Persistent immune activation despite suppressive HAART is associated with higher risk for viral blips in HIV-1 infected individuals

Alexander Zoufaly1*, Jan G Kiepe1*, Sandra Hertling1, Anja Hüfner1, Olaf Degen1, Torsten Feldt2
Stefan Schmiedel1, Michael Kurovski3, Jan van Lunzen1

1) Department of Medicine 1/Infectious Diseases Unit, University Medical Center Hamburg-Eppendorf, Germany
2) Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany
3) HIV Laboratory Therapia, Auguste-Viktoria Clinic, Berlin, Germany

Introduction

Viral blips are thought to represent random biological variations around a steady state of residual HIV viremia and to lack clinical significance. However, blips may be the consequence of shedding from activated immune cells and persistent immune activation has recently been linked with increased morbidity and mortality. In this study we aimed to analyze the association between viral blips and systemic immune activation.

Methods

Patients from our HIV outpatient cohort were included in this nested case-control study if they developed a blip after having been on fully suppressive HAART for at least 180 days. Cases were matched with controls without blips according to duration of time of complete viral suppression (CVS), age, sex, and CDC stage.

All used viral load assays (Amplicoq and faqman HIV-1 PCR) had, at least, a lower limit of detection of ≤50 HIV RNA copies/ml. Flow cytometry was used to measure CD3, CD4, CD8, HLA-DR+, CD45RA+, CD16+, CD56, and CD19+ on longitudinal blood samples from cases and controls.

Domain averaged areas under the curve were calculated for these cellular markers as well as C-reactive protein levels from first date of CVS until index date (date of viral blip or corresponding date in blip-free controls). A univariate and multivariable conditional logistic regression model was used to assess risk factors for viral blips.

Adherence to HAART was assessed by measuring prescribed NNRTI or PI plasma levels at index date in a subset of 57 patients who had available serum samples.

Results

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Controls without blips (n = 82)</th>
<th>Cases with blips (n = 82)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex*</td>
<td>46 (59.5)</td>
<td>66 (80.5)</td>
<td>1</td>
</tr>
<tr>
<td>Age in years, mean (SD)</td>
<td>47.8 (12.4)</td>
<td>46.6 (11.9)</td>
<td>0.6</td>
</tr>
<tr>
<td>Lymphocyte count at HAART initiation, median (IQR)</td>
<td>(707)</td>
<td>(757)</td>
<td>0.1</td>
</tr>
<tr>
<td>Viral load at HAART initiation, median log10 (IQR)</td>
<td>4.93 (4.29-5.48)</td>
<td>4.10 (4.08-5.64)</td>
<td>0.8</td>
</tr>
<tr>
<td>Duration of complete viral suppression (baseline to index date), median (IQR)</td>
<td>433 (243-952)</td>
<td>427 (252-1038)</td>
<td>0.2</td>
</tr>
<tr>
<td>Number of regimen switches (baseline to index date)</td>
<td>1 (0-1)</td>
<td>0 (0-2)</td>
<td>0.8</td>
</tr>
<tr>
<td>CD4 Stage at index date*</td>
<td>35 (24.7)</td>
<td>35 (24.7)</td>
<td>1</td>
</tr>
<tr>
<td>Viral load at index date, median cop/ml (IQR)</td>
<td>&gt;50</td>
<td>9 (70-150)</td>
<td>0.02</td>
</tr>
<tr>
<td>Regimen at index date*</td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
</tbody>
</table>

References:

Corresponding author:
Prof. Jan van Lunzen, MD, University Medical Center Hamburg-Eppendorf, Department of Medicine 1/Infectious Diseases Unit, v.lunzen@uke.de, Phone: 004940741053964

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Limitations

• Activation markers were not assessed on CD4 and CD8 cells separately
• Plasma drug levels only assessed on a subset of patients
• Clinical endpoints not investigated here

Conclusion

• Higher levels of activated T-lymphocytes (CD3+HLA-DR+) in patients who developed a blip
• No such association found regarding C-reactive protein and other cellular markers including CD4 and CD8
• Blips not explained by lack of adherence
• Viral blips could help to identify patients with higher levels of immune activation and potentially higher risk for disease progression