ASPECTOS METABÓLICOS DEL PACIENTE VIH

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Hospital Universitari Germans Trias i Pujol  
Badalona
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Weight gain and ARVs. An unexpected link
Weight gain with DTG (or INSTI) not a new problem

Retrospective observational cohort of 495 subjects on EFV/TDF/FTC* switching to INSTI or PI.
• 18 months F-U: INSTI +2.9 kg, DTG +5.3 kg, PI +0.7 kg, remain EFV/TDF/FTC +0.9 kg (p<0.05)
EFV>2 years, VL<50 c/mL

INSTI greater weight gain than PIs or EFV

J Noorwood. JAIDS 2017;76:527–531
Obesity following ART initiation is common

1794 naives, Rio de Janeiro. **18.3% developed obesity** (BMI ≥ 30kg/m²; incidence 37.4/1000 p/y)

No treatment change. Limited number of INSTI.

<table>
<thead>
<tr>
<th></th>
<th>aHR</th>
<th>Lower CI</th>
<th>Upper CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at ART Initiation (per 10 year increase)</td>
<td>0.82</td>
<td>0.72</td>
<td>0.94</td>
</tr>
<tr>
<td>Sex: Female (reference male)</td>
<td>1.66</td>
<td>1.26</td>
<td>2.20</td>
</tr>
<tr>
<td>Sex: TW</td>
<td>0.87</td>
<td>0.55</td>
<td>1.36</td>
</tr>
<tr>
<td>Baseline Viral Load (copies/mL) $\log_{10}^a$</td>
<td>1.16</td>
<td>1.02</td>
<td>1.33</td>
</tr>
<tr>
<td>NRTI: AZT (reference TDF)</td>
<td>0.86</td>
<td>0.67</td>
<td>1.10</td>
</tr>
<tr>
<td>ART Core Drug: PI (reference NNRTI)</td>
<td>0.91</td>
<td>0.70</td>
<td>1.18</td>
</tr>
<tr>
<td>ART Core Drug: INSTI</td>
<td>7.12</td>
<td>2.97</td>
<td>17.09</td>
</tr>
<tr>
<td>Baseline Diagnosis of Hypertension</td>
<td>1.54</td>
<td>1.09</td>
<td>2.16</td>
</tr>
<tr>
<td>Baseline Diagnosis of Diabetes Mellitus</td>
<td>1.92</td>
<td>1.09</td>
<td>3.36</td>
</tr>
</tbody>
</table>

**INSTI more obesity**

**Obesity: not a return to normal health**

RISK FACTORS FOR EXCESS WEIGHT GAIN FOLLOWING SWITCH TO INTEGRASE INHIBITOR-BASED ART
Jordan E. Lake, Kunling Wu, Kristine M. Erlandson, Sara H. Bares, Paula Debroy, Catherine Godfrey, John R. Koethe, Grace A. McComsey, Frank J. Palella, Katherine Tassiopoulou

GREATER WEIGHT GAIN AMONG TREATMENT-NAÏVE PERSONS STARTING INTEGRASE INHIBITORS
Kassem Bourgi, Cathy Jenkins, Peter F. Rebeiro, Jordan E. Lake, Richard D. Moore, W. C. Mathews, Michael A. Horberg, Amanda Willig, Michelle Floris-Moore, Michael John Gill, Angel M. Mayor, Ronald Bosch, Timothy R. Sterling, John R. Koethe, for the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) for iDeA

WEIGHT GAIN DURING TREATMENT AMONG 3,468 TREATMENT-EXPERIENCED ADULTS WITH HIV
Grace A. McComsey, Joseph J. Eron, Steven Santiago, Karam Mounzer, Graeme Moyle, Thanes Vanig, Paul E. Sax, Keri N. Althoff, Scott Milligan, Michael Marks, Richard Haubrich, Richard A. Elion

INTEGRASE STRAND TRANSFER INHIBITORS ARE ASSOCIATED WITH WEIGHT GAIN IN WOMEN
Anne M. Kerchberger, Anandi N. Sheth, Christine D. Angert, Cyra Christina Mehta, Nathan A. Summers, Igbo Ototokun, Deborah Gustafson, Sheri Weiser, Seble Kassaye, Deborah Konkle-Parker, Anjali Sharma, Adaora Adimora, Hector Bolivar, Cecile D. Labiri

