

# Weight gain e comorbidità cardio-metabolica

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# Intersection of HIV and Obesity Epidemics:

## Obesity in the World:

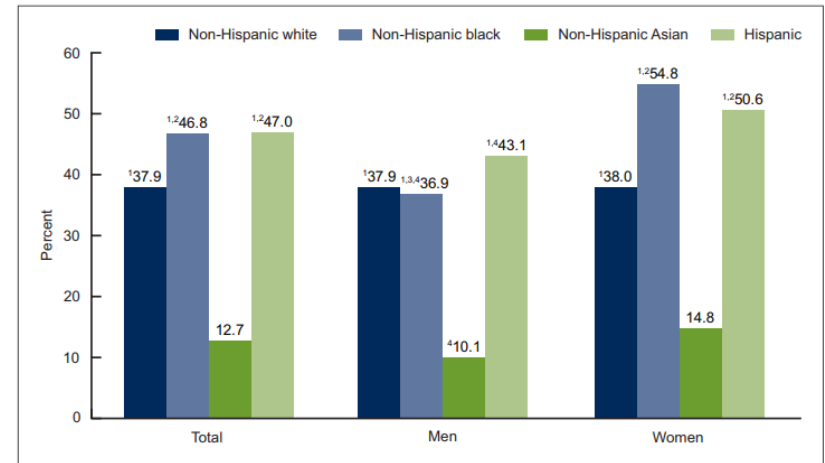
- Worldwide obesity has nearly tripled since 1975.
- In 2016, more than 1.9 billion adults, 18 years and older, were overweight. Of these over 650 million were obese.
- 39% of adults aged 18 years and over were overweight in 2016, and 13% were obese.

WHO. Health topics. <https://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight>

## Obesity in the US:

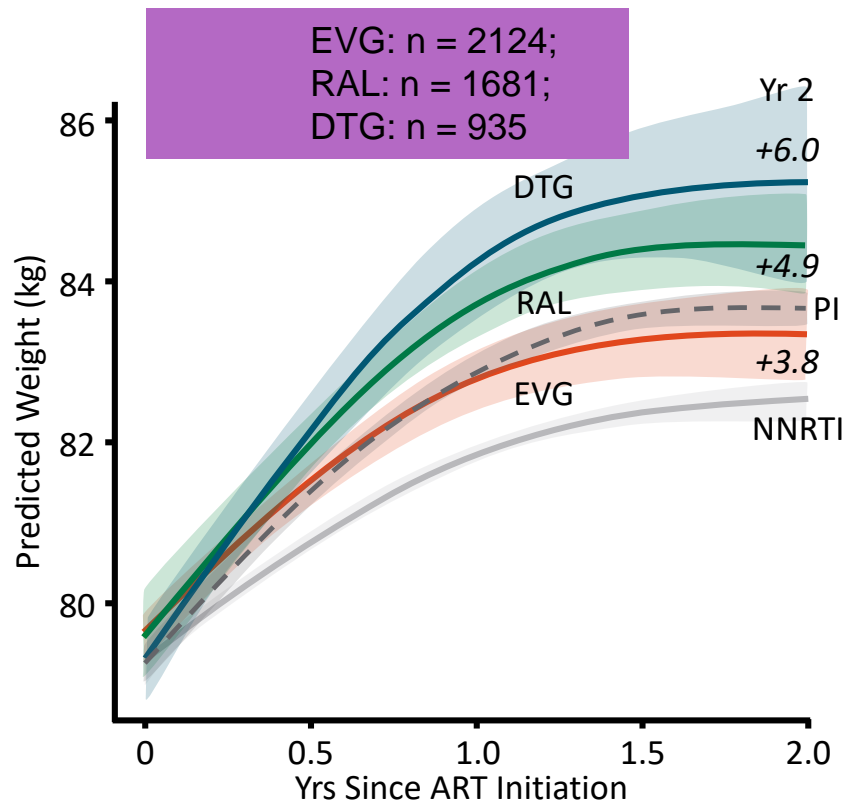
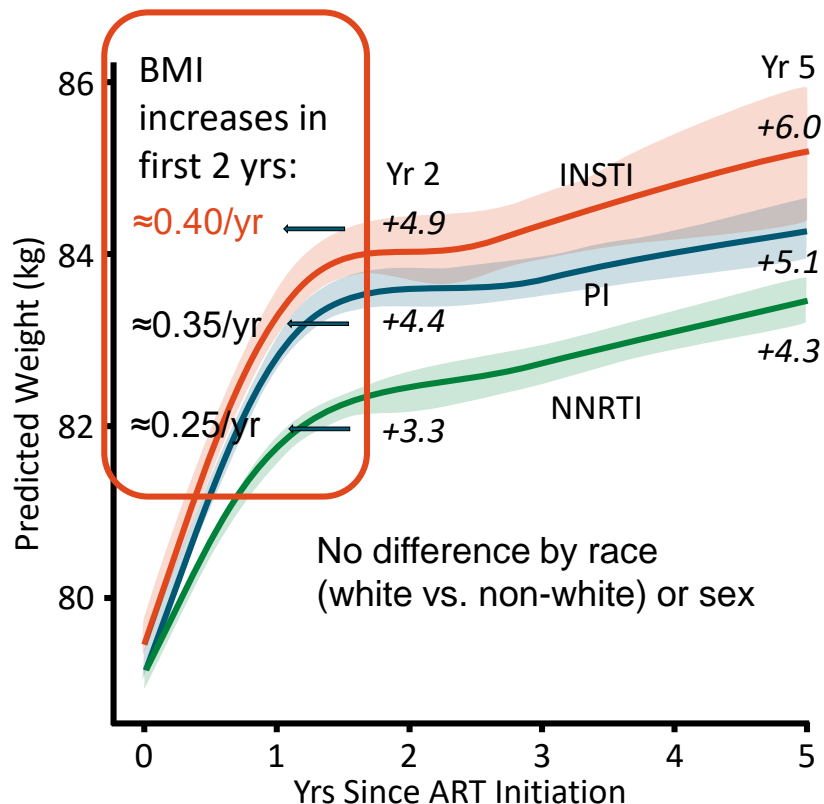
- The prevalence of 39.8% in 2016.  
**Affected mostly Blacks and Hispanics**

Figure 2. Age-adjusted prevalence of obesity among adults aged 20 and over, by sex and race and Hispanic origin: United States, 2015–2016



