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
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.

Obesity in the US:
- The prevalence of 39.8% in 2016.
  Affected mostly Blacks and Hispanics

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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 = 5880)
  - 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

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*Color coded to match respective comparators, denoting F: NNRTI (third 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


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

Men
Women

≥10% change in body weight (%)
25%
13%
11%

Treatment-emergent obesity (BMI ≥30 kg/m²; %)
19%
8%
4


Estimated BMI increase @ 1 year:
≈ 1.5 in males,
≈ 2 in females
Doravirine Weight Gain In Treatment Naive 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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOR</td>
<td>665</td>
</tr>
<tr>
<td>DRV+r</td>
<td>383</td>
</tr>
<tr>
<td>EFV</td>
<td>472</td>
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</table>


Weight Change with Cabotegravir/Rilpivirine: Week 48

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

Magnitude of Weight Gain with INSTI: Rx Experienced

ACTG: A5001 & A5322 (n=981)

Adjusted yearly weight change (kg/yr):
- DTG: 1.0 (p=0.001; EVG: 0.5 (p=0.11); RAL: -0.2 (p=0.17)

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 Rs)

Lake. CROI 2019; Abstract669; 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

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

Slow down of weight gain with switch from a PI

Weight Gain after Switch from TDF to TAF

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.

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

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!

**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 getting less heretical?

Grant: NEJM 2010;363: 2587-99

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**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)

Grant: NEJM 2010;363: 2587-99

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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.

ADVANCE: Changes in body composition: women

Week 48

Week 96

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. 17th EACS. Basel. November 2019

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


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)

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<thead>
<tr>
<th>Treatment</th>
<th>DM/DM Events Rate/1000 Yrs</th>
<th>CVD Events Rate/1000 Yrs</th>
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<tbody>
<tr>
<td>DTG + FTC/TAF</td>
<td>3.2</td>
<td>5.9</td>
</tr>
<tr>
<td>DTG + FTC/TDF</td>
<td>4.8</td>
<td>7.2</td>
</tr>
<tr>
<td>EFV/FTC/TDF</td>
<td>4.6</td>
<td>6.6</td>
</tr>
</tbody>
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*Data after Wk 96 are incomplete. †P = .03 for comparison between DTG + FTC/TAF and EFV/FTC/TDF. All other comparisons were not significant.

Slide credit: clinicaloptions.com

The virtual 2021 Ryan White HIV/AIDS Program (RWHAP) CLINICAL CONFERENCE, October 3-6, 2021
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-INSTITI
Janet Lo. CROI 2021

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-INSTITI or non-TAF regimen help?

Question-and-Answer Session