THE IMPACT OF WEIGHT GAIN AND SEX ON IMMUNE ACTIVATION FOLLOWING INITIATION OF ART
Sara H. Bares, Laura M. Smeaton, Vincent Vu, Beth A. Zavoda-Smith, Sarah E. Scott, Catherine Godfrey, Grace A. McComsey

ACTG 5001/5322 RCT. Retrosp, n=691. **Switch from PI or NNRTI. 2007-17.** Slope of weight change prior INSTI. DTG, black race, age, ≥60 and BMI ≥30: greater weight increase

Retrospect, NA-ACCORD. n=24001. **Naïve. 2007-2016.** Weight gain greater DTG or RAL vs EVG (or NNRTIs).

RETROSPECT, n=3,468. TRIO health cohort. EMR. **Switch.** BMI ≥ 3% gain annually psych disorders, not in obese. INSTI NOT associated. PI protective effect.

Retrospec, WIHS. Women (60% AA), n=1118, **switch. INSTI more gain, BMI, waist circumf, and.. blood pressure!.**

ACTG 5202 & 5257. Post hoc Naïve. **More gain with ↓CD4, more inflammation, and women. No info INSTI.**
Observational follow-up post ACTG RCTs. Weight gain.

A5001 or A5332 from 2007-17. Switched to INSTI from PI/r or NNRTI during follow-up N=691. 63% on PI/r.

Difference pre-post 0.9 kg/year (p=0.04)

INSTI greater weight gain

DTG greater weight gain

Not a return to health

Figure 1: Change in weight before and after switch to INSTI

Figure 3: Annual weight gain by pre-switch ART class

JE Lake. CROI 2019. #669.
Greater weight gain with INSTI (and DTG). NA-ACCORD

NA-ACCORD: 24,001 naives (2007-2016) initiate a sustained ART: 11.825 NNRTI, 6.436 PI, 4740 INSTI.

Similar weight gain men or women

Weight gain not a return to health

DTG and INSTI greater weight gain

Figure 1. Predicted weight changes within: (A) 5-years of ART initiation by ART class (B) 2-years of ART initiation by INSTI drug and ART class
¿Cuánto pesabais al acabar la carrera?
¿Cuánto pesabais al acabar la especialidad?
¿Os habéis pesado hace poco?
¿Qué ganancia por año tenéis?
¿Pero 40 kilos en 40 años?
Cambio de peso por edad

<table>
<thead>
<tr>
<th>Age</th>
<th>Women</th>
<th>Mean body weight at baseline (kg)</th>
<th>Weight change (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>kg [95% CI]</td>
<td>kg [95% CI]</td>
</tr>
<tr>
<td>40</td>
<td>1075</td>
<td>67.2 [66.4-67.9]</td>
<td>3.1 [2.7-3.4]</td>
</tr>
<tr>
<td>45</td>
<td>1150</td>
<td>67.6 [66.9-68.4]</td>
<td>3.1 [2.7-3.4]</td>
</tr>
<tr>
<td>50</td>
<td>1198</td>
<td>67.5 [66.8-68.2]</td>
<td>1.9 [1.6-2.3]</td>
</tr>
<tr>
<td>55</td>
<td>1330</td>
<td>70.1 [69.4-70.8]</td>
<td>1.0 [0.7-1.4]</td>
</tr>
<tr>
<td>60</td>
<td>617</td>
<td>70.5 [69.5-71.5]</td>
<td>0.0 [-0.5-0.4]</td>
</tr>
<tr>
<td>All</td>
<td>5370</td>
<td>68.5 [68.2-68.9]</td>
<td>1.8 [1.7-2.0]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>Men</th>
<th>Mean body weight at baseline (kg)</th>
<th>Weight change (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>kg [95% CI]</td>
<td>kg [95% CI]</td>
</tr>
<tr>
<td>40</td>
<td>208</td>
<td>82.0 [80.1-83.8]</td>
<td>2.8 [2.1-3.6]</td>
</tr>
<tr>
<td>45</td>
<td>226</td>
<td>84.3 [82.5-86.0]</td>
<td>1.9 [1.2-2.7]</td>
</tr>
<tr>
<td>50</td>
<td>252</td>
<td>84.4 [82.8-86.1]</td>
<td>1.8 [1.1-2.5]</td>
</tr>
<tr>
<td>55</td>
<td>361</td>
<td>83.4 [82.0-84.8]</td>
<td>0.8 [0.2-1.4]</td>
</tr>
<tr>
<td>60</td>
<td>205</td>
<td>84.5 [82.6-86.3]</td>
<td>-0.8 [-1.6-0.0]</td>
</tr>
<tr>
<td>All</td>
<td>1252</td>
<td>83.7 [82.9-84.5]</td>
<td>1.3 [1.0-1.6]</td>
</tr>
</tbody>
</table>
### Cambio de IMC por edad

