Use of nucleos(t)ide reverse transcriptase inhibitors (NRTIs) and risk of myocardial infarction in HIV-infected patients enrolled in the SMART study

SMART/INSIGHT and D:A:D Study Groups

Late breaker session, track B
International AIDS Conference,
Mexico City, 7th August 2008
Background

- **D:A:D Study (Lancet, April 2008)**
  - Abacavir (ABC) associated with excess risk of myocardial infarction
    - Present for current use (not not cumulative or past)
      - Suggesting that abacavir may increase the chance that existing atherosclerosis converts to cardiovascular disease (CVD)
    - Robust after adjustment for CV risk factors = channelling bias for known CV risk factors is less likely
Aims and objectives

• To establish whether this finding can be reproduced in an other data set where utilization of various NRTIs* differed from that in D:A:D
• To explore plausible biological mechanisms

*: NRTI=nucleos(t)ide reverse transcriptase inhibitor
CD4+ Count–Guided Interruption of Antiretroviral Treatment

The Strategies for Management of Antiretroviral Therapy (SMART) Study Group∗

CD4+ cell count >350 cells/mm³

- n = 2752
  - Continuous Strategy: Virologic Suppression (VS)

- n = 2720
  - Intermittent Strategy: Drug Conservation (DC)

Clinical outcome: All patients in VS group (n=2752)

Biomarkers: levels of 6 markers of inflammation or coagulation at study entry among patients on NRTI when enrolling (n=791)
Considerations in design of analyses (I)

• Use of NRTI’s*
  - Abacavir (but not didanosine)
    • “ABC (no ddI)”
  - Didanosine (with abacavir or with other NRTIs)
    • “ddI (w/wo ABC)”
  - NRTIs other than ABC and ddI
    • “Other NRTIs”

*: NRTI=nucleos(t)ide reverse transcriptase inhibitor
Patient characteristics according to use of NRTIs at study entry (I)

<table>
<thead>
<tr>
<th></th>
<th>ABC (not ddI)</th>
<th>ddl (w/wo ABC)</th>
<th>Other NRTI’s</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>1019</td>
<td>643</td>
<td>2882</td>
<td>4544</td>
</tr>
<tr>
<td>Age (median, IQR)</td>
<td>45 (39-51)</td>
<td>44 (38-49)</td>
<td>44 (38-50)</td>
<td>44 (38-50)</td>
</tr>
<tr>
<td>% female</td>
<td>23</td>
<td>23</td>
<td>28</td>
<td>27</td>
</tr>
<tr>
<td>%HIV-RNA ≤ 400 cop./mL</td>
<td>82</td>
<td>78</td>
<td>84</td>
<td>83</td>
</tr>
<tr>
<td>CD4 (median, IQR), c/µL</td>
<td>639 (495-836)</td>
<td>596 (475-794)</td>
<td>630 (486-814)</td>
<td>630 (487-819)</td>
</tr>
<tr>
<td>% prior CV disease</td>
<td>4</td>
<td>5</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>% current smokers</td>
<td>38</td>
<td>41</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>% ischemic abnorm.¹</td>
<td>36</td>
<td>35</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>% diabetes</td>
<td>7</td>
<td>6</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

¹Q-wave, ST depression, T-wave inversion, any bundle branch block or QTb > 112%

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### Patient characteristics according to use of NRTIs at study entry (II)

<table>
<thead>
<tr>
<th></th>
<th>ABC (no ddl)</th>
<th>ddl (w/wo ABC)</th>
<th>Other NRTI’s</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>1019</td>
<td>643</td>
<td>2882</td>
<td>4544</td>
</tr>
<tr>
<td><strong>% BP lowering drugs</strong></td>
<td>21</td>
<td>20</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td><strong>% lipid lowering drugs</strong></td>
<td>21</td>
<td>21</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td><strong>Total/HDL ratio (median, IQR)</strong></td>
<td>4.6 (3.6-5.9)</td>
<td>4.7 (3.6-5.9)</td>
<td>4.6 (3.6-5.9)</td>
<td>4.6 (3.6-5.9)</td>
</tr>
<tr>
<td><strong>% past/current ABC use</strong></td>
<td>100</td>
<td>28</td>
<td>7</td>
<td>31</td>
</tr>
<tr>
<td><strong>% NRTI only</strong></td>
<td>39</td>
<td>6</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td><strong>% using tenofovir</strong></td>
<td>17</td>
<td>25</td>
<td>22</td>
<td>21</td>
</tr>
<tr>
<td><strong>% &gt; 5 CV risk factors</strong></td>
<td>18</td>
<td>17</td>
<td>14</td>
<td>15</td>
</tr>
</tbody>
</table>
Considerations in design of analyses(II)

- CVD events*
  - CVD, major
    - Clinical and silent MI, stroke, surgery for coronary artery disease (CAD), and CVD death
    - Clinical MI as considered in D:A:D
  - CVD, major, expanded version
    - Major CVD plus peripheral vascular disease, Congestive heart failure (CHF), drug treatment for CAD, and unwitnessed deaths.
  - CVD, minor
    - CHF, peripheral vascular disease or CAD requiring drug treatment

