BHIVA
British HIV Association

2023 Spring Conference

Mon 24th - Wed 26th April
Gateshead, UK

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Longer-term safety of integrase inhibitors

Chair:
Jonathan Underwood
Longer-term safety of integrase inhibitors

Andrew Carr
St Vincent’s Hospital, Sydney, Australia
Integrase Inhibitors, Weight Gain, and Cardiovascular Disease

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HIV and Immunology Unit
St Vincent’s Hospital, Sydney
Professor of Medicine, University of New South Wales
Disclosures

- Research funding / support: MSD, ViiV
- Advisory boards: Gilead, MSD, ViiV
INSTIs, weight gain and CVD

Epidemiology of overweight

- **Obesity** = BMI $>$ 30 kg/m$^2$
- **Global prevalence (2016)** = 13%
  - nearly tripled since 1975
  - $>$30% in 7 countries (USA 36.2%)
  - Australia-Europe 20-30%
- **HIV+ adults** (15% to 39%)
- **Complications**
  - Hypertension – cardiovascular disease
  - Type-2 diabetes – CVD, kidney disease, retinopathy, peripheral neuropathy
  - Other – osteoarthritis, cancers, sleep apnoea, fatty liver disease
  - 4 million deaths a year (70% from CVD; 85% in LMIC)
  - 5 kg/m$^2$ BMI increment increases risk of death by $\sim$30% (HIV no different?)

Comorbidities more common in HIV
Incidence of new comorbidities similar for HIV+ vs HIV-
Each comorbidity was associated with a 3-fold greater risk of death
HIV+ patients had greater loss of DALYs
INSTIs, weight gain and CVD

INSTIs: Associations with weight gain in cohorts

Average US adult gains 0.5-1.0 kg / yr from early to middle adulthood

Initial ART

<table>
<thead>
<tr>
<th>Drug Category</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>INSTIs</td>
<td>4,093</td>
</tr>
<tr>
<td>PI</td>
<td>7,063</td>
</tr>
<tr>
<td>NNRTI</td>
<td>10,711</td>
</tr>
</tbody>
</table>

ART switching

Bourgi et al, J Int AIDS Soc 2020
https://jamanetwork.com/journals/jama/fullarticle/2643761
Norwood et al, JAIDS 2017; Zheng et al. JAMA 2017
INSTIs, weight gain and CVD

Association does **not** always mean causality

A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors

Andrew Carr*, Katherine Samaras†, Samantha Burton*, Matthew Law‡, Judith Freund§, Donald J. Chisholm† and David A. Cooper**

Carr et al, AIDS 1998
## INSTIs, weight gain and CVD

### Comorbidities: Delayed recognition

<table>
<thead>
<tr>
<th>Drug / class</th>
<th>FDA approval</th>
<th>Toxicity</th>
<th>Strong signal</th>
<th>Delay (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine</td>
<td>1987</td>
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<td>2003</td>
<td>7</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>1998</td>
<td>suicidality</td>
<td>2013</td>
<td>15</td>
</tr>
<tr>
<td>Abacavir</td>
<td>1998</td>
<td>myocardial infarction</td>
<td>2008</td>
<td>10</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>2001</td>
<td>kidney disease</td>
<td>2006</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>fracture</td>
<td>2012</td>
<td>11</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>2003</td>
<td>kidney stones</td>
<td>2007</td>
<td>4</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>2007</td>
<td>myopathy</td>
<td>2012</td>
<td>5</td>
</tr>
</tbody>
</table>

INSTIs, weight gain and CVD

Initial ART: Pre-INSTITI era (START trial)

Initial ART suppressed weight gain in pre-INSTITI era (mostly TDF-EFV)
INSTIs, weight gain and CVD
Initial ART: Gilead RCTs

