Antiretroviral Therapy and Weight Gain

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Sincere appreciations to Raj Gandhi and Pablo Tebas

Case

- A 34 y/o African American woman diagnosed with HIV disease in 2017.
- Baseline CD4 count and viral load were 45 and 170,000 respectively.
- Antiretroviral therapy initiated with TAF/FTC/BIC
- Gained 20 pounds over ensuing 2 years
- She reports no change in diet and activity level.
- She asks you if her weight gain is related to her medicines

- Which of the following statements are true about her antiretroviral therapy and weight gain?

A. Likely associated with BIC

B. Likely associated with TAF

C. Likely associated with both BIC and TAF

D. Not Associated with her antiretroviral therapy.

Antiretrovirals and Weight Gain: Outline

- Some Perspective
- How Much?: Magnitude of the Problem
- Who's Affected?: Determinants of Weight Gain
- How and Why?: Patterns and Purported Mechanisms
- What Does it Mean?: Metabolic and Clinical Implications
- Gaps in Knowledge and Future Directions

Perspective: The Obesity Epidemic and HIV

Intersection of HIV and Obesity Epidemics:

Obesity in the World:

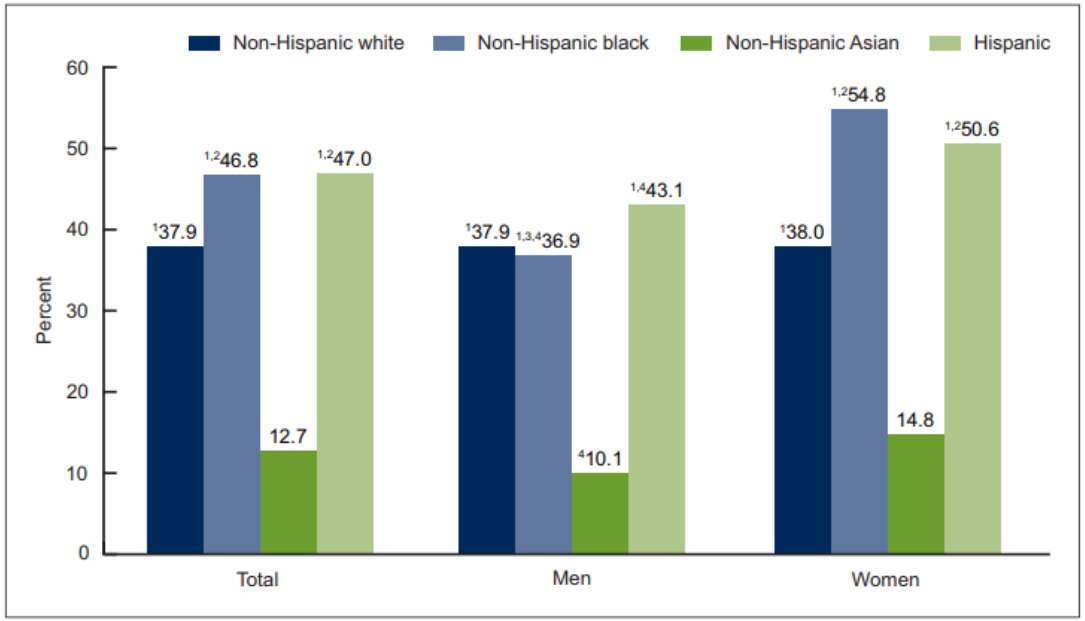
- Worldwide obesity has nearly tripled since 1975.
- In 2016, more than 1.9 billion adults, 18 years and older, were overweight. Of these over 650 million were obese.
- 39% of adults aged 18 years and over were overweight in 2016, and 13% were obese.

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

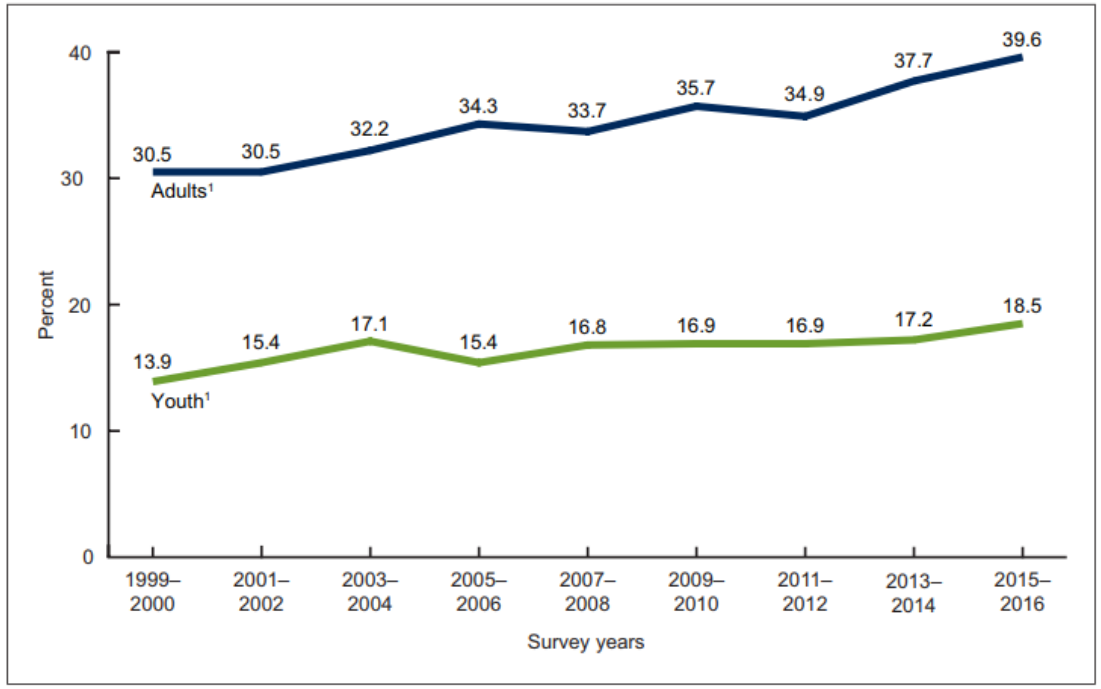


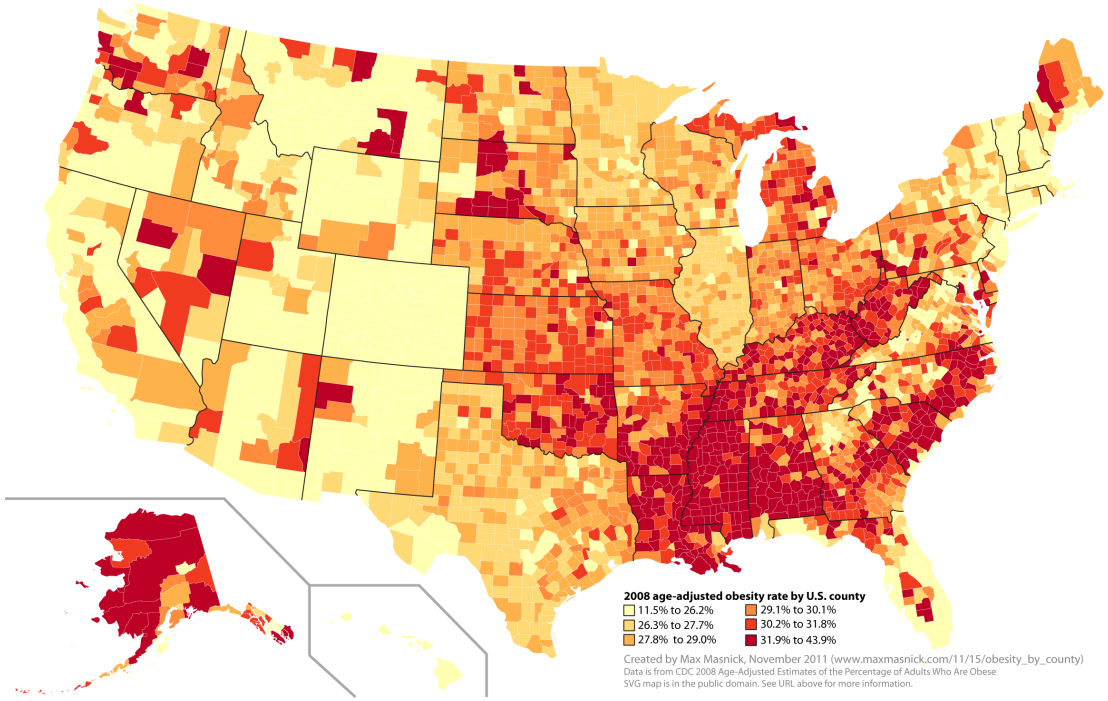
https://www.cdc.gov/nchs/data/databriefs/db288.pdf

Obesity is getting worse

And overlaps with poverty and HIV

Figure 5. Trends in obesity prevalence among adults aged 20 and over (age adjusted) and youth aged 2–19 years: United States, 1999–2000 through 2015–2016





Like HIV, higher prevalence of obesity in the South, in Blacks & Hispanics, in low income households

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

Magnitude and Determinants of Weight Gain with Integrase Inhibitors

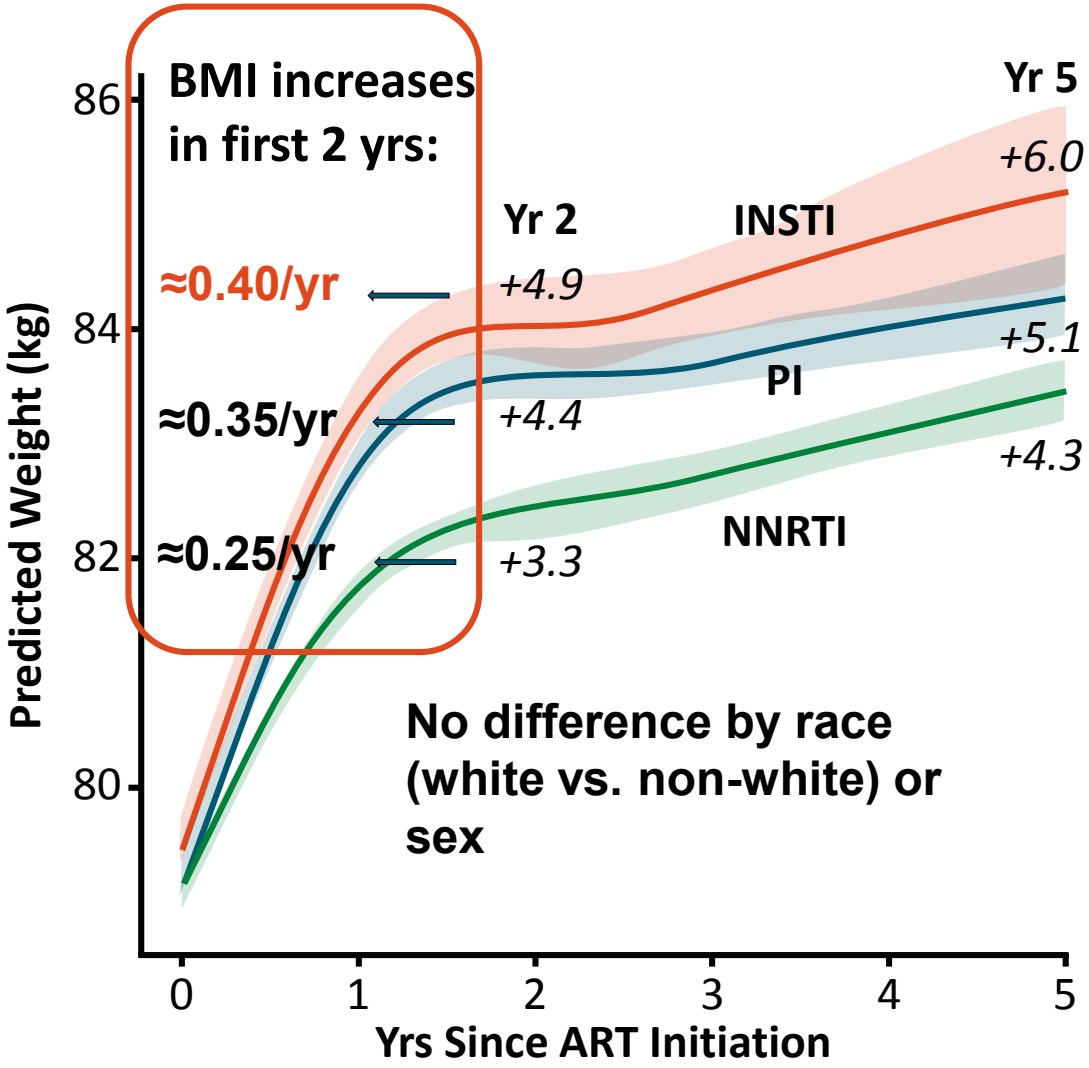
Magnitude of Weight Gain with INSTI: Rx Naïve (RCTs)

Study	Comparisons	BMI Change (kg/m²/year)	INSTI vs. Comparator	Other Predictors of Weight Gain			
				Sex	Race/Ethnicity	Low B/l CD4	High B/l VL
McComsey 2016 (n=328) A5260s	TDF/FTC/RAL TDF/FTC/DRV/r TDF/FTC/ATV/r	0.9 – 1.1 @ wk 96 **(≈0.5/yr)**	No difference Vs. ATV/r & DRV/r		Black	Estimate: −0.86	Estimate:1.34
Bhagwat 2017 A5257 (n=1809)	TDF/FTC/RAL TDF/FTC/DRV/r TDF/FTC/ATV/r	+3.8 kg @ wk 96 →BMI **(≈0.6/yr)**	OR: 1.4 for severe weight gain	Women	Black OR: 1.55	OR: 0.78	OR: 2.52
Bernadino 2019 (n=126) NEAT001	DRV/r+RAL. DRV/r /TDF/FTC	**≈0.51(+2.2%)** **≈0.23(+1.0%)**	Greater weight gain with RAL				
Stellbrink Gilead 1490 (n=645)	TAF/FTC/DTG TAF/FTC/BIC	**≈0.5(1.8kg/y)** **≈0.5(1.7kg/y)**	No diff b/w DTG and BIC				

Remarkable concordance of findings in RCT in the U.S.: INSTI-based ART associated with 0.5 annual increase in BMI

McComsey. CID 2016; Bhagwat. CROI 2017; Bernardino. PLoS Med 2019; Stellbrink. Glasgow 2018

Weight Gain by Class: NA-ACCORD

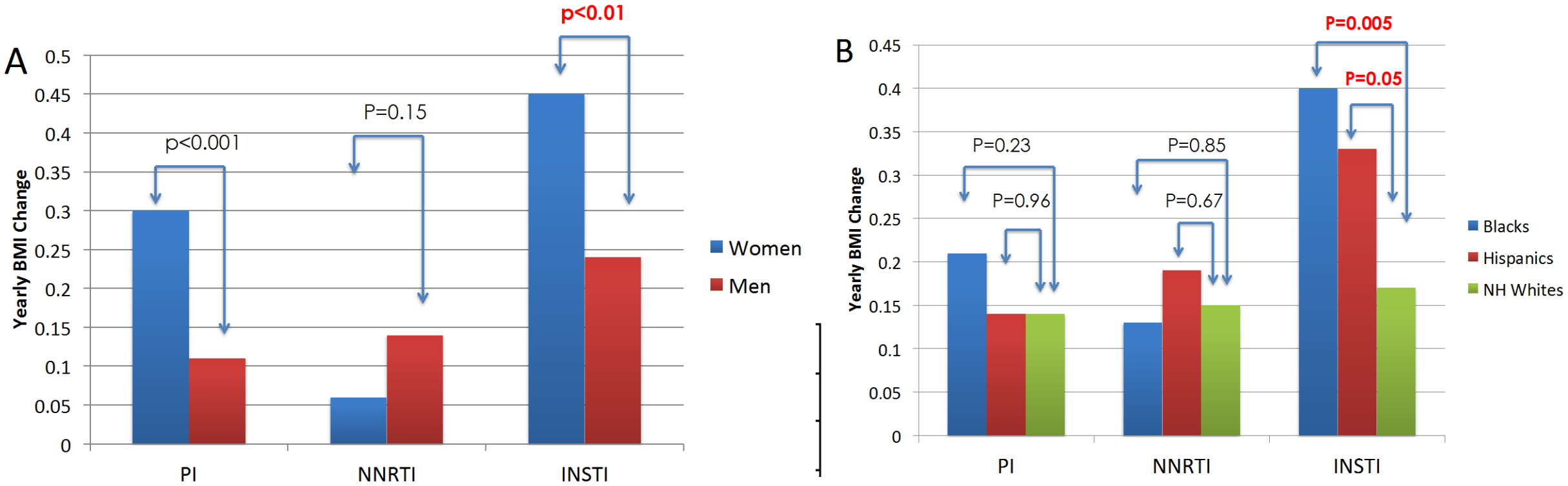


Bourgi. CROI 2019. Abstr 670.

