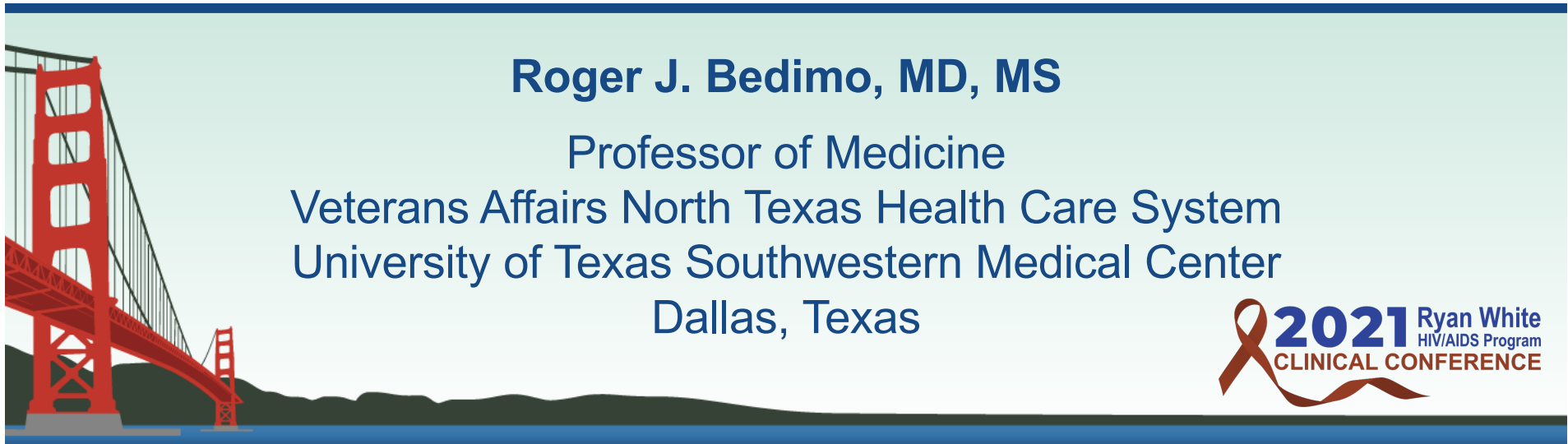


Antiretroviral Therapy and Weight Gain

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Financial Relationships With Ineligible Companies (Formerly Described as Commercial Interests by the ACCME) Within the Last 2 Years

Dr Bedimo has received grant funding from ViiV Healthcare and serves on the Scientific Advisory Board for Merck & Co, Inc, ViiV Healthcare, and Gilead Sciences, Inc. (Updated 9/30/21)

Learning Objectives

After attending this presentation, learners will be able to:

- Assess the magnitude of weight gain associated with antiretroviral therapy

- Identify predictors of weight gain on antiretroviral therapy

- List potential mechanisms and metabolic complications of weight gain during antiretroviral therapy

Case #1

- 27 y/o African-American woman recently diagnosed with HIV. CD4 count is 198, HIV VL: 649,000. She's HBV immune and HCV antibody negative. She's eager to start antiretroviral therapy but has heard of potential of weight gain. You tell her the greatest potential for weight gain is associated with:
 - 1) Male sex and White race
 - 2) Integrase inhibitor-based regimens
 - 3) Protease inhibitor-based regimens
 - 4) Non-nucleoside reverse transcriptase inhibitor-based regimens
 - 5) The jury is still out

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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.

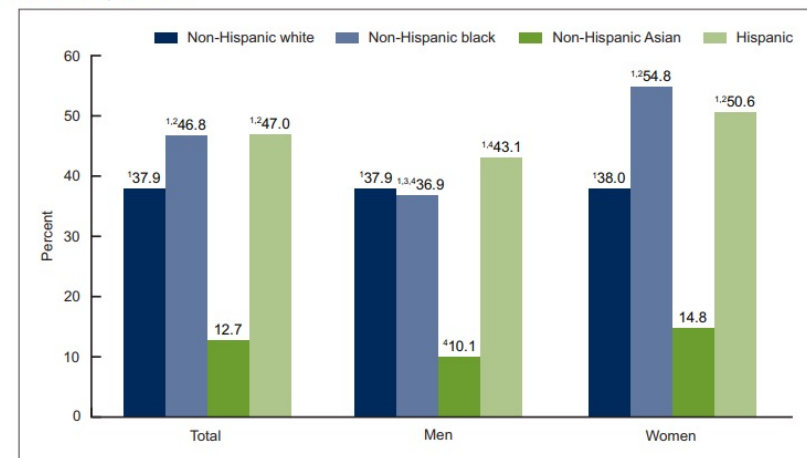
WHO. Health topics. <https://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight>

Slide 6 of 30

Obesity in the US:

