HIV, CARDIOVASCULAR DISEASE AND WEIGHT GAIN- CROI 2021

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DISCLAIMERS

- No funding for this presentation

EPIDEMIOLOGY

- Multiple studies have shown an average of 1.5 to 2 fold increased risk of CV events in HIV patients as compared to non-HIV patients.
- In a large meta-analyses, the crude rate of CV disease in HIV **was 61.8 (95% CI, 45.8-83.4)** per 10 000 person-years vs. individuals without HIV, the risk ratio of 2.16 (95% CI, 1.68-2.77).
  - From 1990 to 2015, 80 studies, 154 nations, 793K HIV patients, 3.5 million person years.
- HIV contribution to CV disease has increased from 0.36% to 0.92% for the global burden of disease
- **PLWH risk ratio of CV disease vs non-HIV patients is 2.16 (95% CI, 1.68-2.77) for myocardial infarction and 2.56 for Stroke.**

Shah ASV. Circulation, 2018

CHRONIC CVD DISEASE IN PLWH- TREATMENT AND REVASCULARIZATION- STENTING

- **Estimates indicate that by 2030, over 70% of PLWH will be over 50 yo, and 80% will have ASCVD**
- Obstacles in treatment are related to major adverse CV events (MACE) after revascularization
- Mixed results in studies regarding the use of bare and DES stents in PLWH
- Higher target lesions revascularization rate has been reported
- Recurrent ACS has been reported more frequent in PLWH
- The recurrent events are likely related to a combination of stent thrombosis, and accelerated in-stent and de novo atherosclerosis

Smit M, Lancet Infect Dis, 2015; McCutcheon K, Trends in Cardiovascular Medicine, 2021

CVD & ART EPIDEMIOLOGY

- PI and CVD Risk
  - As before some but not all studies suggested a risk of increase CVD disease with PI therapy
  - Primarily this was seen with older PI agents (Indinavir, Lopinavir-ritonavir)
  - Now considered NOT a class effect. Atazanavir and Darunavir do not appear to have increased CVD risk
  - CVD risk was thought to be related to increased lipids with PIs; Atazanavir reduces lipids.
- Abacavir
  - Controversial risk for MI, especially in those with high CVD risk at baseline
  - D:A:D cohort showed increased risk for MI with ABC+DDI combination within 6 months of the MI event, relative rate for ABC was 1.90 (95% CI, 1.47-2.45), 1.89 increased 10 year risk after adjustment.
  - Follow up D:A:D study showed the rate of MI was 0.47 among those receiving abacavir at the time and 0.21 among those not receiving abacavir (adjusted risk ratio 1.98, 95% CI 1.72-2.29)
  - This represents a 98% increase in MI rate with ABC use.

DAD Study Group. JID, 2010; DAD Study Group, Lancet, 2008. Sabin CA, BMC Med. 2016.

CVD AND HIV STATUS

- Several studies indicate that higher CD4 cell counts are associated with decreased MI risk.
  - CD4: 350-499 cells/μL: aIRR = **1.32** (0.98 to 1.77); 200-349 cells/μL: aIRR = **1.37** (1.01 to 1.86); 100-199 cells/μL: aIRR = 1.60 (1.09 to 2.34);**<100** cells/μL: aIRR = **2.19** (1.44 to 3.33)]
  - **CD4 declines** are associated with increased risk of CVD, cancer, and death within 6 mo after the decline, incidence rate ratio (incidence rate ratio, **11.7** [95% CI, 3.6-37.4] and 13.7 [95% CI, 4.3-43.6], respectively, and mortality rate ratio **4.3** [95% CI, 1.1-17.6]).

- Similarly, lower or suppressed HIV RNA levels are associated with decreased MI risk.
  - Odds ratios of **1.51** (95% confidence interval, 1.09-2.10) for MI if HIV RNA level >50 copies/mL

Van Levveld SF, AIDS, 2012; Lang S, CID 2012; Bucher HC, JAIDS, 2012; Helleberg M, CID, 2013; Drozd DR, JAIDS, 2017;

CVD, HIV AND STOPPING ART

- Most importantly, in a key trial- **SMART,** the hazard ratios for death from any CV, renal or hepatic disease were increased to 1.8 (95% CI, 1.2-2.9) in patients who were in the ART conservation arm (stopped therapy) as opposed to those remaining on ART. (HFH-Dr. Markowitz participated in this study)
- This ended the debate on whether ART or HIV was worse for PLWH and CVD disease; HIV disease is worse and treatment discontinuation has worse outcomes.
- Outcomes were thought to be due to:
  - HIV viral suppression is cardioprotective?
  - Reduction in pro-inflammatory cytokines (IL-6), D-dimer
  - Discontinuation of ART lead to reduction of HDL which was associated with increased MI cases.

Strategies for Management of Antiretroviral Therapy (SMART) Study Group, NEJM, 2006. Kuller LH, PLoS Med, 2008; Duprez DA, Atherosclerosis, 2009.