<table>
<thead>
<tr>
<th>Edad</th>
<th>Hombres</th>
<th>Mujeres</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peso insuficiente (&lt; 18,5 kg/m²)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De 18 a 24 años</td>
<td>3,5</td>
<td>12,7</td>
</tr>
<tr>
<td>De 25 a 34 años</td>
<td>0,4</td>
<td>6,9</td>
</tr>
<tr>
<td>De 35 a 44 años</td>
<td>0,5</td>
<td>3,4</td>
</tr>
<tr>
<td>De 45 a 54 años</td>
<td>0,7</td>
<td>2,0</td>
</tr>
<tr>
<td>De 55 a 64 años</td>
<td>0,4</td>
<td>1,3</td>
</tr>
<tr>
<td>De 65 a 74 años</td>
<td>0,2</td>
<td>1,5</td>
</tr>
<tr>
<td><strong>Normopeso (18,5-24,9 kg/m²)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De 18 a 24 años</td>
<td>68,4</td>
<td>64,5</td>
</tr>
<tr>
<td>De 25 a 34 años</td>
<td>52,8</td>
<td>60,8</td>
</tr>
<tr>
<td>De 35 a 44 años</td>
<td>40,0</td>
<td>59,3</td>
</tr>
<tr>
<td>De 45 a 54 años</td>
<td>29,1</td>
<td>53,0</td>
</tr>
<tr>
<td>De 55 a 64 años</td>
<td>24,7</td>
<td>40,5</td>
</tr>
<tr>
<td>De 65 a 74 años</td>
<td>24,5</td>
<td>33,0</td>
</tr>
<tr>
<td><strong>Sobrepeso (25,0-29,9 kg/m²)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De 18 a 24 años</td>
<td>19,6</td>
<td>15,0</td>
</tr>
<tr>
<td>De 25 a 34 años</td>
<td>35,7</td>
<td>21,8</td>
</tr>
<tr>
<td>De 35 a 44 años</td>
<td>43,4</td>
<td>24,4</td>
</tr>
<tr>
<td>De 45 a 54 años</td>
<td>49,7</td>
<td>29,3</td>
</tr>
<tr>
<td>De 55 a 64 años</td>
<td>49,7</td>
<td>39,5</td>
</tr>
<tr>
<td>De 65 a 74 años</td>
<td>50,6</td>
<td>39,1</td>
</tr>
<tr>
<td><strong>Obesidad (&gt;= 30 kg/m²)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De 18 a 24 años</td>
<td>8,4</td>
<td>7,9</td>
</tr>
<tr>
<td>De 25 a 34 años</td>
<td>11,1</td>
<td>10,6</td>
</tr>
<tr>
<td>De 35 a 44 años</td>
<td>16,2</td>
<td>12,9</td>
</tr>
<tr>
<td>De 45 a 54 años</td>
<td>20,5</td>
<td>15,7</td>
</tr>
<tr>
<td>De 55 a 64 años</td>
<td>25,2</td>
<td>18,8</td>
</tr>
<tr>
<td>De 65 a 74 años</td>
<td>24,7</td>
<td>26,3</td>
</tr>
</tbody>
</table>

Encuesta Nacional de Salud 2017. MSCBS-INE  
Encuesta Europea de Salud en España 2014. INE-MSCBS

GeSIDA 2019
Relación IMC-exceso de mortalidad

**Hombres: RR a 10-a de DM, HTA, CAD y ACVA**

**Sobre todo si es abdominal**

<table>
<thead>
<tr>
<th>BMI</th>
<th>DM</th>
<th>HTA</th>
<th>CAD</th>
<th>ACVS</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.5–21.9</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>22.0–24.9</td>
<td>1.8</td>
<td>1.5</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>25.0–29.9</td>
<td>5.6</td>
<td>2.4</td>
<td>1.7</td>
<td>1.3</td>
</tr>
<tr>
<td>30.0–34.9</td>
<td>18.2</td>
<td>3.8</td>
<td>2.2</td>
<td>2.1</td>
</tr>
<tr>
<td>&gt; 35.0</td>
<td>41.2</td>
<td>4.2</td>
<td>2.4</td>
<td>2.5</td>
</tr>
</tbody>
</table>

GeSIDA 2019
Let’s look for the greatest scientific evidence

Research Clinical Trials

- Randomization
- Identical baseline characteristics
- No uncontrolled biases
Greater waist circumference increases with RAL vs DRV ACTG 5257/ACTG 5260s. n=1809.