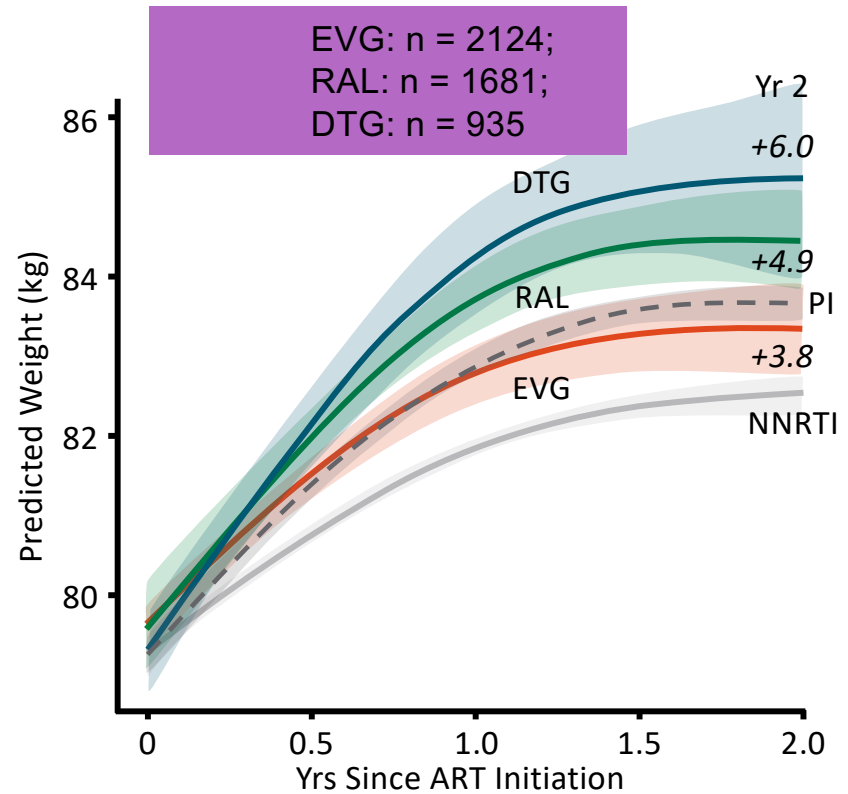
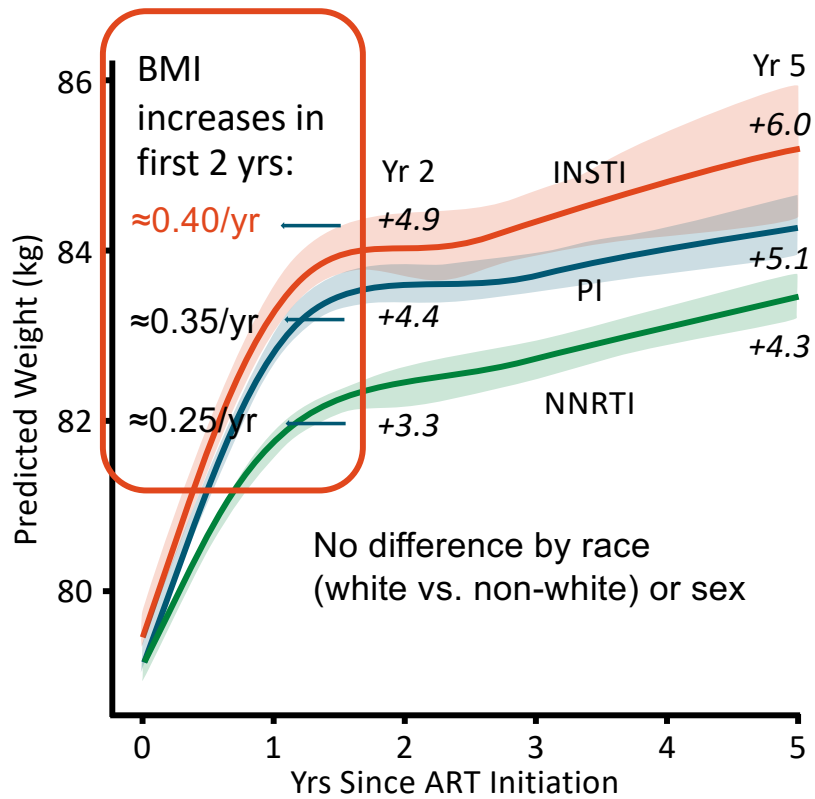
- The prevalence of 39.8% in 2016.
Affected mostly Blacks and Hispanics

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



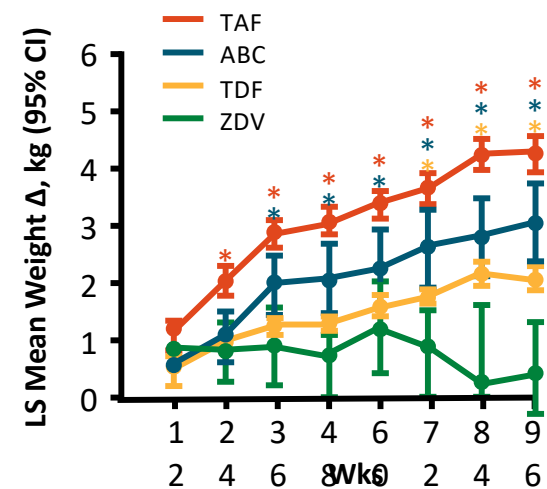
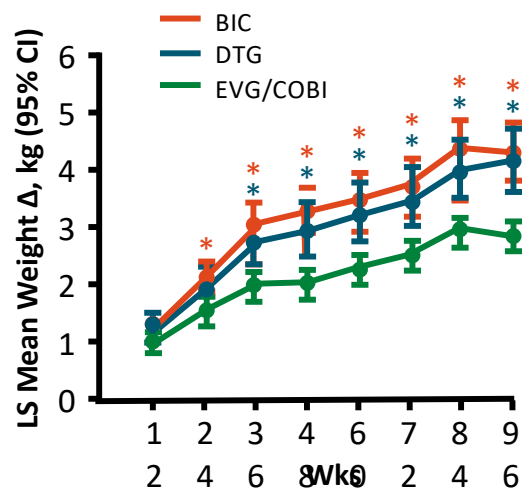
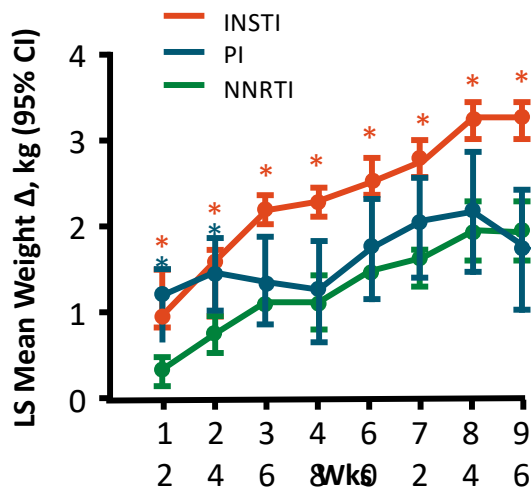
<https://www.cdc.gov/nchs/data/databriefs/db288.pdf>

Weight Gain by Class or Specific INSTI: NA-ACCORD



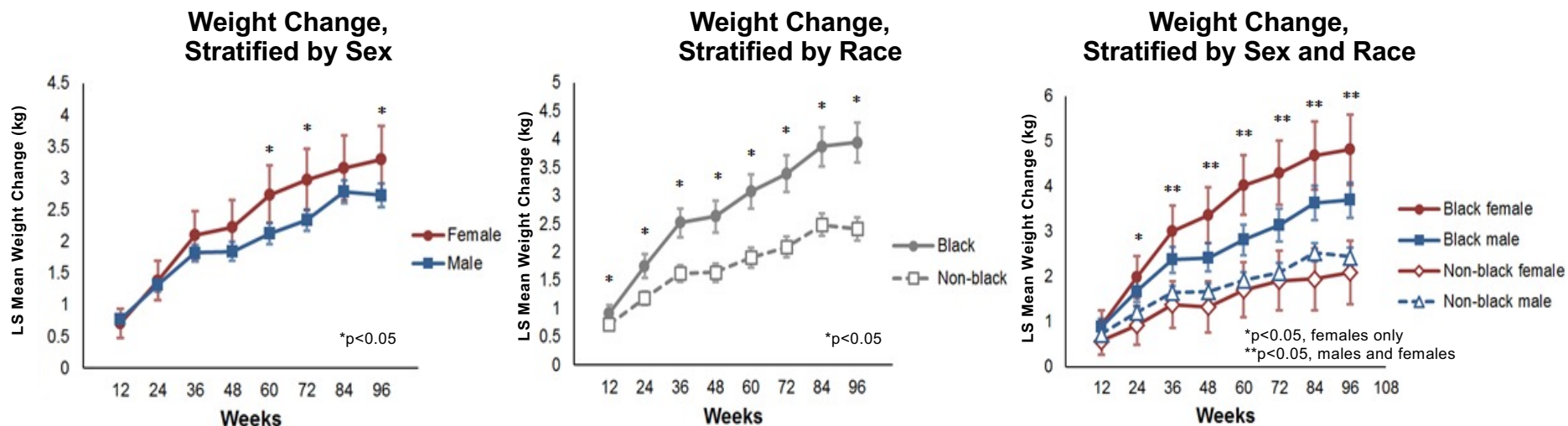
Multivariate Analysis of Weight Gain After ART Start

- 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).