TRADITIONAL RISK FACTORS AND HIV

- CVD Risk Factors for:
  - Coronary Heart Disease
  - Cerebrovascular Disease
  - Peripheral Artery Disease
  - Aortic Atherosclerosis, Thoracic or Abdominal Aortic Aneurysms

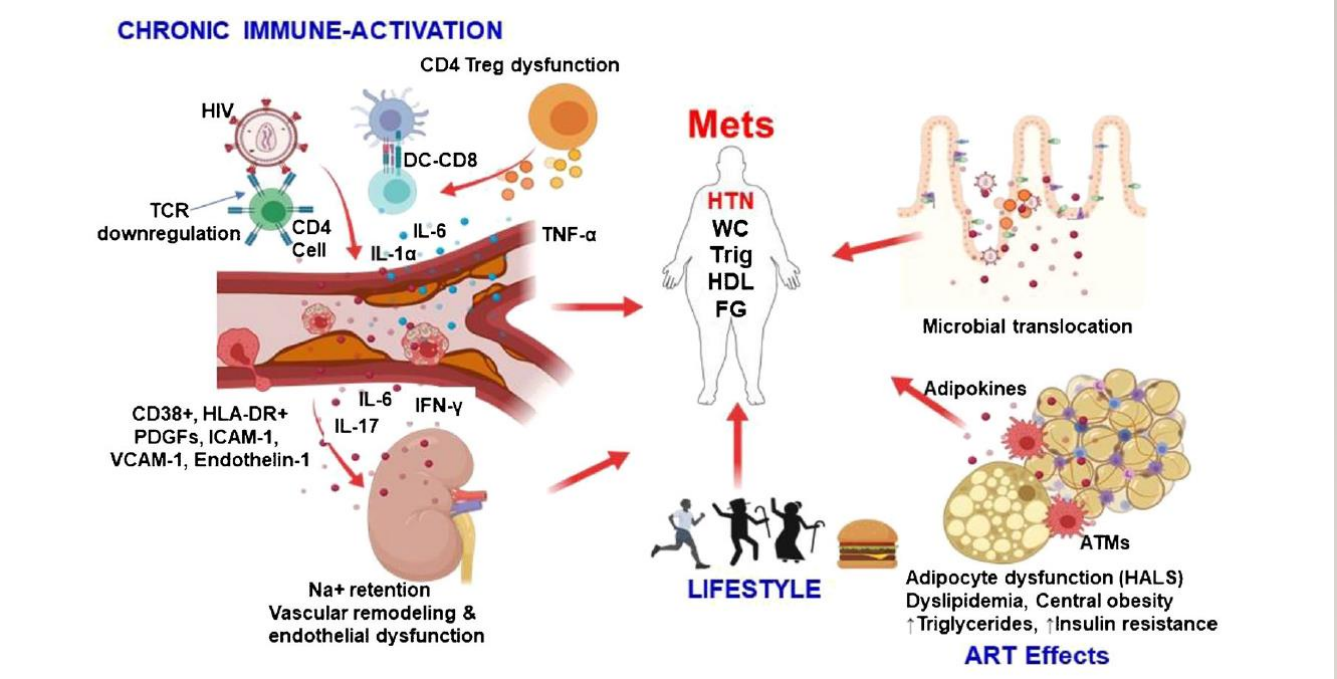
- Variables as risks:
  - Age
  - Gender (male)
  - Total Cholesterol
  - HDL Cholesterol (protective higher)
  - Systolic blood pressure
  - Diabetes Mellitus (type I or II)
  - Current Smoking

ADDITIONAL RISK FACTORS FOR CVD

- Blood pressure treatment
- Family history of CVD
- Rheumatoid Arthritis
- Body Mass Index
- Waist Circumference
- Geographic region (used in some scores)
- Urbanization (used in China)
- C-reactive protein
- Chronic kidney disease
- Atrial fibrillation
- Lipid lowering treatment
- Coronary artery calcium score
- Statin use at baseline

HIV AND METABOLIC SYNDROME

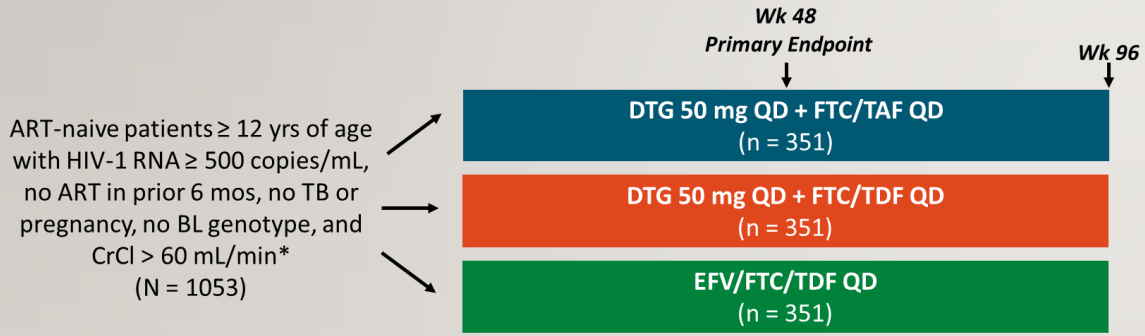
- Metabolic syndrome is a collection of risk factors including
  - Abdominal obesity
  - Atherogenic dyslipidemia
  - Elevated blood pressure
  - Insulin resistance/glucose intolerance
  - Pro-inflammatory state (elevated CRP)
  - Pro-thrombotic state (elevated plasminogen activator inhibitor 1, fibrinogen)
- Ranges between 11-48% in PLWH
- Associated with CVD risk and global neurocognitive deficits in PLWH