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient</strong></td>
<td></td>
</tr>
<tr>
<td>CD4 &lt;200 vs. &gt;200</td>
<td>4.36</td>
</tr>
<tr>
<td>RNA &gt;100,000 vs. &lt;100,000</td>
<td>1.98</td>
</tr>
<tr>
<td>BMI &gt;25, &gt;30 vs. &lt;25</td>
<td>1.54, 1.66</td>
</tr>
<tr>
<td>Women vs. men</td>
<td>1.54</td>
</tr>
<tr>
<td>Black race vs. other races</td>
<td>1.32</td>
</tr>
<tr>
<td><strong>INSTIs</strong></td>
<td></td>
</tr>
<tr>
<td>BIC / DTG vs. EFV</td>
<td>1.82</td>
</tr>
<tr>
<td>RPV vs. EFV</td>
<td>1.51</td>
</tr>
<tr>
<td>TAF vs. ABC</td>
<td>1.90</td>
</tr>
<tr>
<td>TAF vs. TDF</td>
<td>1.47</td>
</tr>
</tbody>
</table>

Sax et al, Clin Infect Dis 2020
INSTIs, weight gain and CVD
Initial ART: Dolutegravir, TAF/TDF and efavirenz (ADVANCE)

- Fat gain >> muscle gain
- Fat gain peripherally and centrally
- Less fat gain with EFV in slow EFV metabolisers

INSTIs, weight gain and CVD

Initial ART: Dolutegravir, TAF/TDF and efavirenz (ADVANCE)

ADVANCE – Week 144 vs South African general population

Similar findings in Kaiser cohort

### INSTIs, weight gain and CVD

**Initial ART: Pregnancy (IMPAACT 2010)**

<table>
<thead>
<tr>
<th>INSTIs regimen</th>
<th>Weight gain / week</th>
<th>Adverse pregnancy outcome</th>
<th>Low weight gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG-F-TAF</td>
<td>0.38 kg</td>
<td>24%</td>
<td>15%</td>
</tr>
<tr>
<td>DTG-F-TDF</td>
<td>0.32 kg</td>
<td>33%</td>
<td>24%</td>
</tr>
<tr>
<td>EFV/F/TDF</td>
<td>0.29 kg</td>
<td>33%</td>
<td>30%</td>
</tr>
<tr>
<td><strong>Recommended</strong></td>
<td><strong>0.42 kg</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Less weight gain associated with
  - more adverse pregnancy outcome (HR 1.4)
  - more small-for-gestational age babies (HR 1.5)

INSTIs, weight gain and CVD
Initial ART: Weight change is not normally distributed

TDF-3TC-DOR vs TDF-3TC-DRVc (DRIVE)

Mean changes

Median changes

Orkin et al, AIDS 2021
INSTIs, weight gain and CVD
Switch cohort: TDF to TAF (OPERA)

- All patients undetectable
- Switched TDF to TAF only or also switched non-INSTI anchor to INSTI

<table>
<thead>
<tr>
<th>Time to switch (months)</th>
<th>INSTI (n=3281)</th>
<th>NNRTI (n=1452)</th>
<th>PIx (n=746)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-60 to 0</td>
<td>0.42</td>
<td>0.66</td>
<td>0.31</td>
</tr>
<tr>
<td>0 to 9</td>
<td>2.64</td>
<td>2.25</td>
<td>1.98</td>
</tr>
<tr>
<td>9+</td>
<td>0.29</td>
<td>0.20</td>
<td>-0.11</td>
</tr>
</tbody>
</table>

- Similar findings in Asian cohort from TDF-Art to EVGc/F-TAF (+0.5 kg in 48 weeks pre-switch vs. +1.8 kg in 48 weeks after switch)

INSTIs, weight gain and CVD
Switch RCTs: TDF / TAF

NRTI switch to TDF-FTC or ABC-3TC (STEAL)

- TDF-FTC
- ABC-3TC

TAF-based ART to DTG-3TC (TANGO)

Martin et al, Clin Infect Dis 2009; Osiyemi et al, ID Week 2021
INSTIs, weight gain and CVD
Switch RCTs: PIr to Dolutegravir (NEAT022)

Note very wide confidence intervals

P=0.008
INSTIs, weight gain and CVD
Switch RCTs: Gilead

- >10% weight gain associated with
  - younger age
  - lower baseline weight
INSTIs, weight gain and CVD
Switch RCTs: Gilead

Erlandson et al, Clin Infect Dis, 2021 May 14;ciab444. doi: 10.1093/cid/ciab444
INSTIs, weight gain and CVD
PrEP: Cabotegravir vs. placebo or TDF