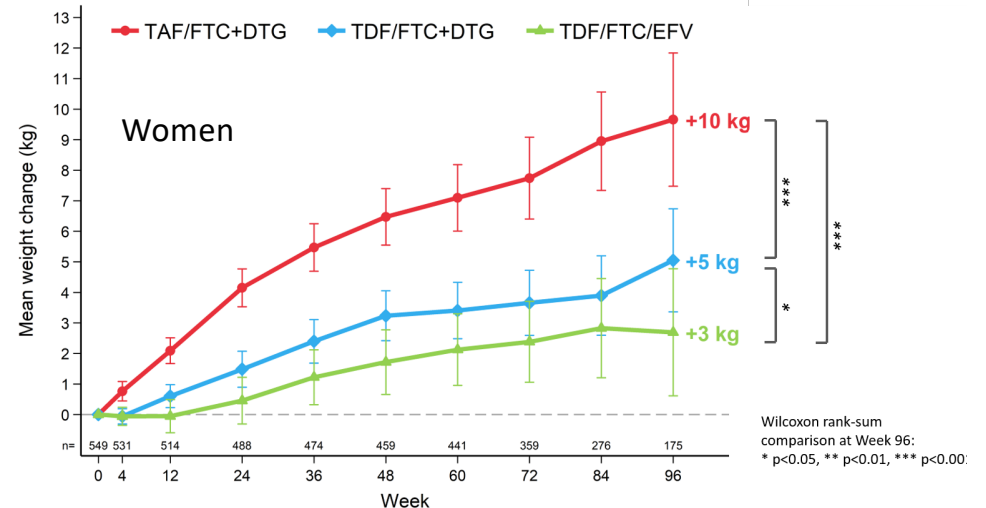
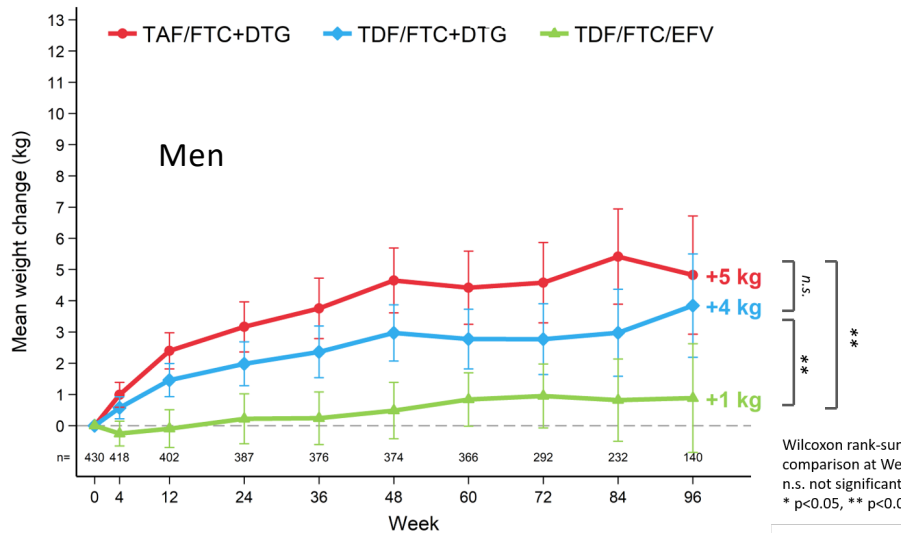
Effect of Sex and Race on Weight Change



- 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

Sax et al. Clin Infect Dis. 2020 Sep 12;71(6):1379-1389

Magnitude & Determinants in Africa: ADVANCE - Mean Change in Weight to Wk 96 by Sex

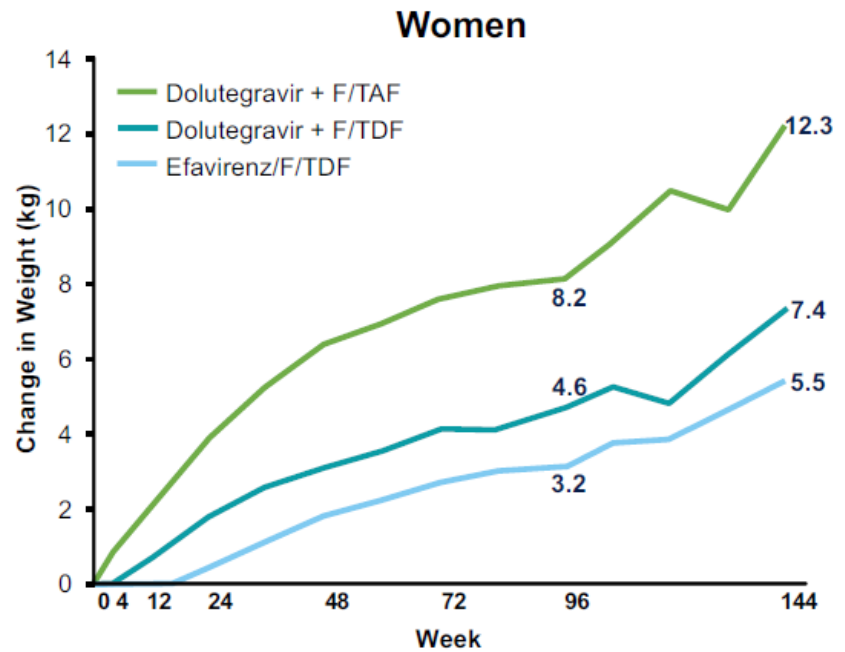
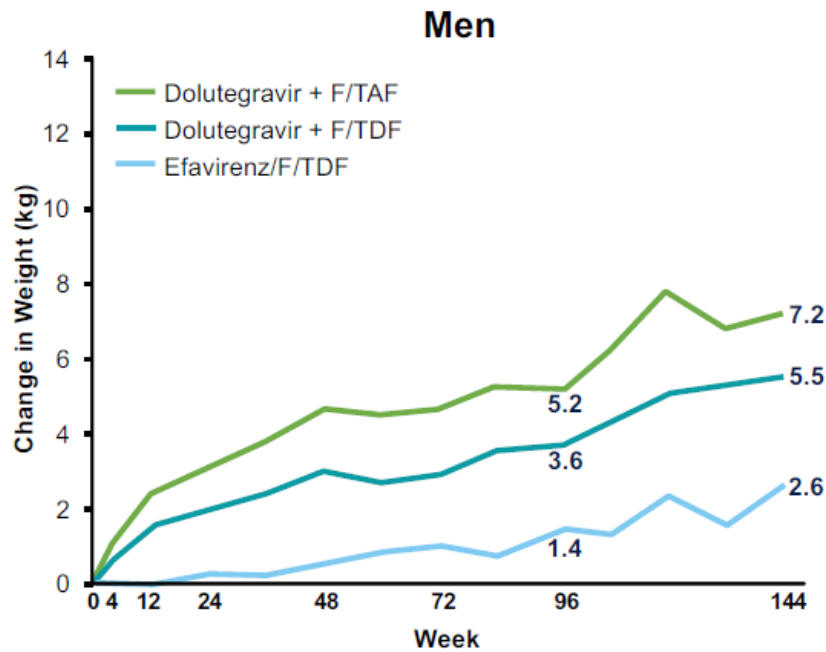


