Antiretroviral Therapy and Weight Gain

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Antiretrovirals and Weight Gain: Learning Objectives

Upon completion of this presentation, learners will be better able to:

1. Assess the magnitude of weight gain associated with antiretroviral therapy.
2. Identify predictors of weight gain on antiretroviral therapy.
3. Describe options for the health care team for the management and education of patients with weight gain during 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
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 the potential for 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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3) Protease inhibitor-based regimens

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5) The jury is still out
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.


Obesity in the US:

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

Magnitude and Determinants of Weight Gain with Antiretroviral Therapy Initiation
Weight Gain by Class or Specific INSTI: NA-ACCORD

BMI increases in first 2 yrs:
- ≈0.40/yr
- ≈0.35/yr
- ≈0.25/yr

No difference by race (white vs. non-white) or sex

Predicted Weight (kg)

Yrs Since ART Initiation


Slide credit: clinicaloptions.com
ADVANCE: Phase III Trial of First-line DTG + FTC/(TAF or TDF) vs EFV/FTC/TDF in South Africa

- Multicenter, randomized, open-label phase III trial conducted in South Africa
  - Primary efficacy endpoint: HIV-1 RNA < 50 copies/mL at Wk 48 by ITT (M=F) analysis
    - DTG + FTC/TAF and DTG + FTC/TDF noninferior to EFV/FTC/TDF at Wk 48: 84% vs 85% vs 79%
  - Secondary endpoints: safety, weight gain

ART-naive patients ≥ 12 yrs of age with HIV-1 RNA ≥ 500 copies/mL, no ART in prior 6 mos, no TB or pregnancy, no BL genotype, and CrCl > 60 mL/min (N = 1053)

Wk 48 Primary Endpoint
- DTG 50 mg QD + FTC/TAF QD (n = 351) 79%
- DTG 50 mg QD + FTC/TDF QD (n = 351) 78%
- EFV/FTC/TDF QD (n = 351) 74%

Wk 96 Current Analysis
- Wk 96 HIV-1 RNA < 50 c/mL
  - Differences between arms not statistically significant.


Slide credit: clinicaloptions.com
Magnitude and Determinants: ADVANCE - Mean Change in Weight to Wk 96 by Sex

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

≥10% change in body weight (%)

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

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
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
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

<table>
<thead>
<tr>
<th></th>
<th>DOR</th>
<th>DRV+r</th>
<th>EFV</th>
</tr>
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<tbody>
<tr>
<td>N=</td>
<td>855</td>
<td>383</td>
<td>472</td>
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</table>

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

- **INSTI**: Significant weight gain. Greater magnitude of weight gain in people of African descent and women:
  - Yearly BMI gain: ≈ 1.7/year in NAMSAL (65% female); ≈ 2.0/year in females in ADVANCE vs. 0.5 in US studies. ¹,²,³,⁴
  - Among INSTIs, probably greater with DTG and BIC, than RAL and EVG. ⁴,⁵,⁶

- **NRTIs**: Greater weight gain with TAF vs. ABC and TDF; ⁵,⁶ and greater weight gain with INSTI in conjunction with TAF. ¹

- **NNRTI** and PI probably less conducive to weight gain. ⁵,⁶,⁷,⁸

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Weight Gain with ART Initiation: Return to Health Versus Obesity?

Hypothesis:
• Starting “modern” ART and controlling viremia decreases inflammation and reduces the catabolic effects of HIV infection
• The better and faster viremia is controlled (e.g. with INSTI) the more “return to health” gain.
• Greater gain with higher baseline viremia
• Calorie intake might improve with better clinical status, healthcare services, etc…

Is it really ART or are people living with HIV gaining more weight than the general population?
BMI Changes Over Time in PWH Initiating ART

- Comparison of BMI over time in PWH vs uninfected controls from Kaiser Permanente EMR database (N = 138,222)
  - Study included PWH ≥ 21 yrs of age who initiated ART between 2006-2016 with available baseline BMI
  - Uninfected controls were matched 1:10 by age, sex, race/ethnicity, clinic, yr
- Linear mixed effects modeling* to compare BMI over time by HIV status and baseline BMI

