Antiretroviral Therapy and Weight Gain

Roger Bedimo
VA North Texas Health Care System
UT Southwestern Medical Center

Sincere appreciations to Raj Gandhi and Pablo Tebas
Case

• 43 yo African American woman diagnosed with HIV in the 1990s

• Previous regimens: TDF/FTC/EFV; DRV/r + ETR + TAF/FTC (because of drug resistant virus)

• Switched to DTG + DRV/r + TAF/FTC

• Gained 40 lb over ensuing 2 years (from 210 lb to 250 lb)

• She asks you if her weight gain is related to her medicines

Weight gain is associated with:

1) All antiretroviral regimens
2) Integrase inhibitor-based regimens
3) Protease inhibitor-based regimens
4) Non-nucleoside reverse transcriptase inhibitor-based regimens
5) The jury is still out
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.


Obesity in the US:

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

Obesity is getting worse and overlaps with poverty and HIV.

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

Magnitude of Weight Gain with Integrase Inhibitors

1. Treatment-Naïve
2. Treatment-Experienced
3. PrEP?
## Magnitude of Weight Gain with INSTI: Rx Naïve (RCTs)

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

Weight Gain by Sex and Race/Ethnicity

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/m² (6.4).
### NAMSAL: Changes in body weight/BMI by arm at Week 48

<table>
<thead>
<tr>
<th>Week 48</th>
<th>TDF/3TC+DTG (n=293)</th>
<th>TDF/3TC+EFV400 (n=278)</th>
<th>p-value for difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change from baseline:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>+5</td>
<td>+3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>+1.7</td>
<td>+1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treatment-emergent overweight (BMI 25 – 29.9), n (%)</td>
<td>16%</td>
<td>17%</td>
<td>n.s.</td>
</tr>
<tr>
<td>Treatment-emergent obesity (BMI ≥ 30), n (%)</td>
<td>12%</td>
<td>5%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Highly significant differences in weight and BMI change between arms
Clinical obesity (BMI 30 kg/m²) TDF/3TC+DTG higher than TDF/3TC/EFV

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

Hill et al. IAS 2019
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/m² (6.4).

<table>
<thead>
<tr>
<th>Antiretrovirals (n; PY of exposure)</th>
<th>Protease Inhibitors</th>
<th>Integrase Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV* (n=780; 1934 PY)</td>
<td>0.25</td>
<td>0.06</td>
</tr>
<tr>
<td>DRV* (n=1278; 2998 PY)</td>
<td>0.18</td>
<td>0.16</td>
</tr>
<tr>
<td>LPV/RTV (n=223; 388 PY)</td>
<td>0.06</td>
<td>0.39</td>
</tr>
<tr>
<td>RAL (n=591; 1334 PY)</td>
<td></td>
<td>0.23</td>
</tr>
<tr>
<td>EVG (n=405; 423 PY)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTG (n=2037; 2473 PY)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Yearly BMI Change:

Bar charts A and B illustrate yearly BMI change by sex and race for the different antiretrovirals.

Bedimo. CROI 2019
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

Yr 2
INSTI
+4.9
PI
NNRTI
+4.4
+3.3

Yr 5
+6.0

Yr 2
DTG
RAL
EVG
+6.0
+4.9
+3.8


EVG: n = 2124;
RAL: n = 1681;
DTG: n = 935

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

Yr 2
DTG
RAL
EVG
+6.0
+4.9
+3.8


EVG: n = 2124;
RAL: n = 1681;
DTG: n = 935

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

Yr 2
DTG
RAL
EVG
+6.0
+4.9
+3.8


EVG: n = 2124;
RAL: n = 1681;
DTG: n = 935
So Far…

- Weight gain with ART initiation; Greater with INSTI (BMI increase of 0.3 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 metabolic rate: (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

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)

Fig 1: Change in weight (kg) according to modelled slopes see adjacent text for p-values

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/m² were associated with greater weight gain
Switch to INSTI + ABC and EVG + TAF predictor (small #s)

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

Lake. CROI 2019; Abstract 669
Norwood. JAIDS 2017 Dec 15;76(5):527-531
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: \(^{5-7}\)

---

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

1053 Participants

Phase 3 (South Africa, Zimbabwe)
Open-label
Treatment-naïve
HIV RNA ≥500 copies/mL
No TB or pregnancy
No baseline genotyping

96 Weeks
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

## ADVANCE: Changes in Weight at Week 96

### Outcomes at Week 96

<table>
<thead>
<tr>
<th></th>
<th>Dolutegravir + F/TAF (n=351)</th>
<th>Dolutegravir + F/TDF (n=351)</th>
<th>Efavirenz/F/TDF (n=351)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean weight change (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>+8*†</td>
<td>+5*</td>
<td>+2</td>
</tr>
<tr>
<td>Men</td>
<td>+5*</td>
<td>+4*</td>
<td>+1</td>
</tr>
<tr>
<td>Women</td>
<td>+10*‡</td>
<td>+5*</td>
<td>+3</td>
</tr>
<tr>
<td>≥10% change in body weight (%)</td>
<td>25*†</td>
<td>13*</td>
<td>11</td>
</tr>
<tr>
<td>Treatment-emergent obesity (BMI ≥30 kg/m²; %)</td>
<td>19*†</td>
<td>8*</td>
<td>4</td>
</tr>
</tbody>
</table>

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


Weight Gain with ART Initiation – Risk Factors in RCTs

- Pooled analysis of 8 RCTs of ARV naïve patients: 2003-2015
- 5,000 participants and 10,000 person-years of follow-up.
- Weight gain was greater in more recent trials and with the use of newer ART regimens.
- Demographic factors: lower CD4, higher HIV-1 RNA, no IDU, female sex and black race.
- Regimens: INSTI > PI > NNRTI
- INSTIs: DTG and BIC > EVG/c; NRTIs: TAF > TDF, ABC, AZT

Other risk factors

- Demographics:
  - Blacks, Hispanics
  - Women
- Non-obese at baseline:
- Co-Morbidities & Concomitant Meds?
- Diet?