Estimated BMI increase @ 1 year: ≈ 1.5 in males, ≈ 2 in females

	DTG + F/TAF	DTG + F/TDF	EFV/F/TDF
≥10% change in body weight (%)	25*†	13*	11
Treatment-emergent obesity (BMI ≥30 kg/m ² ; %)	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

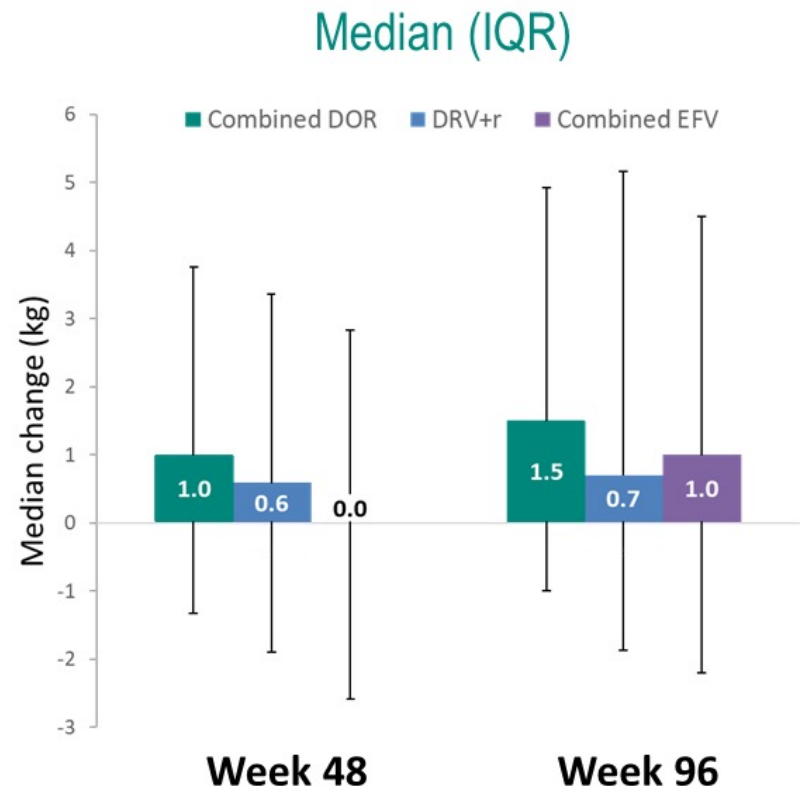
Magnitude & Determinants in Africa: ADVANCE - Mean Change in Weight to Wk 144 by Sex



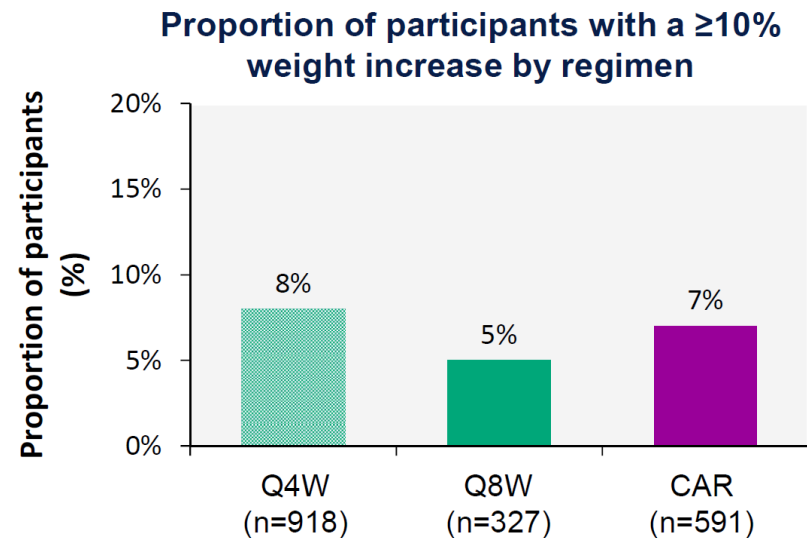
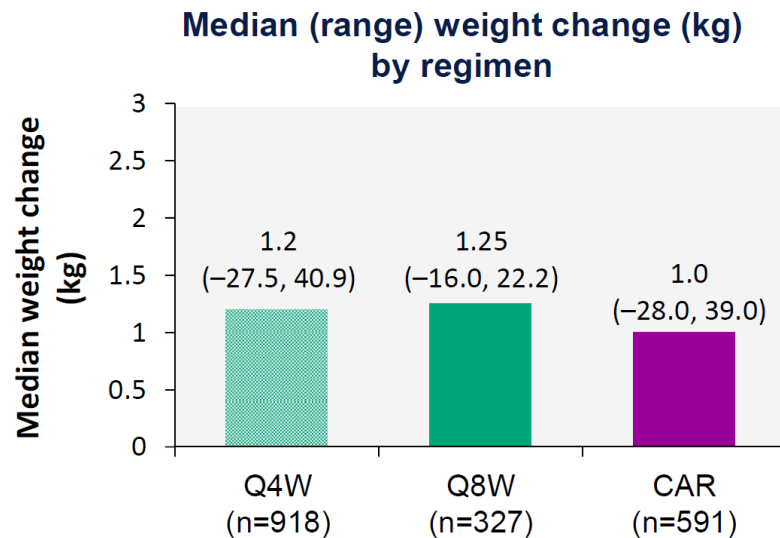
Doravirine Weight Gain In Treatment Naïve Individuals

- 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.