Yu B, JAIDS, 2019; Masenga S, Current Hypertension Reports, 2020

ADVANCE TRIAL

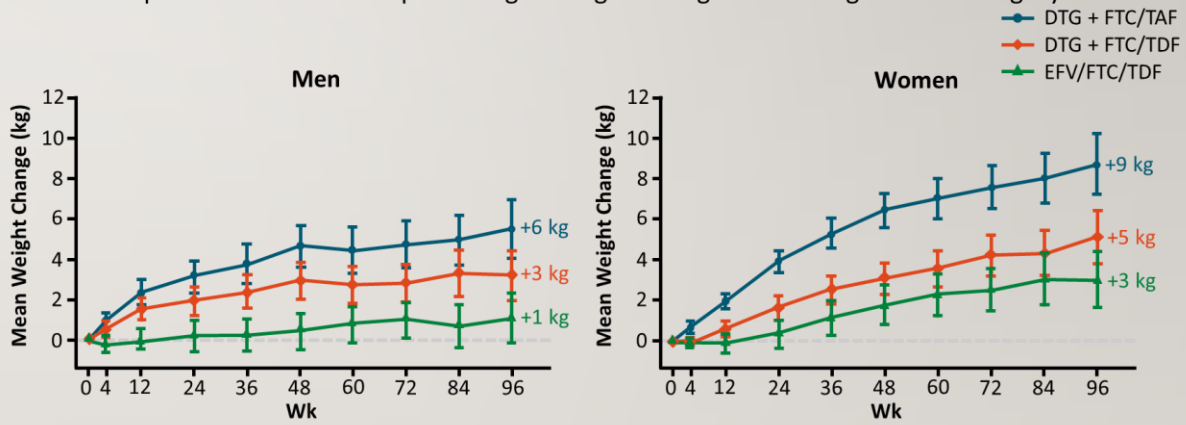
- Randomized, open-label phase III noninferiority trial in Johannesburg



*CrCl > 80 mL/min if 12-18 yrs of age.

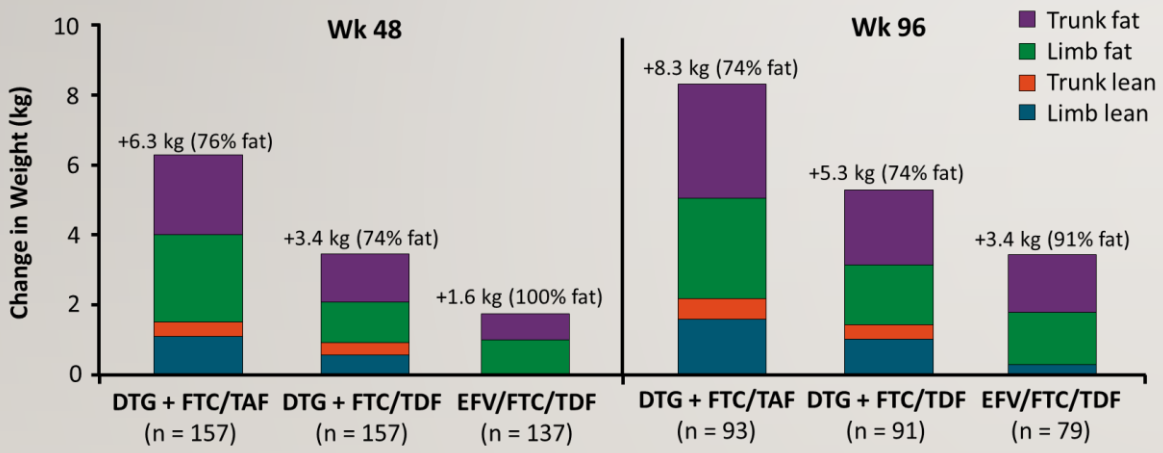
- Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48 by FDA Snapshot in ITT population

- 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
  - Same patterns observed for percentage change in weight and change in BMI category over time

