

## Antiretroviral Therapy and Weight Gain

Roger J. Bedimo, MD, MS

Professor of Medicine  
Veterans Affairs North Texas Health Care System  
University of Texas Southwestern Medical Center  
Dallas, Texas



---

---

---

---

---

---

---

---

### 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 with weight gain during antiretroviral therapy

---

---

---

---

---

---

---

---

## Intersection of HIV and Obesity Epidemics:

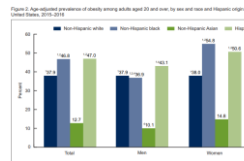
### Obesity in the World:

- 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:

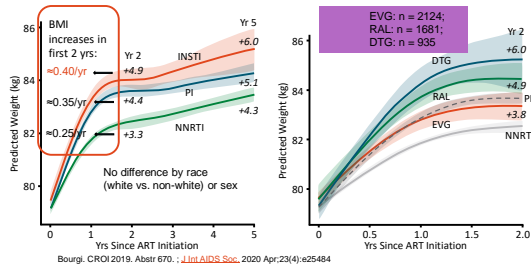
- The prevalence of 39.8% in 2016. **Affected mostly Blacks and Hispanics**



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



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

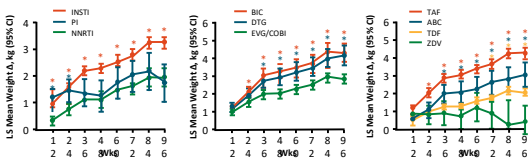


Bourg. CROI 2019. Abstr 670. [J Int AIDS Soc. 2020 Apr;23\(4\):e25484](https://doi.org/10.1093/aids/34.4.625-634)



## 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 < .05 vs NNRTI (first panel), EVG/COBI (second panel), or ZDV (third panel).

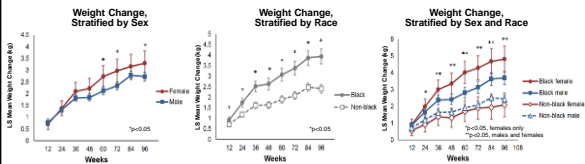
Sax et al. Clin Infect Dis. 2020 Sep 12;71(6):1379-1389

Slide credit: [clinicaltrials.gov](https://clinicaltrials.gov)



Weight Changes in Treatment-Naïve PLHIV: Pooled Analysis of 8 Phase 3 Clinical Trials

### 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

---

---

---

---

---

---

---

---

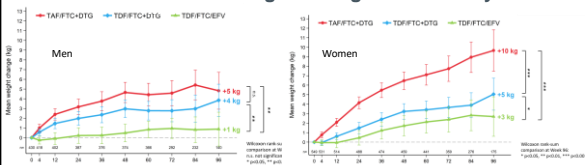
---

---

---

---

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



Estimated BMI increase @ 1 year:  $\approx 1.5$  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

---

---

---

---

---

---

---

---

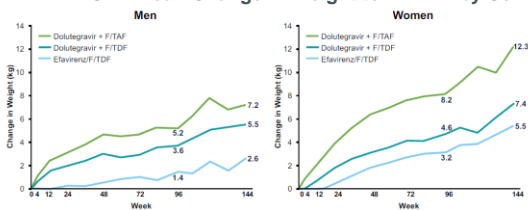
---

---

---

---

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



AIDS 2020: 23rd International AIDS Conference Virtual, July 6-10, 2020. Abstract OAXLB0104