Cabotegravir vs. Placebo (HPTN077)
CAB: +1.1kg, Pbo: +1.0, P=0.66

Cabotegravir vs. TDF-FTC (HPTN083)
CAB: +1.3kg, TDF-FTC: +0.3, P<0.001

**INSTIs, weight gain and CVD**

**PrEP / HBV: TDF vs. placebo or TAF**

**TDF-FTC vs. Placebo (iPrEx)**
Difference Wk 24 = -0.8%, P=0.02

**TAF-FTC vs. TDF-FTC (DISCOVER)**

**TAF vs. TDF** (HBV monoinfection)

## INSTIs, weight gain and CVD

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<td>2001</td>
<td>kidney disease, fracture</td>
<td>2006</td>
<td>5</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>2001</td>
<td>weight loss</td>
<td>2019</td>
<td>18</td>
</tr>
<tr>
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<td>2003</td>
<td>kidney stones</td>
<td>2007</td>
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<td>Raltegravir</td>
<td>2007</td>
<td>myopathy</td>
<td>2012</td>
<td>5</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>2013</td>
<td>weight gain</td>
<td>2019</td>
<td>6</td>
</tr>
<tr>
<td>Bictegravir</td>
<td>2018</td>
<td>weight gain</td>
<td>2020</td>
<td>2</td>
</tr>
</tbody>
</table>

Cooper et al, Clin Infect Dis 2010; Bedimo et al, AIDS 2012; Lee et al, JAIDS 2013; Mollan et al, IDSA 2013
INSTIs, weight gain and CVD

Significance

- **Average Australian man:**
  86 kg, BMI 27.8 kg/m²

- **Starts TAF / INSTI, weight gain of**
  - 2 kg, so BMI → to 28.5 kg/m²
  - 10 kg, so BMI → to 31.0 kg/m²

- **BMI increase of 5 kg/m² requires**
  a weight increase of 15.6 kg

- **However, remember that**
  - 40% of weight-related deaths occur in adults who are not obese
  - so more morbidity is possible with smaller BMI increments

---

Pathogenesis of weight gain

Australians consume ≈ 0.45kg of food a day (+3 litres of water)

Nutrient intake data: Australian Bureau of Statistics; Australian Health Survey: Nutrition First Results - Foods and Nutrients; https://ketoschool.com/the-science-behind-fat-metabolism-60f7a3f678d0
## INSTIs, weight gain and CVD

### Pathogenesis of weight gain

Add an extra 0.3kg of food a day with physical activity unchanged

<table>
<thead>
<tr>
<th>Intake</th>
<th>Output</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fat storage</td>
</tr>
<tr>
<td></td>
<td>Urea</td>
</tr>
<tr>
<td></td>
<td>CO2</td>
</tr>
<tr>
<td></td>
<td>Oxygen</td>
</tr>
<tr>
<td></td>
<td>Water</td>
</tr>
<tr>
<td></td>
<td>Fibre</td>
</tr>
<tr>
<td></td>
<td>Protein / fat / carbohydrate</td>
</tr>
</tbody>
</table>

Nutrient intake data: Australian Bureau of Statistics; Australian Health Survey: Nutrition First Results - Foods and Nutrients; [https://ketoschool.com/the-science-behind-fat-metabolism-60f7a3f678d0](https://ketoschool.com/the-science-behind-fat-metabolism-60f7a3f678d0)
How do we lose weight?

Definitely
- Calorie restriction (dietician)
  +
- More physical activity

Possibilities
- Switch INSTI / TAF
- (Medication – no data)
- (Bariatric surgery – cases reports only)

Meerman and Brown, BMJ 2014
INSTIs, weight gain and CVD

Interventions for overweight: Reduced intake and more exercise

- **Reduce energy intake (WHO)**
  - total fat <30% of calories
  - free sugars <10% of calories
  - 0.3 kg weight loss at 6 months

- **Increase physical activity (WHO)**
  - 150 minutes of exercise / week
  - reduce sedentary work
  - change transport
  - more public exercise space

- **Specific diets (121 RCTs, n=21,942)**
  - mean 4-5 kg at 6 mths, 3 kg at 12 mths
  - declines appear greater than with INSTI switching

