Discordant Early Immune Responses Distinguish TB-IRIS and Death in HIV/TB Co-infection

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Background

Study design: Prospective cohort study of ART-naïve, HIV-infected adults with CD4 counts <125/mm3 and active pulmonary TB at enrollment.

Exposures measured at baseline and week 4 post-ART initiation:

1. HIV- plasma viral load and CD4 counts.
2. Levels of 28 soluble plasma biomarkers by Luminex in all available samples. TNF-α, IL-4, and IL-13 were below the limit of detection.
3. MTB-specific cellular immune response using fresh peripheral blood mononuclear cells (PBMCs) by Purified Protein Derivative (PPD) stimulation and IFN-γ ELISPOT.

Outcomes determined during monthly follow-ups for 6 months post-ART initiation:

1. Non-traumatic death
2. Paradigmatic TB-IRIS assessed retrospectively using INSHI and ACTG guidelines2
3. Controls were non-TB-IRIS survivors

Methods

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Analyses

1. Association between pre-ART biomarker levels in TB-IRIS and death vs. controls.
2. Association between change from baseline to week 4 post-ART levels in TB-IRIS and death to controls.

Rank-sum tests and logistic regression were used for analysis.

Results

Background

Advanced HIV/TB patients are at high risk for both mortality and TB-immune reconstitution inflammatory syndrome (TB-IRIS) despite timely commencement of antiretroviral therapy (ART) following anti-tuberculosis initiation.1, 2 Because TB-IRIS and early mortality appear to be related to rapid and minimal immune recovery respectively, we hypothesized that these two outcomes are characterized by distinct immunological profiles after ART initiation. We evaluated various immunologic variables to determine factors that distinguish early mortality, TB-IRIS, and non-TB-IRIS survivors at baseline and week 4 post-ART initiation among a cohort of advanced HIV/TB co-infected adults in Botswana.

Table 1. Baseline characteristics of cohort. *One TB-IRIS event preceded death after ART initiation. **P-value for interquartile range; N=Non-NA, V0=Week 0, V4=Week 4.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Control (n=116)</th>
<th>TB-IRIS (n=32)</th>
<th>P value*</th>
<th>Death (n=10)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>G-CSF</td>
<td>124 (98-174)</td>
<td>88 (62-132)</td>
<td>0·01</td>
<td>10 (7-145)</td>
<td>0·03</td>
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<tr>
<td>GM-CSF</td>
<td>34·5 (20·0-51·4)</td>
<td>18·3 (12·2-31·9)</td>
<td>0·0008</td>
<td>46·9 (35·5-66·1)</td>
<td>0·03</td>
</tr>
<tr>
<td>IL-2</td>
<td>2·4 (1·0-7·3)</td>
<td>1·0 (0·3-2·0)</td>
<td>0·02</td>
<td>3·7 (1·1-11·4)</td>
<td>0·40</td>
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<tr>
<td>IL-4</td>
<td>3·7 (1·2-10·8)</td>
<td>2·3 (0·1-12·3)</td>
<td>0·007</td>
<td>2·4 (0·3-11·5)</td>
<td>0·09</td>
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<tr>
<td>IL-6</td>
<td>14·7 (5·8-20·8)</td>
<td>10·3 (3·0-21·3)</td>
<td>0·04</td>
<td>19·6 (11·3-31·2)</td>
<td>0·11</td>
</tr>
<tr>
<td>IL-10</td>
<td>22·4 (16·0-45·1)</td>
<td>14·5 (3·2-31·3)</td>
<td>0·07</td>
<td>39·8 (13·1-68·2)</td>
<td>0·03</td>
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<tr>
<td>IL-12p40</td>
<td>15·0 (9·4-23·6)</td>
<td>5·4 (1·7-15·9)</td>
<td>0·003</td>
<td>20·1 (7·4-37·1)</td>
<td>0·05</td>
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<tr>
<td>IL-12p70</td>
<td>9·8 (5·8-17·8)</td>
<td>6·3 (3·2-12·0)</td>
<td>0·01</td>
<td>11·4 (6·1-19·9)</td>
<td>0·49</td>
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<td>IL-15</td>
<td>43·1 (12·1-10·0)</td>
<td>1·7 (1·2-8·4)</td>
<td>0·02</td>
<td>5·8 (2·5-13·3)</td>
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<tr>
<td>IL-17a</td>
<td>3·3 (1·6-5·9)</td>
<td>3·0 (1·6-7·3)</td>
<td>0·005</td>
<td>4·2 (2·4-6·4)</td>
<td>0·35</td>
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<tr>
<td>MCP-1</td>
<td>548·7 (388-477·4)</td>
<td>649·3 (379-244·6)</td>
<td>0·71</td>
<td>832·2 (652-1331·2)</td>
<td>0·003</td>
</tr>
</tbody>
</table>

Table 2. Baseline, pre-ART, biomarker levels associated significantly with TB-IRIS or death compared to controls among patients with advanced HIV/TB initiating ART.

Table 3. Adjusted odds ratios (OR) per quartile change in immunostactic variable from baseline to week 4 post-ART initiation with TB-IRIS and death. TB-IRIS associations were adjusted for BMI and NVP. **Model included pre-ART CD4 count, female sex, and baseline OI. 

Table 4. Table 5. Adjusted odds ratios (OR) per quartile change in immunostactic variable from baseline to week 4 post-ART initiation with TB-IRIS and death. TB-IRIS associations were adjusted for BMI and NVP. **Model included pre-ART CD4 count, female sex, and baseline OI. 

Table 5. Adjusted odds ratios (OR) per quartile change in immunostactic variable from baseline to week 4 post-ART initiation with TB-IRIS and death. TB-IRIS associations were adjusted for BMI and NVP. Model included pre-ART CD4 count, female sex, and baseline OI. **Independent association between biomarker and outcome.

Table 6. Adjusted odds ratios (OR) per quartile change in immunostactic variable from baseline to week 4 post-ART initiation with TB-IRIS and death. TB-IRIS associations were adjusted for BMI and NVP. Model included pre-ART CD4 count, female sex, and baseline OI. **Independent association between biomarker and outcome.

Conclusion

Distinct inflammatory biomarker profiles and cellular immune responses characterize early mortality, TB-IRIS pre- and post-ART initiation. Interventions that decrease inflammation without inhibiting adaptive immune function hold promise in treatment of advanced HIV/TB.