- RAL greater increases than DRV (p=0.01), greater in **women** vs men (p<0.01) and **blacks** (p<0.01).
- Higher baseline VL and lower CD4 associated with greater WC increases.
- No lipodystrophy distribution in abdominal CT scans and whole body DEXA².

![Graph showing WC over 96 weeks by treatment group](image)

**This does not resemble lipodystrophy but obesity**

Weight Gain in PrEP Trials

- No HIV infection. No 3RD ARV drug. Double-blinded RCTs. Good model.

**iPrEx**

- Placebo: +0.5 kg
- F/TDF: -0.3 kg

Less fat gain on TDF/FTC (P= .025) DEXA scans

**DISCOVER**

- Placebo: 0 kg
- F/TDF: +1.0 kg
- F/TAF: +0.5 kg

\[ p=0.02 \]

**HPTN 077**

- CAB: +1.1 kg
- PBO: +1.0 kg

\[ p=0.66 \]

*p <0.05 analysis of covariance (ANCOVA) model including baseline F/TDF for PrEP and treatment as fixed effects and baseline weight as a covariate.

TDF and TAF and Weight: Data from HBV Monoinfection Studies (no HIV)

- Data from **HBV clinical trials** (double-blinded)
  - Studies 108\(^1\) (n=425) and 110 (n=873)\(^2\), pivotal trials of TAF for HBV treatment:

<table>
<thead>
<tr>
<th>Study</th>
<th>TAF</th>
<th>TDF</th>
<th>Difference (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS-US-320-0108</td>
<td>0.8</td>
<td>-0.7</td>
<td>1.5</td>
</tr>
<tr>
<td>GS-US-320-0110</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- A low proportion of subjects across both TDF and TAF treatment groups (1.2%) experienced a weight increase of ≥ 10 kg at Week 48

- A tenofovir (TFV) PK/PD analysis revealed that a **decrease in weight** was **associated with the highest quartile of plasma TFV concentrations**, which occurred with TDF

DRV/c + TAF? Another TDF vs TAF comparison: AMBER Study, naives.

Double-blind RCT. Naives

DRV/c/F/TAF (n=362) vs DRV/c + F/TDF (n=363). Blacks 12%, women 11%.

Weight increase at 48 weeks:
+1.8 kg (TAF) vs 0.8 kg (TDF)

TAF not equal to TDF
No/Low impact of DRV/c

Effect of Baseline ARV on Weight: TAF, BIC, DTG, 96 weeks

Weight Changes in Participants Initiating ART, Stratified by INSTI, and NRTI

Integrated analysis of 8 Phase 3 RCT of PLHIV initiating ART from 2003-2015 (N=5,680) with >10,000 PY of follow-up

Weight Change in Participants Initiating ART, Stratified by INSTI, and NRTI

- Stratified by INSTI
  - 4.24 kg
  - 4.07 kg

- Stratified by NRTI
  - 4.25 kg
  - 2.07 kg

Double-blinded trial: DTG + 3TC (n=716) vs DTG + TDF/FTC (n=717). Median CD4 432 cells, only 8.5% < 200 cells. No OIs. Only difference between arms addition of TDF.

- Increased weight reported as an AE in 13 (1.8%) participants treated with DTG + 3TC and in 10 (1.4%) treated with DTG + TDF/FTC.
- Overall mean change from baseline was +3.1 kg in the DTG + 3TC group and +2.1 kg in the DTG + TDF/FTC group.
BIC vs DTG in RCTs. Impact on body weight, 96 weeks

GS-1490. BIC/F/TAF vs DTG + F/TAF.¹
- Direct comparison of DTG vs BIC. Double-blinded. 96 weeks. N=645.
- Median change: BIC/F/TAF 3.5 kg (IQR 0.1–8.2), DTG+ F/TAF 3.9 kg (0.8–7.4).