---

---

---

---

---

---

---

---

---

---

---

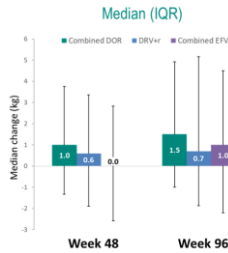
---

### Doravirine Weight Gain In Treatment Naïve Individuals

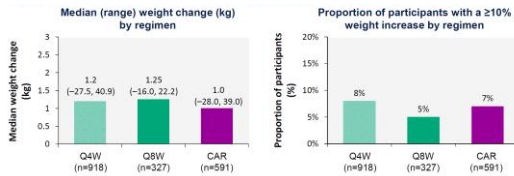
- Post hoc, pooled data analysis of 3 Phase 2/3 clinical trials in treatment naïve patients
  - DOR 100 mg vs EFV 600 mg, with FTC/TDF
  - DOR 100 mg vs DRV+r 800/100, with FTC/TDF or ABC/3TC
  - DOR/3TC/TDF vs EFV/FTC/TDF
- Double blind data through week 96 combined by treatment group

Treatment Group	N
DOR	855
DRV+r	383
EFV	472

Orkin C. EACS 2019; AIDS 2021 Jan 1;35(1):91-99



### 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 ≥10% weight increase was similar for the CAB + RPV LA regimens and CAR

\*Median weight gain at baseline: Q4W: 70.0 (67.0, 73.0); Q8W: 71.0 (68.0, 74.0); CAR: 70.0 (67.0, 73.0). CAR: 68.0 (65.0, 71.0). Q4W: 69.0 (66.0, 72.0). Q8W: 69.0 (66.0, 72.0). CAR: 69.0 (66.0, 72.0).

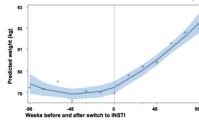
Patel et al. CROI 2021; Virtual. Science Spotlight 1297



### 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/m<sup>2</sup> were associated with greater weight gain  
 Switch to INSTI + ABC and EVG + TAF predictor (small #)

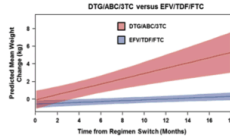


Lake. CROI 2019; Abstract 669; CID 2020 [Epub ahead of print]

Retrospective, single-site study (n=495)

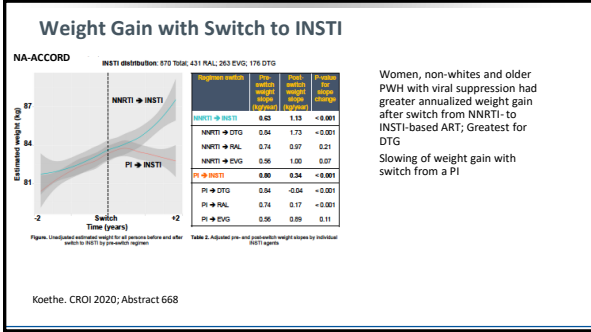
Patients on EFV/TDF/FTC switched to INSTI (DTG/ABC/3TC; RAL/TDF/FTC or EVG/c/TDF/FTC) vs. continued

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



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





\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

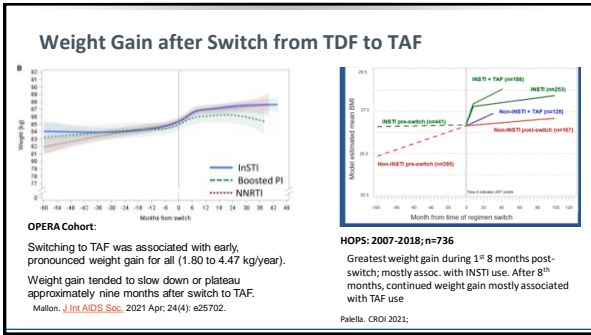
\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_



\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

### 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.<sup>4,5,6</sup>
  - Possible mechanism(s): INSTIs induce adipocyte dysfunction: adipogenesis, lipogenesis, oxidative stress, fibrosis, and insulin resistance.<sup>7</sup>
- NRTIs: Greater weight gain with TAF vs. ABC and TDF;<sup>5,6</sup> and greater weight gain with INSTI in conjunction with TAF.<sup>1</sup>
- NNRTI less conducive to weight gain.<sup>5,6,8,9</sup>
- 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. Orlin. EACS 2019; 9. Moestrup. EACS 2019.