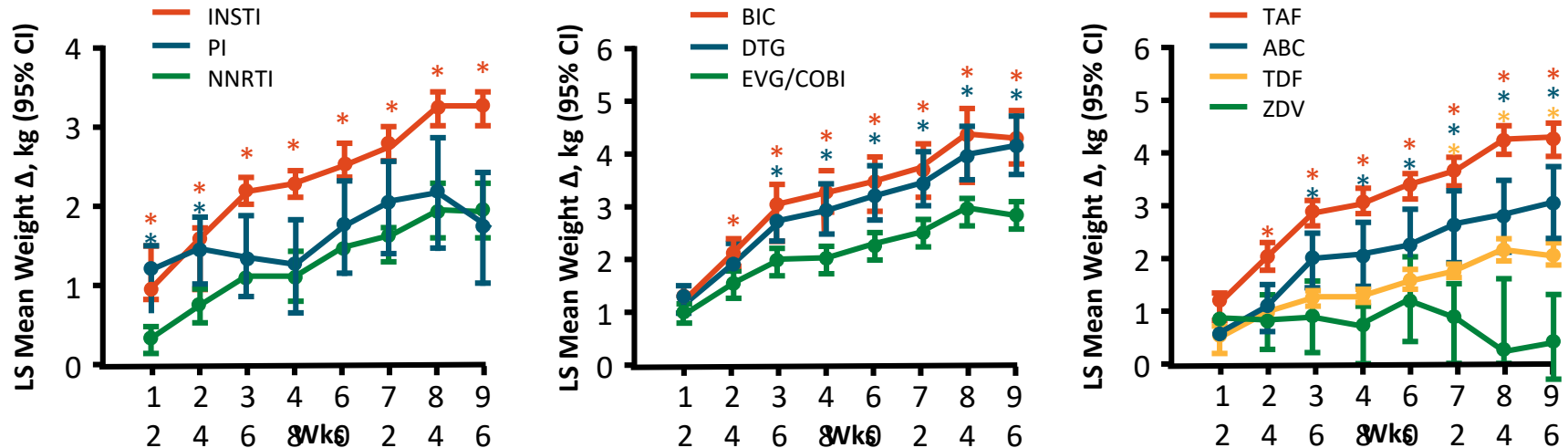
<https://www.cdc.gov/nchs/data/databriefs/db288.pdf>

# Weight Gain by Class or Specific INSTI: NA-ACCORD



# Multivariate Analysis of Weight Gain After ART Start

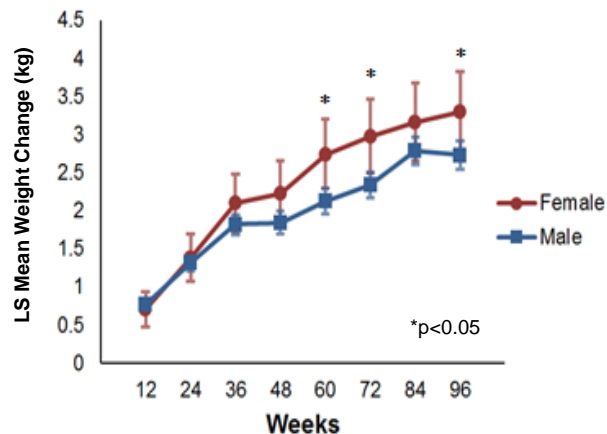
- Pooled analysis of 8 phase III RCTs of first-line ART initiation during 2003-2015 (N = 5680)
  - Baseline factors associated with weight gain: lower CD4+ cell count, higher HIV-1 RNA level, no IDU, female sex, black race, symptomatic HIV, younger age (< 50 vs ≥ 50 yrs), and higher BMI



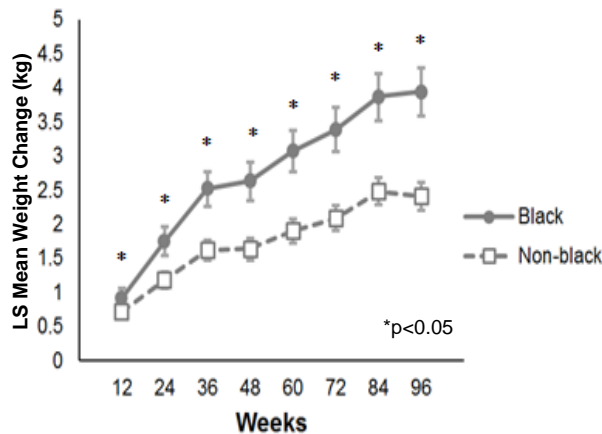
\*Color-coded to match respective comparators, denoting  $P \leq .05$  vs NNRTI (first panel), EVG/COBI (second panel), or ZDV (third panel).