N=3,468. Virally suppressed

Annualized weight gain was ≥3% for 1,045 (30%).

Predictors of ≥3% weight gain

McComsey. CROI 2019; Abstract 671
What happens if you keep HIV out of the equation?
PREP Studies
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.

Risk reduction and adherence counseling
Wk 48
Wk 96
Open-label switch up to Wk 144

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)

*Prior PrEP use allowed.

Hare. CROI 2019. Abstr 104LB.
Primary Outcome: Changes in weight

CAB vs. PBO

<table>
<thead>
<tr>
<th>Observation Period</th>
<th>CAB</th>
<th>PBO</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (W0 → 41)</td>
<td>+1.1 (-0.9, 3)</td>
<td>+1.0 (-1.2, 3.2)</td>
<td>0.66</td>
</tr>
<tr>
<td>Oral phase (W0 → 4)</td>
<td>+0.4 (-0.4, 1)</td>
<td>+0.1 (-0.6, 1)</td>
<td>0.60</td>
</tr>
<tr>
<td>Injection phase (W5 → 41)</td>
<td>+0.9 (-1.2, 2.8)</td>
<td>+0.7 (-1.5, 2)</td>
<td>0.65</td>
</tr>
</tbody>
</table>

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

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

ADVANCE: Changes in body composition: men

Week 48

TAF/FTC+DTG (n=109) +5.2 kg
TDF/FTC+DTG (n=124) +2.8 kg
TDF/FTC/EFV (n=114) +0.7 kg

Week 96

TAF/FTC+DTG (n=43) +5.4 kg
TDF/FTC+DTG (n=42) +4.3 kg
TDF/FTC/EFV (n=40) +0.5 kg
ADVANCE: Changes in body composition: women

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Week 48</th>
<th>Week 96</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAF/FTC+DTG (n=158)</td>
<td>+6.7 kg</td>
<td>+9.2 kg</td>
</tr>
<tr>
<td>TDF/FTC+DTG (n=156)</td>
<td>+3.4 kg</td>
<td>+5.4 kg</td>
</tr>
<tr>
<td>TDF/FTC/EFV (n=137)</td>
<td>+1.8 kg</td>
<td>+2.8 kg</td>
</tr>
</tbody>
</table>

Mean change in weight (kg)

- **Limb Lean**
- **Trunk Lean**
- **Limb Fat**
- **Trunk Fat**
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 truck 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

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: Changes in lipids to Week 48

<table>
<thead>
<tr>
<th>Lipid (mmol/L)</th>
<th>TAF/FTC+DTG</th>
<th>TDF/FTC+DTG</th>
<th>TDF/FTC/EFV</th>
</tr>
</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>
</tr>
<tr>
<td>HDL, median</td>
<td>+0.1</td>
<td>+0.1</td>
<td>+0.3</td>
</tr>
</tbody>
</table>

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

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


Need to understand mechanisms and metabolic implications of weight gain in HIV
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.\(^3\)

Potential Clinical Implications of INSTI-Associated Weight Gain
Future Directions?
The average BMI change on INSTI is 0.3 to 0.5/year (2 to 3 lbs). In and of itself not impressive. Outliers (5-20 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

Determinants of weight gain on INSTI across studies:

- Female, Blacks & Hispanics; Baseline values: low weight, High VL, low CD4

TAF associated with weight gain in HIV and uninfected...

Mechanisms unclear.

- Reversal of HIV-induced inflammatory changes in adipose tissue?; vs.
- Phenotypic (pro-inflammatory) modulation of adipose tissue
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.

Clinical implications of obesity in HIV-negative (BMI ≥ 30kg/m²)

Obstetric/Birth outcomes
Alzheimer’s disease
Type 2 diabetes
CVS disease/hypertension
Mobility/ability to work
4-year reduction in life expectancy


Slide from Hill et al. IAS 2019
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

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

Adiponectin, Weight Gain and ASCVD in HIV

- **With available data/samples (ALLRT)**
  - **Aim 1**: To determine the association of race/ethnicity and sex with baseline adiponectin in HIV and changes in adiponectin on ART.
  - **Aim 2**: To determine whether levels of adiponectin in PWH on ART are associated with ASCVD risk, and whether this association is modulated by sex and race/ethnicity.

- **Subsequent goal:**
  - To correlate baseline and changes in adiponectin levels with BMI gains in HIV
Metformin for DM Prevention in the General Population

- DPP (Diabetes Prevention Program): RCT that compared weight loss with metformin, intensive lifestyle intervention (ILS), or placebo in population at high risk for DM.

- Effects of Metformin: 31% reduction in diabetes incidence (DPP); More effective in obesity
  - Induced weight loss explained 64% of beneficial effects on diabetes risk

- 1066 lost at least 5% of baseline weight in the first year and were followed for 15 years (Outcomes Study – DPPOS)

- Those originally randomly assigned to metformin had the greatest loss during years 6 to 15: -6.2% vs. -3.7% (ILS), and -2.8% (Placebo).

Aroda. Diabetologia 2017 Sep;60(9):1601-1611; Apolzan. Ann Intern Med 2019; April 23
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?