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

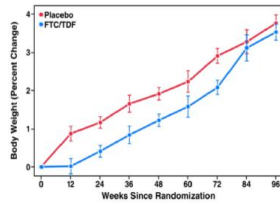
\_\_\_\_\_

**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




---

---

---

---

---

---

---

---

---

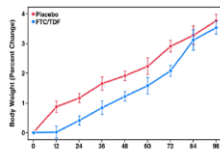
---

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

**HPTN 083**

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

- 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)



Grant. NEJM 2010;363: 2587-99

Landovitz. AIDS 2020. Abstr OAXLB0101

---

---

---

---

---

---

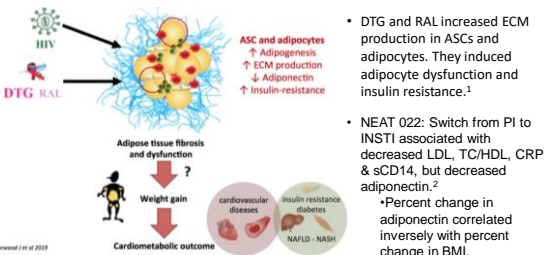
---

---

---

---

**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.

Revised 1st ed 2018  
 Copyright © 2018

1. Gorwood et al. 2019; 2. J Antimicrob Chemother. 2021 Jun13;dkab158. doi: 10.1093/jac/dkab158

---

---

---

---

---

---

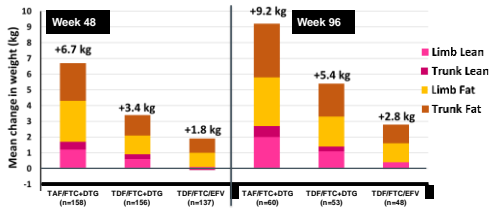
---

---

---

---

### 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

McCann. 17<sup>th</sup> EACS. Basel, November 2019

---

---

---

---

---

---

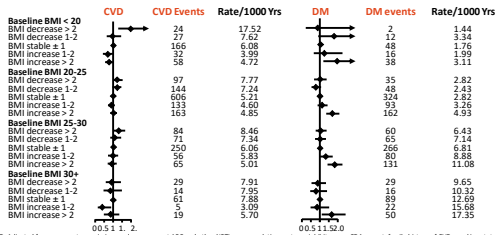
---

---

---

---

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



CVD: Adjusted for age, race, waist, transmission route, 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 HbA1c  
Peto method, CI 95% 1.1, 2.0  
Slide credit: clinicaloptions.com

---

---

---

---

---

---

---

---

---

---

### 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>			
<b>Women</b>			
• Wk 96	8.2	4.6	3.2
• Wk 144*	12.3	7.4	5.5
<b>Men</b>			
• 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*	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.  
Source: AIDS 2020, Abstr DA11801. Slide credit: clinicaloptions.com

---

---

---

---

---

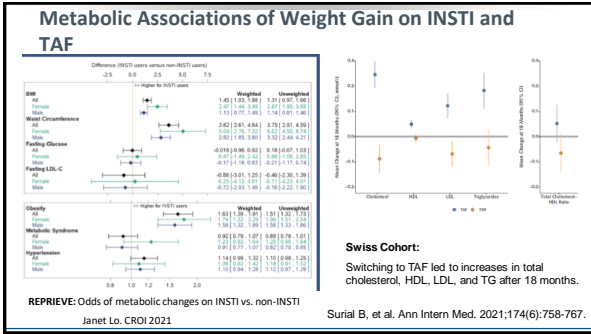
---

---

---

---

---




---

---

---

---

---

---

---

---

---

---

- ### Summary
- Accumulating data that INSTI- and TAF-based regimens are associated with greater weight gain than other regimens (also, Pls 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?

---

---

---

---

---

---

---

---

---

---




---

---

---

---

---

---

---

---

---

---