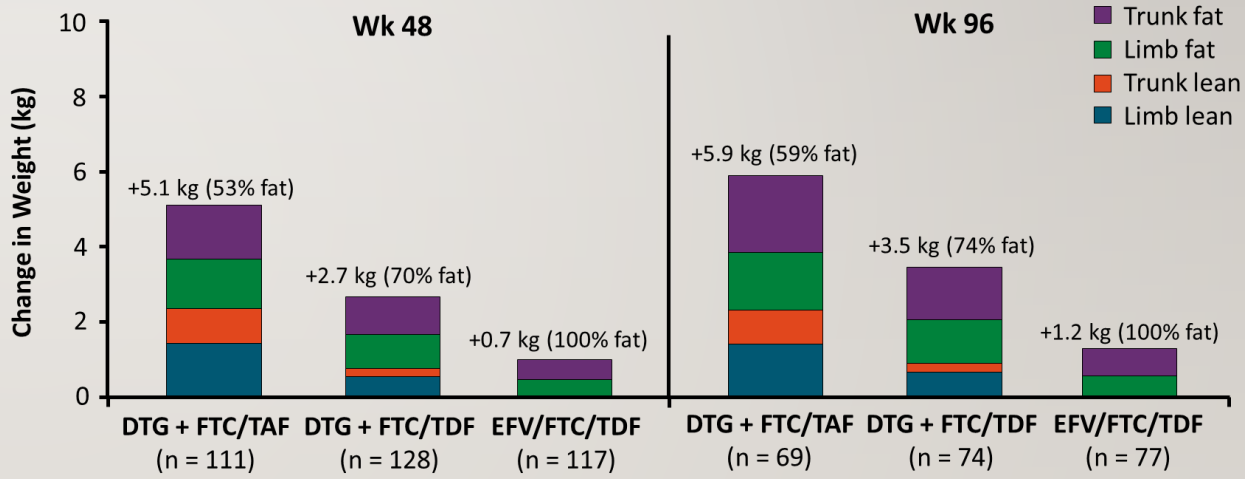


ADVANCE TRIAL

WOMEN



MEN



McCann. EACS 2019. Abstr PS3/3. Venter. NEJM. 2019;381:803

ADVANCE TRIAL

Outcome	DTG + FTC/TAF	DTG + FTC/TDF	EFV/FTC/TDF
> 10% body weight increase at Wk 96, %			
▪ Men	42	27	18
▪ Women	51	32	23
Treatment-emergent obesity at Wk 96, %			
▪ Men	7	3	2
▪ Women	27	17	11
Treatment-emergent metabolic syndrome,* n/N (%)			
▪ Wk 48	20/290 (7)	16/297 (5)	9/275 (3)
▪ Wk 96	17/189 (9)†	9/189 (5)	6/180 (3)

*Based on International Diabetes Federation definition. †*P* = .025 vs EFV/FTC/TDF.

McCann. EACS 2019. Abstr PS3/3. Venter. NEJM. 2019;381:803

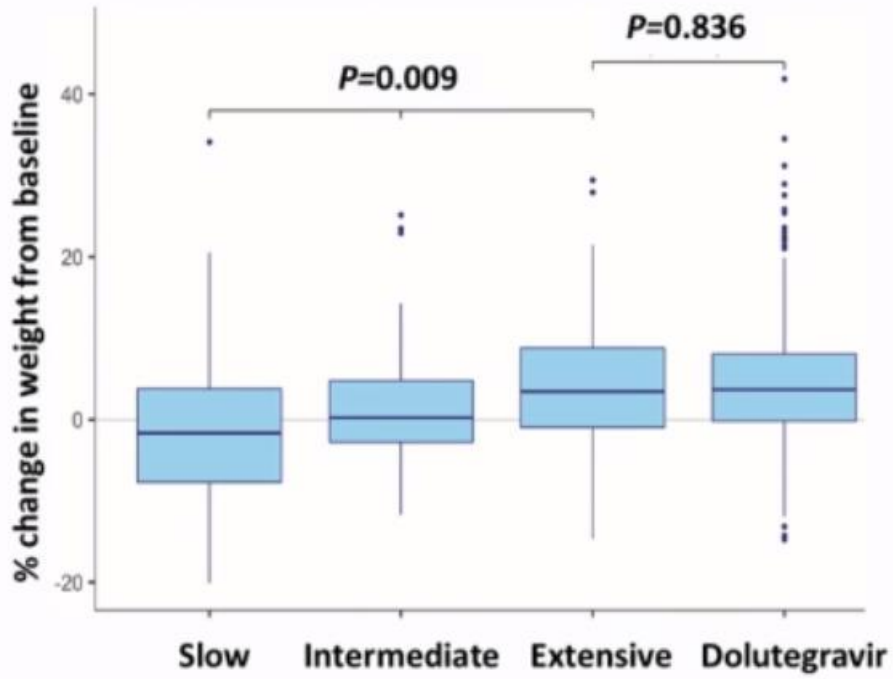
Are older treatments playing a role?

