Do Integrase Inhibitors Cause Weight Gain?

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Antiretroviral Therapy and Weight Gain

- Weight gain is frequent in the year following ART initiation\(^1,2\)
- May be associated with lower mortality for those who are not initially overweight\(^3\)
- However, may lead to higher rates of DM and CVD\(^4,5\)
- May be more likely with a PI,\(^2\) though change in lean mass or regional fat similar b/w RAL, DRV/r, & ATV/r after 96 weeks\(^6\)

2. Lakey W et al. AIDS Res Hum Retroviruses, March 2013  
3. Yuh B et al. CID, June 2015  
Guidelines-Based Regimens for Initial ART

Recommended Regimens

### HHS Guidelines (October 2017)

**Recommended Regimens for Most People**
- Dolutegravir-Abacavir-Lamivudine
- Dolutegravir + Emtricitabine-TDF
- Dolutegravir + Emtricitabine-TAF
- Elvitegravir-Cobicistat-Emtricitabine-TDF
- Elvitegravir-Cobicistat-Emtricitabine-TAF
- Raltegravir + Emtricitabine-TDF
- Raltegravir + Emtricitabine-TAF

### IAS-USA Guidelines (July 2016)

**Recommended Regimens**
- Dolutegravir-Abacavir-Lamivudine
- Dolutegravir + Emtricitabine-TAF
- Elvitegravir-Cobicistat-Emtricitabine-TAF
- Raltegravir + Emtricitabine-TAF

**Sources:**
- 2016 IAS-USA Antiretroviral Therapy Guidelines. IAS-USA. (www.iasusa.org)
### The Integrase Inhibitor Era
Superiority of Integrase Strand Transfer Inhibitors (INSTI’s)

<table>
<thead>
<tr>
<th>INSTI</th>
<th>Treatment-Naïve Study</th>
<th>Compared to…</th>
<th>Virologic efficacy (RNA &lt;50 copies/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dolutegravir</td>
<td>SINGLE FLAMINGO ARIA (♀)</td>
<td>Efavirenz Darunavir/r</td>
<td>88% vs. 81%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atazanavir/r</td>
<td>90% vs. 83%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>82% vs. 71%*</td>
</tr>
<tr>
<td>Elvitegravir</td>
<td>Study 102 Study 103 WAVES (♀)</td>
<td>Efavirenz Atazanavir/r</td>
<td>88% vs. 84%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atazanavir/r</td>
<td>90% vs. 87%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>87% vs. 81%*</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>ACTG 5257</td>
<td>Darunavir/r</td>
<td>93.9% vs. 89.4%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atazanavir/r</td>
<td>vs. 88.3%*</td>
</tr>
</tbody>
</table>

*Reduced virologic failure, risk of resistance or regimen changes with INSTI’s

*Zero cases of virologic failure with resistance in dolutegravir trials

Sources: adapted from a talk by Dr. Joe Eron at ID Week 2017 and other sources, including Davy-Mendez T et al. JAIDS, Oct 2017.
However, INSTI’s are not Free of Risks

- Several studies found an association between INSTI’s and CNS side effects/intolerability
  - Strongest association with DTG
  - Also DTG+ABC, women, older individuals
    - See ECHO talk from 4/14/17 (www.hivecho.org)

- Now, studies implicate INSTI’s as a case of weight gain…
Study #1
Research Letter from Investigators in France

- Analyzed reason for discontinuation of DTG-based ART
- Of 517 patients, 55 (10.6%) stopped DTG d/t side effects
- Unexpectedly, reason in 4 (7%) was weight gain (4-7 kg)
- Then analyzed 462 pts who received DTG for ≥6 months
  - Mean age 50.1, 65% male
  - Mean CD4 591 (range 5-2,010), 94% already on ART, HIV RNA suppressed for 92%, ABC/3TC in 48% & TDF/FTC in 32%
  - Baseline BMI: <18 kg/m² (6%), 18-25 kg/m² (59%), 25-30 kg/m² (24%), >30 kg/m² (6%)