GS-1489. BIC/F/TAF vs DTG/3TC/ABC.²
- Median change: BIC/F/TAF 3.6 kg (IQR 0.0–8.5), DTG/ABC/3TC 2.4 kg (−0.4 to 5.8).

TANGO. Switch from TAF-based 3DR to DTG/3TC. 48 weeks

Switch, open-label. TAF-based 3DR: 67% EVG/C, 12% RPV, 7% bDRV. N=740.

- **Similar mean increase** from baseline in weight of **0.8 kg** in both groups.
- Increased weight was reported as an AE in 3 (1%) DTG/3TC and in 6 (2%) treated with a TAF-based regimen.

Mixed counterbalancing effects
## ADVANCE: Changes in body weight/BMI by arm

<table>
<thead>
<tr>
<th></th>
<th>TAF/FTC+DTG</th>
<th>TDF/FTC+DTG</th>
<th>TDF/FTC/EFV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change in weight (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 48</td>
<td>+6 kg*</td>
<td>+3 kg*</td>
<td>+1 kg</td>
</tr>
<tr>
<td>Week 96</td>
<td>+8 kg*</td>
<td>+5 kg*</td>
<td>+2 kg</td>
</tr>
<tr>
<td>Treatment-emergent overweight, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 48</td>
<td>23%</td>
<td>14%</td>
<td>9%</td>
</tr>
<tr>
<td>Week 96</td>
<td>25%</td>
<td>13%</td>
<td>11%</td>
</tr>
<tr>
<td>Treatment-emergent obesity, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 48</td>
<td>14%*</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Week 96</td>
<td>19%*</td>
<td>8%</td>
<td>4%</td>
</tr>
</tbody>
</table>

*Highly significant differences in weight change between arms, p<0.001

Clinical obesity (BMI ≥ 30 kg/m²). TAF/FTC+DTG higher than other 2 groups (p<0.01)
Mean change in weight (kg) to Week 96: men & women

DTG/TAF vs DTG/TDF vs no DTG, EFV + TDF

N=351 (overall)  
N=351 (overall)  
N=351 (overall)

DTG greater impact than TAF and EFV in men

DTG and TAF greater impact in black women

* 48-96 week dataset incomplete

F Venter. 10th IAS 2019 Mexico. #WEAB0405LB

Share your thoughts using #IAS2019  
Find this presentation on www.ias2019.org
ADVANCE: BMI category over time: women
(obese at baseline excluded)

No correlation with blood pressure, lipids, glucose or HBA1c across arms.

- DTG and TAF greater impact in women
- Obesity not a return to normal health
ADVANCE: DTG + FTC/TAF, DTG + FTC/TDF or EFV/FTC/TDF (South Africa)

ADVANCE: Obesity rates.

Treatment-emergent obesity at week 96

ADVANCE: Changes in Body Composition

DTG was associated with increases in both fat and lean body mass vs. EFV, with greater increases with FTC/TAF in women vs. men.

ADVANCE: Subjects meeting Metabolic sd. definition.

Intl Diabetes Federation definition:
Central obesity (BMI ≥ 30) plus any two of: hyperTG, low HDL-chol, HTN or hiperglicemia.

Impact not only on weight or obesity but metabolic syndrome

NAMSAL: Changes in body weight/BMI by arm at Week 48

- RCT, open label. DTG + TDF/3TC (n=301) vs EFV400 + TDF/3TC (n=303). **DTG vs EFV400.**
- 66% women, 100% blacks, median weight 64 kg, median BMI 23 kg/m².

<table>
<thead>
<tr>
<th>Week 48</th>
<th>TDF/3TC+DTG (n=293)</th>
<th>TDF/3TC+EFV400 (n=278)</th>
<th>DTG greater impact than EFV400 in weight, BMI and obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change from baseline:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>+5</td>
<td>+3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></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>
Description, Weight Change at Week 96 – Treatment-naïve RCTs


*Mean change data shown for all studies except 1489 and 1490, which show median changes.