## Effect of Sex and Race on Weight Change

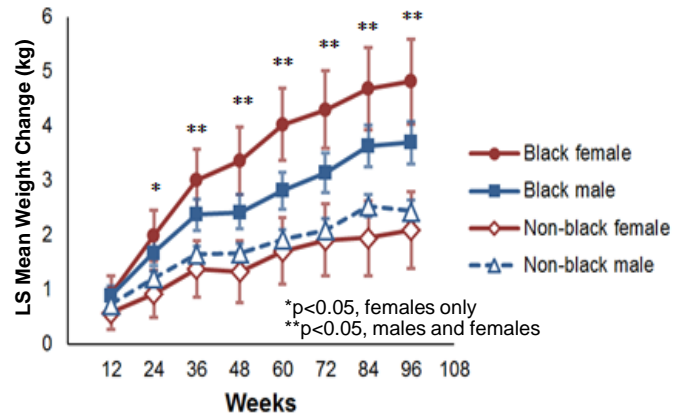
Weight Change,  
Stratified by Sex



Weight Change,  
Stratified by Race



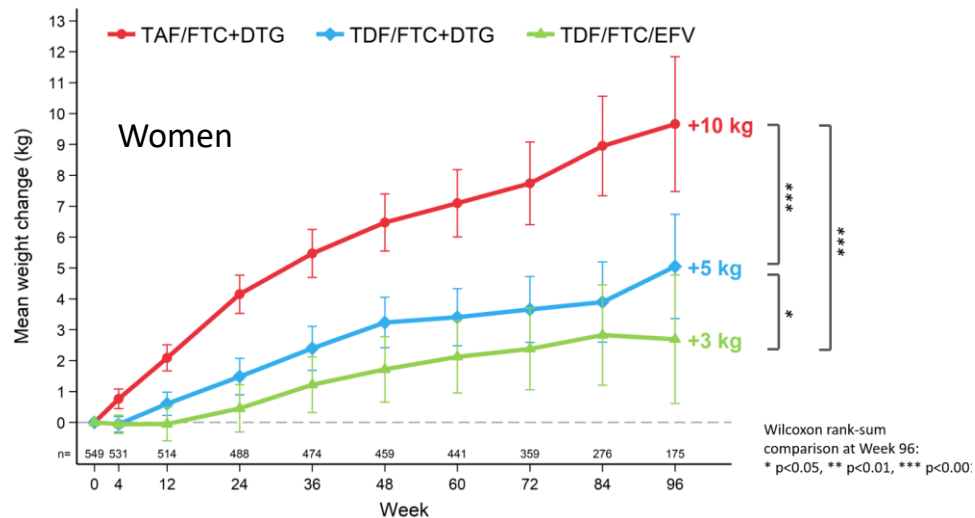
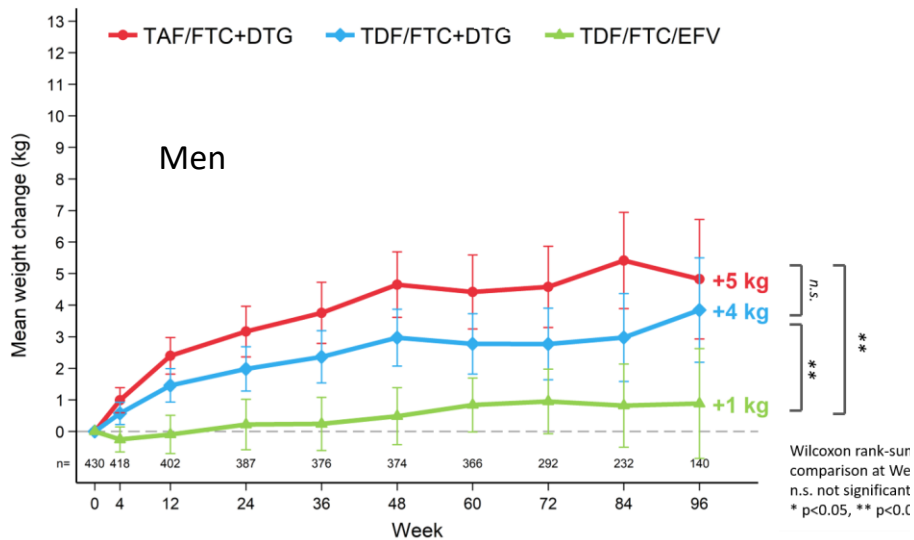
Weight Change,  
Stratified by Sex and Race



- Females gained more weight than males
- Black participants gained significantly more weight than non-Black participants
- The greatest weight gain was seen among Black females, followed by Black males

# Magnitude & Determinants in Africa:

## ADVANCE - Mean Change in Weight to Wk 96 by Sex



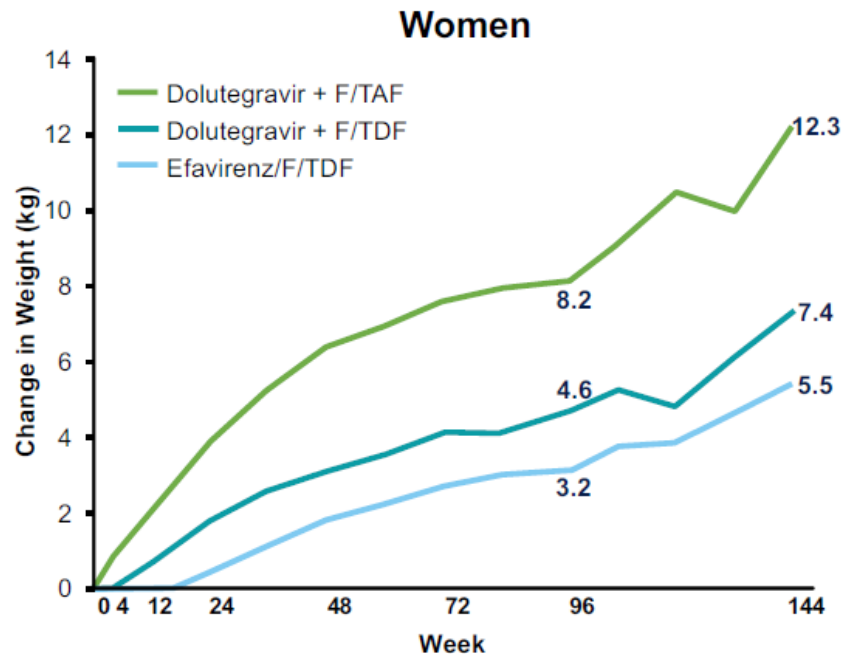
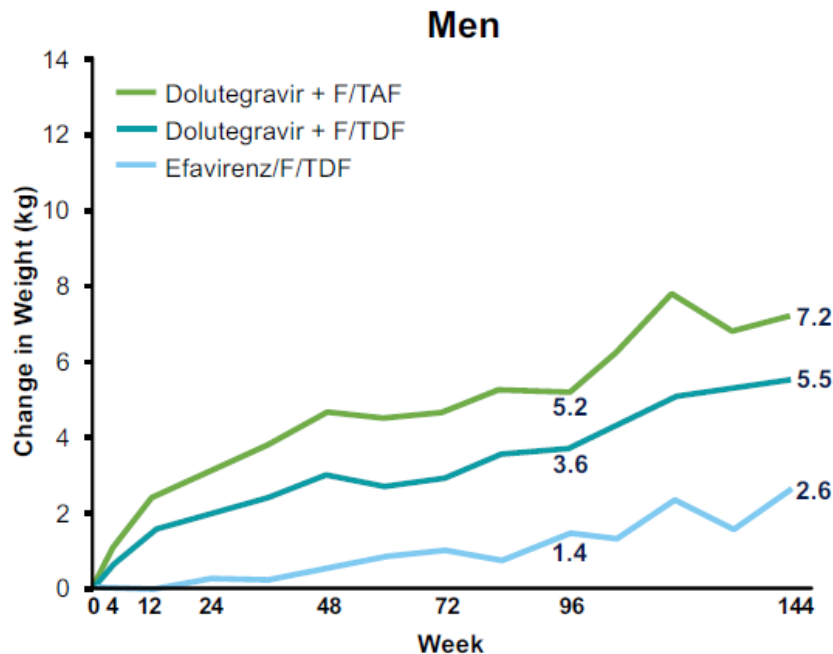
**Estimated BMI increase @ 1 year:  $\approx 1.5$  in males,  $\approx 2$  in females**

	DTG + F/TAF	DTG + F/TDF	EFV/F/TDF
$\geq 10\%$ change in body weight (%)	25*†	13*	11
Treatment-emergent obesity (BMI $\geq 30$ kg/m <sup>2</sup> ; %)	19*†	8*	4

Venter WF, et al. *J Int AIDS Soc.* 2019;22(suppl 5):103-104. Abstract WEAB0405LB. Venter WF, et al. *N Engl J Med.* 2019;July 24, 2019. [Epub ahead of print]. Hill A, et al. *J Int AIDS Soc.* 2019;22(suppl 5):92. Abstract MOAX0102LB