ADVANCE Study

Open-label, 3 arm randomized trial performed in South Africa

Dolutegravir + F/TAF
Dolutegravir +F/TDF
Efavirenz + F/TDF

***CYP2B6* Genotype and Weight Gain Differences Between Dolutegravir and Efavirenz**



Griesel *et al,* Clin Infect Dis; 2020

CROI 2021- WEIGHT AND CVD RISK

In the **ADVANCE trial** (n=1053)

- Mean Weight Gain at 144 weeks
  - +9.5kg (TAF/FTC+DTG),
  - +6.1kg (TDF/FTC+DTG),
  - +3.6kg (TDF/FTC/EFV)
- At week 144, participants on TAF/FTC+DTG had greater predicted 10-year risk of developing CVD compared to TDF/FTC/EFV (p=0.016) and Type 2 DM (p=0,024)
- Men had higher CVD risk (2 additional CVD events per 1000 men)
- Women had higher Type 2 DM risk (9 additional T2DM per 1000 women)
- Multiple studies including ADVANCE looked at gestational weight, weight gains and pregnancy outcomes
  - Higher maternal weight can be associated with poor pregnancy outcomes.

Hindley L, Abstract 510. CROI 2021

Body Weight: HIV, ART, and Lifestyle factors

HIV

- Monocyte activation/Inflammation
- Gut integrity alteration/Microbial translocation
- Adipose tissue distribution
- Alteration of fat quality

Antiretrovirals

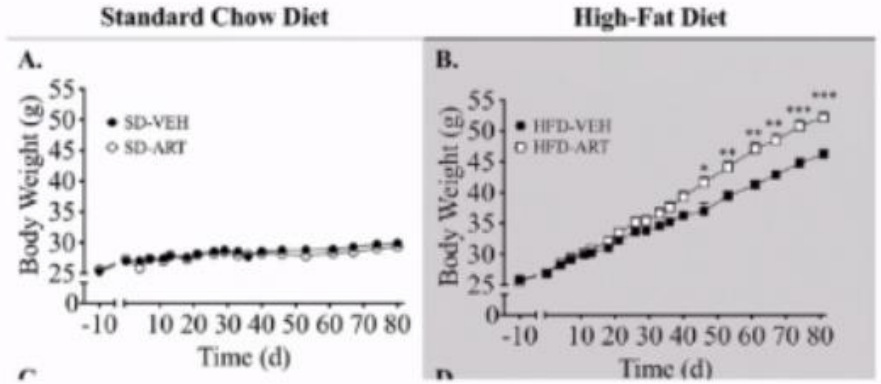
INSTIs
TAF
Others?

Host factors

- Race/ethnicity
- Sex
- Age
- Genetics
- Comorbidities & meds (psych)
- Hormonal abnormalities (GH, sex hormones)

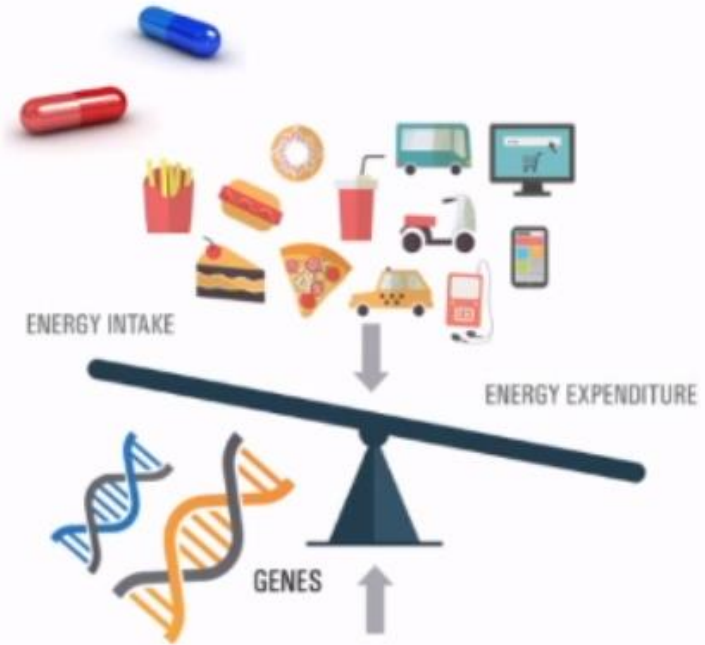
Lifestyle

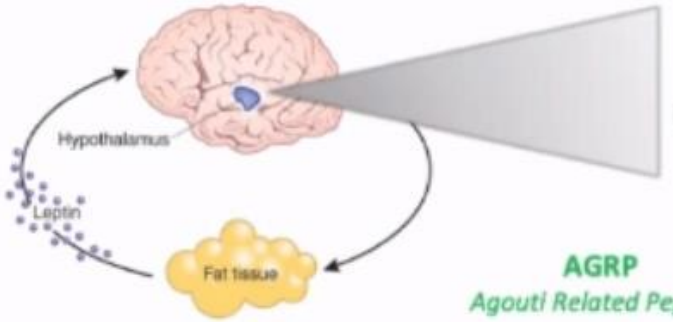
- Food quality (saturated fat and sugar)
- Physical activity
- Socioeconomic and avoiding stigma; weight=healthy (misconception)
- Alcohol
- Drugs, smoking
- Sleep disorders