La obesidad está reconocida como enfermedad y como problema sanitario global

“...la obesidad es una enfermedad primaria, y hay que aplicar todo el caudal de nuestros conocimientos médicos en la prevención y el tratamiento de la obesidad como una entidad patológica primaria”¹

“Reconocer a la obesidad como una enfermedad ayudará a cambiar el modo en que la comunidad médica aborda este complejo asunto, que afecta aproximadamente a uno de cada tres norteamericanos”²

“AACE, American Association of Clinical Endocrinologists (Asociación americana de endocrinólogos clínicos); AMA, American Medical Association (Asociación médica americana); FDA, Food and Drug Administration (Administración de Alimentos y Medicamentos de los Estados Unidos); OMS, Organización Mundial de la Salud

“La obesidad es una enfermedad crónica, frecuente tanto en países desarrollados como en países en desarrollo, y afecta tanto a los niños como a los adultos”³

“La FDA coincide con estas observaciones en que la obesidad es una enfermedad. “No obstante el sobrepeso, en el sentido de tener un peso superior al ideal pero sin llegar a la obesidad, no es una enfermedad”³
Causas de Obesidad: Control de la ingestión calórica
Obesidad: “Contagio” por redes sociales

DOI: 10.1056/NEJMsa066082
La complejidad de la fisiopatología de la obesidad

Metabolism Volume 92, March 2019, Pages 26-36
Tejido adiposo: Adipoquinas, citoquinas e inflamación
Tejido adiposo: Adipoquinas y anti-inflamación

Role of anti-inflammatory adipokines in obesity-related diseases. Trends in Endocrinology & Metabolism, 25(7), 348–355. doi:10.1016/j.tem.2014.03.009
**Weight gain in RCT: switch from PI/r to DTG (NEAT 022).**

Switch from PI/r to DTG, n=415. 53% on DRV/r
- High CVD risk (age > 50 or Framingham >10%), stable & suppressed for ≥6/12 months

**After adjustment for baseline BMI, switching from DRV to DTG was the only independent factor associated with BMI gain (P=0.018).**

L Waters. HIV Glasgow 2018, #102.
Unraveling the brain regulation of appetite: lessons from genetics

Giles S H Yeo & Lora K Heisler

Brain sensing of gut- and adipocyte-derived hormones.
Gut- and adipocyte-derived hormones, reflecting short- and long-term nutritional status, respectively, circulate in the periphery and signal to specific receptors in the brain.
Is there any pathogenic pathway for weight gain with DTG (or INSTI)?

- Melanocortin, leptin, 5-hydroxytryptamine and brain-derived neurotrophic factor signaling axes regulating energy homeostasis and appetite responses.
- In vitro, DTG inhibits binding of melanocyte stimulating hormone (MSH) to the human recombinant melanocortin 4 (MC4R) by 64% at a concentration = Cₘₐₓ (only one among 65 physiological receptors tested [>50%]). Clinical significance unknown.
- MC4R is involved in the regulation of energy homeostasis, food intake and blood pressure.

POMC: pro-opiomelanocortin and its receptors.
The actions of melanocortin (MC) peptides are mediated by 5 receptors: MC1R-MC5R

Adipocyte hypertrophy and increased adipogenic markers in SCAT & VAT of ART-treated macaques

Macaques:
• 9 control
• 5 treated with DTG (4) or RAL (1)
No controls treated with other ARVs

Also increased total and peri-adipocyte fibrosis

Adipogenic markers

Adiponectin

Decreased Adiponectin expression in SCAT of ART-treated macaques

ObeVIH study:
ART-controlled HIV-infected obese patients

Undergoing bariatric surgery

Age: 46.9±2.0 years  
BMI: 41.5±1.3kg/m²  
Known duration of HIV infection: 16.3±1.7 years  
14 women, 4 men

without INSTIs  
(n=5)

with INSTIs  
(n=14)

Non-INSTIT ART

INSTIs  
DTG n=10  
RAL n=2  
EVG n=2

Subcutaneous and visceral adipose tissues  
Surgical samples

Results

Increased fibrosis in SCAT & VAT of INSTIs-treated patients

Sirius red staining

Increased fibrosis + adipocyte hypertrophy and dysfunction

**Results**

DTG (>RAL) induce adipocyte dysfunction and insulin resistance

**Adipokine secretion**

**Insulin resistance**

**Akt activation**

**Insulin-induced Glucose uptake**

**Phospho Akt**

<table>
<thead>
<tr>
<th></th>
<th>DMSO</th>
<th>DTG</th>
<th>RAL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Akt</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tubulin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Protein array expression (% of DMSO)**