# Magnitude & Determinants in Africa:

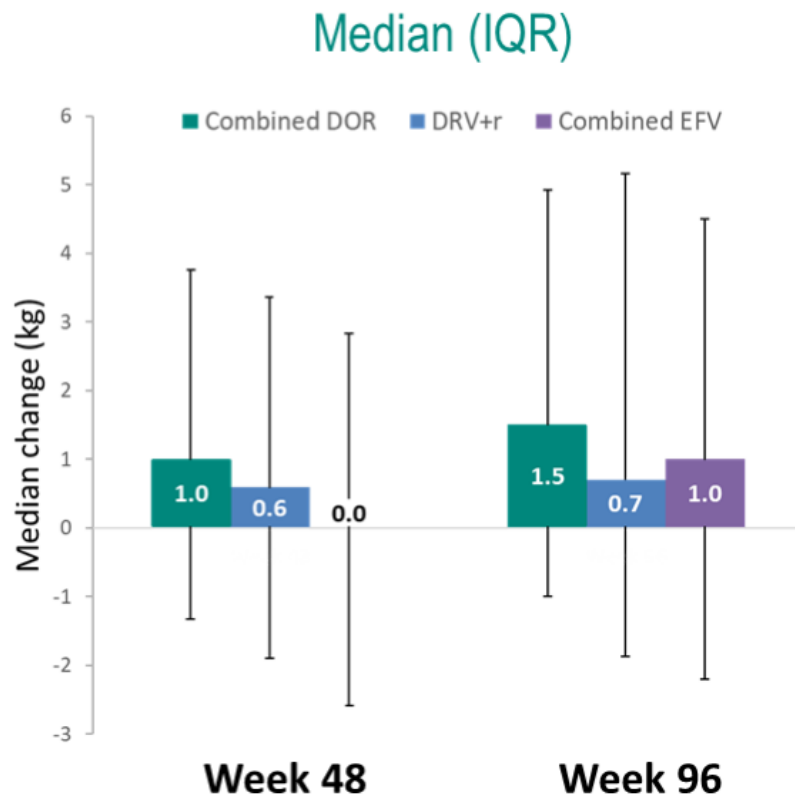
## ADVANCE - Mean Change in Weight to Wk 144 by Sex



# Doravirine Weight Gain In Treatment Naïve Individuals

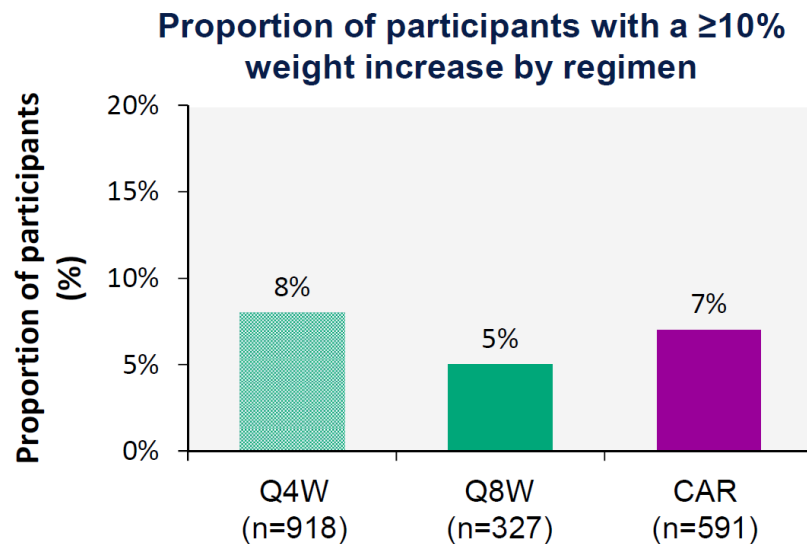
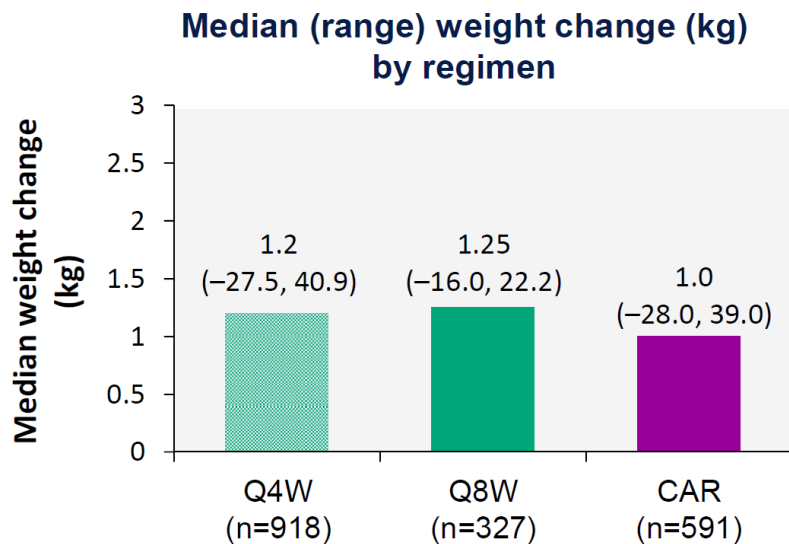
- Post hoc, pooled data analysis of 3 Phase 2/3 clinical trials in treatment naïve patients
  - DOR 100 mg vs EFV 600 mg, with FTC/TDF
  - DOR 100 mg vs DRV+r 800/100, with FTC/TDF or ABC/3TC
  - DOR/3TC/TDF vs EFV/FTC/TDF
- Double blind data through week 96 combined by treatment group

DOR	DRV+r	EFV
N=855	N=383	N=472





# Weight Change with Cabotegravir/Rilpivirine: Week 48



- Median weight increased from baseline\* across all regimens, with slightly higher increases observed in participants receiving CAB + RPV LA vs. those receiving CAR
- The proportion of participants with a  $\geq 10\%$  weight increase was similar for the CAB + RPV LA regimens and CAR

\*Median (IQR) weight (kg) at baseline: Q4W, 76.0 (67.0, 85.9); Q8W, 77.0 (68.0, 87.0); CAR, 75.2 (65.4, 85.7).