Slide credit: clinicaloptions.com

Magnitude and Determinants: Weight Gain by Sex and Race/Ethnicity in Clinic Cohort

4,048 patients, 69% male, 53% Black, 28% Hispanic, and 16% non-Hispanic Whites. Mean age was 46.3 years (SD 11.9). Mean baseline BMI: 27.0 kg/m^2 (6.4).



Bedimo. ID Week 2018

NAMSAL: Changes in body weight/BMI by arm at Week 48

Week 48	TDF/3TC+DTG (n=293)	TDF/3TC+EFV400 (n=278)	p-value for difference
Mean change from baseline:			
Weight (kg)	+5	+3	<0.001
BMI (kg/m^2)	+1.7	+1.2	<0.001
Treatment-emergent overweight (BMI 25 – 29.9), n (%)	16%	17%	n.s.
Treatment-emergent obesity (BMI ≥ 30), n (%)	12%	5%	<0.01

Highly significant differences in weight and BMI change between arms

Clinical obesity (BMI 30 kg/m^2) TDF/3TC+DTG higher than TDF/3TC/EFV

3 Sites in Yaoundé, Cameroon: 100% African Descent; 65% Female

Hill et al. IAS 2019

ADVANCE: DTG with TAF/FTC or TDF/FTC vs. EFV/TDF/FTC

1053 Participants

TAF/FTC+DTG
n = 351

TDF/FTC+DTG
n = 351

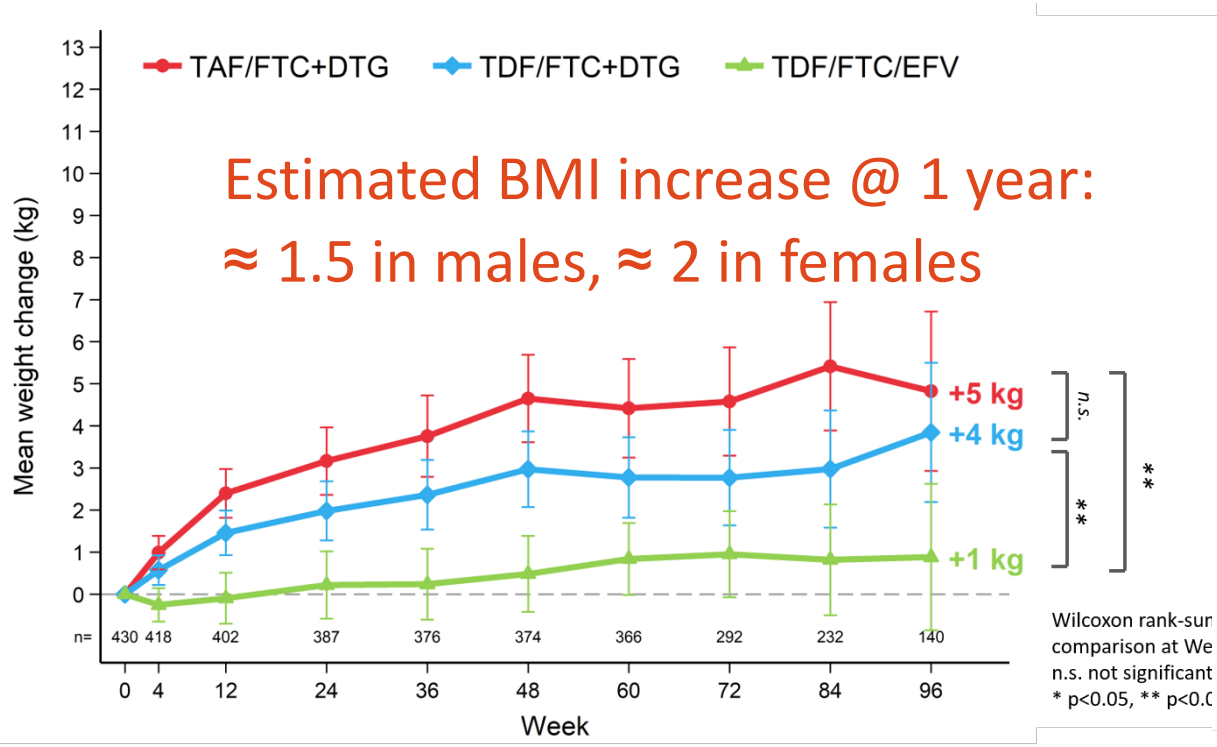
TDF/FTC/EFV
n = 351

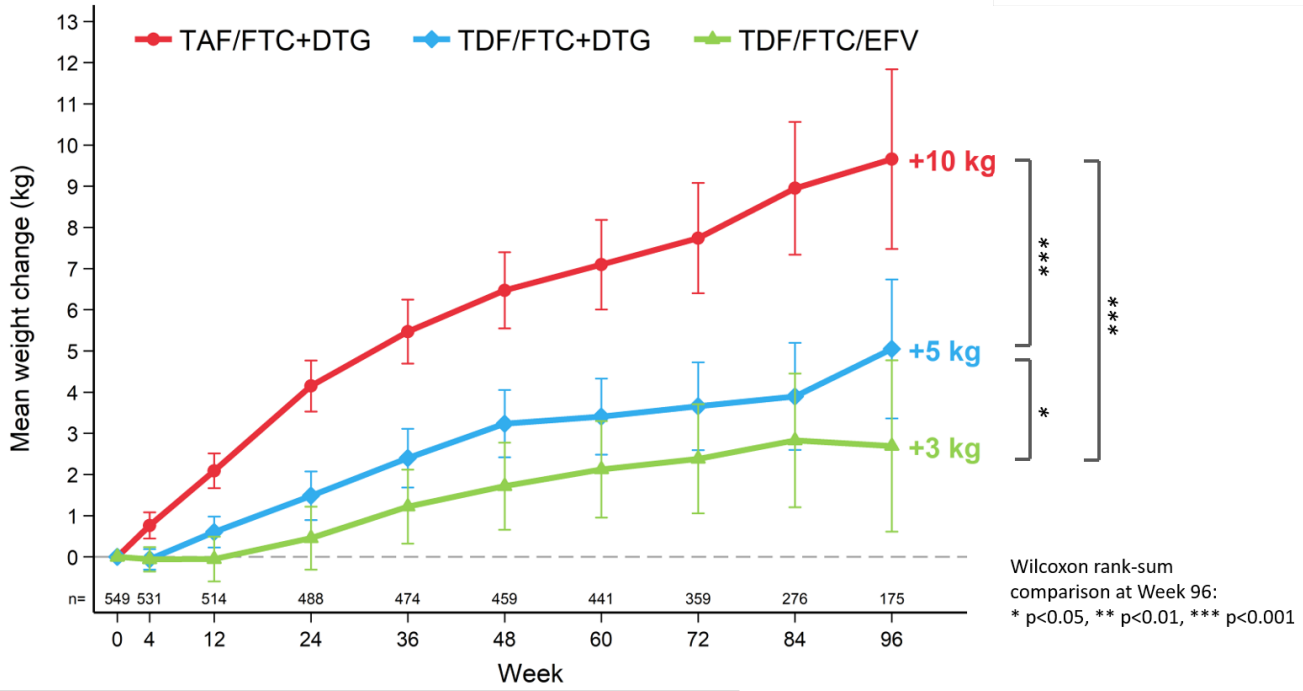
96 Weeks

Phase 3 (South Africa, Zimbabwe)

Open-label
Treatment-naïve
HIV RNA ≥500 copies/mL
No TB or pregnancy
No baseline genotyping

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

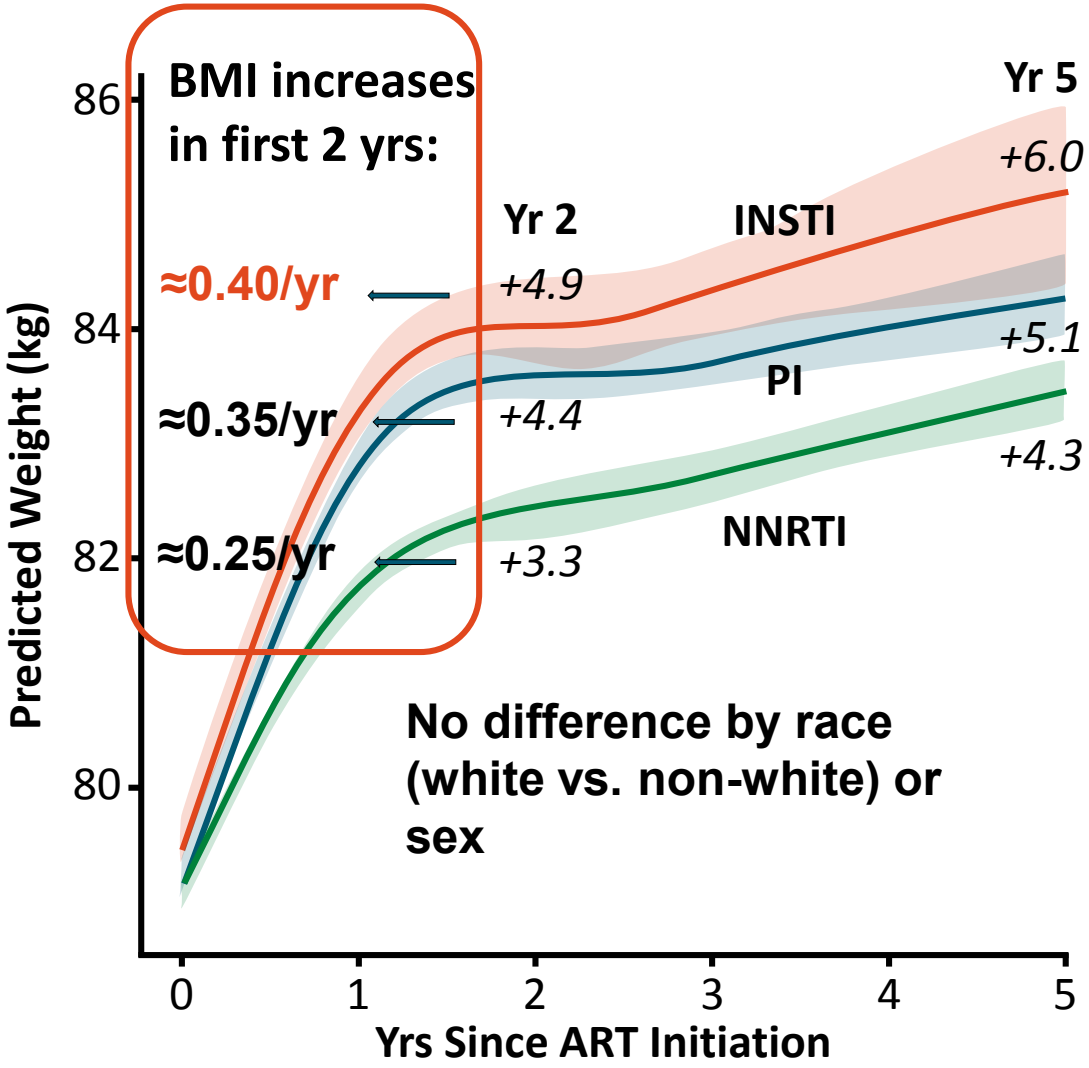


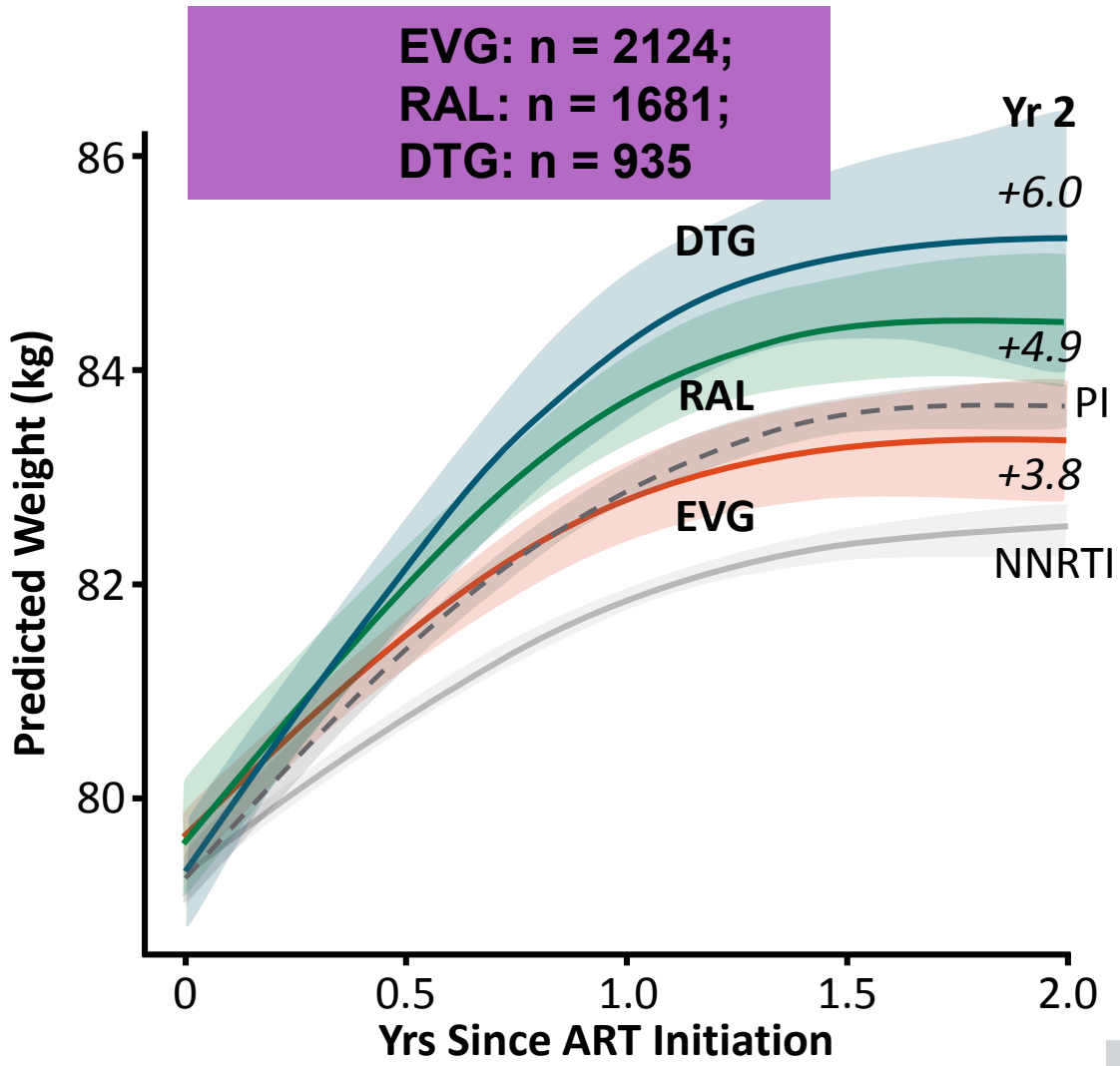


- **Significantly greater weight increase with DTG vs EFV, with TAF vs TDF**
- **Plateau in weight gain after Wk 48 observed in men but not in women**

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**

Weight Gain by Class or Specific INSTI: NA-ACCORD





Bourgi. CROI 2019. Abstr 670.