---


## INSTIs, weight gain and CVD

### Interventions for overweight: Consider other medications

<table>
<thead>
<tr>
<th>Drug family</th>
<th>Medications Associated with weight gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotic</td>
<td>olanzapine, tioridazine, risperidone, clozapine, quetiapine</td>
</tr>
<tr>
<td>Steroids</td>
<td>corticosteroids, progestagens, estrogens</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>MAOIs, tricyclics, paroxetine, citalopram, escitalopram, imipramine, mirtazapine</td>
</tr>
<tr>
<td>Antidiabetic</td>
<td>insulin, sulfonylureas, glitazones, meglitinides</td>
</tr>
<tr>
<td>Mood stabilisers</td>
<td>lithium, carbamazepine, gabapentin, valproate</td>
</tr>
<tr>
<td>Antihistamine</td>
<td>ciproheptadine</td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>terazosin, propranolol</td>
</tr>
</tbody>
</table>
INSTIs, weight gain and CVD
Interventions for overweight: B/F/TAF switch?

**B/F/TAF to DOR/ISL (MK-8591A-018)**

- Placebo-controlled RCT
- Changes in weight at Week 48
  - B/F/TAF (n=302) 0.55 kg (SD 4.40)
  - DOR/ISL (n=306) 0.23 kg (SD 4.19)
  - Δ = 0.30 kg (95% CI -0.99, 0.39); p=0.39

**B/F/TAF to CAB+RPV (SOLAR)**

- BUT
  - most patients were not overweight and had not gained weight on B/F/TAF
  - weight loss after pregnancy or after ceasing steroids / antipsychotics is often limited

Tan et al. CROI 2023 (abstract 146); Ramgopal et al, CROI 2023 abstract 191
INSTIs, weight gain and CVD
Interventions for overweight: Weight loss medication?

Semaglutide (2.4 mg once a week subcut)

- Ongoing RCT in obese HIV+ adults (although no eligibility requirement for weight gain on ART)

Hypertension developed in 23% (12.6 per 100 patient years)

**INSTIs vs NNRTIs**

<table>
<thead>
<tr>
<th>ART status</th>
<th>Model</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All PLWH</td>
<td>Non-Adjusted</td>
<td>1.38 (1.17, 1.63)</td>
</tr>
<tr>
<td></td>
<td>Adjusted</td>
<td>1.76 (1.47, 2.11)</td>
</tr>
<tr>
<td>ART-naïve</td>
<td>Non-Adjusted</td>
<td>1.84 (1.48, 2.29)</td>
</tr>
<tr>
<td></td>
<td>Adjusted</td>
<td>1.92 (1.51, 2.44)</td>
</tr>
<tr>
<td>ART-experienced</td>
<td>Non-Adjusted</td>
<td>1.28 (0.99, 1.68)</td>
</tr>
<tr>
<td></td>
<td>Adjusted</td>
<td>1.43 (1.07, 1.92)</td>
</tr>
</tbody>
</table>

**INSTIs vs PI**

<table>
<thead>
<tr>
<th>ART status</th>
<th>Model</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All PLWH</td>
<td>Non-Adjusted</td>
<td>0.69 (0.58, 0.81)</td>
</tr>
<tr>
<td></td>
<td>Adjusted</td>
<td>1.07 (0.89, 1.29)</td>
</tr>
<tr>
<td>ART-naïve</td>
<td>Non-Adjusted</td>
<td>0.90 (0.74, 1.09)</td>
</tr>
<tr>
<td></td>
<td>Adjusted</td>
<td>1.01 (0.82, 1.25)</td>
</tr>
<tr>
<td>ART-experienced</td>
<td>Non-Adjusted</td>
<td>1.05 (0.65, 1.68)</td>
</tr>
<tr>
<td></td>
<td>Adjusted</td>
<td>1.42 (0.86, 2.35)</td>
</tr>
</tbody>
</table>

Byonanebye et al, HIV Med 2022
INSTIs, weight gain and CVD

INSTIs and diabetes

Weight gain, diabetes, CVD and death

O'Halloran et al, vCROI 2021 (abstract 516); Bannister et al, EACS 2021 (poster PE5/12)
Hepatic steatosis / NAFLD

- 30.5% of 4798 HIV+ adults
- higher risk for significant fibrosis (OR 1.91)
- risk factors
  - diabetes (OR 4.7)
  - BMI (OR 2.1)
  - But not INSTI (OR 0.8)