CAB, cabotegravir; CAR, current antiretroviral regimen; IQR, interquartile range; LA, long-acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

# Magnitude of Weight Gain with INSTI: Rx Experienced

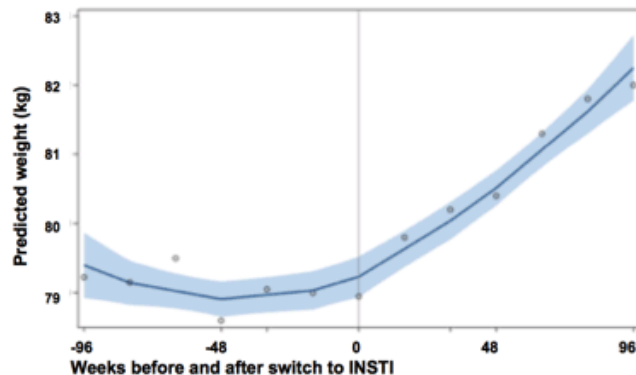
ACTG: A5001 & A5322 (n=691)

Adjusted yearly weight change (Kg/yr):

DTG: 1.0 (p<0.001); EVG: 0.5 (p=0.11); RAL: -0.2 (p=0.37)

In adjusted models, black race, age  $\geq 60$  and BMI  $\geq 30$  kg/m<sup>2</sup> were associated with greater weight gain

Switch to INSTI + ABC and EVG + TAF predictor (small #s)

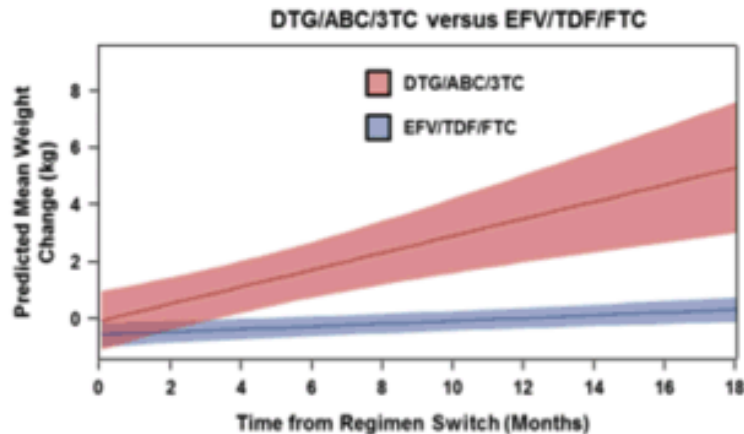


Lake. CROI 2019; Abstract 669; CID 2020 [Epub ahead of print]

Retrospective, single-site study (n=495)

Patients on EFV/TDF/FTC switched to INSTI (DTG/ABC/3TC; RAL/TDF/FTC or EVG/c/TDF/FTC) vs. continued

Weight gain highest with switch to DTG/ABC/3TC



Norwood. JAIDS 2017 Dec 15;76(5):527-531

# Weight Gain with Switch to INSTI

## NA-ACCORD

INSTI distribution: 870 Total; 431 RAL; 263 EVG; 176 DTG

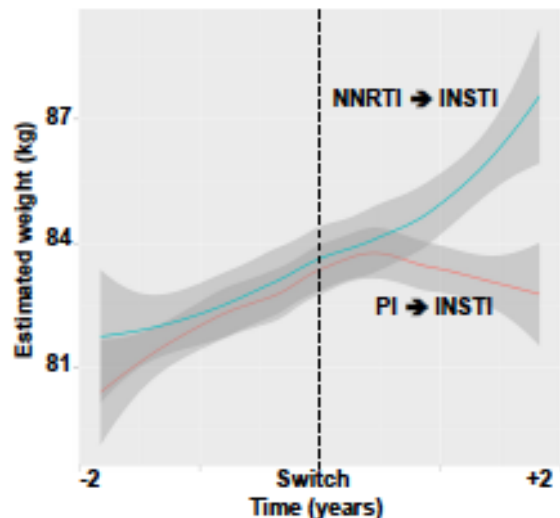


Figure. Unadjusted estimated weight for all persons before and after switch to INSTI by pre-switch regimen

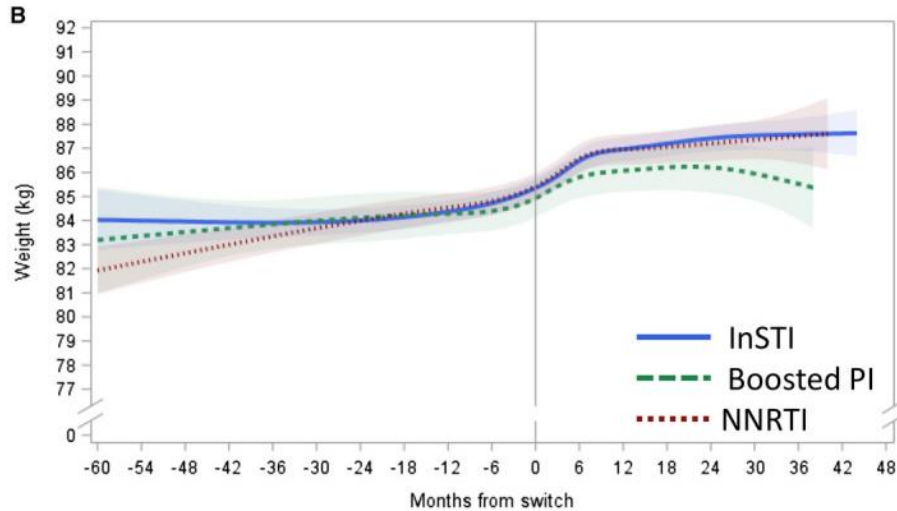
Regimen switch	Pre-switch weight slope (kg/year)	Post-switch weight slope (kg/year)	P-value for slope change
NNRTI → INSTI	0.63	1.13	< 0.001
NNRTI → DTG	0.64	1.73	< 0.001
NNRTI → RAL	0.74	0.97	0.21
NNRTI → EVG	0.56	1.00	0.07
PI → INSTI	0.80	0.34	< 0.001
PI → DTG	0.84	-0.04	< 0.001
PI → RAL	0.74	0.17	< 0.001
PI → EVG	0.56	0.89	0.11

Table 2. Adjusted pre- and post-switch weight slopes by individual INSTI agents

Women, non-whites and older PWH with viral suppression had greater annualized weight gain after switch from NNRTI- to INSTI-based ART; Greatest for DTG

Slowing of weight gain with switch from a PI

# Weight Gain after Switch from TDF to TAF



## OPERA Cohort:

Switching to TAF was associated with early, pronounced weight gain for all (1.80 to 4.47 kg/year).

Weight gain tended to slow down or plateau approximately nine months after switch to TAF.

Mallon. [J Int AIDS Soc.](#) 2021 Apr; 24(4): e25702.



