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PLATELET FUNCTION UPON SWITCHING TO TAF VS CONTINUING ABC: A RANDOMISED SUBSTUDY

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Disclosures

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- Gilead Sciences
- Bristol Myers Squibb
- Janssen Cilag (Tibotec)
- Merck Sharpe and Dohme
Background

- PLWH (People living with HIV) are at increased risk of myocardial infarction

- Cardiovascular (CV) disease in PLWH has multifactorial etiology
  - Traditional risk factors
  - HIV infection
  - Antiretroviral agents

- Many studies (eg, D:A:D) show association of abacavir (ABC) with CV events
  - Others did not, including meta-analysis of randomised studies
  - No CV signal in registrational studies, underlying mechanistic effect likely subtle
  - The association also appears reversible, pointing to platelet dysfunction as a potential mechanism

D:A:D, data collection on adverse events of anti-HIV drugs.
Platelet Activation, Thrombosis and M.I.

Changes in systemic environment:

- Liver
- Inflammation (HIV)
- Acute Coronary Syndrome
- Drugs

- Collagen
- GPVI
- sGPVI
- ADP
- Thromboxane
- Epinephrine
- Thrombin

Platelet

ACTIVATION

Aggregation

Thrombosis

Infarction
Platelet Reactivity - Aggregation

- Increased platelet aggregation associated with CVD events\(^1\)
- Platelet reactivity measured by aggregometry\(^2\)
- ABC associated with more reactive platelets (cross-sectional study)

\[\text{Platelet Aggregation, \%} \]

\[
\begin{align*}
\text{Log [ADP] Concentration, \(\mu\text{M}\)} & \quad 0 & \quad 0.5 & \quad 1.0 & \quad 1.5 \\
\text{Platelet Aggregation, \%} & \quad 0 & \quad 50 & \quad 100 \\
\end{align*}
\]

\(p=0.008\)

Platelet Reactivity - Aggregation

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\[\text{Platelet Aggregation, } \%
\]

\[\log [\text{ADP}] \text{ Concentration, } \mu\text{M}
\]

\[\text{EC}_{50} \quad p=0.008
\]

1. Trip MD et al. NEJM 1990; 322(22):1549-54
2. Satchell CS et al. JID 2011; 204(8):1202-10
Platelet Function: Glycoprotein VI (GPVI) and Abacavir

• Collagen receptor – expressed on platelets

• Conventional wisdom- ‘increases’ in soluble GPVI associated with cardiovascular events – acute ischaemic stroke

Platelet Function: Glycoprotein VI (GPVI) and Abacavir

- ‘Lower’ sGPVI levels in PLWH prior to CAD (Case-control study)³
- Persistently ‘lower’ sGPVI in those remaining on ABC⁴

SWIFT Trial⁴
(virologically suppressed, switching from ABC to TDF vs remaining on ABC)

- Collagen receptor – expressed on platelets¹
- Conventional wisdom- ‘increases’ in soluble GPVI associated with cardiovascular events – acute ischaemic stroke²

Aims

To determine changes in GPVI function and associated platelet reactivity in a group of virologically-suppressed PLWH switching away from ABC to TAF (Study 1717)
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Hypothesis

Switch from ABC to TAF would result in:

1. Decreases in platelet reactivity measured by aggregometry
2. Increases in soluble GPVI (based on findings from the SWIFT study¹)

¹ O’Halloran J et al. AIDS 2018. Feb 12 [Epub ahead of print]
Study Design: Switch from ABC/3TC to TAF/FTC

Phase 3, randomised, double-blind, active-controlled study in US and EU (Study 1717) (Primary endpoint at Week 48)

ABC/3TC + Third Agent
N=556
- HIV-1 RNA <50 c/mL for ≥6 mo
- No CD4 criteria
- Estimated CrCL ≥50 mL/min
- No single tablet regimen allowed

TAF/FTC OD
n=280
Continue Third Agent

ABC/3TC OD
n=276
Continue Third Agent

Week 0 12 48 96
Study 1717 Platelet Substudy

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  • No single tablet regimen allowed

Platelet Substudy
n=61
From four clinical sites in Dublin and London

TAF/FTC QD
Continue Third Agent

ABC/3TC QD
Continue Third Agent

3TC, lamivudine; FTC, emtricitabine
Methods

Platelet reactivity measured using aggregometry at baseline, Week 4 and Week 12

- Five platelet agonists*
- Between-group comparison of population EC$_{50}$ by F-test

*Adenosine diphosphate (ADP), collagen, epinephrine, and thrombin receptor-activating peptide (TRAP) and arachidonic acid;
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Platelet surface markers at baseline and week 12

• GPVI, CD42b [GP1bA] and P-selectin [CD62P]†
• Single-colour flow cytometry
• GPVI shedding induced by collagen-related peptide
• Between-group comparison by Wilcoxon rank sum test

