - Hierarchy of weight gain increase – INSTI > PIs > NNRTI**
- Are there differences between integrase inhibitors? **Maybe: Hierarchy within INSTI class – Dolutegravir > raltegravir > Elvitegravir (no cohort data for bictegravir)**
- Who is at greater risk of weight gain on integrase inhibitors? **Women, black race, older age**
- Are there differences for risk of weight gain between ART naïve PLHIV and those switching regimens? **Greater magnitude of weight gain in ART naïve versus switch INSTI**
- Are there differences with companion NRTI drugs? **Greater weight gain with TAF vs TDF in RCTs**

Summary

- What are the long term consequences of weight gain? **Diabetes, possibly CVD, Longer term follow-up and re-analysis of other studies is required to evaluate consequences of weight gain/clinical obesity**
- What are the consequences of excess adiposity in PLHIV with regard to inflammation and immune activation? **Unknown**
- What is the pathogenesis of weight gain with INSTIs? **Unknown**
- Is the weight gain with INSTIs reversible? **Unknown**