Case #2: Weight Gain with ART Switch

- M.S. is a 35 y/o white male on EFV/3TC/TDF for the past 10 years. He has been very reluctant to change a regimen that “saved his life”. However, willing to consider, due to persistent insomnia, depressive disorder. CD4 count is 700, VL<20 copies/mL. He’s HCV negative and HBV immune. A switch to DTG + FTC/TAF will likely result in:
 - a. No change in weight, as patient was already virologically suppressed.
 - b. Weight loss, since TAF is associated with fewer metabolic complications.
 - c. Weight gain because of switch from TDF to TAF
 - d. Weight gain because of switch from EFV to BIC
 - e. Both c and d.

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Magnitude of Weight Gain with INSTI: Rx Experienced

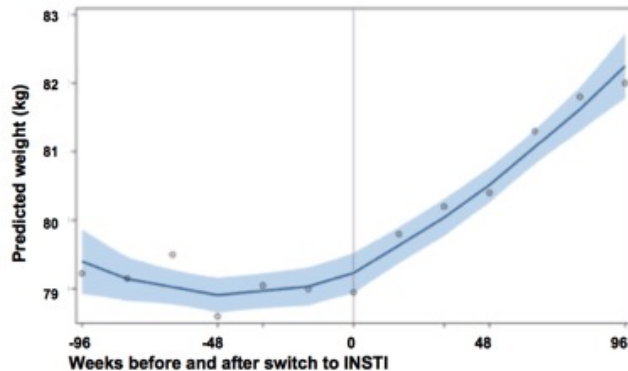
ACTG: A5001 & A5322 (n=691)

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 ≥ 60 and BMI ≥ 30 kg/m² were associated with greater weight gain

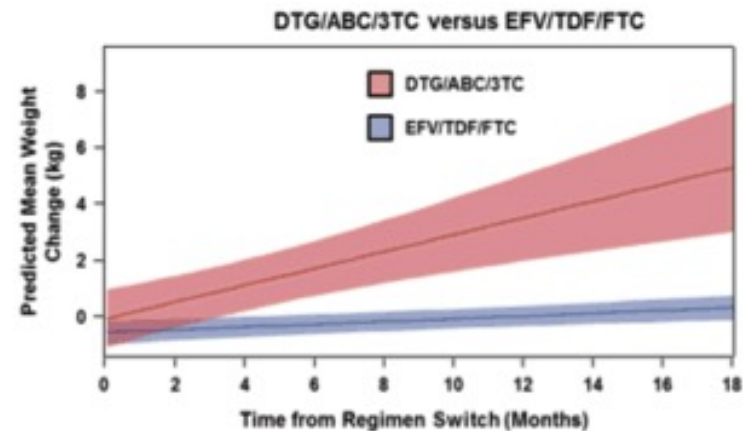
Switch to INSTI + ABC and EVG + TAF predictor (small #s)



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

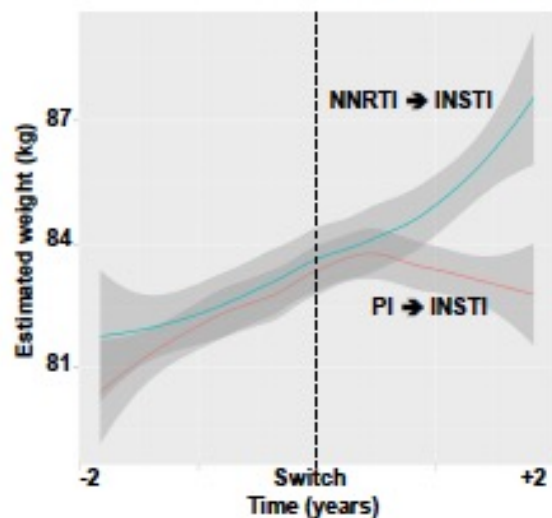


Figure. Unadjusted estimated weight for all persons before and after switch to INSTI by pre-switch regimen

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	0.84	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

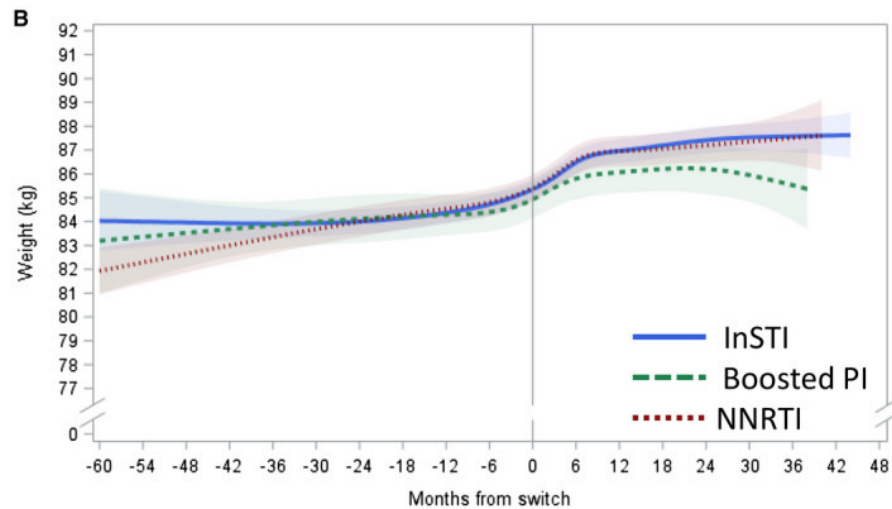
Table 2. Adjusted pre- and post-switch weight slopes by individual INSTI agents

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

Koethe. CROI 2020; Abstract 668

Weight Gain after Switch from TDF to TAF

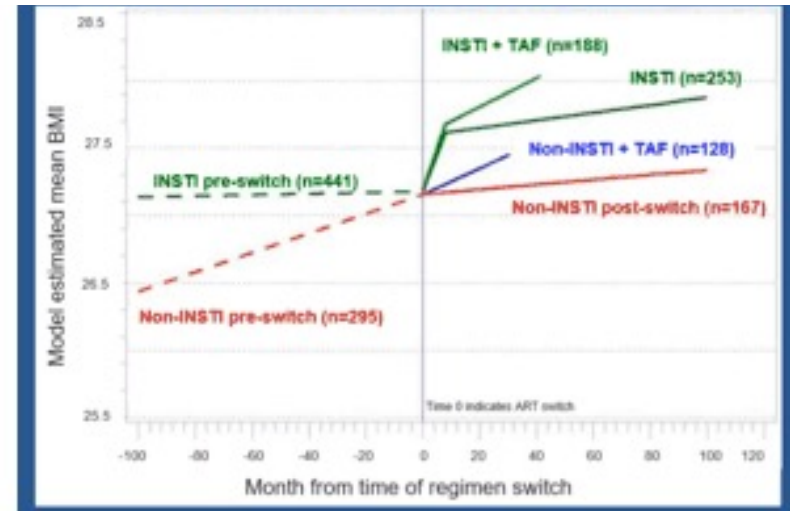


OPERA Cohort:

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 1st 8 months post-switch; mostly assoc. with INSTI use. After 8th months, continued weight gain mostly associated with TAF use

Palella. CROI 2021;

Summary: Magnitude and Determinants of Weight Gain with ART Initiation in Naïve Patients

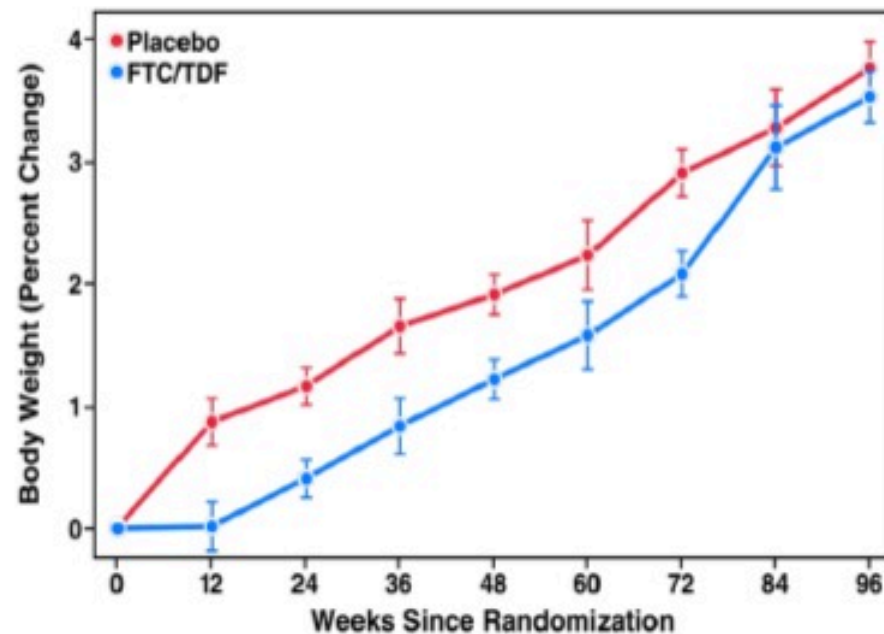
- INSTI: Significant weight gain. Greater magnitude of weight gain in people of African descent and women: Probably greater with DTG and BIC than RAL.^{4,5,6}
 - Possible mechanism(s): INSTIs induce adipocyte dysfunction: adipogenesis, lipogenesis, oxidative stress, fibrosis, and insulin resistance.⁷
- NRTIs: Greater weight gain with TAF vs. ABC and TDF;^{5,6} and greater weight gain with INSTI in conjunction with TAF.¹
- NNRTI less conducive to weight gain.^{5,6,8,9}
- Balance the benefits of INSTIs and TAF with risk of weight gain!

1. Venter. NEJM 2019; 2. Hill. IAS 2019; 3. Bedimo. ID Week 2018; 4. Bourgi. CROI 2019; 5. Bedimo. CROI 2019; 6. Sax. CID 2019; 7. Gorwood. CID 2020; 8. Orkin. EACS 2019; 9. Moestrup. EACS 2019.

iPrEX Trial: FTC/TDF vs. Placebo for PrEP

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

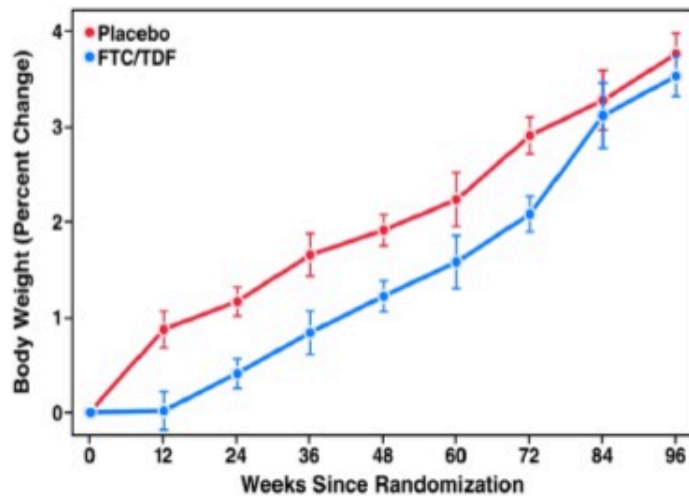
Maybe the thought of some ARVs delaying weight gain is a getting less heretical?



Grant. NEJM 2010;363: 2587-99

Weight Gain on PrEP Studies: iPrEX: FTC/TDF vs. Placebo

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



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)

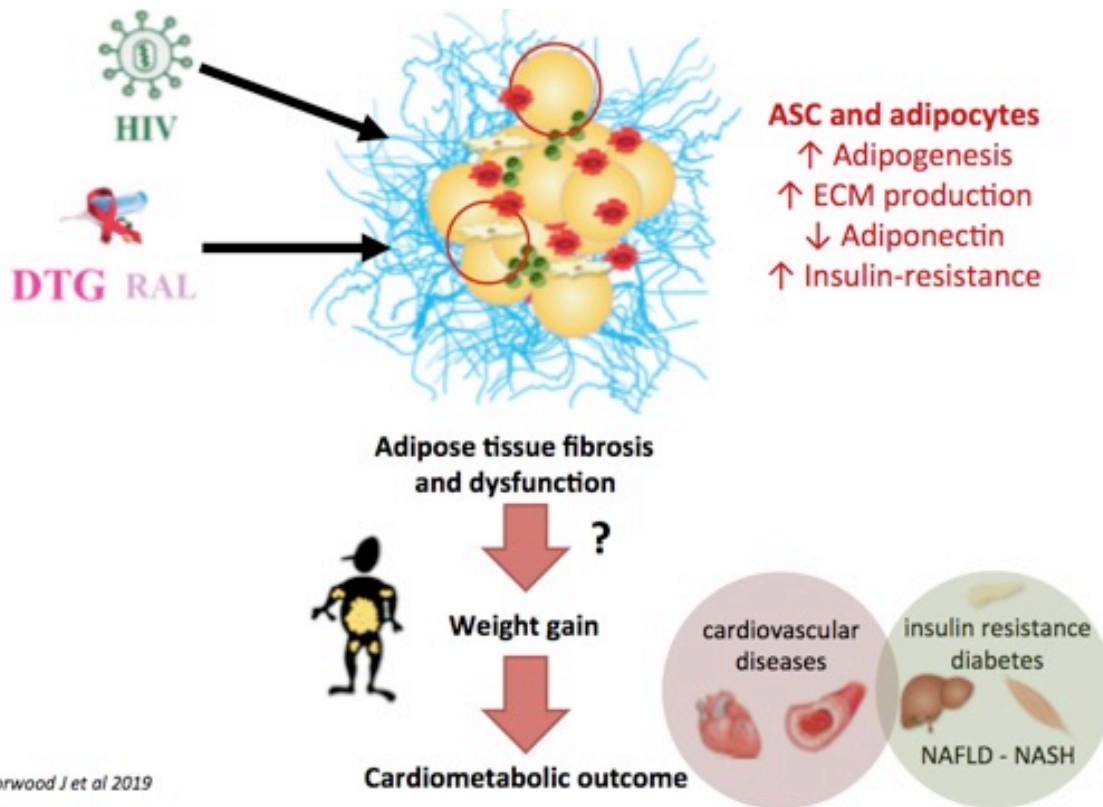
Case #3: Cardiometabolic Risk of Weight Gain on ART