## HOPS: 2007-2018; n=736

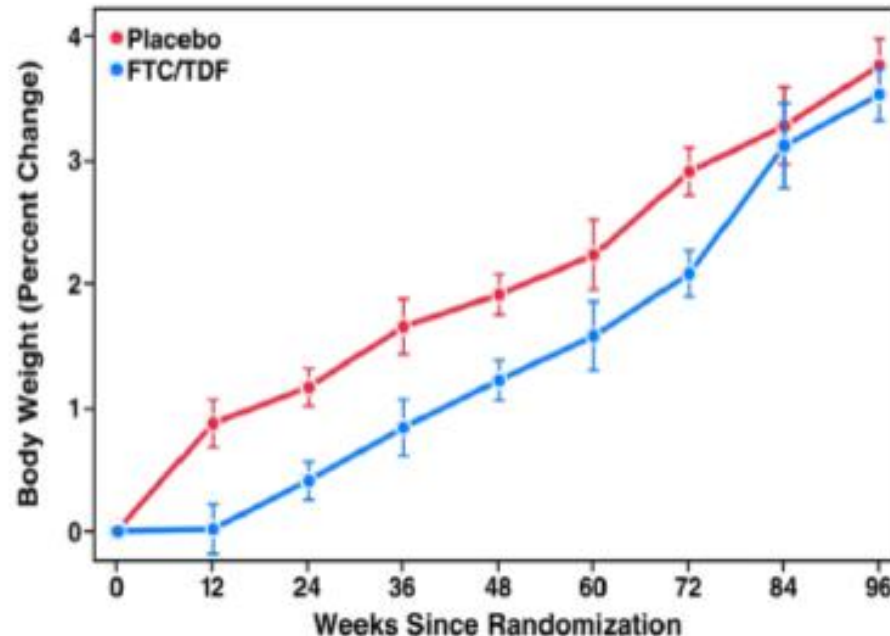
Greatest weight gain during 1<sup>st</sup> 8 months post-switch; mostly assoc. with INSTI use. After 8<sup>th</sup> months, continued weight gain mostly associated with TAF use

Palella. CROI 2021;

# iPrEX Trial: FTC/TDF vs. Placebo for PrEP

- Placebo (n=1225)
- TDF/FTC (n=1226)
- Delayed weight gain in treatment group

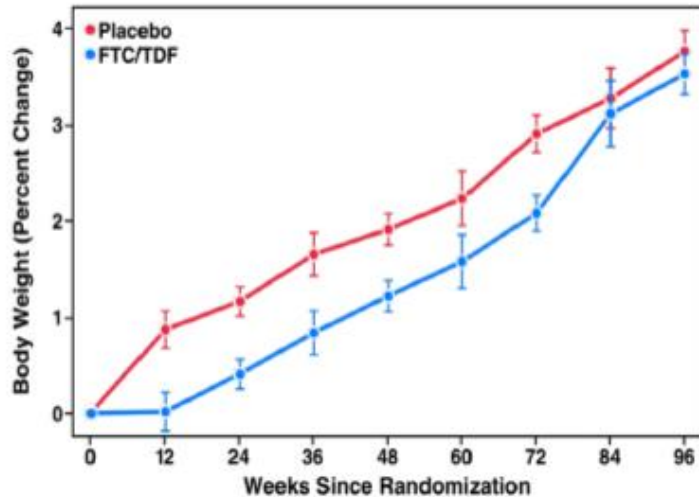
Maybe the thought of  
some ARVs delaying  
weight gain is a  
getting less heretical?



# Weight Gain on PrEP Studies:

## iPrEX: FTC/TDF vs. Placebo

- Placebo (n=1225)
- TDF/FTC (n=1226)
- Delayed weight gain in treatment group



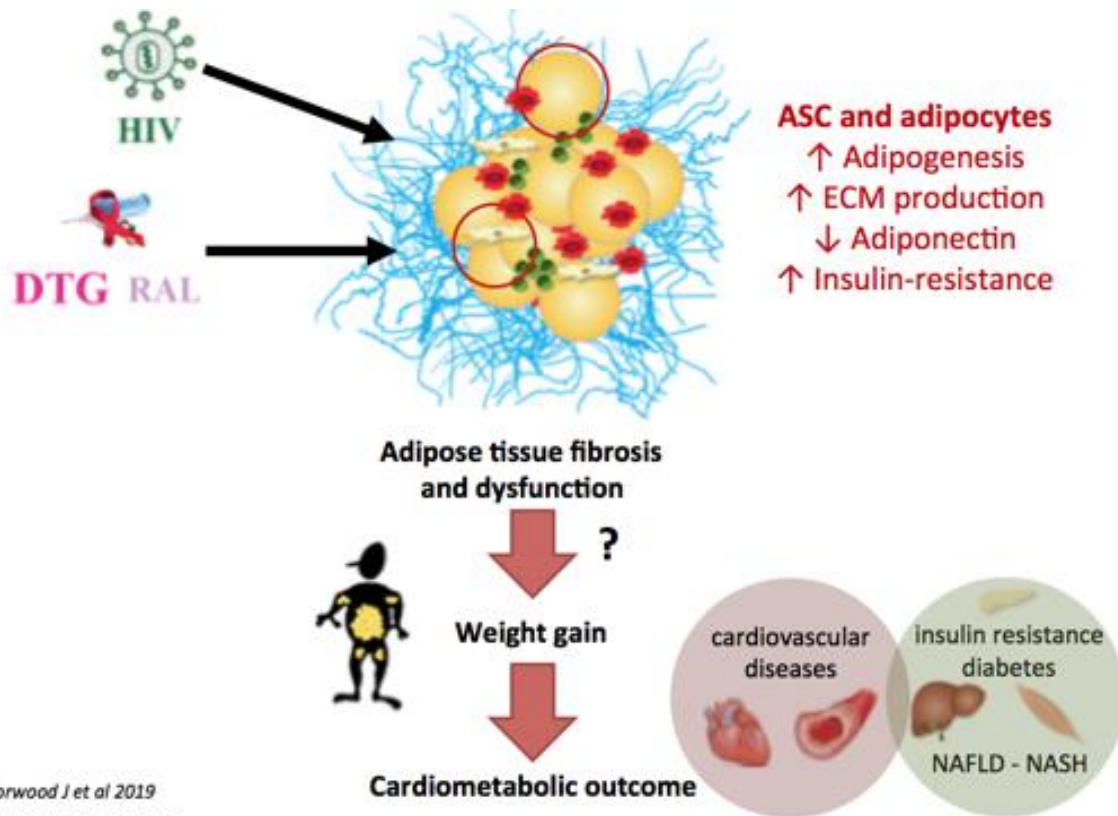
Grant. NEJM 2010;363: 2587-99

## HPTN 083

- Overall, significantly greater median weight increase from BL with CAB vs FTC/TDF ( $P < .001$ )
  - CAB: +1.30 kg/yr (95% CI: 0.99-1.60)
  - FTC/TDF: +0.31 kg/yr (95% CI: -0.12 to -0.49)