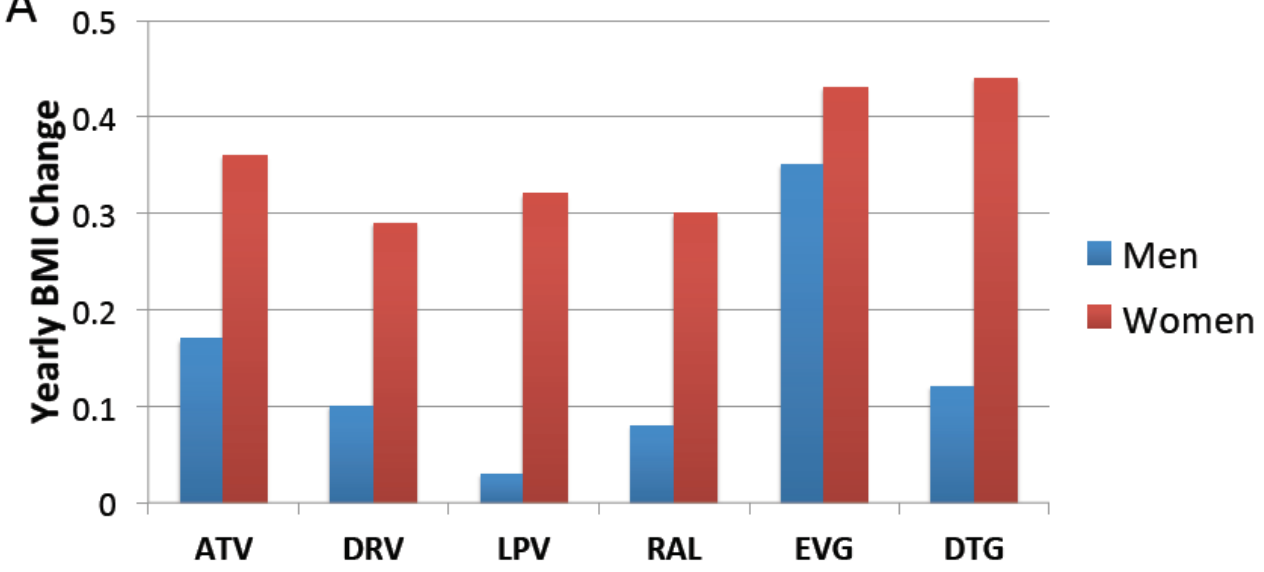
Slide credit: clinicaloptions.com

Weight Gain by Class or Specific INSTI: Clinic Cohort

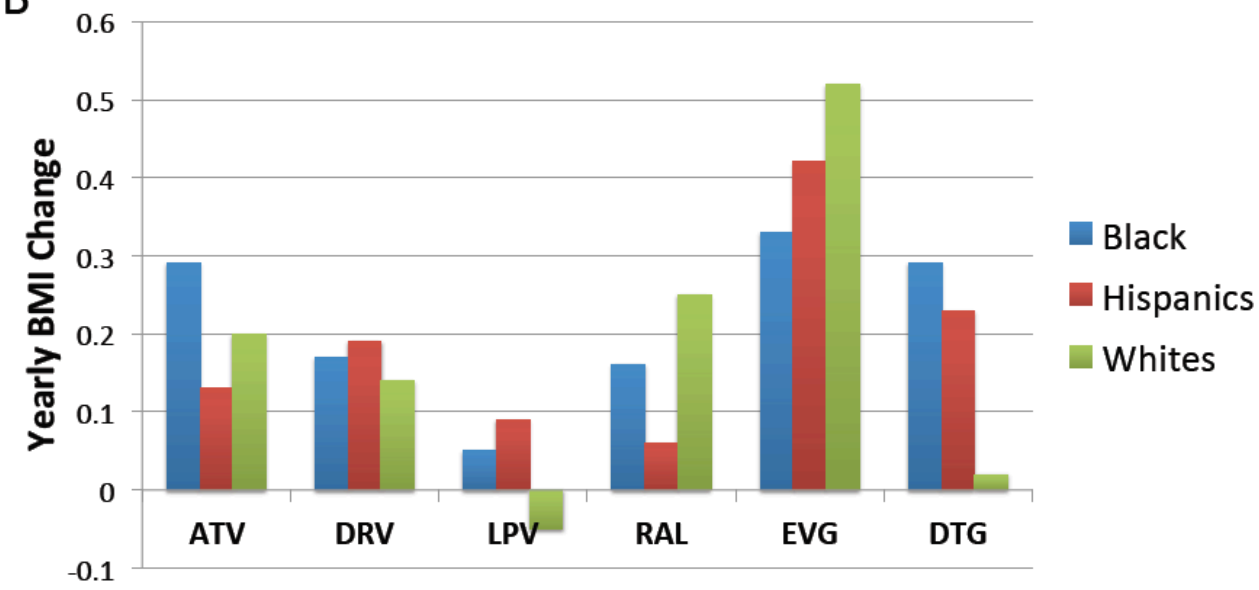
4,048 patients, 69% male, 53% Black, 28% Hispanic, and 16% non-Hispanic Whites. Mean age was 46.3 years (SD 11.9). Mean baseline BMI: 27.0 kg/m^2 (6.4).

	Protease Inhibitors			Integrase Inhibitors		
Antiretrovirals (n; PY of exposure)	ATV* (n=780; 1934 PY)	DRV* (n=1278; 2998 PY)	LPV/RTV (n=223; 388 PY)	RAL (n=591; 1334 PY)	EVG (n=405; 423 PY)	DTG (n=2037; 2473 PY)
Yearly BMI Change:	0.25	0.18	0.06	0.16	0.39	0.23

A



B



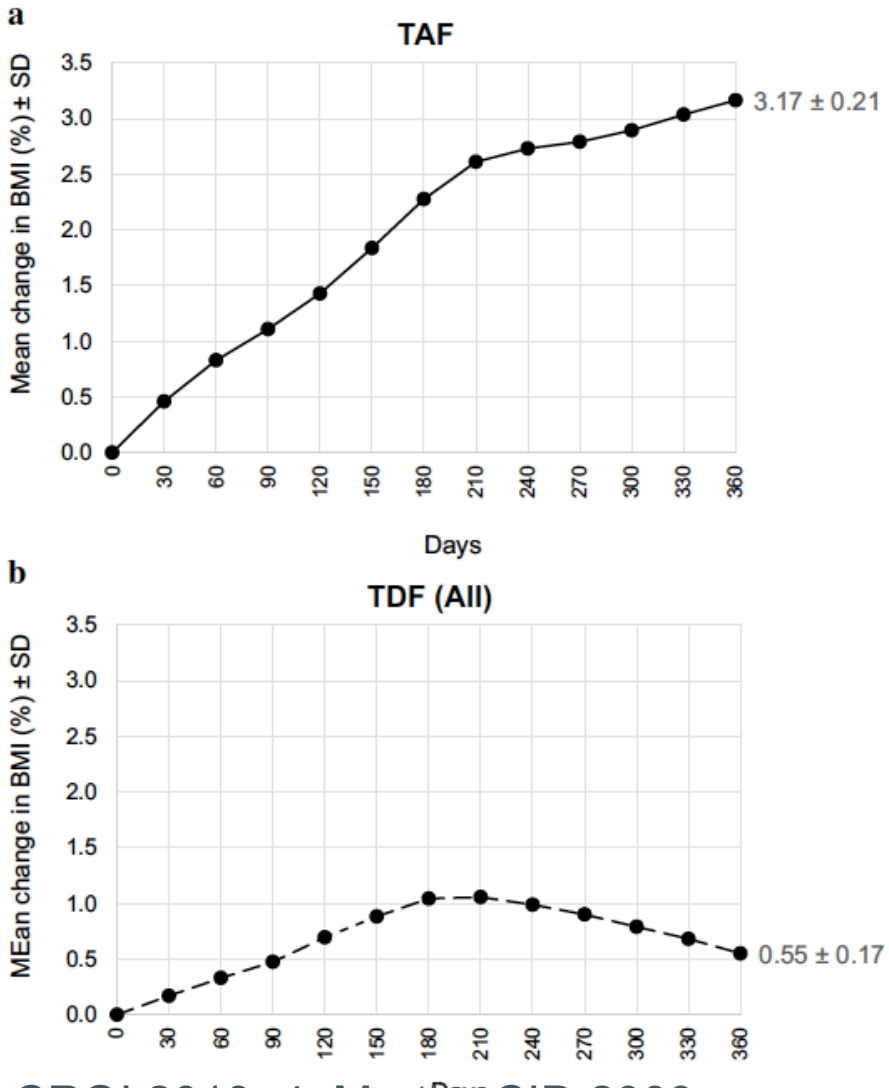
Bedimo. CROI 2019

But it may not be just the INSTIs

Other Potential Predictors of Weight Gain with INSTI

NRTI backbone (needs to be accounted for):

- TAF
  - Switch from TDF to TAF: +2.3 kg.[1]
  - AMBER: TAF/FTC/DRV/c (+1.8 kg) vs. TDF/FTC/DRV/c (0.8 kg).[2]
  - TAF Vs. TDF in HIV-uninfected (DISCOVER):+ 1.1 kg vs. +0 kg @ week 48.[3]
- ABC
  - STEAL: switch to ABC/3TC vs. TDF/FTC: +1Kg.[4]
  - ABC + DTG:[5-7]

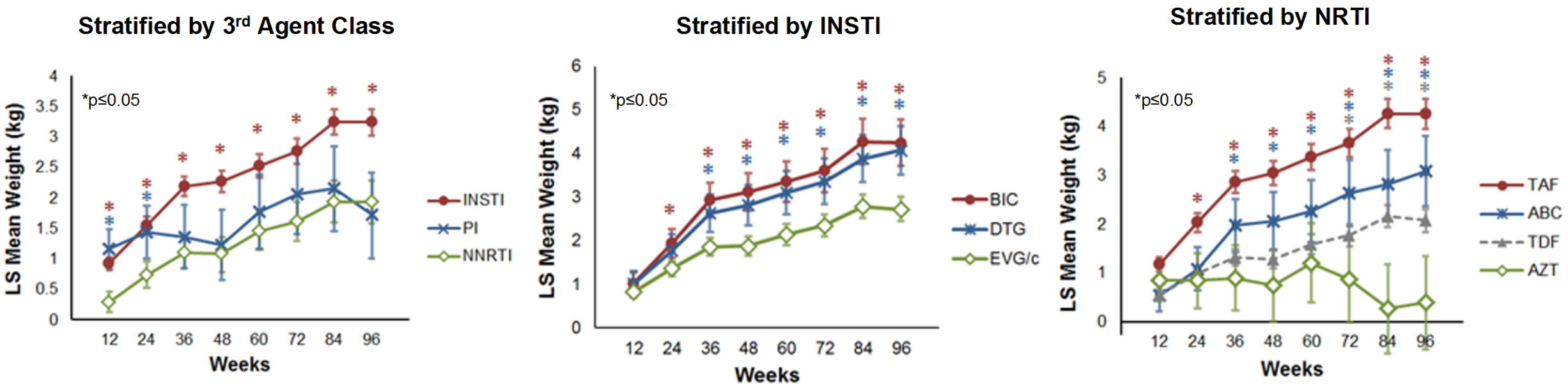


1. Gomez. Infection 2019; 47:95-102; 2. Orkin. HIV Glasgow 2018; 3. Hare. CROI 2019; 4. Martin. CID 2009; 5. Tamarasso 2017; 6. Menard 2018; 7. Lake 2019

Effect of Baseline ARV on Weight Increase

- Participants taking INSTIs experienced the most weight gain (mean: 3.24 kg)
  - Participants taking BIC or DTG demonstrated similar weight gain, both greater than participants taking EVG/c
- Among NRTIs, TAF was associated with an increased risk of ≥ 10% weight gain vs. ABC and TDF
  - Mean weight gain: TAF = 4.25 kg; ABC = 3.08 kg; TDF = 2.07 kg

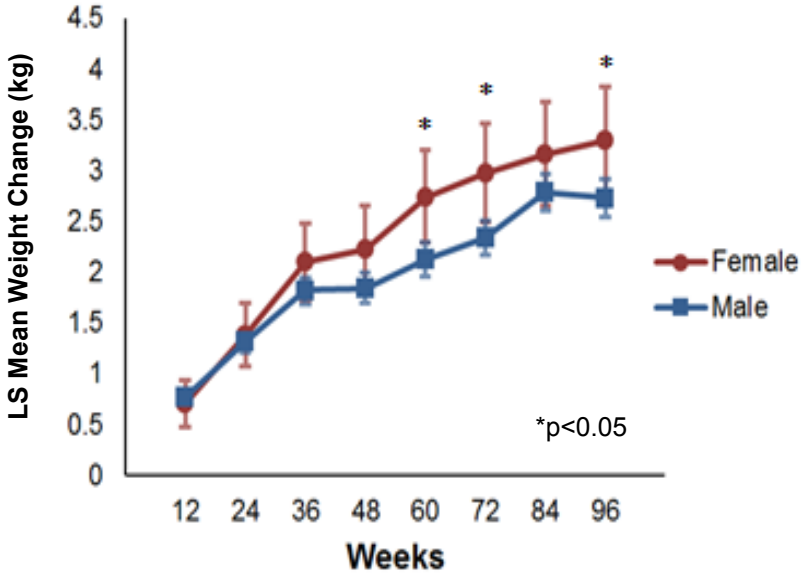
Weight Change in Participants Initiating ARV therapy, Stratified by 3rd agent, INSTI, and NRTI