Assays performed on fresh whole blood (citrate)

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†GPVI kind gift from Liz Gardiner and Rob Andrews from Monash University, Melbourne.
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Assays performed on fresh whole blood (citrate)

Sample size: 40 per arm

- 80% power to determine between-group difference of 15% in platelet aggregation (p <0.05)

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## Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>Main Study</th>
<th>Platelet Substudy</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>TAF/FTC n=280</td>
<td>ABC/3TC n=276</td>
</tr>
<tr>
<td>Age, y (range)</td>
<td>52 (20, 79)</td>
<td>52 (24, 74)</td>
</tr>
<tr>
<td>Female, %</td>
<td>14</td>
<td>22</td>
</tr>
<tr>
<td>White, %</td>
<td>73</td>
<td>72</td>
</tr>
<tr>
<td>CD4 count, cells/mm³</td>
<td>654 (489, 849)</td>
<td>700 (546, 891)</td>
</tr>
<tr>
<td>Duration on ABC/3TC, yrs</td>
<td>8 (3, 11)</td>
<td>8 (4, 11)</td>
</tr>
<tr>
<td>Platelet count, x10⁹/µl</td>
<td>220 (182, 254)</td>
<td>218 (181, 259)</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>27</td>
<td>23</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>47</td>
<td>51</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>39</td>
<td>40</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Cardiovascular disease, %</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

Data are median (IQR) or %, unless specified otherwise.
Platelet Reactivity in Response to Collagen

- Higher collagen EC$_{50}$ (i.e., less reactive platelets) in TAF/FTC group at both Weeks 4 and 12
Platelet Reactivity in Response to Collagen

- Higher collagen EC$_{50}$ (i.e., less reactive platelets) in TAF/FTC group at both Weeks 4 and 12
- Similar results seen with TRAP and ADP but not with Epinephrine or Arachidonic Acid
Platelet Reactivity in Response to TRAP

- Higher TRAP-EC$_{50}$ (i.e., less reactive platelets) in TAF/FTC group at Weeks 4
Platelet Reactivity in Response to ADP

- Higher ADP EC\textsubscript{50} (i.e. less reactive platelets) in TAF/FTC group at Week 4
Platelet Reactivity in Response to ADP

- No evaluable between-group differences with epinephrine or arachidonic acid
Higher platelet surface GPVI expression in the TAF/FTC group at week 12
Soluble GPVI Expression

Higher platelet surface GPVI expression in the TAF/FTC group at week 12
Greater increases in sGPVI expression in the TAF/FTC group to week 48
Higher platelet surface GPVI expression in the TAF/FTC group at week 12

Not mediated through changes in GPVI shedding
Soluble GPVI

Mean Change in sGPVI, %

<table>
<thead>
<tr>
<th></th>
<th>Week 0</th>
<th>Week 4</th>
<th>Week 12</th>
<th>Week 24</th>
<th>Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAF/FTC</td>
<td>0</td>
<td>4</td>
<td>12</td>
<td>24</td>
<td>48</td>
</tr>
<tr>
<td>ABC/3TC</td>
<td>0</td>
<td>4</td>
<td>12</td>
<td>24</td>
<td>48</td>
</tr>
</tbody>
</table>

TAF/FTC, n= 268 261 259 252 229
ABC/3TC, n= 267 259 259 255 243

Platelet surface CD42b and P-selectin expression

No difference in platelet CD42b or P-selectin expression at baseline or week 12.
Limitations

- Did not attain full recruitment targets
- Study not designed to measure clinical cardiovascular events
- Did not recruit participants with pre-existing renal dysfunction
- Aggregometry assay produces population level EC$_{50}$ which are not amenable to normal adjustment for covariates
Conclusions

Switching from ABC/3TC to TAF/FTC was associated with:

- Early (week 4 and week 12) decreases in platelet reactivity induced by collagen

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Conclusions

Switching from ABC/3TC to TAF/FTC was associated with:

• Early (week 4 and week 12) decreases in platelet reactivity induced by collagen

• Increases in expression of collagen receptor - GPVI – on platelets at week 12

• Increases in soluble GPVI that persisted to week 48\(^1\)

Suggests coordinated changes in platelet-collagen interactions mediated through the GPVI pathway with removal of ABC.

Conclusions (2)

Results suggest an inherent platelet defect in participants on ABC:
- increased platelet reactivity
- decreased expression of both platelet surface GPVI and soluble GPVI
- reversed with switch from ABC

These data implicate platelet dysfunction as a viable, robust and consistent mechanism to explain how ABC contributes to a reversible, increased risk of myocardial infarction
Acknowledgements

Study participants

Platelet sub-study team:

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