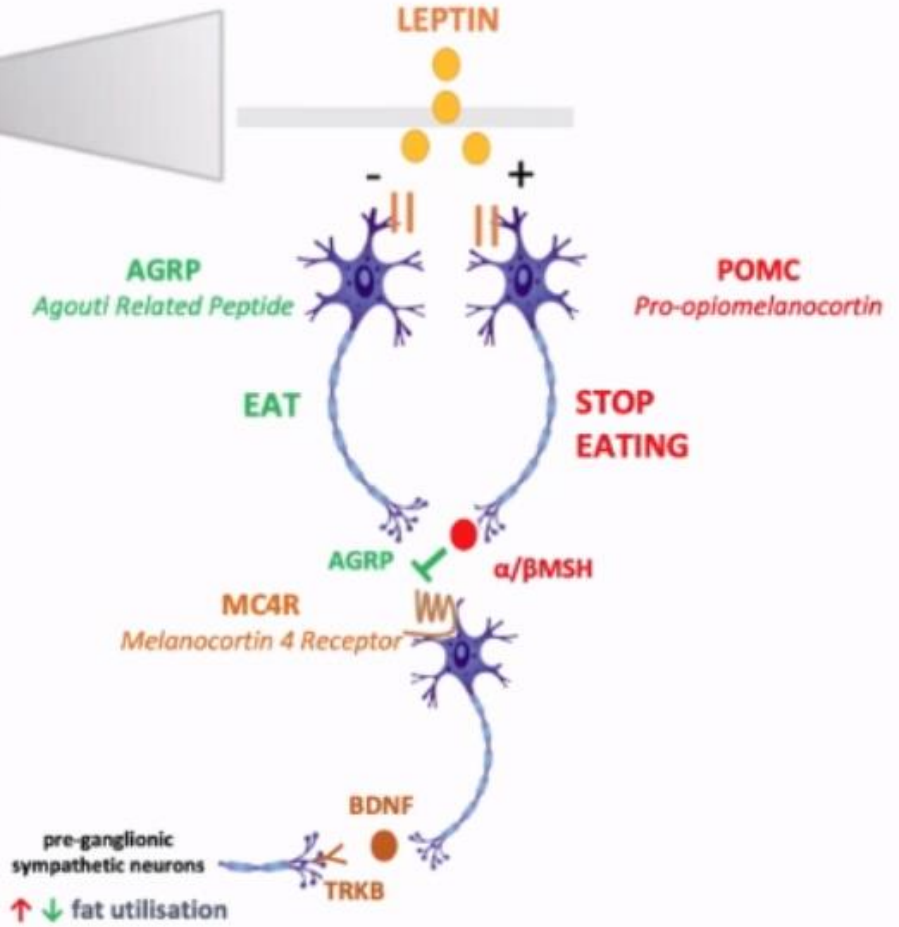


Pepin ME et al. mol Metab 2018

Physiology of weight regulation







- System set-up to defend against starvation (negative energy balance)
- Components detect nutritional state and trigger adaptations to maintain energy homeostasis
- Adapt by changing: i) appetite; hormone secretion; iii) autonomic nervous system activation and fat utilisation

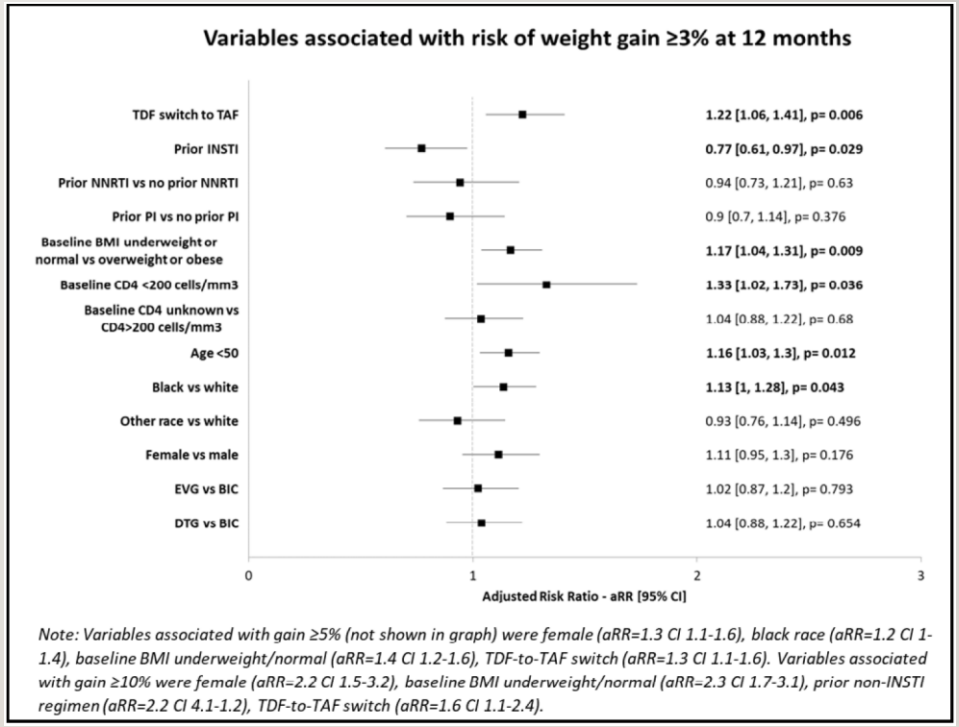
HIV AND WEIGHT GAIN: QUICK CROI 2021 UPDATE

