ASSOCIATION BETWEEN INTEGRASE STRAND TRANSFER INHIBITORS AND CARDIOVASCULAR DISEASE

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Disclosure: Nothing to disclose
Introduction:

Background:
- Associations between cardiovascular disease (CVD) and use of older antiretroviral drugs are well described,[1] as either of:
  - Gradual increased risk with longer cumulative exposure (i.e. certain protease inhibitors). [2-4]
  - Rapid and maintained increased risk, reversible upon discontinuation (i.e. abacavir). [5-7]
- There are limited data on potential associations between longer-term exposure to integrase strand transfer inhibitors (INSTIs) and CVD.

Study objectives:
- To assess if exposure to INSTIs* (raltegravir [RAL], elvitegravir [EVG/c] and dolutegravir [DTG]), is associated with an increased incidence of CVD.

References:

* Due to low number of individuals exposed, bictegravir was not included in the analysis
Methods:

Inclusion:
- INSTI naïve RESPOND participants aged ≥18 years, followed from latest of cohort enrolment or 1st of January 2012 (baseline).

Outcomes:
- CVD - composite endpoint consisting of rigorously defined myocardial infarction (MI), strokes, and invasive cardiovascular procedures (ICP)

Statistical analysis:
- Individuals were followed from baseline to the earliest of first CVD event, last follow-up or 1st of October 2018.
- Exposure to INSTIs was calculated following the methodology developed in D:A:D study. [1]
- Negative binomial regression models, adjusted for common CVD risk factors, HIV characteristics and ARVs previously associated with CVD - factors potentially associated with INSTI use and CVD were fixed at baseline.
- Logistic regression examined odds of starting an INSTI by D:A:D 5-year CVD risk score.

Results:

- A total of 21,267 participants were included; 9,782 (46%) exposed to an INSTI during follow-up. (6372 to DTG, 2385 to EVG/c and 2147 to RAL)

- Overall, 75.5% were white, 73.3% male, 48.9% of Western European origin and 41.2% MSM.

- During a median of 6.3 years of follow-up (IQR 3.5-6.7; 106,870 PYFU); 517 CVD events (IR 4.9/1000 PYFU [CI 95%, 4.5-5.3]) of which, 210 MIs, 162 strokes and 145 ICPs.

- Individuals experiencing CVD were older (median, [IQR]: 53.7 [48.5-61.9] vs. 44.5 [36.2-51.5] years), and a larger proportion had classic risk factors for CVD at baseline, than those without.
  - Greater proportion with a high/very high 5-year estimated D:A:D CVD risk score in the group that experienced CVD (46% vs 12%, P<0.001).

- Odds ratio [95%CI] of initiation INSTI by 5-year estimated D:A:D CVD risk, when compared to low risk (<1%):
  - Moderate risk (1 - <5%): 1.11 [1.00-1.21], high risk (5 - <10%): 1.19 [1.05-1.35], very high risk (>10%): 1.05 [0.89-1.25].
Results:

**Figure A:**
Crude incidence rates of CVD stratified by INSTI exposure

![Graph showing crude incidence rates of CVD stratified by INSTI exposure]

Persons at risk (n)

<table>
<thead>
<tr>
<th>INSTI exposure time (months)</th>
<th>0</th>
<th>0 - 6</th>
<th>6 - 12</th>
<th>12 - 24</th>
<th>24 - 36</th>
<th>&gt;36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persons at risk (n)</td>
<td>21267</td>
<td>9454</td>
<td>8314</td>
<td>7289</td>
<td>5148</td>
<td>2931</td>
</tr>
</tbody>
</table>

PYFU

<table>
<thead>
<tr>
<th>INSTI exposure time (months)</th>
<th>0</th>
<th>0 - 6</th>
<th>6 - 12</th>
<th>12 - 24</th>
<th>24 - 36</th>
<th>&gt;36</th>
</tr>
</thead>
<tbody>
<tr>
<td>PYFU</td>
<td>83237</td>
<td>5423</td>
<td>4327</td>
<td>6576</td>
<td>4132</td>
<td>3175</td>
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</table>

Events (n)

<table>
<thead>
<tr>
<th>INSTI exposure time (months)</th>
<th>0</th>
<th>0 - 6</th>
<th>6 - 12</th>
<th>12 - 24</th>
<th>24 - 36</th>
<th>&gt;36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events (n)</td>
<td>363</td>
<td>58</td>
<td>24</td>
<td>43</td>
<td>17</td>
<td>12</td>
</tr>
</tbody>
</table>

IR [95% Confidence interval]

<table>
<thead>
<tr>
<th>INSTI exposure time (months)</th>
<th>0</th>
<th>0 - 6</th>
<th>6 - 12</th>
<th>12 - 24</th>
<th>24 - 36</th>
<th>&gt;36</th>
</tr>
</thead>
</table>

**Figure B:**
Adjusted IR ratios of CVD stratified by INSTI exposure

![Graph showing adjusted IR ratios of CVD stratified by INSTI exposure]

<table>
<thead>
<tr>
<th>INSTI exposure time (months)</th>
<th>0</th>
<th>0 - 6</th>
<th>6 - 12</th>
<th>12 - 24</th>
<th>24 - 36</th>
<th>&gt;36</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRR [95% Confidence interval]</td>
<td>reference</td>
<td>2.49 [1.86-3.23]</td>
<td>1.37 [0.90-2.10]</td>
<td>1.60 [1.15-2.24]</td>
<td>0.99 [0.60-1.65]</td>
<td>0.87 [0.48-1.58]</td>
</tr>
</tbody>
</table>

Multivariable model adjusted for: Baseline: Calendar year, age, gender, ethnicity, region, body mass index, HIV acquisition risk, antiretroviral treatment status, CD4 count, hypertension, diabetes, prior AIDS, cardiovascular disease, chronic kidney disease and dyslipidaemia. Time-updated: Smoking status, cumulative exposure to lopinavir, indinavir, didanosine, stavudine, darunavir and abacavir use in the past 6 months.
Limitations & Conclusion:

Limitations:
• Due to the observational nature of the study, we cannot exclude the potential for channeling bias or residual confounding.
• Focus on INSTI class rather than individual drugs, and unable to specifically assess ART-naïve individuals due to limited statistical power.

Conclusion:
• The INSTIs examined were associated with a 2.5 times greater incidence of CVD in the first 6 months of exposure when compared to no INSTI exposure, after accounting for known CVD risk factors, and across a wide range of sensitivity analyses.
• These findings call for further investigations in mechanistic studies and other large populations of people living with HIV seen in routine clinical care.

Writing group:

Acknowledgements:
The RESPOND study group (https://chip.dk/Research/Studies/RESPOND/Study-group)