- **Adiponectin**
  - DMSO
  - DTG: **
  - RAL

- **Leptin**
  - DMSO
  - DTG: *
  - RAL

- **Akt activation**
  - DMSO
  - DTG: **
  - RAL: *

- **Glucose uptake**
  - DMSO
  - DTG: *
  - RAL: **

ADIPOCITO ASESINO

- Inflamación
  - IL-6
  - CRP
  - TNFα

- Lipoprotein lipasa

- Angiotensina

- Insulina

- Resistina

- FFA

- Leptina

- Lactato

- Adiponectina

- Inhibidor del Activador del Plasminógeno (PAI-1)

- Aterosclerosis

- Hipertensión

- Dislipemia aterogénica

- Diabetes tipo 2

- Trombosis
## Algunos genes implicados

<table>
<thead>
<tr>
<th>Gene</th>
<th>Gene Product</th>
<th>Mechanism of Obesity</th>
<th>In Human</th>
<th>In Rodent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lep (ob)</td>
<td>Leptin, a fat-derived hormone</td>
<td>Mutations prevent leptin from delivering satiety signal; brain perceives starvation</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>LepR (db)</td>
<td>Leptin receptor</td>
<td>Same as above</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>POMC</td>
<td>Proopiomelanocortin, a precursor of several hormones and neuropeptides</td>
<td>Mutation prevents synthesis of melanocyte-stimulating hormone (MSH), a satiety signal</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>MC4R</td>
<td>Type 4 receptor for MSH</td>
<td>Mutation prevents reception of satiety signal from MSH</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>AgRP</td>
<td>Agouti-related peptide, a neuropeptide expressed in the hypothalamus</td>
<td>Overexpression inhibits signal through MC4R</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>PC-1</td>
<td>Prohormone convertase 1, a processing enzyme</td>
<td>Mutation prevents synthesis of neuropeptide, probably MSH</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Fat</td>
<td>Carboxypeptidase E, a processing enzyme</td>
<td>Same as above</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Tub</td>
<td>Tub, a hypothalamic protein of unknown function</td>
<td>Hypothalamic dysfunction</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>TrkB</td>
<td>TrkB, a neurotrophin receptor</td>
<td>Hyperphagia due to uncharacterized hypothalamic defect</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Control hipotalámico del balance energético

Control of energy balance by two types of neurons of the arcuate nuclei: (1) pro-opiomelanocortin (POMC) neurons that release α-melanocyte-stimulating hormone (α-MSH) and cocaine- and amphetamine-regulated transcript (CART), decreasing food intake and increasing energy expenditure; and (2) neurons that produce agouti-related protein (AGRP) and neuropeptide Y (NPY), increasing food intake and reducing energy expenditure. α-MSH released by POMC neurons stimulates melanocortin receptors (MCR-3 and MCR-4) in the paraventricular nuclei (PVN), which then activate neuronal pathways that project to the nucleus tractus solitarius (NTS) and increase sympathetic activity and energy expenditure. AGRP acts as an antagonist of MCR-4. Insulin, leptin, and cholecystokinin (CCK) are hormones that inhibit AGRP-NPY neurons and stimulate adjacent POMC-CART neurons, thereby reducing food intake. Ghrelin, a hormone secreted from the stomach, activates AGRP-NPY neurons and stimulates food intake. LepR, leptin receptor; Y1R, neuropeptide Y1 receptor. (Redrawn from Barsh GS, Schwartz MW: Nature Rev Genetics 3:589, 2002)
Why haven’t we seen all this at our offices?

- We have a lot of work with a number of HIV-related issues.
- We do not routinely weigh our patients at all visits.
- We see a low number of women.
- We see a low number of blacks.
- We do not use DTG + TAF due to unfavourable price.
- We probably tended to attribute weight gain to other causes...
Weight gain and ARVs. Unknowns.

• Is weight gain associated with other metabolic features: blood pressure, insulin resistance, metabolic syndrome, hepatic steatosis?
• Must it be associated with increased CVR?
• Is the weight protective effect of TDF associated with its safer lipid profile?
• Should we switch ART in subjects with overweight/obesity?
• Will it revert to normal?

• Underlying mechanism...
Summary: Drivers of weight gain/loss in HIV on ART... ... as of Dec 2019

Weight gain

No weight gain

Low CD4 High VL

DTG or BIC

DRV ABC

TAF

Women Black race

TDF
Conclusiones

Dr. Esteban Jódar

Dr. Josep Maria Llibre