- W.G is a 30 y/o white female who has been on DTG + TAF/FTC for the past 2 years. VL <20 copies/mL. CD4 count: 640. Since ART initiation, she gained 30 lbs since (210 lbs to 240 lbs). Her fasting blood glucose increased from 99 to 135 mg/dL. She reports no change in diet or exercise level. Studies have so far shown the following the cardio-metabolic risk of her weight gain.
 - a. There is no risk for metabolic complications. Most of the weight gain is lean, not fat mass.
 - b. Decreased risk of insulin resistance.
 - c. Increased risk of metabolic syndrome.
 - d. Increased risk of cardiovascular disease.

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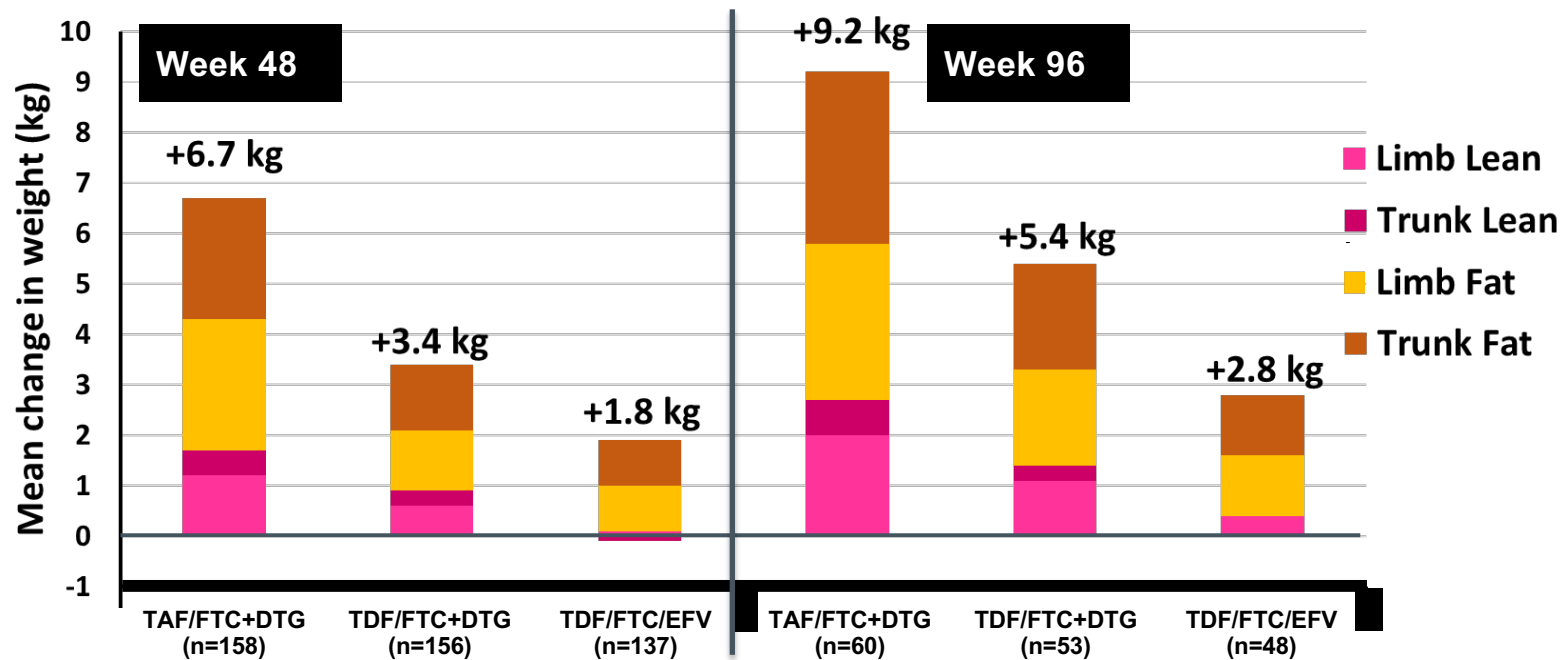
Potential Mechanisms of Weight Gain on ART