Source: Menard A et al. AIDS, June 2017.
Study #1
Research Letter from Investigators in France

- Mean time from baseline to assessment: 276 +/- 79 days
- Mean weight gain: 3 kg (p=0.009)
  - For 20% of patients weight increased >10%
  - For 27% of patients weight increased 4-10%
- Mean BMI increase: 1 kg/m\(^2\) (p=0.002)
- Mean increases in BMI and weight were significant for women, trend towards significant for men
  - Especially significant for women receiving ABC/3TC
DTG-Based ART at Single Center in France
Change in Mean Weight

Source: Menard A et al. AIDS, June 2017.
DTG-Based ART at Single Center in France
Change in Mean BMI

Source: Menard A et al. AIDS, June 2017.
Study #2
Vanderbilt: Switch from EFV to INSTI

- Retrospective observational cohort
- Patients with HIV RNA <1,000 on EFV/TDF/FTC for ≥2 years
- Compared weight change after switch to INSTI or boosted PI vs. staying on EFV (for ≥18 months)
- Also subanalysis comparing DTG/ABC/3TC to other INSTI’s

### Study #2

**Vanderbilt: Switch from EFV to INSTI**

<table>
<thead>
<tr>
<th></th>
<th>Switch to INSTI (N=136)</th>
<th>Switch to PI (N=34)</th>
<th>Continue EFV (N=325)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (years)</td>
<td>39.7</td>
<td>38.6</td>
<td>38.5</td>
</tr>
<tr>
<td>Female, %</td>
<td>14</td>
<td>29</td>
<td>14</td>
</tr>
<tr>
<td>Non-white, %</td>
<td>38</td>
<td>41</td>
<td>46</td>
</tr>
<tr>
<td>CD4 count, median</td>
<td>662*</td>
<td>516</td>
<td>576</td>
</tr>
<tr>
<td>Weight, median (kg)</td>
<td>82.5</td>
<td>75.2</td>
<td>80.3</td>
</tr>
<tr>
<td>Mean weight change after 18 months (kg)</td>
<td>+2.9*</td>
<td>+0.7</td>
<td>+0.9</td>
</tr>
</tbody>
</table>

Those who switched to DTG/ABC/3TC gained the most weight (mean 5.3 kg, p<0.001 compared to EFV/TDF/FTV)

*Source: Norwood et al, JAIDS, Aug 2017.*
Study #3
Retrospective Review at Single Center in Brazil

- Retrospective analysis of non-obese patients initiating ART between 2000-2016 at single center in Rio

- Included adults with BMI <30 kg/m² at ART initiation who had ≥90 days of ART; reviewed for development of obesity

- Variables: time on PI’s, NNRTI’s, INSTI’s, TDF or AZT

- Baseline: n=1,567
  - Median BMI 22.6, age 36.3, 61.3% male, CD4 count 226, VL 4.8 log₁₀
  - 14% BMI<18.5, 56.4% BMI 18.5-24.9, 21.7% BMI 25-29.9

- Median f/u time 4.1 years

Study #3
Retrospective Review at Single Center in Brazil

- Overall, 76.5% gained weight; 18.3% developed obesity
- Median BMI increased from 22.3 to 24.7 (p<0.001)

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>INSTI</th>
<th>NNRTI</th>
<th>PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity incidence rate*</td>
<td>37.4</td>
<td>370.7</td>
<td>36.0</td>
<td>37.8</td>
</tr>
<tr>
<td>Time to obesity diagnosis (years)</td>
<td>1.9</td>
<td>1.0</td>
<td>1.9</td>
<td>1.9</td>
</tr>
<tr>
<td>BMI gain per year</td>
<td>0.4</td>
<td>1.6</td>
<td>0.4</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Factors associated with incident obesity: INSTI (aHR 7.12), younger age, female sex, higher baseline VL or lower CD4, baseline HTN or DM, higher baseline BMI

Have you ever prescribed tesamorelin (Egrifta) for lipodystrophy?

- Yes
- No