Immune Activation during Pregnancy and Postpartum Period in Treated HIV+ Ugandans

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Background

- We recently reported high post-partum maternal mortality in HIV+ women who started ART at low CD4 counts (Hunt et al., AIDS, 2013).
- Most of these deaths were from opportunistic diseases.
- In HIV-uninfected women, the post-partum period is also associated with a 2-fold increased risk of TB (Jerrier, Am J Rep Dss, 2012).
- We sought to understand whether immune changes occurring during pregnancy and the post-partum period might contribute to risk for infectious complications in treated HIV infection.

Methods

- Sampled female HIV+ adults initiating ART in the Uganda AIDS Rural Treatment Outcomes (UARTO) cohort who were pregnant at enrolment or became pregnant (by self-report) during observation (q3 month visits).
- Timing of pregnancy onset estimated from self-reported delivery date.
- Biomarkers assessed on cryopreserved plasma from UARTO visits pre-ART and from ≥2 of the following timepoints: pre-pregnancy, 1st trimester, 2nd trimester, 3rd trimester, and postpartum months 0-3, 3-6, 6-9, 9-12.
- VL<400 required for all timepoints occurring after month 6 of ART.
- Pregnancy-related changes in biomarkers were assessed with linear mixed models adjusted for duration and timing of pregnancy timepoints (with 95% CIs) after adjustment for duration of suppressive ART.

Results

- Characteristics of HIV+ Women at ART Initiation

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>29 (25-33)</td>
</tr>
<tr>
<td>Pregnant at ART initiation, %</td>
<td>16 (30%)</td>
</tr>
<tr>
<td>CD4+ T cell count, cells/μL²</td>
<td>134 (81-216)</td>
</tr>
<tr>
<td>Plasma HIV RNA level, log₁₀ copies/ml</td>
<td>5.0 (4.5-5.5)</td>
</tr>
<tr>
<td>Month of 1st pregnancy onset (relative to ART)</td>
<td>11 (-3 to 24)</td>
</tr>
</tbody>
</table>

- Biomarker Changes during Pregnancy and Postpartum Adjusted for Duration of ART

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Relative Δ from Pre-Pregnancy</th>
<th>Pregnancy</th>
<th>Post-Partum</th>
<th>Month</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>sCD14</td>
<td>1.4</td>
<td>1st</td>
<td>0.7</td>
<td>9-12</td>
<td>1</td>
</tr>
<tr>
<td>sCD163</td>
<td>1.4</td>
<td>1st</td>
<td>0.7</td>
<td>9-12</td>
<td>1</td>
</tr>
<tr>
<td>sCD27</td>
<td>1.4</td>
<td>1st</td>
<td>0.7</td>
<td>9-12</td>
<td>1</td>
</tr>
<tr>
<td>IL-6</td>
<td>1.4</td>
<td>1st</td>
<td>0.7</td>
<td>9-12</td>
<td>1</td>
</tr>
<tr>
<td>D-dimer</td>
<td>1.4</td>
<td>1st</td>
<td>0.7</td>
<td>9-12</td>
<td>1</td>
</tr>
<tr>
<td>I-FABP</td>
<td>1.4</td>
<td>1st</td>
<td>0.7</td>
<td>9-12</td>
<td>1</td>
</tr>
</tbody>
</table>

- sCD14 and sCD163 are both soluble markers of monocyte activation and may increase as a consequence of LPS-driven activation of monocytes and neutrophils.

Conclusions / Implications

- Pregnancy and the post-partum period have major effects on several biomarkers relevant to HIV pathogenesis.
- Most markers of immune activation and inflammation decline during pregnancy in treated HIV+ women.
- KT ratio (marker of IDO-1 activity) increases above pre-pregnancy levels for at least 9 months postpartum.
- IDO-1 suppresses T cell proliferation and function, and higher activity strongly predicts mortality in UARTO (see poster #317).
- Monocyte activation (sCD14) and interferon responses (IP-10) appear to remain suppressed for ≥1 year postpartum.
- While D-dimer increases during pregnancy, presumably as a consequence of venous stasis, it declines postpartum and is unlikely to explain postpartum morbidity/mortality.

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