Dynamics of T Cell Activation Accompanying CD4 Recovery in Antiretroviral-Treated HIV-Infected Ugandan Children

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Background
- HIV-infection leads to many derangements of T cells, including depletion of naïve pools and increased expression of activation markers, including CD38 and HLADR.
- Data suggest that CD4 recovery with antiretroviral therapy (ART) depends on the reduction of activation levels in both adults and children.
- Africans seem to have elevated T-cell activation compared to residents of Europe and the USA.
- There has been, to date, no study on T-cell activation and ART in African children.

Objective
To characterize changes in T-cell activation in relation to CD4 recovery following the initiation of ART in African children.

Methods
Design
- Cross sectional study of ART-naïve, ART-treated (≥24 weeks), and HIV-uninfected children, comparing levels of T-cell activation (% CD4 or CD8 with CD38 and HLADR expression).
- Prospective study of a small group of HIV-infected children, to examine early change in T-cell activation, comparing levels before and after ART initiation.

Subjects

Prospective Analysis: CHAMP children who became immunosuppressed after enrolment had ART initiated per WHO guidelines; for 8 children, levels of T-cell activation were available before and 10-14 weeks after initiation of ART.

Laboratory Techniques
- Incubating fresh peripheral blood mononuclear cells with CD3 APC, CD8 PerCP-Cy5.5, HLA-DR, FITC, and CD38 PE.
- Minimum of 30,000 CD3+ cells per sample using 4-color flow cytometry (FACS Calibur, BD Biosciences) and FLOWJO software (TreeStar, Inc., Ashland, CA).
- Plasma HIV RNA (Roche Amplicor Version 1.5, level of detection 400 copies/ml).

Table 1. Characteristics of participants
**Table 2. CD38 and HLADR surface expression in HIV-infected and uninfected Ugandan children**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Number (n)</th>
<th>CD4%</th>
<th>CD8%</th>
<th>CD38+ HLADR+</th>
<th>Median (IQR: 25%-75%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 year</td>
<td>305</td>
<td>50</td>
<td>30</td>
<td>10</td>
<td>37.9 (32.0 - 60.1)</td>
</tr>
<tr>
<td>1-5 year</td>
<td>199</td>
<td>25</td>
<td>51</td>
<td>5</td>
<td>51.1 (40.0 - 75.0)</td>
</tr>
<tr>
<td>6-12 year</td>
<td>30</td>
<td>20</td>
<td>50</td>
<td>20</td>
<td>38.5 (30.0 - 50.0)</td>
</tr>
</tbody>
</table>

Results
- Low CD4 activation correlated with high CD4% among both ART-naïve (p = 0.004) and ART-suppressed children (p = 0.05, p = 0.001).
- Low CD8 activation correlated with high CD8% among both ART-naïve (p = 0.05, p = 0.001) and ART-suppressed children (p = 0.047, p = 0.001).

Figure 1a. CD4 activation by CD4 % strata in Ugandan children

- Among untreated children, plasma HIV RNA levels were tested using Spearman’s rank correlation analysis and the Pearson product-moment correlation to reduce activation.

Figure 1b. CD8 activation by CD4 % strata in Ugandan children

- Children with undetectable HIV plasma RNA and high CD4% (<25%) had the lowest median levels of CD4 (6.8%) and CD8 (25.1%) activation, while those with low CD4% (>15%) had the highest CD4 (24.4%) and CD8 activation levels (46.4%) (Figures 1a and 1b).

Discussion
- In the context of elevated T-cell activation, significant and rapid decreases in activation levels accompany CD4 recovery in ART treated HIV-infected African children.
- Levels of activation in ART-untreated children with CD4 recovery approach, but do not reach, those in uninfected children.
- Children with the lowest levels of CD8 activation following treatment have the greatest CD4 recovery.

- Further study identifying the determinants of activation such as HIV subtype, host genetic factors, or non-HIV infectious burden will be important and may lead to novel treatment strategies for this population.

References

Figure 2a. Early change in CD4 activation with antiretroviral therapy

- In prospective study, median CD4 % recovery was 6.5 % points after 10-14 weeks of ART, the levels of CD38 and HLADR had decreased in all 8 children by median 8.7 % points (p = 0.01), and levels of CD8 activation by a median 17.2% points (p = 0.01). The degree of CD4 recovery was associated with post-treatment CD8 activation levels (p = 0.008).