*Potential confounders: sex, age, race/ethnicity, yr, smoking, substance abuse disorder, education/income, insurance, comorbidities.
START: Immediate vs Deferred Therapy in ART-Naïve

- International, randomized trial

HIV-positive, ART-naïve adults with CD4+ cell count > 500 cells/mm³ (N = 4685)

Immediate ART
ART initiated immediately following randomization (n = 2326)

Deferred ART
Deferred until CD4+ cell count ≤ 350 cells/mm³, AIDS, or event requiring ART (n = 2359)

Study closed by DSMB following interim analysis

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

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 (650), and rather low median viremia (12.7K).

Heretical thought: ART with NNRTI might actually prevent weight gain that would have occurred; especially if b/l CD4 is high and b/l viremia is low...

Moestrup. EACS 2019
What if Viremia was Already Controlled?
Differential Weight Gain with ART Switch to INSTI or TAF
Case #2

- M.S. is a 35 y/o while male on EFV/3TC/TDF for the past 10 years. Has been very reluctant to change a regimen that “saved his life”. However, due to persistent insomnia, depressive disorder. CD4 count is 700, VL<20 copies/mL. A switch to BIC/FTC/TAF will likely result in:

  a. No change in weight, as patient was already virologically suppressed.
  b. Weight loss, given that 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)

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
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
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
NRTI Switch and Weight Gain

- **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

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OPERA: Weight Change With Switch From TDF to TAF While Maintaining Other ARVs by Class of Anchor Agent

Estimated Weight Δ by Time From TDF to TAF Switch, kg/yr (95% CI)

<table>
<thead>
<tr>
<th>Time (mos)</th>
<th>INSTI (n = 3281)</th>
<th>NNRTI (n = 1452)</th>
<th>Boosted PI (n = 746)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-60 to 0</td>
<td>0.42 (0.26 to 0.59)</td>
<td>0.66 (0.51 to 0.81)</td>
<td>0.31 (-0.02 to 0.64)</td>
</tr>
<tr>
<td>0 to 9</td>
<td>2.64 (2.26 to 3.01)</td>
<td>2.25 (1.78 to 2.71)</td>
<td>1.98 (1.13 to 2.83)</td>
</tr>
<tr>
<td>9+</td>
<td>0.29 (0.08 to 0.51)</td>
<td>0.20 (-0.14 to 0.54)</td>
<td>-0.11 (-0.57 to -0.35)</td>
</tr>
</tbody>
</table>

What Happens if You Keep HIV Out of the Equation?
Weight Gain with ART in PrEP Studies
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
DISCOVER Trial: FTC/TAF vs. FTC/TDF for PrEP

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

- 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.

*Prior PrEP use allowed.

** cis-MSM and TG women at high risk of HIV (≥ 2 episodes of condomless anal sex in past 12 wks or rectal gonorrhea/chlamydia or syphilis in past 24 wks), HBV negative, and eGFR ≥ 60 mL/min* (N = 5387)

Hare. CROI 2019. Abstr 104LB.
Weight Gain with ART – Summary

- Weight gain 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.), Outliers (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
- Predictors: Demographics (women, Blacks), VL, CD4, CYP2B6 genotype
Patterns of Weight Gain on ART
Potential Metabolic Risk and Clinical Implications
Case #3

- W.G is a 30 y/o while female who has been on DTG + TAF/FTC for the past 2 years. VL <20 copies/mL. CD4 count: 640. She gained 30 lbs since ART initiation (210 lbs 240 lbs). 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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b. Decreased risk of insulin resistance.

c. **Increased risk of metabolic syndrome.**

d. Increased risk of cardiovascular disease.
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
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\(^4\).

