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Elevated leukocyte adhesion marker VCAM-1 in HIV-1 infected in women during pregnancy

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Background

• Elevated preterm delivery (PTD <37 wks) in HIV infected women pre ART era (16%\(^1\) vs 8%\(^2\) general population)

• Associated with specific classes of therapy
  – Mma Bana RCT\(^3\): 2 fold risk with PI-based ART vs ABC/3TC/ZDV

• Importance of timing
  – St Mary’s Hospital\(^4\): 22% new cART vs 10% preconception cART vs ZDV 6%
  – 36% new PI cART (eligible for ZDV)

• Hypothesis: underlying inflammation fetal-placental unit

Inflammation

- Cytokine environment in pregnancy (IL10)$^1,2$
- Leukocyte adhesion proteins VCAM-1 and ICAM-1, have been associated with chorioamnionitis and PTD$^3,4$
- Elevated ICAM-1 in placentas of HIV-infected vs uninfected women$^5$
- Elevated ICAM-1 in placentas of women initiating cART before 36 weeks vs post 36 weeks$^5$
- Role in HIV associated PTD unknown

Objective

• To characterize maternal plasma leukocyte adhesion markers throughout gestation in HIV-infected and uninfected pregnancies

• To compare by antiretroviral therapy class and timing of initiation

• To correlate with gestational age at delivery
Methods

HIV-1 + and - pregnant women recruited St Mary’s and St Thomas’ Hospitals, London 2007 and 2011

- Whole blood at 12, 20, 28, 34 and 38 weeks

- Plasma fraction separated from unstimulated PBMCs and stored at -80°C.
- VCAM-1, ICAM-1, SSA and CRP concentrations measured using multiplex immunoassays (Human vascular injury panel II, MSD)

Therapy classified:
cART (PI/NNRTI based) or NRTI-only (ZDVm or ZDV/3TC/ABC)

Routine CD4 cell and HIV plasma RNA quantification

- Maternal demographics, expected delivery date and pregnancy outcome

Analyses: Mean biomarker concentrations, linear regression, mixed ANOVA to compare by HIV status, ART, ART timing & PTD
## Results

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>PI/NNRTI cART (n=39)</th>
<th>NRTI only (n=12)</th>
<th>HIV uninfected (n=12)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age /years (SD)</td>
<td>30 (7)</td>
<td>29 (6)</td>
<td>33 (5)</td>
<td>0.42</td>
</tr>
<tr>
<td>PI based cART (%)</td>
<td>22 (56)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Conceived on cART (%)</td>
<td>22 (56)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Conceived on PI cART (%)</td>
<td>10 (25)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median gestation at ART initiation /weeks (range)</td>
<td>0 (0-28)</td>
<td>26 (19-28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median CD4 at entry cells/mm(^3) (range)</td>
<td>390 (170-1520)</td>
<td>492 (260-810)</td>
<td></td>
<td>0.18</td>
</tr>
<tr>
<td>Median gestational age at delivery /weeks (range)</td>
<td>39 (32-41)</td>
<td>38 (38-42)</td>
<td>40 (37-44)</td>
<td>0.20</td>
</tr>
<tr>
<td>PTD &lt;37 weeks (%)</td>
<td>6 (15)*</td>
<td>0 (0)</td>
<td>1 (8)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

* 4 PI/ 2 NNRTI
Mean maternal plasma vascular marker concentrations across gestation by HIV status

VCAM-1 & ICAM-1 2-3 fold higher at week 12, 20

* p <0.002
Mean maternal plasma vascular marker concentrations across gestation comparing HIV-1 women initiating PI cART versus women conceiving on PI cART.

VCAM-1

ICAM-1

2 fold higher at weeks 12-34  * = p <0.01
Mean maternal plasma vascular marker concentrations across gestation comparing HIV-1 women in HIV infected women by treatment and in HIV uninfected women.
Associations with VCAM-1

• No correlation with:
  – Log HIV VL   R= 0.16 p=0.862
  – CD4 count    R=0.10 p=0.606
  – Gestational age at sampling R= -0.07 p=0.690
Mean maternal plasma VCAM-1 concentrations across gestation comparing women experiencing PTD versus term deliveries.
Limitations

- Potential confounders: different pt groups, other PTD risk factors
- Small numbers not powered to associate with delivery outcome or type of PTD (PROM/SPTB/PET)
Summary

• Significantly higher leukocyte adhesion molecules in women initiating PI cART vs preconception PI cART, NRTI-only and uninfected women

• VCAM-1 was higher in women delivering preterm (not statistically significant)

• No association with CD4 cell count or viral load

• High VCAM-1 predated treatment initiation, declined through gestation suggestive of confounding
Acknowledgments

• NIHR, Imperial BRC, BHIVA, Save the Baby Fund, Abbvie

• St Thomas’ hospital, LHPRG