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

Gorwood J et al 2019
Gorwood J et al submitted

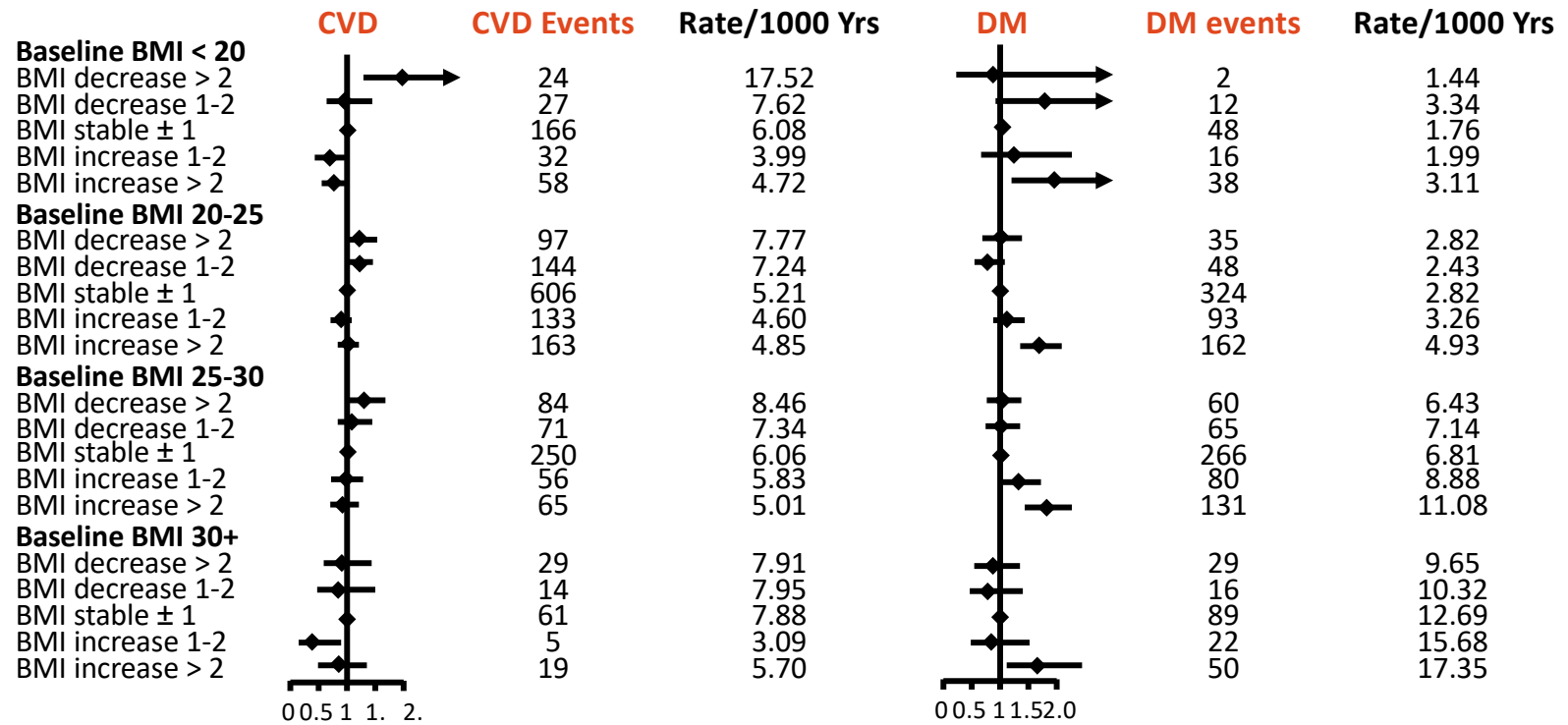
ADVANCE: Changes in body composition: women



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



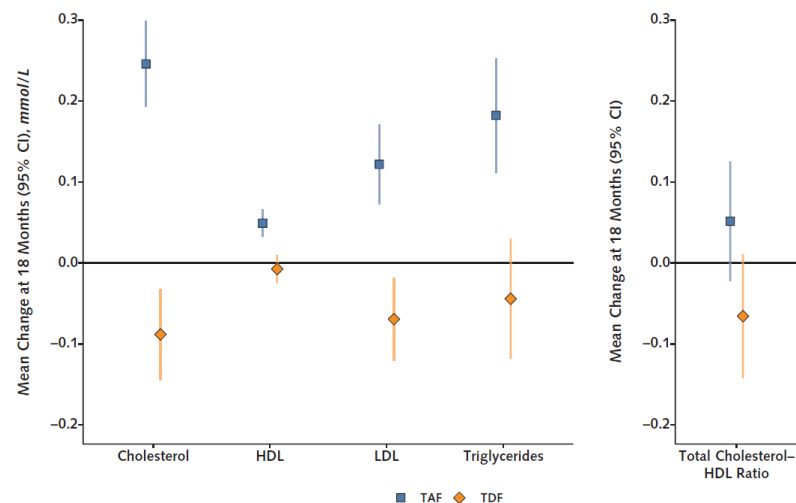
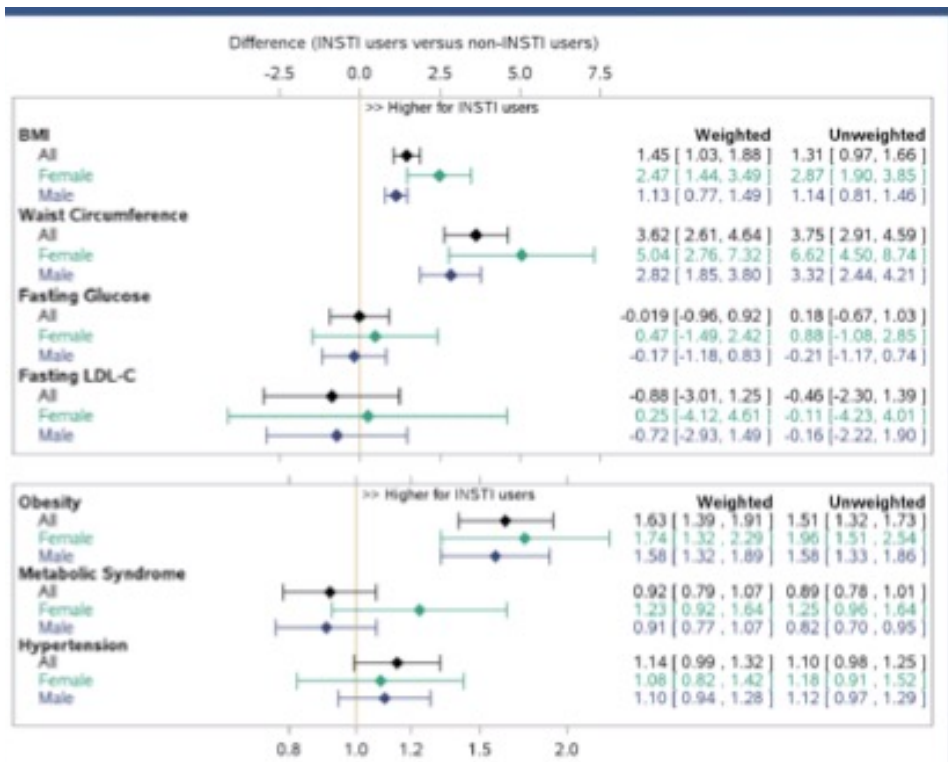
ADVANCE Study: Weight Gain and Metabolic Syndrome Through Wk 96

- 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)
Mean weight gain from BL, kg			
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
Treatment-emergent metabolic syndrome at Wk 96, %			
All patients	8.4 [†]	5.9	3.9 [†]
Women	10.9	8.1	5.6
Men	4.6	3.3	1.8

*Data after Wk 96 are incomplete. [†] $P = .03$ 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



Swiss Cohort:

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

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

Summary

- Accumulating data that INSTI- and TAF-based regimens are associated with greater weight gain than other regimens (also, PIs to some extent)
 - Increases in weight on DTG are higher in women, Blacks (and Hispanics?)
- Initial data on patterns and mechanism of weight gain: mostly fat, with INSTI. Need to evaluate effect on appetite, caloric intake, energy expenditure
- Metabolic Complications: Increased lipids and with TAF; probably metabolic syndrome and insulin resistance with TAF and INSTI
- In patients with significant weight gain: does changing to non-INSTI or non-TAF regimen help?



Question-and-Answer Session

 **2021** Ryan White
HIV/AIDS Program
CLINICAL CONFERENCE