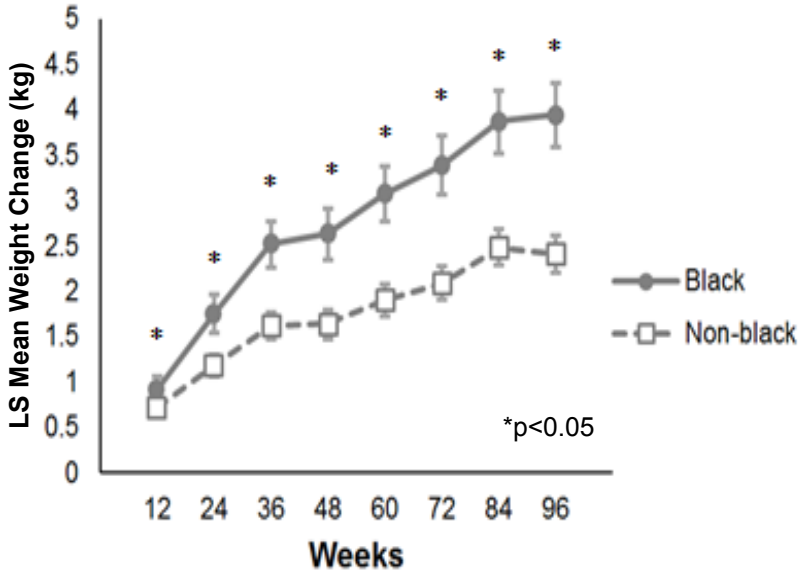
Sax P, et al. CID 2019. 14 Oct epub

Effect of Sex and Race on Weight Change

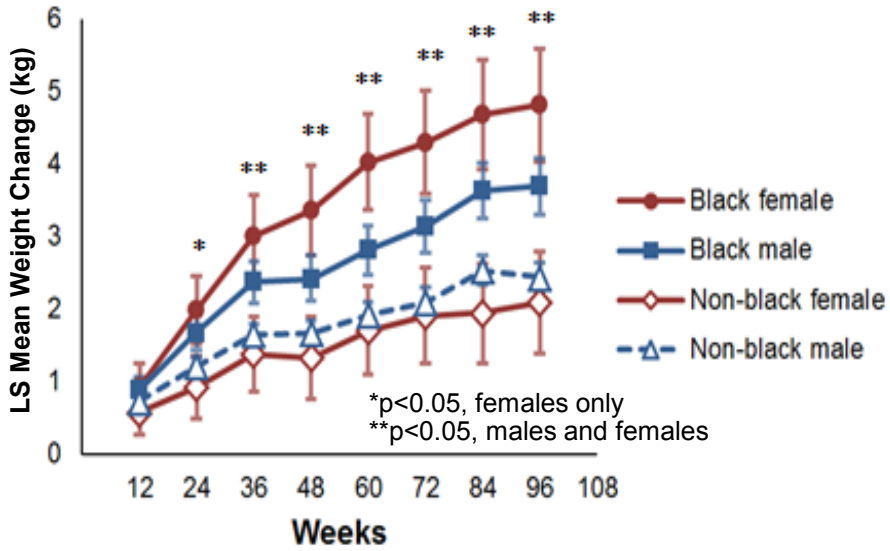
Weight Change, Stratified by Sex



Weight Change, Stratified by Race

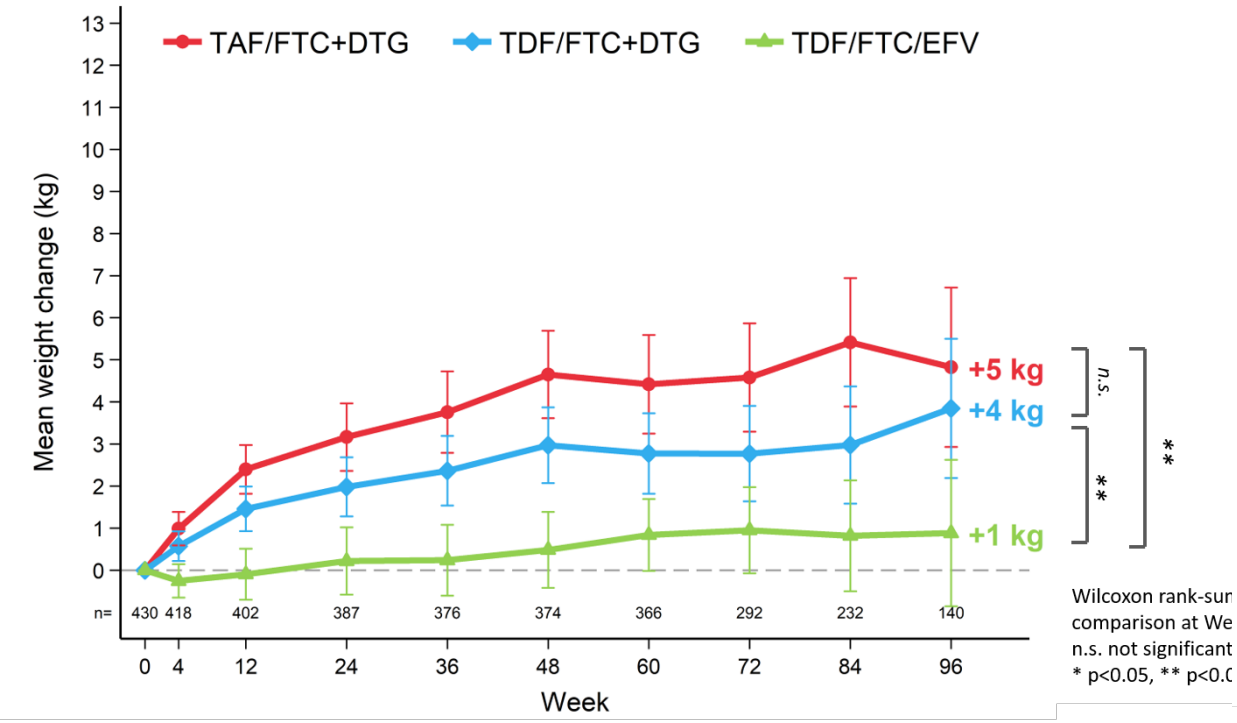


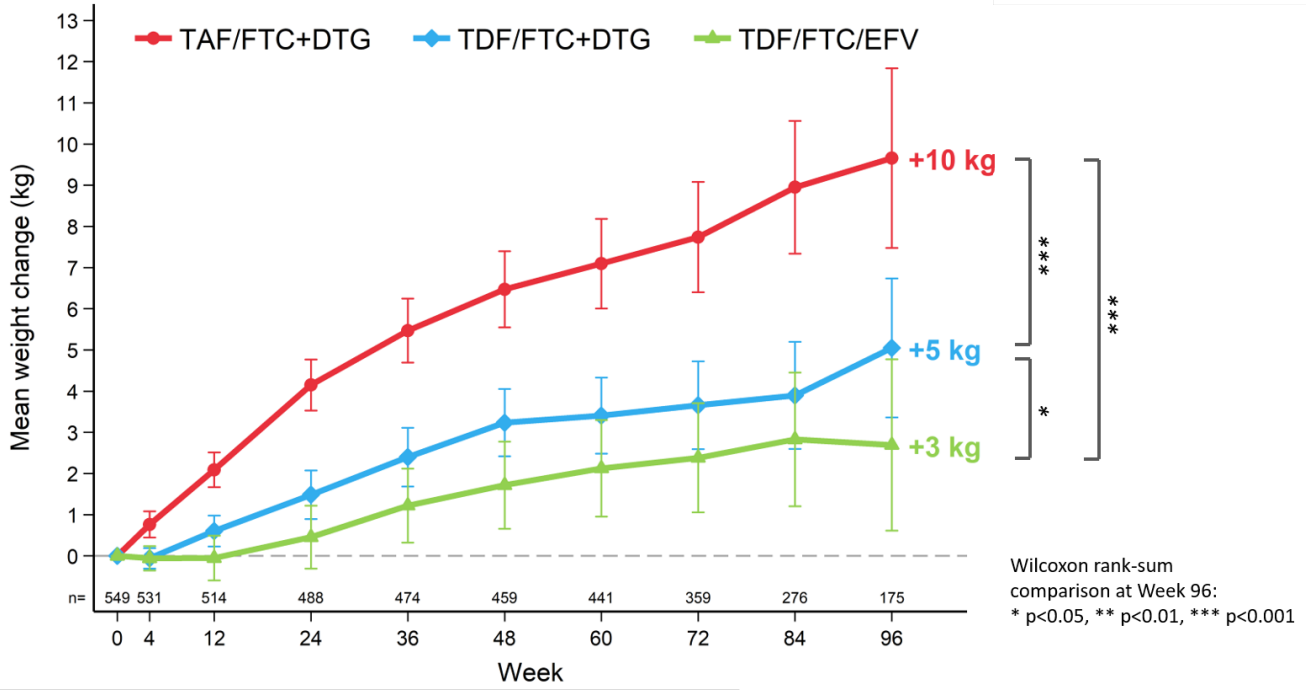
Weight Change, Stratified by Sex and Race



- 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

ADVANCE: Mean Change in Weight to Wk 96 by Sex





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**

ADVANCE: Changes in Weight at Week 96

Outcomes at Week 96

	Dolutegravir +F/TAF (n=351)	Dolutegravir + F/TDF (n=351)	Efavirenz/F/TDF (n=351)
Mean weight change (kg)			
Overall	+8*†	+5*	+2
Men	+5*	+4*	+1
Women	+10*‡	+5*	+3
≥10% change in body weight (%)	25*†	13*	11
Treatment-emergent obesity (BMI ≥30 kg/m^2; %)	19*†	8*	4

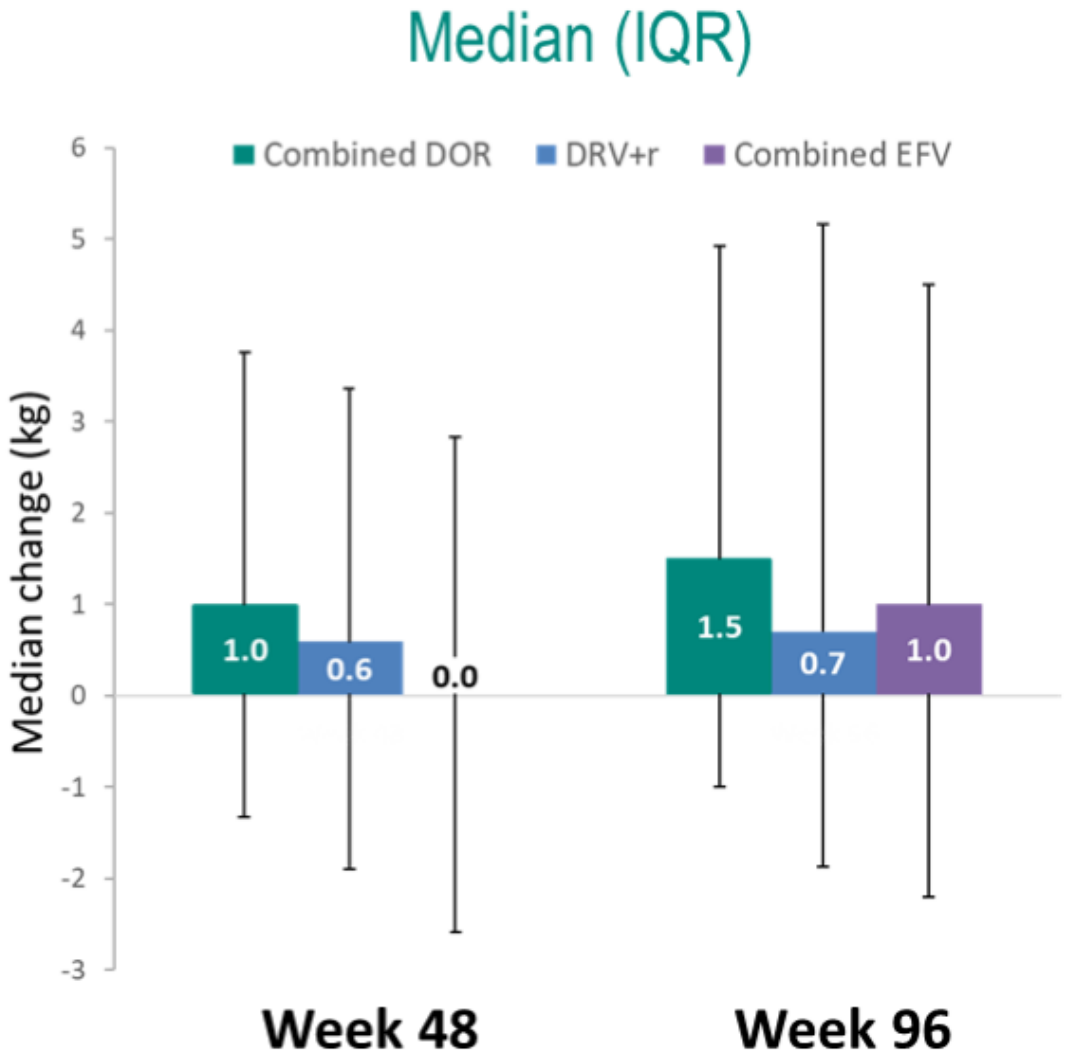
*P<0.001 versus efavirenz/F/TDF; †P<0.01 versus dolutegravir + F/TAF, and ‡P<0.001 versus dolutegravir + F/TDF.

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

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

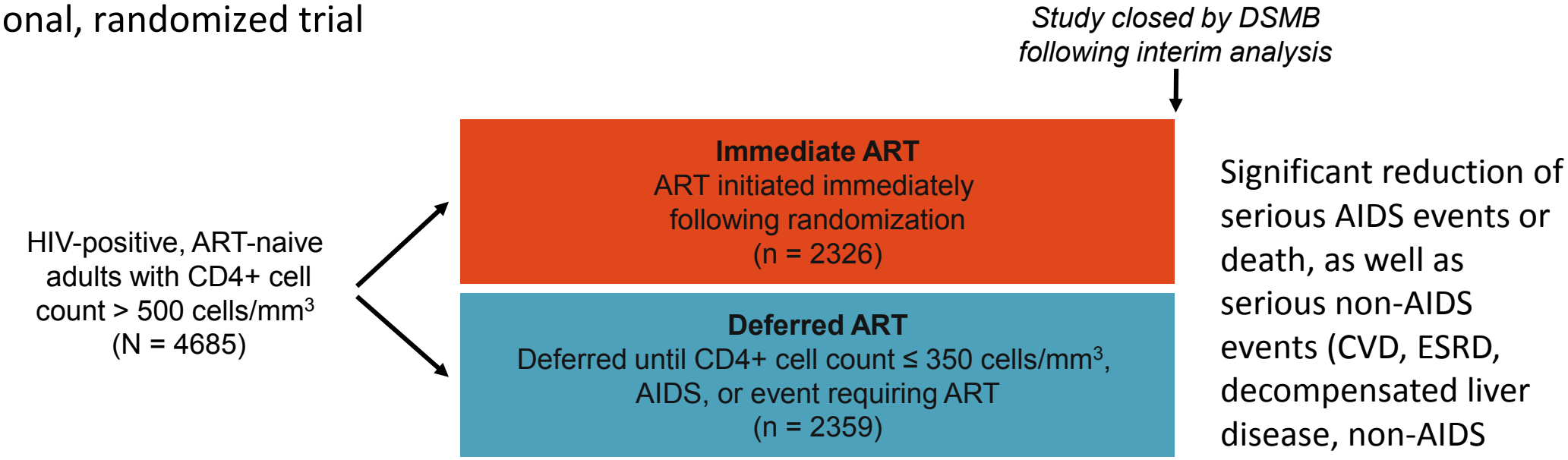
DOR	DRV+r	EFV
N=855	N=383	N=472



Orkin C. Presented at 2019 EACS. November 7, 2019. Session PS3.

START: Immediate vs Deferred Therapy for Asymptomatic, ART-Naive Pts

- International, randomized trial

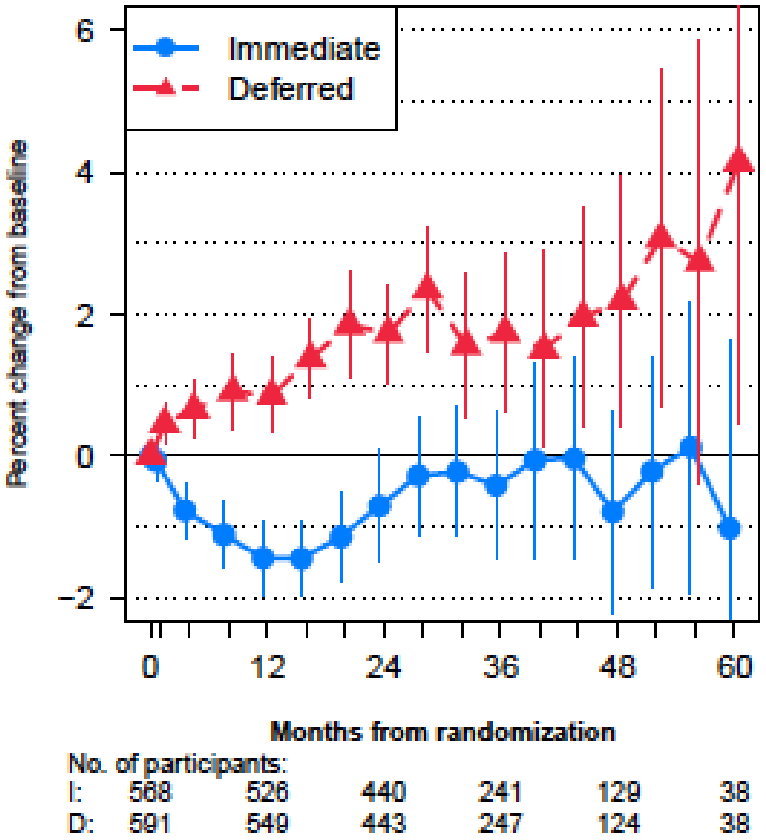


Significant reduction of serious AIDS events or death, as well as serious non-AIDS events (CVD, ESRD, decompensated liver disease, non-AIDS cancer.