*: Pre-specified (SMART Study Group, NEJM 2006; Phillips et al, AVT, 2008)
All events adjudicated by Endpoint Review Committee
Hazard ratios for four types of CVD while receiving "ABC (no ddl)" versus using "Other NRTIs"

- **CVD, major** (n=70)
- **Myocardial infarction** (n=19)
- **CVD, expanded def.** (n=112)
- **CVD, minor** (n=58)

Hazard ratio (95% CI) of CVD:
- **Unadjusted**
  - Myocardial infarction: 1.8 (12.6, 13.0)
  - CVD, expanded def.: 1.9 (4.3)
  - CVD, minor: 2.7

- **Adjusted for CV risk factors**
  - Myocardial infarction: 1.8
  - CVD, expanded def.: 1.9
  - CVD, minor: 2.7

Favors "Other" ▶
Favors ABC ◀

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Comparison of hazard ratios* for "ABC (no ddI)" and for "ddI (w/wo ABC)" versus "Other NRTIs"

- CVD, major (n=70)
- MI (n=19)
- CVD, expanded def. (n=112)
- CVD, minor (n=58)

Hazard ratio* (95% CI) of CVD

* Favors ABC/ddI
* Favors “Other”

*: Adjusted for CV risk factors

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Hazards ratios* for using "ABC (no ddl)" versus using "Other NRTIs" according to CV risk status at study entry

At study entry:

- ≥ 5 cardiovascular risk factors
  - Yes
  - No

- Ischemic abnormalities on ECG
  - Yes
  - No

*Hazard ratio* (95% CI) of CVD (expanded definition)

- Favors ABC
- Favors “Other”

P-value for interaction:
* = 0.1; ** > 0.4

*: Adjusted for CV risk factors
Adjusted mean differences in biomarker levels at study entry for using "ABC (no ddI)" or "ddI (w/wo ABC)" versus using "Other NRTIs"
Limitations

• Possibility of channeling effect; i.e. patients at an a priori excess underlying risk of CVD may have been preferentially placed on abacavir
  - CV risk factor profile fairly comparable between groups
  - Adjustment for known and quantifiable CV risk factors failed to affect the association!
  - Definitive solution: randomised controlled trial
• Possibility that patients on abacavir had elevated hsCRP and IL-6 for reasons other than use of abacavir
  - Prospective follow-up
    • preferably in randomised controlled trial setting
• Reduced power for some endpoints
• Overlap in patient populations
  - Analyses of sites not participants in D:A:D - >90% of endpoints – consistent results
Summary

• Consistent with D:A:D, current use of abacavir, during follow-up in SMART
  - associated with an excess risk of CVD
• Abacavir use at study entry
  - associated with increased levels of IL-6 and hs-CRP
Proposed mechanisms of action for how abacavir may increase CVD risk

- The drug causes an increased propensity for subclinical atherosclerosis to cause CVD
  - Data not consistent with abacavir affecting atherosclerosis
- The increased propensity maybe caused by proinflammatory properties of the drug
  - IL-6 and hs-CRP surrogates of ongoing inflammatory reactions in coronary arterial wall leading to instability of existing plaques
Conclusions

• Abacavir associated with excess CVD risk in two observational studies

• The drug
  - does not appear to affect the underlying atherosclerotic process per se
  - may cause coronary artheritis ➔ instability of plaques

• This adverse effect appears to be only clinically relevant to consider among patients with elevated underlying CV risk

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- D:A:D Study Group including Steering Committee
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- SMART Clinical Trials.gov identifier: NCT00027352
Back-up slides
Association with didanosine and abacavir use and risk of MI: Additional adjustment for factors that may be influenced by cART

Adjustment for:
- Latest CD4
- Latest HIV RNA
- Latest lipids
- Latest blood pressure
- Diabetes
- Fat loss/gain
- Latest glucose

*: Adjusted for demographic factors, calendar year, cohort, CV risk factors that are unlikely to be modified strongly by cART use and cumulative exposure to other antiretroviral drugs

D:A:D Study Group, Lancet 2008
XVII IAC, Mexico, 2008. Abstract THAB0305
Channelling and how to assess this bias statistically

Selection

Abacavir

Inflammation+
Lipids+
Diabetes mellitus+
CV history+
Smoking+

"Other NRTIs"

Testing for association:

Abacavir

Cardiovascular disease

If channelling bias explains association between ABC and CVD, adjustment for shown CV factors would tend to remove the association.
Relationship with specific drugs
cumulative and recent use

- Zidovudine
- Didanosine
- Stavudine
- Lamivudine
- Abacavir

Adjusted relative rate of myocardial infarction (95% CI)

Cumulative (/ yr, adjusted for recent)
Recent (currently on or received < 6 mts ago (adjusted for cumulative))

D:A:D Study Group, Lancet 2008

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