**Changes in platelet function following abacavir administration: a pilot study**

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**Background**

- Abacavir has been associated with increased rates of cardiovascular disease (CVD) but the mechanism by which this occurs remains unknown.
- The association shows strongest with current use and the elevated risk returns to baseline within 6 months of stopping therapy.
- It is physiologically plausible that alterations in platelet function may be playing a role.
- Carbohydrate phosphates (the active anabolite of abacavir) may affect intracellular glycogen/cytoplasm activity leading to increased platelet activation.

**Aims:**

1. To determine if abacavir administration is associated with changes in platelet function
2. To identify if any abacavir-induced changes are reversible on cessation of the drug

**Methods**

- An open label, single centre intervention study was performed in twenty (20) adult males, all the stable non-abacavir containing antiretroviral (ARV) regimen with an undetectable HIV viral load.
- Participants received abacavir 600mg daily for 15 days in addition to their usual ARV regimen.
- Participants were excluded if they had a history of cardiovascular disease (CVD) or were at high baseline risk for CVD, or if they were those who switched to tenofovir-based regimens.

**Results**

- Participants received abacavir 600mg daily for 15 days in addition to their usual ARV regimen. Plasma, serum and whole blood was collected prior to commencing abacavir, on day 15 and then again following a 28 day washout.
- Flow cytometric approaches were used to measure levels of VASP activation following incubation with PGE1 (alone (resting platelets)) or PGE1 & ADP (activated platelets).
- Platelet receptors were also isolated using flow cytometric methods: GPⅡb, GPⅢa, integrin αⅡb and (III and tetratin CD9), while GPⅡb levels were unchanged on cessation of the drug.

**Discussion**

- Short course abacavir therapy (in addition to suppressive ART) is associated with significant and reversible changes in platelet profile.
- The clinical impact of these changes remains unclear.

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**Conclusions**

- VASP phosphorylation in the presence of PGE1 was stable across all time points.
- The de phosphorylation of VASP promoted by ADP was decreased following 15 days of abacavir therapy, as demonstrated by a higher VASP/P concentration and lower VASP index.
- The mechanism by which abacavir may be decreasing ADP responsiveness (and the clinical implication of that change) in platelets is unknown.
- The observed results may be the consequence of a direct effect on the P2Y12 receptor or represent a negative feedback mechanism responding to pro-thrombotic alterations in other pathways within the platelet or systems external to the platelet (such as alterations in endothelial function).
- Lower integrin (III and platelet receptor levels may suggest the presence of immature platelets; and hence a megakaryocyte effect.

**Limitations:**

- The small sample size and homogeneous study population means that the results of this pilot study need to be interpreted with caution until they have been replicated in a larger more heterogeneous group.
- However they do raise doubt in the current hypothesis that abacavir association with CVD is mediated through the guanylyl cyclase-cGMP pathway of platelet activation.

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**Table 1: Baseline Characteristics**

<table>
<thead>
<tr>
<th>n = 20 male participants</th>
<th>Median(IQR) or n(%)</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>40 (20.5–50.5)</td>
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<tr>
<td>Ethnicity</td>
<td>Caucasian Asian</td>
</tr>
<tr>
<td></td>
<td>18 (90%)</td>
</tr>
<tr>
<td></td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Duration of know HIV infection, years</td>
<td>6 (2–12)</td>
</tr>
<tr>
<td>CDH + T cell nad, cells/μL</td>
<td>270 (210–371)</td>
</tr>
<tr>
<td>Current CDH + T cell count, cells/μL</td>
<td>650 (575–963)</td>
</tr>
</tbody>
</table>

**ARV regimen**

<table>
<thead>
<tr>
<th>Tenofovir/Emtricitabine (NRTI)</th>
<th>PI</th>
<th>Integrase</th>
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<tr>
<td>19 (9)</td>
<td>9 (45)</td>
<td>6 (30)</td>
</tr>
<tr>
<td>20 (9)</td>
<td>6 (30)</td>
<td>9 (45)</td>
</tr>
</tbody>
</table>

**FRS, 10 year % risk**

- Cardiovascular Disease: 5 (3–7)

**Creactive Protein**, mg/ml

- 115 (81.2–127.2)

**Platelet count, cells x 10^11**

- 210 (177–233)