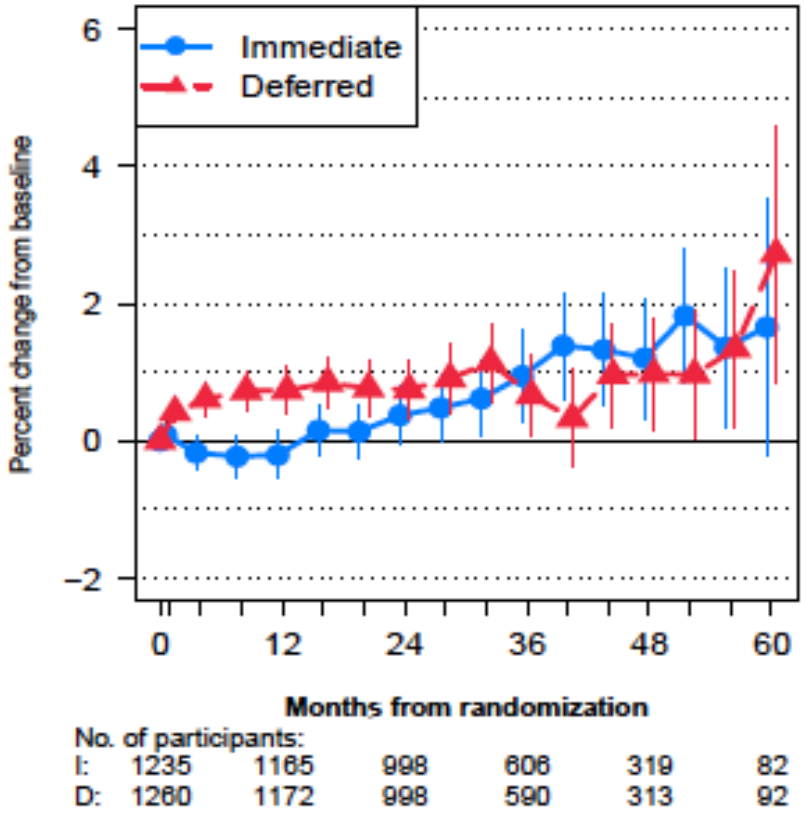
- Primary composite endpoint (target = 213)
  - Serious AIDS or death from AIDS:
  - Serious non-AIDS events and death not attributable to AIDS
    - CVD, ESRD, decompensated liver disease, non-AIDS–defining cancers

INSIGHT START Group. N Engl J Med. 2015;373:795-807. Lundgren J, et al. IAS 2015. Abstract MOSY0302. Slide credit: clinicaloptions.com

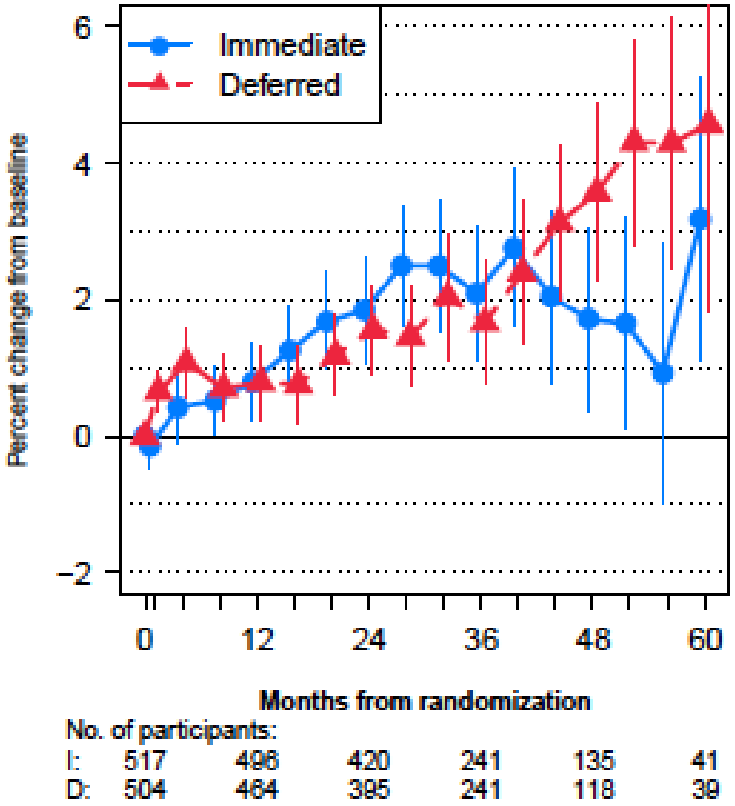
START: Weight Change by Baseline Viremia



Baseline VL <3000



Baseline VL: 3000 to 50,000



Baseline VL >50,000

Moestrup. EACS 2019

START: Immediate vs Deferred ART

Values at study entry	
Median weight	74 kg
Median age	36
% female	26.8%
% smokers	32.0%
Median CD4	651
Median HIV RNA	12761
High income country	46.0%
Low-mid income country	54.0%
ART Class (pre-specified)	
NNRTI	78.7%
INSTI	3.9%
PI	17.4%
NRTI class (pre-specified)	
TDF	88.9%
Other	11.1%

- Mean percent change in weight from baseline:
  - Immediate: 1.1% (95% CI: 0.9 – 1.5)
  - Deferred: 1.9% (95% CI: 1.7 – 2.2)
- Important to note:
  - Most patients (80%) are on NNRTI; <4% on INSTI
  - Very high median CD4 count, and rather low median viremia.

Moestrup. EACS 2019

Magnitude and Determinants of Weight Gain with ARTs

- INSTI: Greater magnitude of weight gain in people of African descent and women:
  - Delta BMI of ≈ 1.7/year in NAMSAL (65% female); ≈ 1.5/year in females in ADVANCE vs. 0.5 in US studies. [1, 2,3,4]
  - Discordant findings on relative risk of individual INSTIs.[4,5,6]
- NRTIs: Greater weight gain with TAF vs. ABC and TDF;[5] and greater weight gain with INSTI in conjunction with TAF.[1]
- NNRTI and PI probably less conducive to weight gain.[5,6,7,8]

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. Orkin. EACS 2019; 8. Moestrup. EACS 2019.

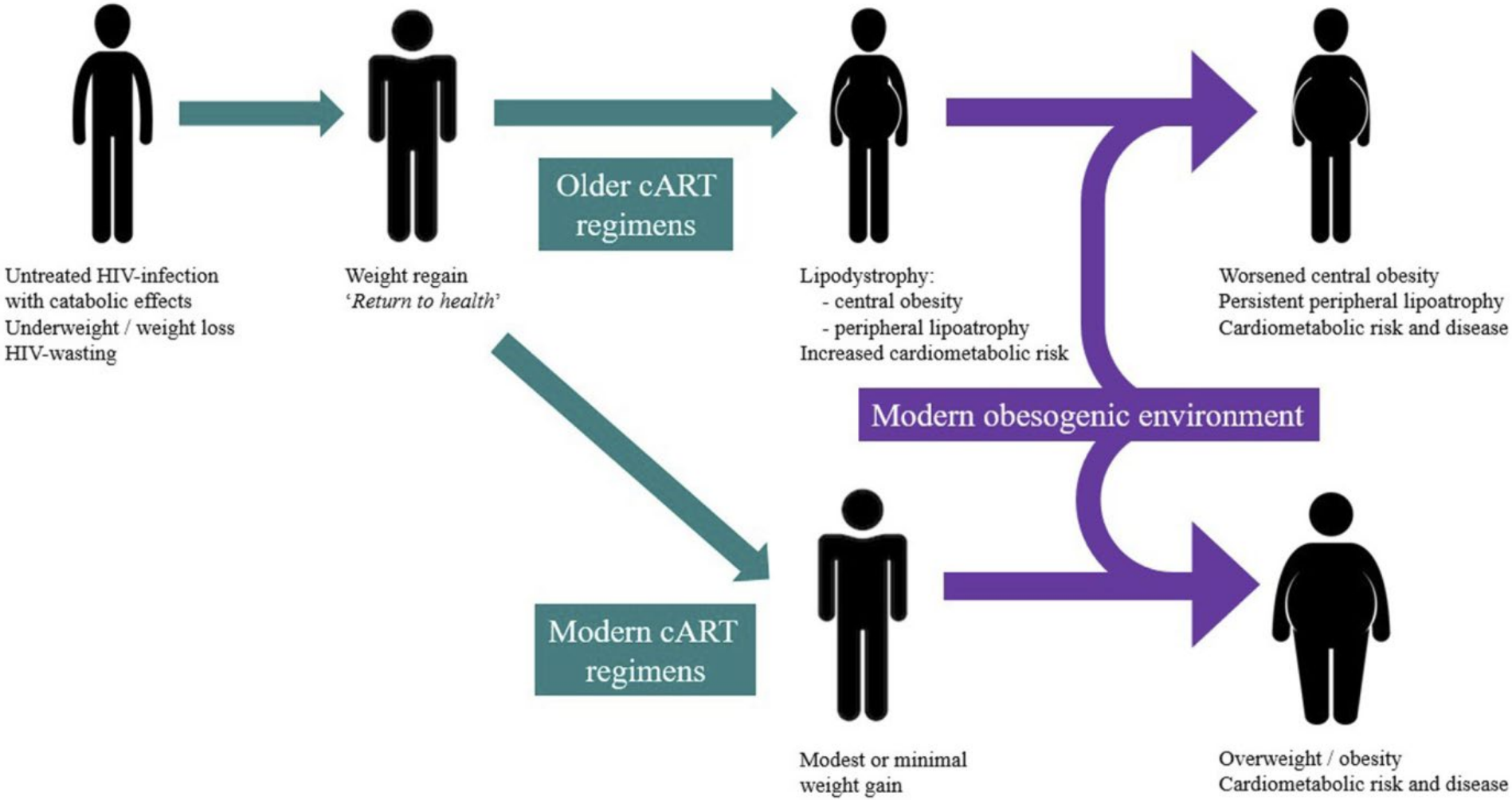
So Far…

- Weight gain with ART initiation; Greater with INSTI (BMI increase of 0.4 to 0.5 per year); Likely greater for Blacks, Hispanics and Women

Why?…

- The fundamental cause of obesity and overweight is an energy imbalance between calories consumed and calories expended.
  - Starting ART and controlling HIV decreases inflammation and reduces the catabolic effects of HIV infection; Mostly in those with high viremia. (HIV was called “slim disease”; and TNF was called cachectin). If you consume the same amount of calories, you will gain weight.
  - It should not be surprising that a group of drugs that control better HIV leads to more weight gain

Weight Gain During ART: Return to Health Versus Obesity



Kumar S, et al. *Front Endocrinol.* 2018;9:705.

Is there differential weight gain with switch to INSI in the setting of virologic control?

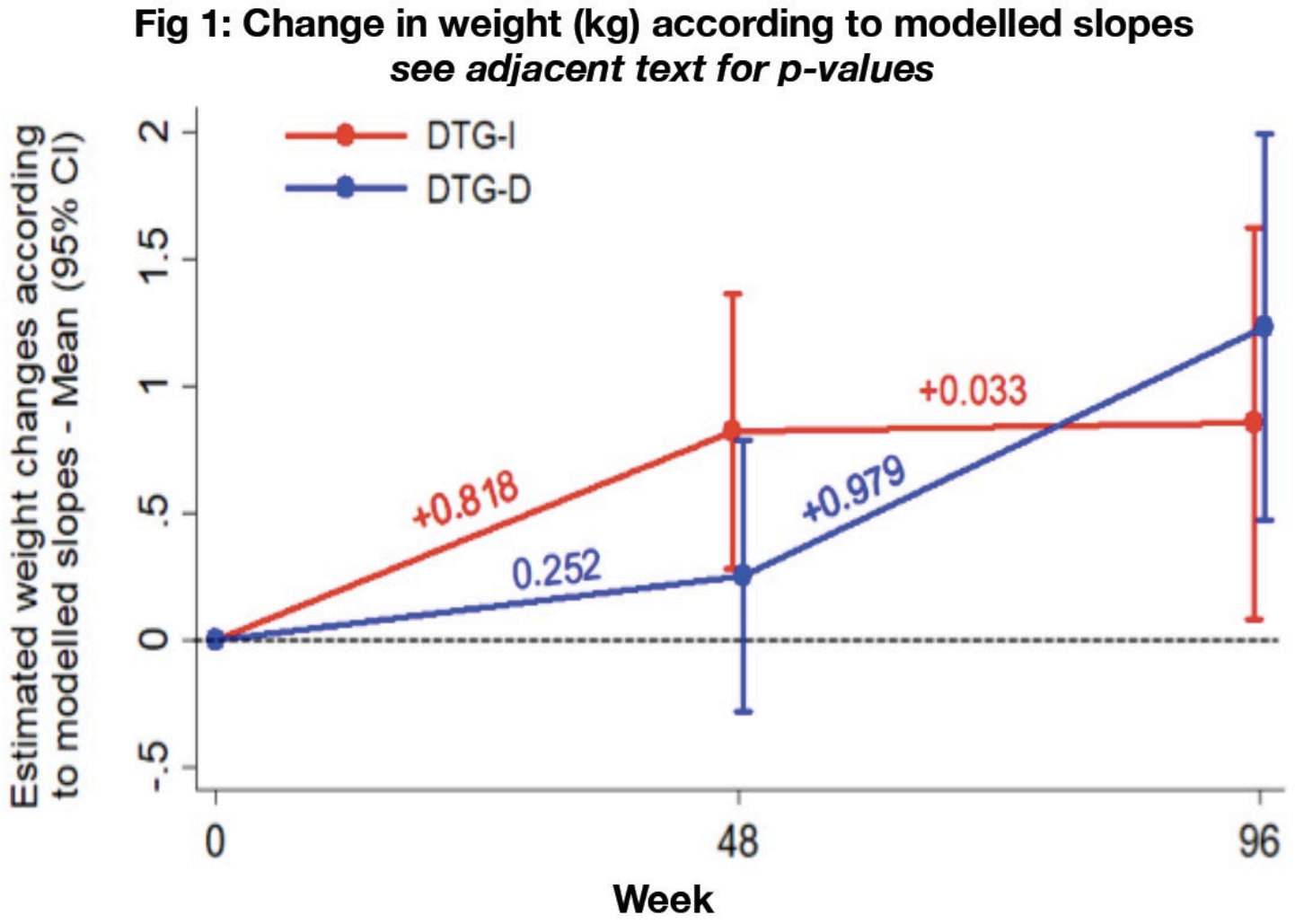
Magnitude of Weight Gain with INSTI: Rx Experienced

NEAT 022 (n=415): High CVD risk (>50 or Framingham >10)
On PI: Immediate (DTG-I) or delayed (DTG-D) switch to DTG

Mean BMI Changes:

Week 0 to Week 48:
DTG-Immed: +0.27 (p=0.003)
DTG-Delayed: +0.06 (p=0.471)

Week 48 to Week 96:
DTG-Immed.: -0.00 (p=0.984)
DTG-Delayed: +0.33 (p=0.004)