Landovitz. AIDS 2020. Abstr OAXLB0101

# Potential Mechanisms of Weight Gain on ART

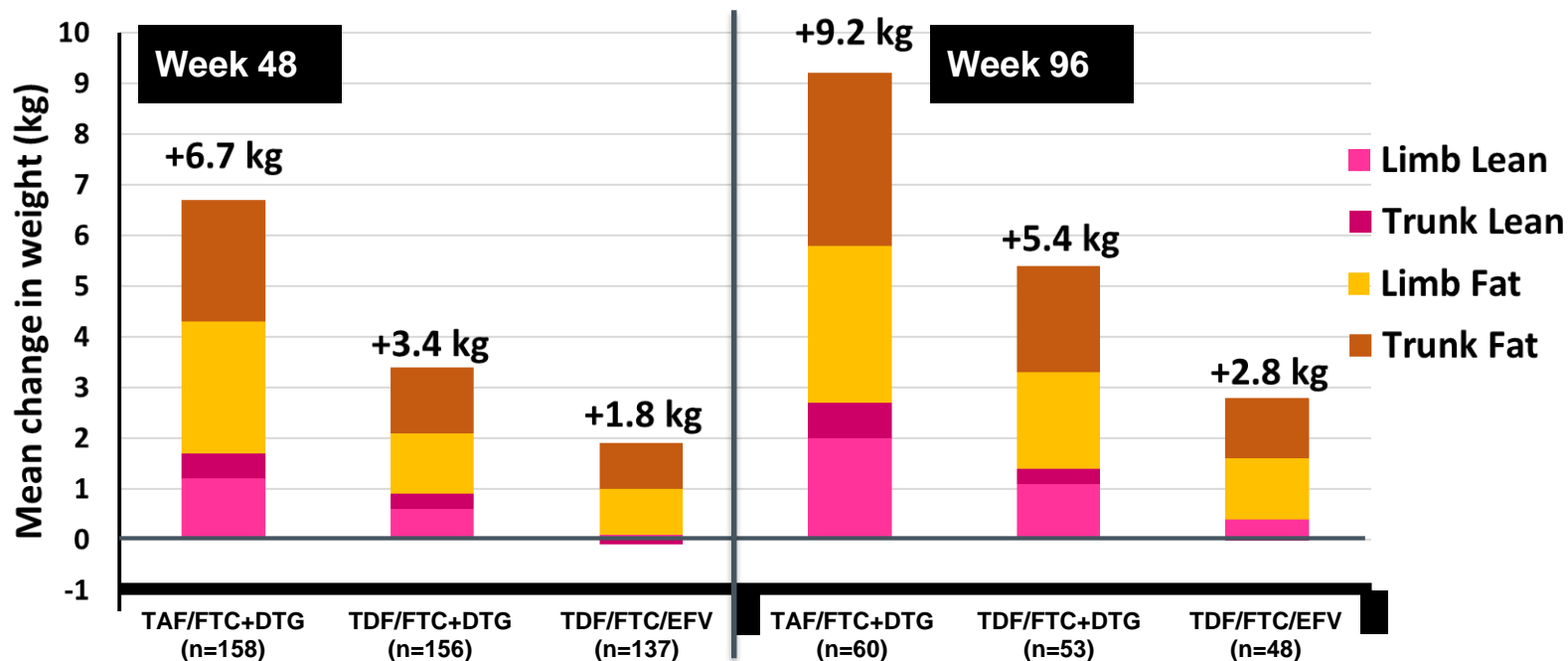


- DTG and RAL increased ECM production in ASCs and adipocytes. They induced adipocyte dysfunction and insulin resistance.<sup>1</sup>
- NEAT 022: Switch from PI to INSTI associated with decreased LDL, TC/HDL, CRP & sCD14, but decreased adiponectin.<sup>2</sup>
  - Percent change in adiponectin correlated inversely with percent change in BMI.