- Session to see:
  - Session 17- Case based discussion on weight gain in HIV and ART
- Antepartum weight gain and adverse pregnancy outcomes in **IMPAACT 2010**
  - Weekly average weight gain was highest with DTG+FTC/TAF (0.378kg) compared to DTG+FTC/TDF (0.319kg, p=0.011) and EFV/FTC/TDF (0.291kg, p<0.001)
  - For women in the DTG+FTC/TAF arm, **low weight gain** was also associated with **higher risk** of stillbirth (HR 6.2, 95%CI 1.16,32.81) and preterm delivery (HR 3.7, 95%CI 1.14,11.92) compared with normal weight gain.
  - No associations between high weight gain and adverse pregnancy outcomes or low or high weight gain and neonatal death

Hoffman, RM. Abstract 176. CROI 2021

HIV AND WEIGHT GAIN: QUICK CROI 2021 UPDATE

- Retrospective study using the Trio Health HIV database to look at weight gain after switching to different InSTIs
  - There was no difference in weight gains among different InSTIs agents at 3%, 5% or >10% gains.
  - Pts with prior TDF were more likely to gain ≥3% (aRR=1.2 CI 1-1.4) and ≥5% (aRR=1.4 CI 1.1-1.7) but not ≥10% (aRR=1.5 CI 0.9-2.4).
  - **Switch from TDF to TAF or from TDF was the major driver of the gains.**



Note: Variables associated with gain ≥5% (not shown in graph) were female (aRR=1.3 CI 1.1-1.6), black race (aRR=1.2 CI 1-1.4), baseline BMI underweight/normal (aRR=1.4 CI 1.2-1.6), TDF-to-TAF switch (aRR=1.3 CI 1.1-1.6). Variables associated with gain ≥10% were female (aRR=2.2 CI 1.5-3.2), baseline BMI underweight/normal (aRR=2.3 CI 1.7-3.1), prior non-INSTI regimen (aRR=2.2 CI 4.1-1.2), TDF-to-TAF switch (aRR=1.6 CI 1.1-2.4).

McComsey GA. Abstract 503. CROI 2021

HIV AND WEIGHT GAIN: QUICK CROI 2021 UPDATE

- EMR review of 2007-2018 medical records data of patients who were InSTI-naive and virally suppressed (VS) for ≥ 1 year on non-InSTI-based ART, switched ART and remained VS.
- 736 persons, 5,316 person-years of follow up.
- Key finding: Both InSTI and TAF use were independently associated with weight gain
  - **InSTI early gains (<8mo)**
  - **TAF continued gains (after 8 mo)**
- For non-InSTI TAF-based ART, 84% of weight gain was associated with TAF both during and after the first 8 months post switch.

Group/Stratum after switch*	Trajectory 0-8 months after switch	Trajectory 8+ months after switch	Trajectory before switch	Difference (before switch vs 0-8 month after switch	Difference (before switch vs 8+ month after switch
INSTI with TAF (n =188)	0.062 (0.049, 0.075)	0.011 (0.001, 0.02)	0.000 (0.000, 0.001)	0.061 (0.048, 0.074)	0.010 (0.001, 0.0200)
INSTI without TAF (n = 253)	0.054 (0.043, 0.07)	0.003 (0.000, 0.006)	0.000 (0.000, 0.001)	0.054 (0.042, 0.065)	0.003 (-0.001, 0.006)
Non-INSTI TAF (n = 128)	0.010 (0.001, 0.019)	0.011 (0.002, 0.02)	0.007 (0.006, 0.008)	0.007 (0.006, 0.008)	0.007 (0.006, 0.009) **
Non-INSTI non TAF (n = 167)	0.002 (0.000, 0.004)	0.002 (0.000, 0.004)	0.007 (0.006, 0.008)	-0.005 (-0.008, -0.002)	-0.005 (-0.008, -0.002)

Analyses were made using Generalized Linear Mixed Effects Model (GLMM)