Waters. HIV Glasgow 2018

Magnitude of Weight Gain with INSTI: Rx Experienced

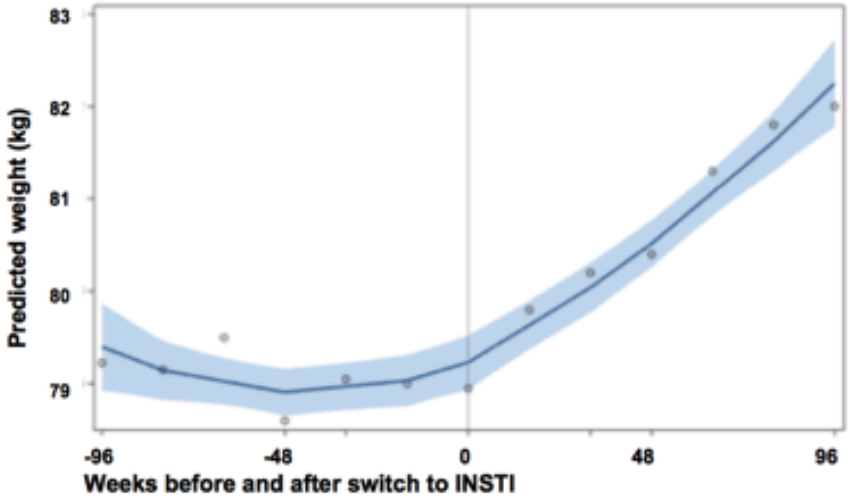
ACTG: A5001 & A5322 (n=691)

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, white or black race, age ≥60 and BMI ≥30 kg/m^2 were associated with greater weight gain

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

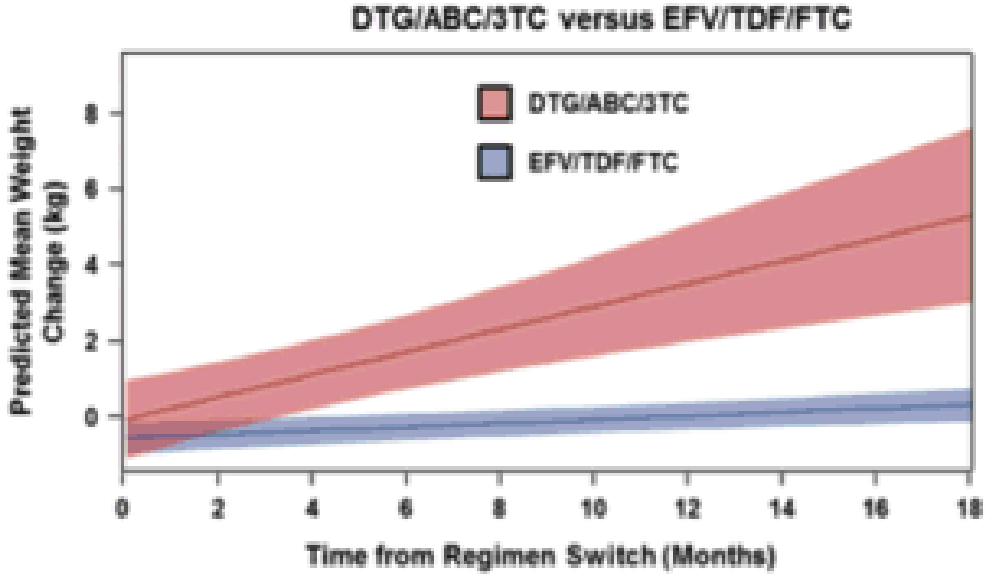


Lake. CROI 2019; Abstract 669

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

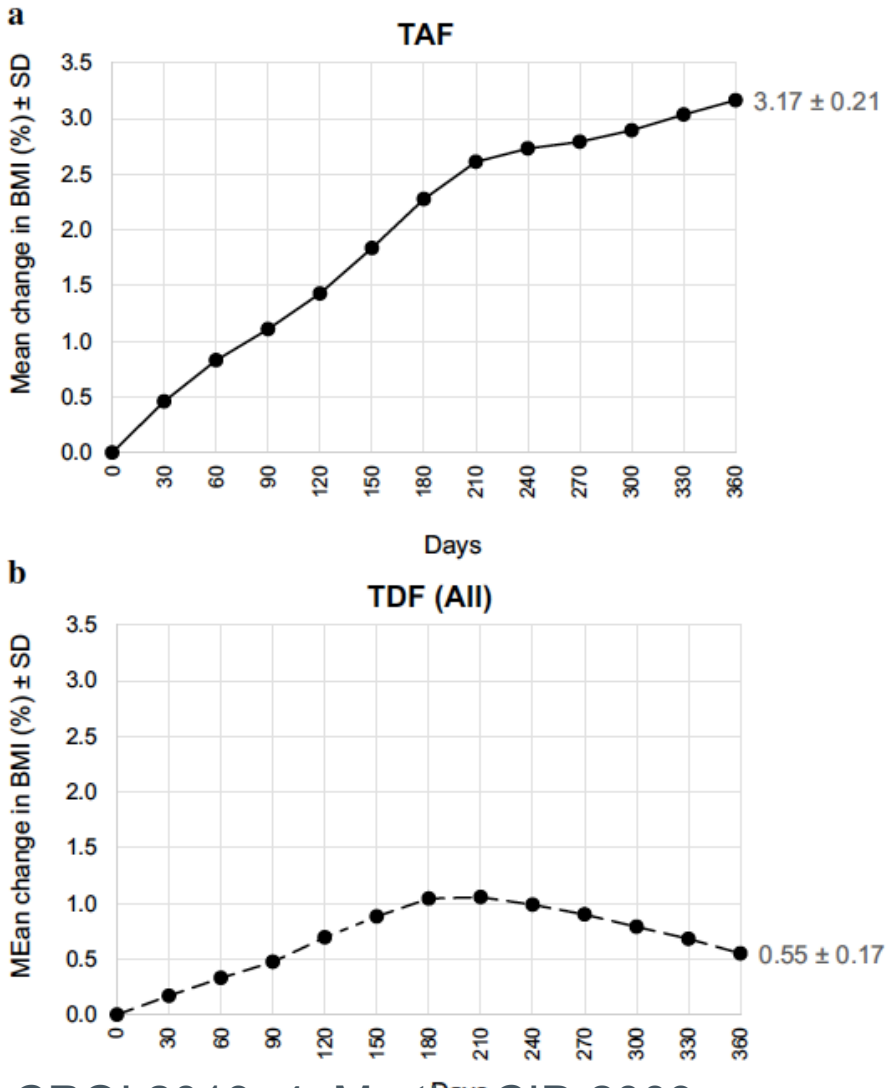


Norwood. JAIDS 2017 Dec 15;76(5):527-531

Other Potential Predictors of Weight Gain with INSTI

NRTI backbone (needs to be accounted for):

- TAF
  - Switch from TDF to TAF: +2.3 kg.[1]
  - AMBER: TAF/FTC/DRV/c (+1.8 kg) vs. TDF/FTC/DRV/c (0.8 kg).[2]
  - TAF Vs. TDF in HIV-uninfected (DISCOVER):+ 1.1 kg vs. +0 kg @ week 48.[3]
- ABC
  - STEAL: switch to ABC/3TC vs. TDF/FTC: +1Kg.[4]
  - ABC + DTG:[5-7]

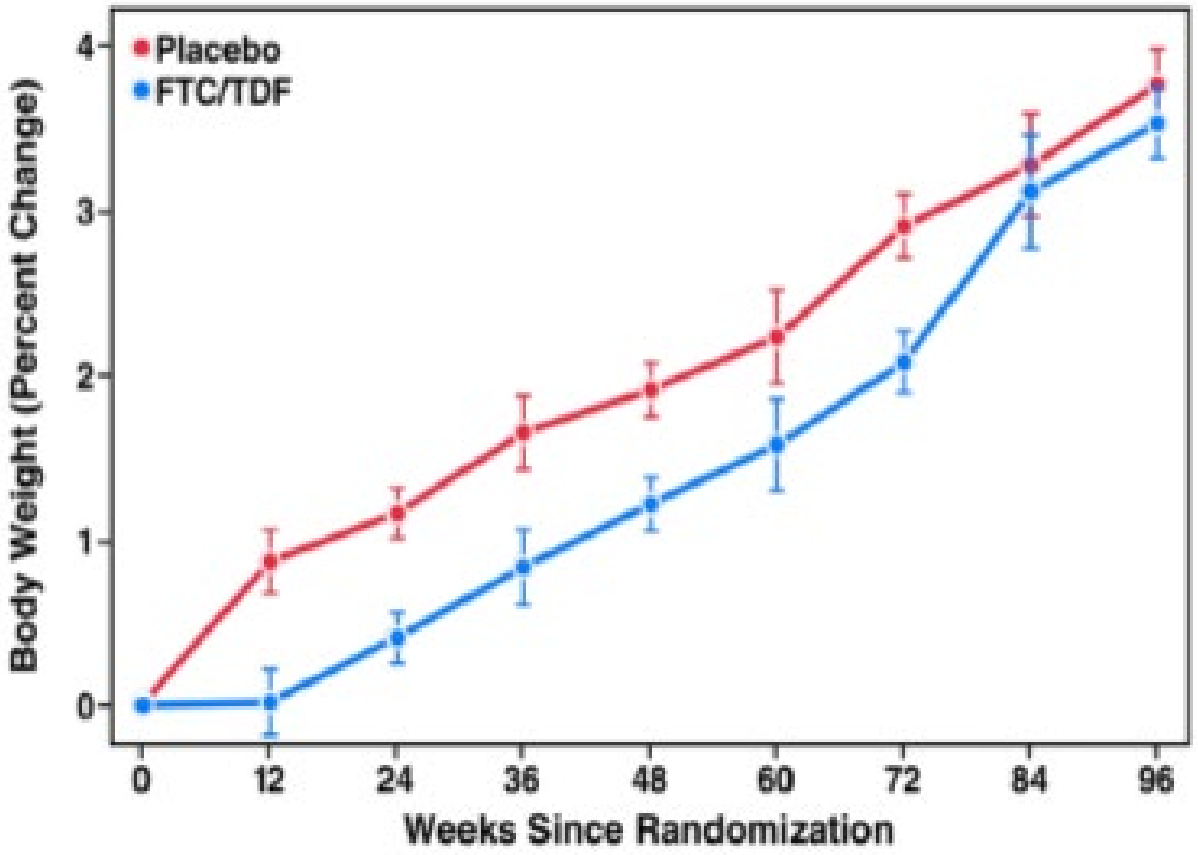


1. Gomez. Infection 2019; 47:95-102; 2. Orkin. HIV Glasgow 2018; 3. Hare. CROI 2019; 4. Martin. CID 2009; 5. Tamarasso 2017; 6. Menard 2018; 7. Lake 2019

What happens if you keep HIV out of the equation?
PREP Studies

iPrEX Trial: FTC/TDF vs. Placebo for PrEP

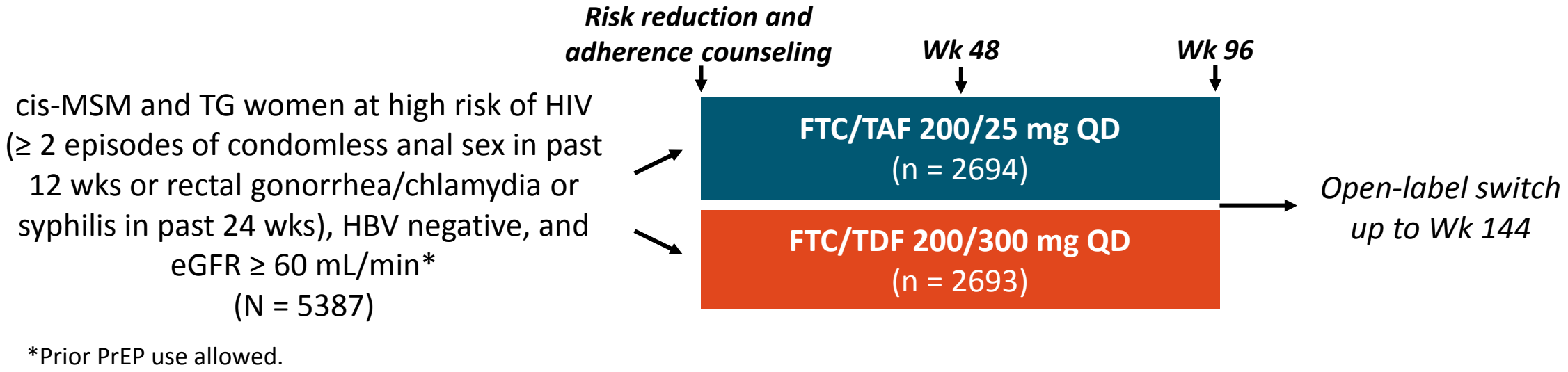
- Placebo (n=1225)
- TDF/FTC (n=1226)
- Delayed weight gain in treatment group



Grant. NEJM 2010;363: 2587-99

DISCOVER Trial: FTC/TAF vs. FTC/TDF for PrEP

- Randomized, double-blind, active-controlled, international, multicenter phase III trial



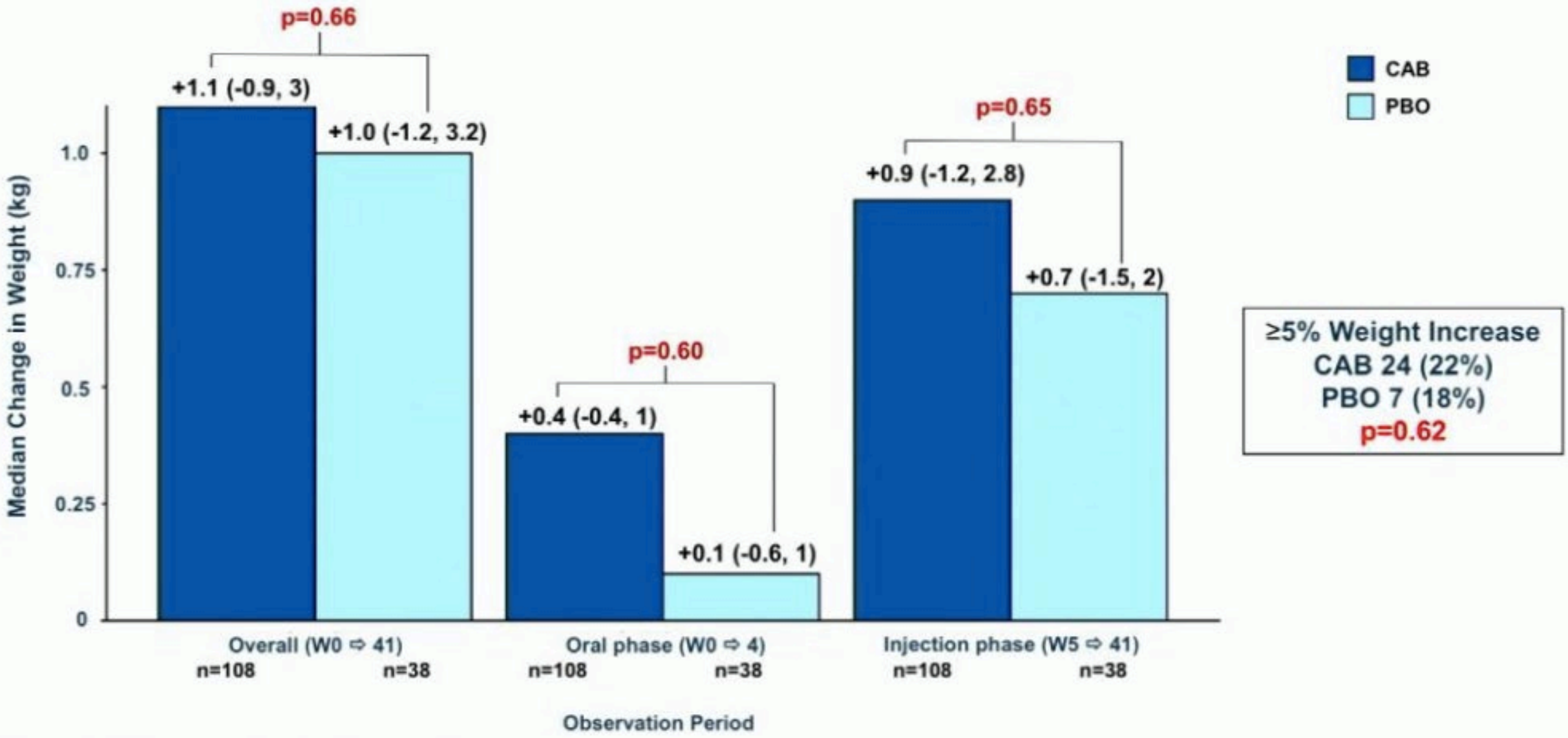
*Prior PrEP use allowed.