Gorwood J et al 2019

Gorwood J et al submitted

# ADVANCE: Changes in body composition: women

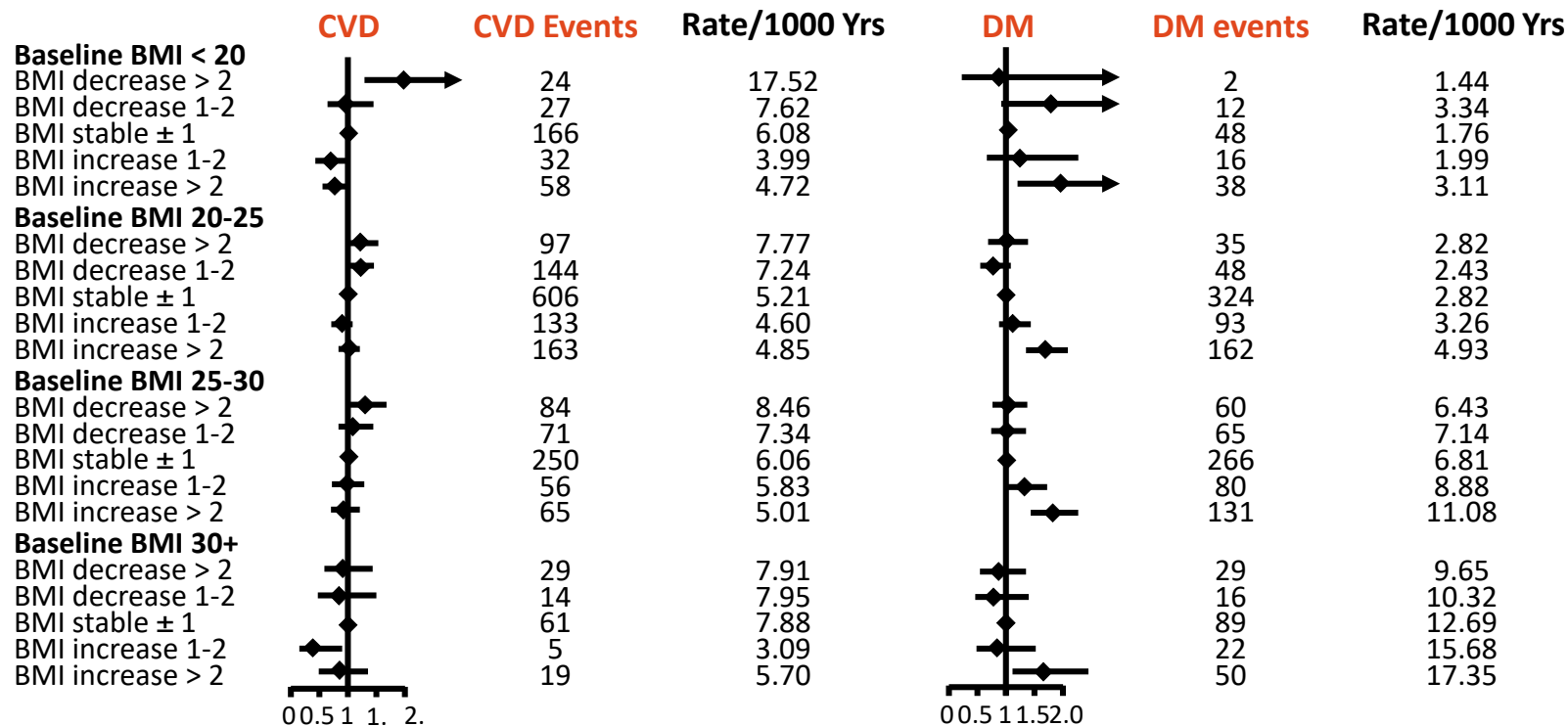


**Most of the weight gain in DTG arms is fat gain, both trunk and limb. Higher with TAF**

**Increases in lean mass (both limb and trunk) also higher in DTG arms vs. EFV**



# D:A:D Study: Risk of CVD After BMI Changes on ART



CVD: Adjusted for age, race, transmission mode, sex, recent ABC and other NRTI use, cumulative protease inhibitor use, CD4+ count, family history of CVD, smoking status  
 DM: Adjusted for age, race, mode of transmission, sex, stavudine use, triglycerides, CD4+ count, smoking status, and HDL

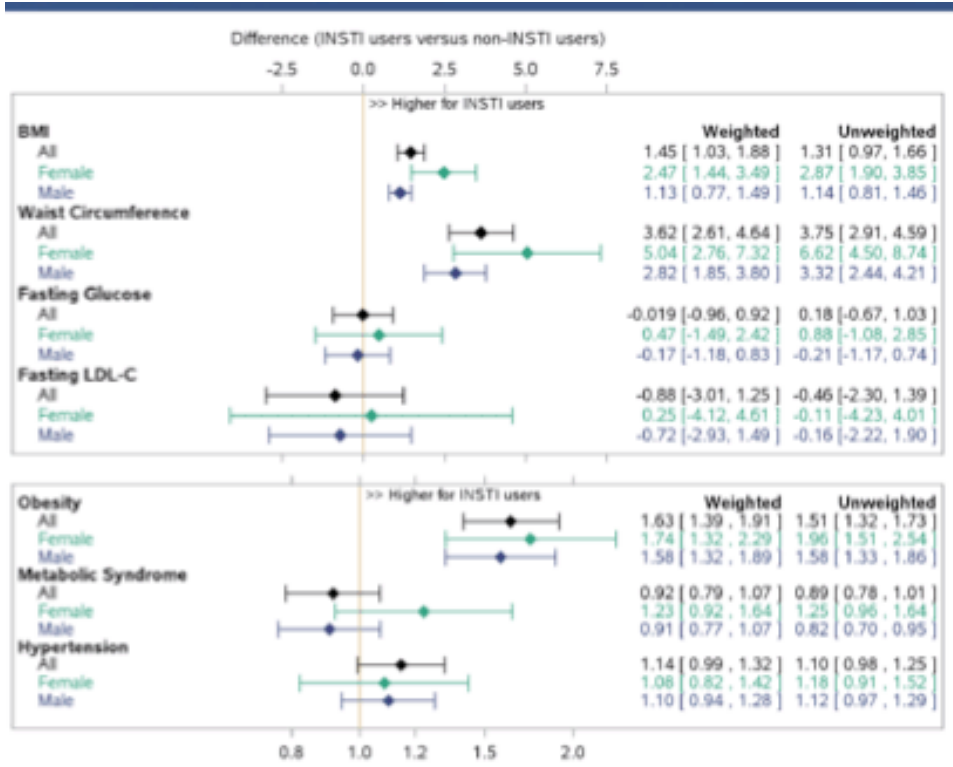
# ADVANCE Study: Weight Gain and Metabolic Syndrome Through Wk 96

- Gained weight was predominantly fat mass rather than lean mass; women gained significantly more fat mass than men ( $P < .001$ )

Outcome	DTG + FTC/TAF (n = 351)	DTG + FTC/TDF (n = 351)	EFV/FTC/TDF (n = 351)
<b>Mean weight gain from BL, kg</b>			
Women			
▪ Wk 96	8.2	4.6	3.2
▪ Wk 144*	12.3	7.4	5.5
Men			
▪ Wk 96	5.2	3.6	1.4
▪ Wk 144*	7.2	5.5	2.6
<b>Treatment-emergent metabolic syndrome at Wk 96, %</b>			
All patients	8.4 <sup>†</sup>	5.9	3.9 <sup>†</sup>
Women	10.9	8.1	5.6
Men	4.6	3.3	1.8

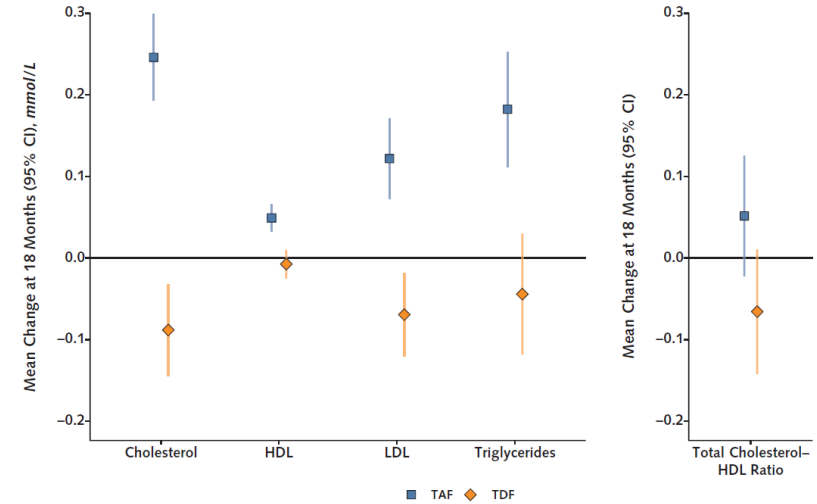
\*Data after Wk 96 are incomplete. <sup>†</sup> $P = .03$  for comparison between DTG + FTC/TAF and EFV/FTC/TDF. All other comparisons were not significant.

# Metabolic Associations of Weight Gain on INSTI and TAF



REPRIEVE: Odds of metabolic changes on INSTI vs. non-INSTI

Janet Lo. CROI 2021



## Swiss Cohort:

Switching to TAF led to increases in total cholesterol, HDL, LDL, and TG after 18 months.

Surial B, et al. Ann Intern Med. 2021;174(6):758-767.

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