Novel Biomarkers Predictive of Non-AIDS Events during ART-mediated Viral Suppression

Abstract Nr: 529
Poster Nr: 763
March 4 – 7, 2018
Boston, MA

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Background

Despite effective antiretroviral therapy (ART), HIV infection remains associated with morbidity/mortality, driven - in part - by increased inflammation.

Potential contributors to inflammation include translocation of bacterial/fungal products from the gut into systemic circulation and pro-inflammatory lipids, but direct linkages between these indices and clinical events have not been adequately demonstrated.

Objective

To identify associations between levels of plasma biomarkers of chronic inflammation, microbial translocation, and monocyte activation with non-AIDS events during suppressive ART.

Methods

• Design: Matched Case-control study.
• Participants: 143 cases with non-AIDS events, 315 matched controls from the ACTG ALLRT trial; all were virally suppressed on ART at year 1, and thereafter (Tenorio, PMID:24794574). Controls had an event-free follow-up equal or greater than that of the relevant case, and participants were matched on age (median 45 years), sex (85% male), pre-ART CD4+ count (median 215 cells/mm3), ART regimen, and parent study.
• Events: Non-AIDS events were defined as myocardial infarction, stroke, cancer, serious bacterial infection and non-accidental death and occurred at a median of 2.9 years after ART initiation.
• Samples: Plasma samples from three time-points: pre-ART initiation, 1-year post-ART, and immediately preceding an event (cases).
• Measures: Markers of gut epithelial dysfunction (i.e. lipopolysaccharide binding protein [LBP]), beta-D-glucan [BDG], intestinal fatty acid binding protein [I-FABP], oxidized [oxLDL], and markers of chronic inflammation/monocyte activation (soluble urokinase plasminogen activator receptor [suPAR], soluble CD163 [sCD163]) were measured at all timepoints.
• Analysis: At each timepoint, conditional logistic regression analysis assessed associations of the biomarkers with events, and adjusted individually for relevant covariates (including diabetes, smoking).

Results

• At all timepoints, higher levels of suPAR were associated with increased risk of non-AIDS events in unadjusted and adjusted conditional logistic regression models (Figure 1: Table 1).
• At year 1 of ART and pre-event, higher levels of BDG and LBP were associated with increased risk of non-AIDS events in unadjusted and adjusted analyses (Table 1: Figure 1).
• No associations were observed for I-FABP, sCD163 and oxLDL.
• Correlations between suPAR, BDG and LBP and other biomarkers are displayed in Figure 2.

Table 1: Associations between Biomarkers and non-AIDS events

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Baseline</th>
<th>Year 1</th>
<th>Pre-Event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=305</td>
<td>N=187</td>
<td>N=377</td>
</tr>
<tr>
<td>suPAR</td>
<td>1.7 (1.2-2.3)</td>
<td>p=0.002</td>
<td>2.1 (1.6-2.7)</td>
</tr>
<tr>
<td>BDG</td>
<td>1.0 (0.8-1.3)</td>
<td>p=0.81</td>
<td>1.4 (1.1-1.7)</td>
</tr>
<tr>
<td>LBP</td>
<td>1.1 (0.9-1.4)</td>
<td>p=0.01</td>
<td>1.3 (1.0-1.8)</td>
</tr>
<tr>
<td>I-FABP</td>
<td>0.9 (0.6-1.4)</td>
<td>p=0.64</td>
<td>0.9 (0.7-1.3)</td>
</tr>
<tr>
<td>sCD163</td>
<td>1.2 (0.9-1.7)</td>
<td>p=0.12</td>
<td>1.2 (1.0-1.6)</td>
</tr>
<tr>
<td>oxLDL</td>
<td>0.9 (0.7-1.2)</td>
<td>p=0.46</td>
<td>0.8 (0.6-1.1)</td>
</tr>
</tbody>
</table>

Conclusions

• Elevated levels of suPAR were most strongly and consistently predictive of non-AIDS events.
• suPAR showed strong correlation with other plasma inflammatory markers before ART; correlations became weaker while on ART.
• After 1 year of ART, elevated BDG and LBP were also predictive of non-AIDS events, similar to IL-6, D-dimer, and sTNFR-I and –II (Tenorio, JID 2014, PMID: 24794574).
• These biomarkers may be used for future larger cohort studies aimed at predicting specific (e.g., cardiovascular, cancer) morbidity/mortality in ART-treated HIV infection.

This research was supported by funds from the following: Grants from the National Institutes of Health: AI 68036, AI 68648, MH082512, AI010039-05, MH113474, AI343209, AI313185, AI188422, DA04978, KO8NR46, KO802783 and AO806741, and grants from the California HIV/AIDS Research Program (CRHP) HD15-SD-059 and PR15-SD-021.

Acknowledgments

Table: Distributions of suPAR, BDG and LBP

Figure 2: Heatmap of Correlations between Biomarkers

References:

Boehme et al., JID 2014, PMID: 24794574.

* Adjusted p-values used for multiple comparisons.