### ADVANCE STUDY: Lipid (mmol/L)

<table>
<thead>
<tr>
<th></th>
<th>TAF/FTC+DTG</th>
<th>TDF/FTC+DTG</th>
<th>TDF/FTC/EFV</th>
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</thead>
<tbody>
<tr>
<td>Total cholesterol, median</td>
<td>+0.1</td>
<td>-0.1</td>
<td>+0.3</td>
</tr>
<tr>
<td>LDL, median</td>
<td>+0.1</td>
<td>0.0</td>
<td>+0.1</td>
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ADVANCE: 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 ($P < .001$)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>DTG + FTC/TAF (n = 351)</th>
<th>DTG + FTC/TDF (n = 351)</th>
<th>EFV/FTC/TDF (n = 351)</th>
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</thead>
<tbody>
<tr>
<td><strong>Mean weight gain from BL, kg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wk 96</td>
<td>8.2</td>
<td>4.6</td>
<td>3.2</td>
</tr>
<tr>
<td>Wk 144*</td>
<td>12.3</td>
<td>7.4</td>
<td>5.5</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wk 96</td>
<td>5.2</td>
<td>3.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Wk 144*</td>
<td>7.2</td>
<td>5.5</td>
<td>2.6</td>
</tr>
<tr>
<td><strong>Treatment-emergent metabolic syndrome at Wk 96, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>8.4†</td>
<td>5.9</td>
<td>3.9†</td>
</tr>
<tr>
<td>Women</td>
<td>10.9</td>
<td>8.1</td>
<td>5.6</td>
</tr>
<tr>
<td>Men</td>
<td>4.6</td>
<td>3.3</td>
<td>1.8</td>
</tr>
</tbody>
</table>

*Data after Wk 96 are incomplete. †$P = .03$ for comparison between DTG + FTC/TAF and EFV/FTC/TDF. All other comparisons were not significant.

Potential Mechanism(s) of Weight Gain with INSTI
Unlike NRTI, INSTI Penetrate Adipocyte Tissue

Detection of antiretroviral drugs in tissues of HIV patients

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

Obesity-Induced Inflammatory Changes in Adipose Tissue – Phenotypic Modulation

**Lean with normal metabolic function**
- Inflammation
- Metabolic control
- Vascular function

**Obese with mild metabolic dysfunction**
- Inflammation
- Metabolic control
- Vascular function

**Obese with full metabolic dysfunction**
- Inflammation
- Metabolic control
- Vascular function

**Anti-inflammatory adipokines**
- Adiponectin
- SFRP5

**Pro-inflammatory adipokines**
- Leptin
- ANGPTL2
- Resistin
- TNF
- RBP4
- IL-6
- Lipocalin 2
- IL-18
- CCL2
- CXCL5
- NAMPT

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

Need to understand mechanisms and metabolic implications of weight gain in HIV
DTG and RAL increased ECM production in ASCs and adipocytes.

DTG had greater effect than RAL in increasing adipocyte differentiation and triglyceride accumulation.

DTG and RAL induced adipocyte dysfunction and insulin resistance.
Management of Weight Gain with Antiretroviral Therapy  
(Can Anything Be Done?)
Suggested Approach for the Health Care Team

- **Before Prescribing Antiretroviral Therapy:**
  - Counseling: Discuss the possibility of weight gain (esp. Women, Blacks)

- **If weight Gain Occurs on ART:**
  - No good data on reversibility with switch; limited data on metabolic impact; balance with other potential benefits (virologic, lipids, CVD, renal, bone)
  - TANGO trial: switch to DTG/3TC vs continued TAF-based 3- or 4-drug ART in virologically suppressed adults (Week 48 analysis):¹
    - No difference in weight gain (0.80 kg vs. 0.76 kg); Decreased odds for insulin resistance, but not metabolic syndrome.
  - DRIVE-SHIFT: switch to DOR/3TC/TDF in virologically suppressed adults²
    - Mean change in weight less than 1kg at 6 months and 12 months

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?)
- NNRTI exposure might be protective
- Initial data on patterns and mechanism of weight gain: mostly fat, adipocyte dysfunction with INSTI. Need to evaluate effect on appetite, caloric intake, energy expenditure
- In patients with significant weight gain: does changing to non-INSTITI or non-TAF regimen help?
- Metabolic risk: probable increase in DM risk