- Renal and bone safety outcomes more favorable with FTC/TAF vs FTC/TDF
- Weight Change: FTC/TAF Vs. FTC/TDF:+ 1.1 kg vs. +0 kg @ week 48.

Hare. CROI 2019. Abstr 104LB.

Primary Outcome: Changes in weight

CAB vs. PBO



≥5% Weight Increase
CAB 24 (22%)
PBO 7 (18%)
p=0.62

Landovitz, R et al. CROI, Seattle, 2019. Abstract #34LB

Weight Gain with ART – Summary

- Weight gain with occurs in both ARV-naïve and ARV-experienced (INSTI and TAF) and in uninfected (TAF)
  - This suggests different/additional mechanism(s) of action than reversal of catabolism/inflammatory changes in adipose tissue.
  - Phenotypic (pro-inflammatory) modulation of adipose tissue?
- Even if magnitude on average are low (in the U.S.), 0utliers (10-30+ lbs gain) might be concerning:
  - ACTG 5260s: No difference in weight change b/w RAL and PIs. However, odds of “severe weight gain” greater with RAL than with the PIs.
  - ADVANCE: 25% had “severe weight gain” (>10% increase) with DTG/TAF/FTC

Potential Cardiometabolic Risk Associated with Weight Gain on Antiretroviral Therapy

Pathogenesis of Chronic Complications of HIV Infection

#1: THE PATIENT
- Individual and social factors
- Higher rate of traditional risk factors: smoking, dyslipidemia, HTN, diabetes, obesity

Metabolic Complications:
Cardiovascular Disease
Renal Disease
Osteoporosis
Non-AIDS Cancers

#2: THE VIRUS(ES)
- HIV infection itself
- Inflammation and immune activation
- Coinfections: HCV

#3: THE TREATMENT
- ART and toxicity

Slide credit: clinicaloptions.com

Implications of obesity in the general population

- Raised BMI is a major risk factor for non-communicable diseases such as:
  - ASCVD (MI & Stroke) – the leading cause of death in 2012.
  - DM
  - Musculoskeletal disorders (especially osteoarthritis) – a highly disabling degenerative disease of the joints);
  - Some cancers (including endometrial, breast, ovarian, prostate, liver, gallbladder, kidney, and colon).
- These are the leading causes of morbidity and mortality in virologically suppressed PWH.

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

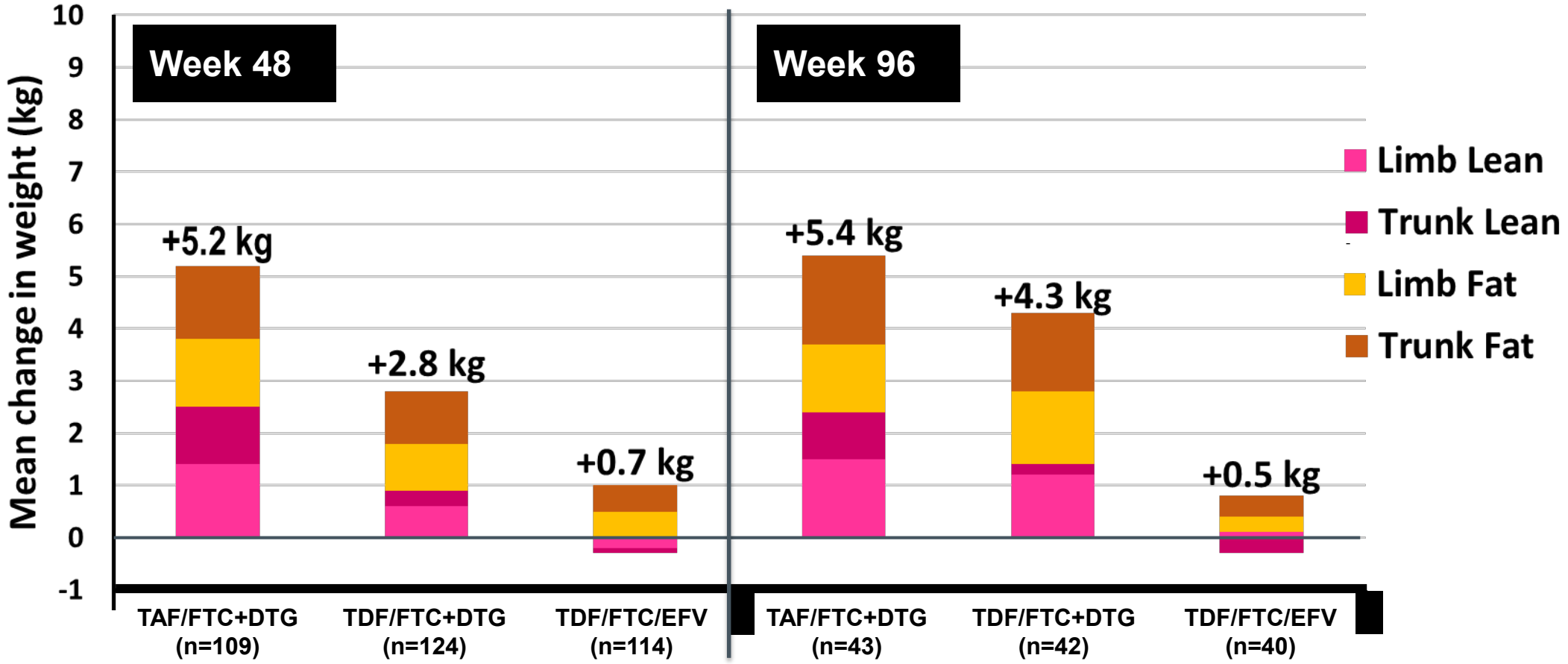
Weight Gain with INSTI – Metabolic Implications Unclear

- Reversibility of weight gain on INSTI? No evidence yet
- Increased CVD Risk?
  - If Central obesity, could correlate with increased CVD risk.
  - Imbalance of pro- and anti-inflammatory adipokines: ⇧ adiponectin → ⇧ CVD risk?
- Incident DM?
  - No apparent risk of incident DM[1]; but case report of INSTI-associated DKA in a diabetic.[2]
- DM risk with weight gain at ART initiation is greater than comparable gain in non-HIV comparators.[3]
  - 5 lbs weight gain → 15% increased risk of DM in PWH vs. 8% in controls

1. Kerchberger, CROI 2019; 2. Horikawa. Tokai J Exp Clin Med., 2018; 3. Herring. JAIDS. 2016 Oct 1;73(2):228-36

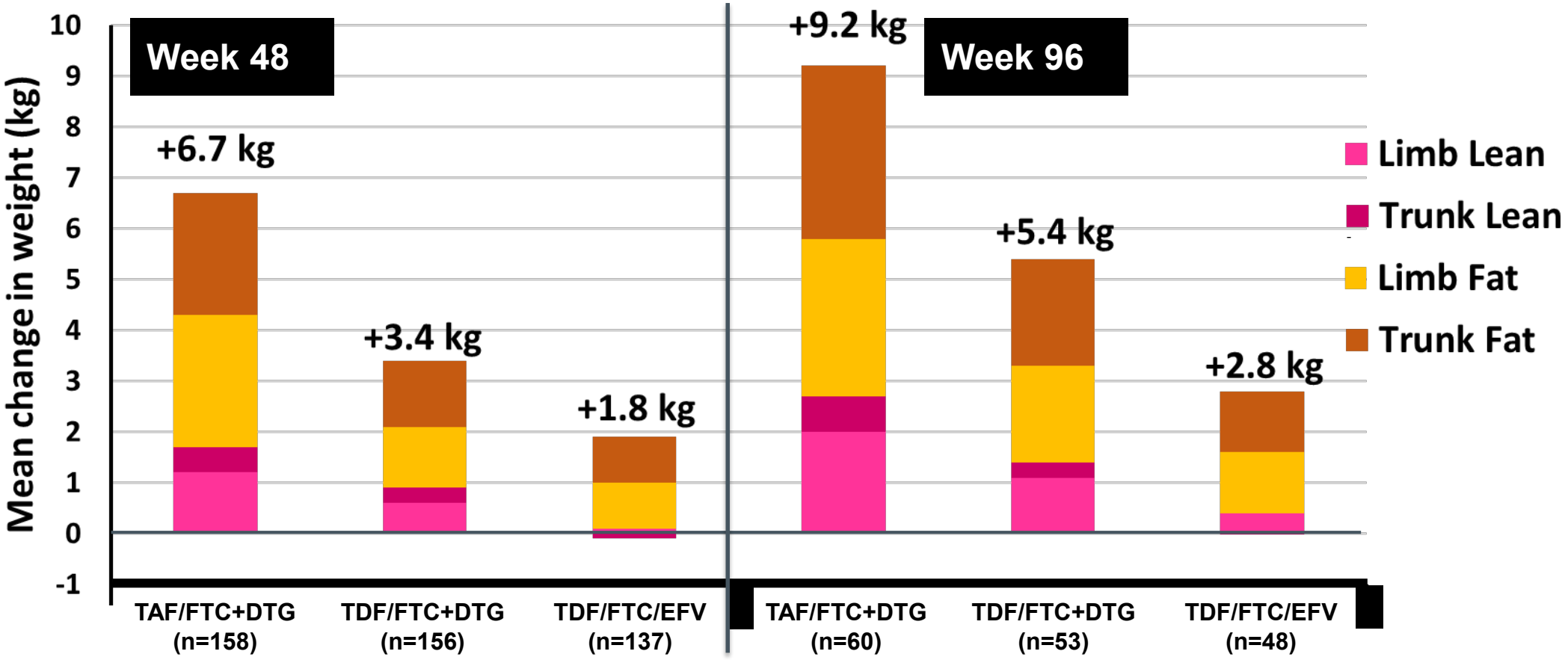
Body Composition – Patterns of Weight Gain on ART

ADVANCE: Changes in body composition: men



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

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

Patterns of Weight Gain - Likely central obesity

- A5260s: Waist Circumference greater with INSTI.[1]
- NEAT 001: DEXA sub-study: trunk fat 7.3% higher DRV/r/RAL vs TDF/FTC/RAL at week 96 (P=0.021); but not higher limb fat or total lean mass.[2]
- ADVANCE Trial: DEXA shows mostly trunk and limb fat gain.

Potential Implications:

- Central Obesity associated with CVD even in normal weight
- Dallas Heart Study: Adiponectin positively assoc. with lower extremity fat, but negatively assoc. with truncal fat.[3]

1. Bhagwat. OFID 2018; 2. Bernardino. PLoS Med 2019; Turer. 3. Diabetologia 2011

Is Weight Change Associated with Changes in Lipids and Glucose Resistance?

- Switching to INSTI:
  - Beneficial changes in lipids[1], modest changes in lipids and glycemic control[2].
  - Increased risk of incident DM for INSTI and PI vs. NNRTI. Only RAL?[3]
- Switching from TDF to TAF:
  - Increase in BMI: 0.45 kg/m^2 , total cholesterol, LDL, HDL, and ASCVD score[4].

1. Martinez. HIV Drug Therapy. Glasgow 2018; 2. Aldredge. WIHS. IDWeek 2019;

3. Rebeiro. IDWeek 2019. Abstract LB9; 4. Schafer. IDWeek 2019; Abstract 979;

ADVANCE: Changes in lipids to Week 48

Lipid (mmol/L)	TAF/FTC+DTG	TDF/FTC+DTG	TDF/FTC/EFV
Total cholesterol, median	+0.1	-0.1	+0.3
LDL, median	+0.1	0.0	+0.1
HDL, median	+0.1	+0.1	+0.3

Some statistically significant differences between arms; however, of small magnitude (not clinically significant)

Total cholesterol: gr1v3 <0.001; gr2v3 <0.001; gr1v2 <0.001

ADVANCE Trial: Metabolic Syndrome

- **Assessed using the International Diabetes Federation (IDF) definition:**
  - **Central obesity (BMI > 30 kg/m^2)**
  - **AND any two of the following factors**

Raised triglycerides	≥ 1.7 mmol/L *OR* on treatment for this lipid abnormality
Reduced HDL cholesterol	Males: ≤ 1.03 mmol/L Females: ≤ 1.29 mmol/L *OR* on treatment for this lipid abnormality
Raised blood pressure	Systolic BP ≥ 130 mmHg Diastolic BP ≥ 85 mmHg *OR* on treatment for previously diagnosed hypertension
Raised fasting glucose	≥ 5.6 mmol/L *OR* diagnosis of Type 2 diabetes

ADVANCE: Metabolic syndrome at Weeks 48 and 96

	TAF/FTC+DTG	TDF/FTC+DTG	TDF/FTC/EFV
Baseline prevalence	16/350 (5%)	21/351 (6%)	14/351 (4%)
Treatment-emergent metabolic syndrome			
Week 48	20/290 (7%)	16/297 (5%)	9/275 (3%)
Week 96	17/189 (9%)	9/189 (5%)	6/180 (3%)

- **Statistically significant differences between TAF/FTC+DTG and TDF/FTC/EFV at week 96, p=0.025**

Potential Mechanism(s) of Weight Gain with INSTI

Adipokines and INSTI-Associated Weight Gain; Potential Insights for Cardiovascular Risk

- MACS: Lower adiponectin is associated with subclinical cardiovascular disease among HIV-infected men.[1]
- A5260s: lower baseline leptin and higher adiponectin were associated with greater gains in VAT.[2]
- NEAT 022: Switch from PI to INSTI associated with decreased LDL, TC/HDL, CRP & sCD14, but decreased adiponectin.[3]
  - Percent change in adiponectin correlated inversely with percent change in BMI (coefficient -0.227, $P < 0.001$).
- Adiponectin levels associated with – and appear to protect against – obesity-linked inflammation and metabolic dysfunction.[4]