Palella F. Abstract 504. CROI 2021

HIV AND WEIGHT GAIN: QUICK CROI 2021 UPDATE

- Weight and Lipid Changes with CAB+RPV LA trials (Patel P, et al)
- Median (range) change in weight from baseline to Week 48 was
  - 1.20 kg (-27.5, 40.9) in Q4W, LA group
  - 1.25 kg (-16.0, 22.2) in Q8W, LA group
  - 1.00 kg (-28.0, 39.0) in the CAR group
- No changes in lipids between the groups
- Clinical obesity developed during the trial on
  - 3.9% in the Q4W LA group
  - 4.1% in the Q8W LA group
  - 4.7% in the CAR groups

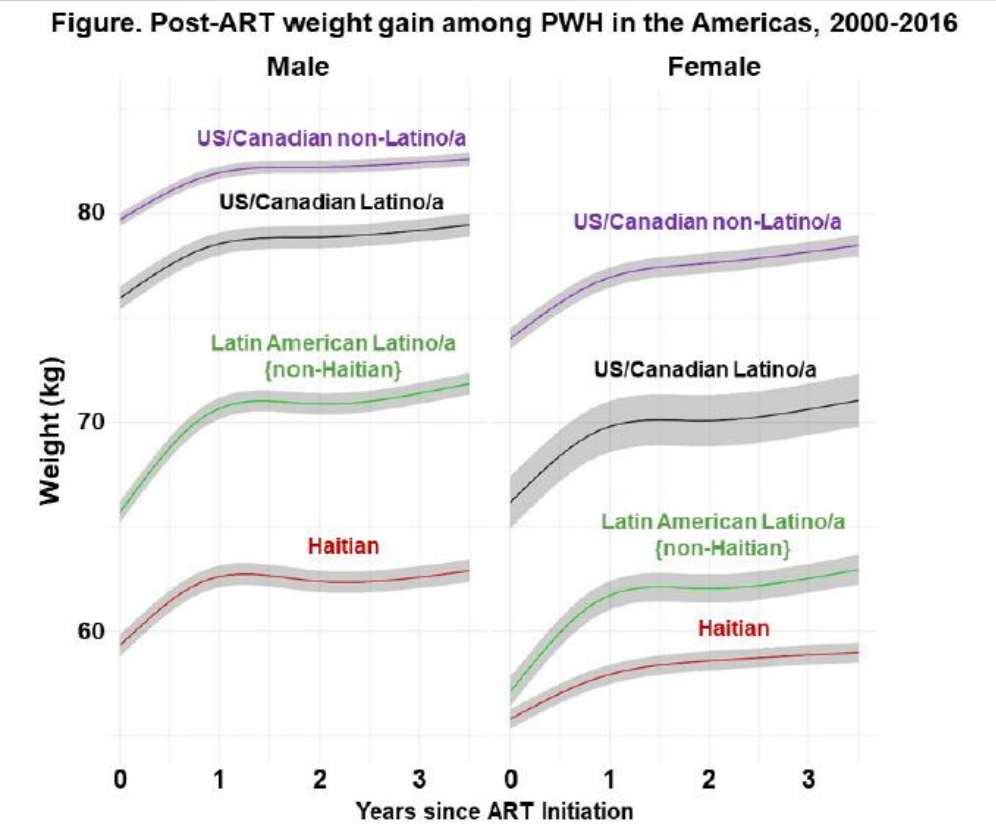
Patel P Abstract 505. CROI 2021

HIV AND WEIGHT GAIN: QUICK CROI 2021 UPDATE

- Reprieve data (Kileel E, et al)
  - InSTI use was associated with higher BMI (+1.6kg)
    - Higher odds of obesity (+65%)
    - Higher waist circumference (+5 cm)
- Kenya's AMPATH program
  - Starting ART 1/2015 to 9/2018, n=17,088
  - Both men and women experience similar weight gains with DTG (6.4 kg for males, 6.3 kg for females, p-value = 0.250).
- RESPOND study
  - 14703 patients (UK)
  - Use of DTG, RAL and TAF, low pre ARV BMI and Black ethnicity were sig associated with **>7% BMI** increase
  - Both DTG (2.02), TAF (2.09) modified OR of achieving **>30% BMI** increase as compared to 3TC
  - But in patients with BL pre-ART CD4 >350, only DTG (1.32 OR) of >7% BMI was seen
  - **Low pre ARV BMI was the strongest independent predictor of >7% BMI increase**

Kileel E, Abstract 506. CROI 2021; Bansi-Matharu L, Abstract 507, CROI 2021; Bourgi K, Abstract 509, CROI 2021.

HIV AND WEIGHT GAIN: QUICK CROI 2021 UPDATE



- Potential for amino acid pathway changes reflective of insulin resistance leading to weight gain, due to changes at the mitochondrial level were attributed to InSTI use for cause of weight gain.
- Decrease in Leptin (a major satiety hormone) may explain weight gain in InSTI patients.

Coelho L, Abstract 510. CROI 2021; Lahiri CD, Abstract 512, CROI 2021; Pickering RT, Abstract 514. CROI 2021

THANK YOU