NAFLD associations with hepatic fibrosis

- prior tNRTI use (OR 75.4)
- female (OR 7.3)
- higher BMI (OR 1.4)
- older age (OR 1.2)

Liver fibrosis (n=1,183)

- median 53 yrs, 77% male
- progression of fibrosis 3.4% / yr

<table>
<thead>
<tr>
<th>Factor</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current INSTI</td>
<td>1.47</td>
<td>0.61, 3.52</td>
<td>0.39</td>
</tr>
<tr>
<td>Current TAF</td>
<td>0.85</td>
<td>0.39, 1.87</td>
<td>0.68</td>
</tr>
<tr>
<td>Current NNRTI</td>
<td>0.83</td>
<td>0.32, 2.18</td>
<td>0.70</td>
</tr>
<tr>
<td>Current PI</td>
<td>1.53</td>
<td>0.64, 3.63</td>
<td>0.34</td>
</tr>
<tr>
<td>Nadir CD4 &lt; 200</td>
<td>0.56</td>
<td>0.27, 1.17</td>
<td>0.12</td>
</tr>
<tr>
<td>Chronic HBV</td>
<td>2.08</td>
<td>0.56, 7.69</td>
<td>0.27</td>
</tr>
<tr>
<td>Chronic HCV</td>
<td>1.08</td>
<td>0.45, 2.57</td>
<td>0.87</td>
</tr>
<tr>
<td>MAFLD</td>
<td>2.50</td>
<td>1.06, 5.89</td>
<td>0.036</td>
</tr>
<tr>
<td>BMI gain &gt; 5%</td>
<td>2.64</td>
<td>1.32, 5.26</td>
<td>0.006</td>
</tr>
</tbody>
</table>

INSTIs, weight gain and CVD

INSTIs and CVD (RESPOND)

- ART-experienced and ART-naïve adults starting an INSTI
- Unadjusted analysis: incidence rate ratio for CVD increased over 3 years
- Adjusted analysis: risk increased only over first 6 months
- Reduced risk in adjusted analysis suggests those who received INSTIs may have been at greater CVD risk than average

Neesgaard et al, Lancet HIV 2022
CROI 2023

INSTIs and CVD with initial ART (Swiss HIV Cohort Study)

- Risk of AMI or stroke with INSTI (34.3%) or no INSTI (65.7%)
- n = 5,362
  - median age 38 yrs
  - 21% women
  - median follow-up 4.9 yrs
  - big switch to INSTI-ART 2013-16 after change in EACS ART guideline recommendations

Adjusted Cumulative CVD Incidence*
INSTIs, weight gain and CVD
CVD risk factors: Conventional vs ART

Traditional risk factors had greater impact than ART in pre-INSTI era

![Image of bar graph showing the percentage reduction in CVD cases by different interventions.](Image)
INSTIs, weight gain and CVD
My perspective
INSTIs, weight gain and CVD
My perspective
INSTIs, weight gain and CVD

Conclusions: Weight gain

- Generally not severe after 2 years, but outliers / subgroups exist
- Likely to cause more NCDs and deaths, even without obesity
- Greater after INSTI initiation than with switching or PrEP, partially reflecting “return-to-health” and / or “return-to-societal norm”
- Inhibited by TDF (vs. placebo, ABC and TAF)
- Inhibited by EFV (vs. RPV and DTG)
- Induced by INSTIs one DTG switch RCT
- Induced by TAF? can tenofovir cause fat loss at one plasma concentration (TDF) but fat gain at a lower plasma concentration (TAF)?
- Calorie restriction and exercise vs INSTI switching vs both?
INSTIs, weight gain and CVD

Conclusions: Hypertension, diabetes, hepatic steatosis and CVD

- Cohort data only
- Randomised trials of initial ART with INSTI/TAF vs. non-INSTI/non-TAF (e.g. ISL-DOR) will hopefully be reported later this year
- Traditional interventions to prevent and treat established CVD likely to be more beneficial than INSTI/TAF switching (but doing both might be additive)
INSTIs, weight gain and CVD

Acknowledgements

- Anton Pozniak
- Alexandra Calmy
BHIVA
British HIV Association

2023 Spring Conference

Mon 24th - Wed 26th April
Gateshead, UK

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