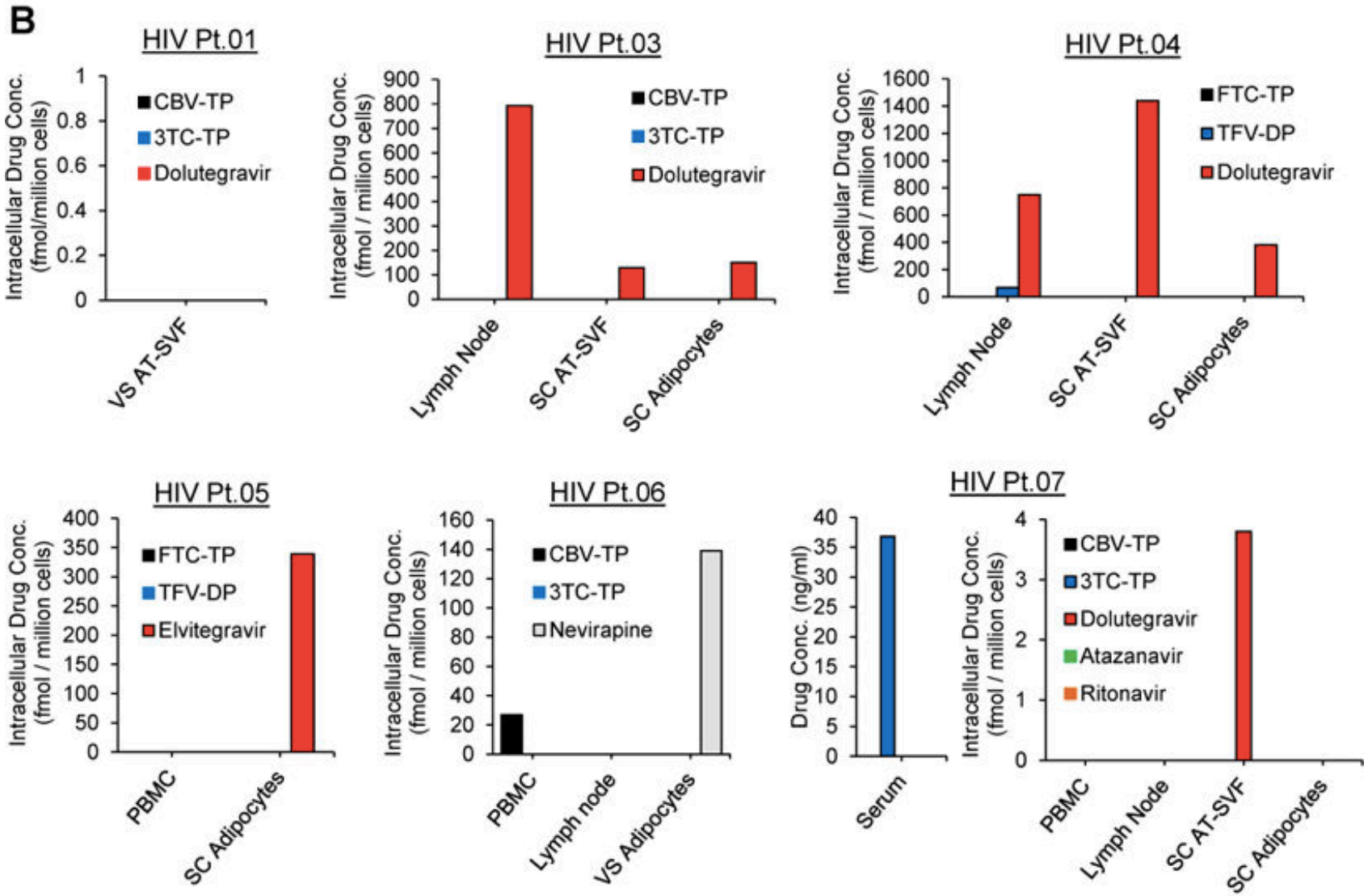
1. Ketlogetswe; AIDS 2014;28:901-9; 2. McComsey. CID 2016; 3. Martinez. HIV Drug Therapy. Glasgow 2018

4. Ouchi. Nat Rev Immunol. 2011 February ; 11(2): 85–97.

Unlike NRTI, INSTI Penetrate Adipocyte Tissue

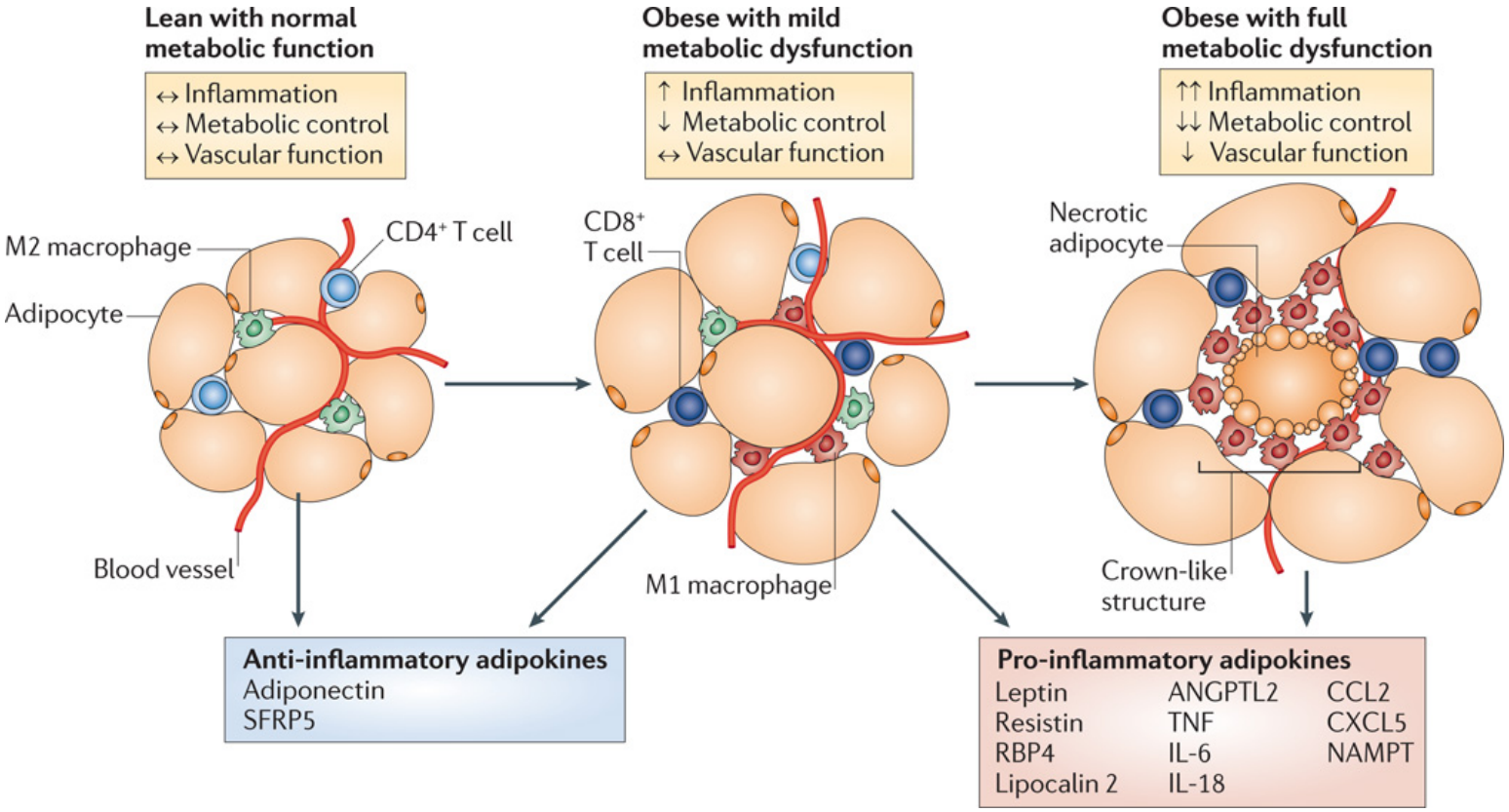
Detection of antiretroviral drugs in tissues of HIV patients

AT-SVF: Adipose Tissue Stromal-vascular-fraction cells

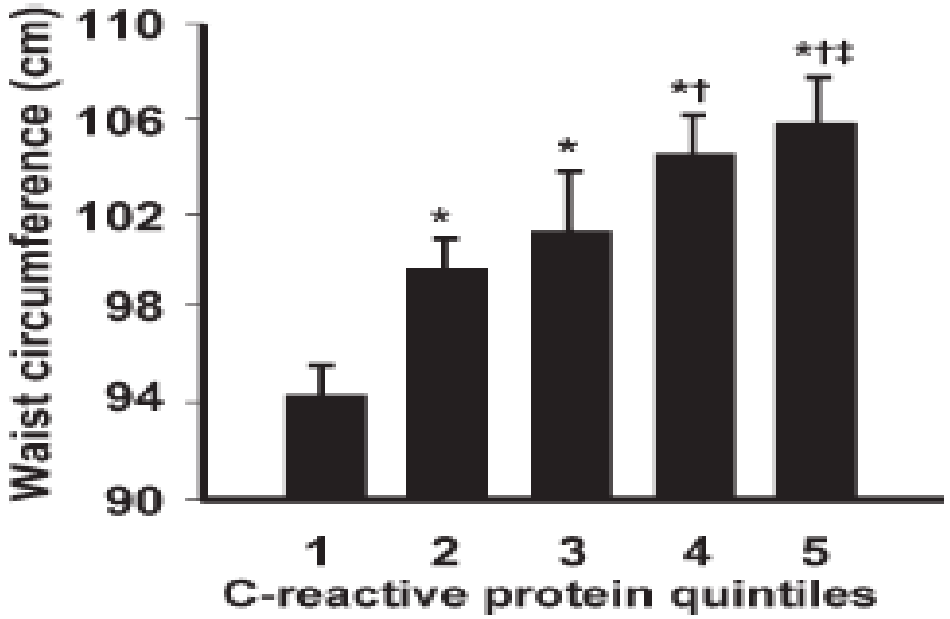


Couturier. Antiviral Res. 2018 Jun;154:140-148.

Obesity-Induced Inflammatory Changes in Adipose Tissue – Phenotypic Modulation



Ouchi et al. Nat Rev Immunol. 2011 Feb;11(2):85-97

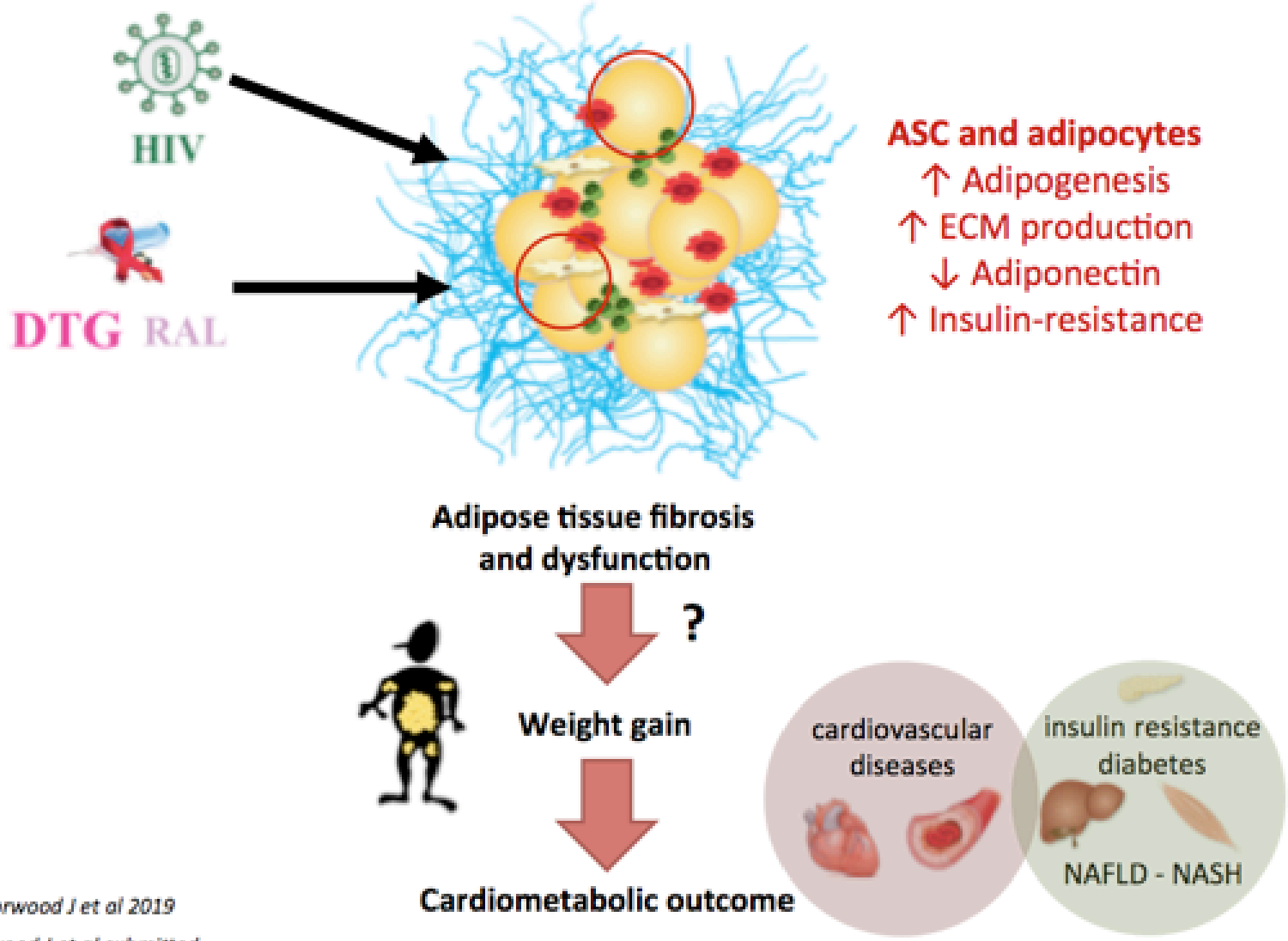


Samaras K et al. Obesity 2008;17:53-59

Need to understand mechanisms and metabolic implications of weight gain in HIV

Conclusion

Impact of INSTIs on Adipose tissue



Gorwood J et al 2019

Gorwood J et al submitted

DTG/RAL increased ECM production in ASCs and adipocytes

DTG have a greater effect than RAL increased adipocyte differentiation

DTG have a greater effect than RAL increased adipocyte differentiation and triglyceride accumulation

DTG/RAL induce adipocyte dysfunction and insulin resistance

Baseline Obesity, Inflammation and Weight Gain on ART

- Baseline markers of inflammation and coagulation (IL-6, D-Dimer) correlated with limb fat and lean mass but not VAT.[1]
- Baseline BMI correlated with inflammatory markers (CRP, IL-6, sTNF-RII, and sCD163.[2]
- In patients with normal pre-ART BMI, pre-ART IL-6, sTNF-RII, IP-10, and sCD163 were higher for weight gainers versus maintainers.[3]
  - Women who gained weight had smaller declines in biomarkers compared to men who gained.[3]

1. McComsey. ACTG 5260s. CID 2016; 2. Koethe. JAIDS 2018; 3. Bares. CROI 2019; Abstract 673

Potential Clinical Implications of INSTI-Associated Weight Gain
Future Directions?

What do we need to do?

- Better understanding of predictors:
  - Sex and Race/Ethnicity associations suggest genetic and hormonal factors
  - Association with low b/l CD4, high b/l viremia, and low b/l weight suggest reversal of HIV-induced chronic inflammation and immune activation?
- Better understand mechanisms:
  - Insights from uninfected (PrEP): Weight gain with TAF but not Cabotegravir?
  - Regional fat deposition? Pro- and anti-inflammatory adipokines
  - What happens to appetite and metabolic rates when you start INSTIs?
- Better understand metabolic risk (or benefit?)
- Reversibility? Mitigating factors?

How to get the necessary information?

- For trials of INSTI and other ARVs, there's need for:
  - A standardized assessment of magnitude and patterns of weight gain in trials of INSTI and other ARVs
  - Analysis of association of weight gain with inflammatory & metabolic markers
- Could be the reverse of FDA guidance on weight loss products:[1]
  - Primary endpoints: Mean % weight loss, and proportion losing >5% weight
  - Secondary endpoints: BP, lipids, glucose & insulin, HbA1c & DM, Waist circumference

1. https://www.fda.gov/downloads/%20Drugs/Guidances/ucm071612.pdf

Summary

- Accumulating data that INSTI-based regimens are associated with greater weight gain than other regimens (also, PI>NNRTI)
  - Increases in weight on DTG are higher in women, Blacks (and Hispanics?)
- Whether there are differences between INSTIs is less certain
- Role of NRTIs must be defined:
  - Greater in combination with TAF as compared with TDF; likely ABC >TDF
- Mechanism of weight gain and distribution of fat must be evaluated: effect on appetite, caloric intake, energy expenditure? Visceral fat, subcutaneous fat, both?
- In patients with significant weight gain: does changing to non-INSTI or non-TAF regimen help?