CD4 T cell depletion, and not age, may be a driver of abnormal CD4 cell compartments in HIV-infected children initiating ART in Uganda

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The naïve CD4 T-cell pool is maintained by:
- Production of new cells by the thymus
- Proliferation within the naïve pool
- Cell loss through death or differentiation to memory cells

The homeostatic mechanisms operating to maintain naïve and memory pools are not fully understood in healthy children.

Even less is known in HIV infection, particularly in resource-limited settings where ART is often initiated with advanced immunodeficiency.
CD4 T-cell homeostasis

CD4 homeostasis

naïve T cells (CD45RA+)

thymus

activity decreases with age

CD31+ TREC

RTE

t

CD31+ Ki67+

t

CD31- TREC

central naive

CD31- Ki67+

t

CD31+ TREC

memory T cells (CD45RA-RO+)

CD31- CD45RO+

CD31- CD45RO+

antigen

effect of HIV
Study objective

- To determine the CD4 T-cell populations in HIV infected Ugandan children initiating antiretroviral therapy
Methods

• 1207 ART-naive children meeting WHO criteria for ART in Uganda/Zimbabwe were enrolled into the ARROW clinical trial and started on ART

• 199 children in Uganda underwent CD4 immunophenotyping at ART initiation using a combination of CD4, CD45RA and CD31 antibodies

• Study participants were:
  – 54% girls
  – Aged 5months to 18yrs
• Three CD4 cell sub populations were investigated:
  - CD4RA+CD31+ : Recent Thymic Emigrants (RTE)
  - CD45+CD31- : Central Naïve (CN)
  - CD45RA-CD31- : Memory (M)
Results: Variations of CD4 cell sub-populations with age

Percentage of CD4 Tcells

<table>
<thead>
<tr>
<th>Age at ART initiation (median, CD4 for age, n)</th>
<th>RTE</th>
<th>CN</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5-2years (778, 2.3, n=75)</td>
<td>15</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td>3-6years (458, 3.2, n=49)</td>
<td>20</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>7-12years (256, 5.3, n=50)</td>
<td>25</td>
<td>15</td>
<td>35</td>
</tr>
<tr>
<td>13-18years (215, 7.3, n=25)</td>
<td>35</td>
<td>20</td>
<td>40</td>
</tr>
</tbody>
</table>
Results: Pre ART CD4 depletion Versus Age as a predictor of CD4 sub populations

<table>
<thead>
<tr>
<th>At ART initiation</th>
<th>Effect (95% CI) of Pre-ART factors on:</th>
<th>%RTE</th>
<th>%CN</th>
<th>%M</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 unit lower CD4 count for age Z-score</td>
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<td>-4.4% (-5.4%, -3.5%) P&lt;0.001</td>
<td>+2.1% (+1.5%, +2.7%) P&lt;0.001</td>
<td>+3.6% (+2.6%, 4.6%) P&lt;0.001</td>
</tr>
<tr>
<td>1 year older age</td>
<td>1 year older age</td>
<td>+0.4% (-0.2%, 1.4%) P=0.16</td>
<td>-0.1% (0.4%, +0.3%) P=0.78</td>
<td>-0.2% (-0.8%, 0.4%) P=0.55</td>
</tr>
<tr>
<td>1 unit lower weight for age</td>
<td>1 unit lower weight for age</td>
<td>-0.0% (-1.5%, +1.4%) P=0.96</td>
<td>+0.7% (-0.2%, +1.6%) P=0.12</td>
<td>-0.5% (-2.0%, +0.9%) P=0.47</td>
</tr>
<tr>
<td>Girl Vs Boy</td>
<td>Girl Vs Boy</td>
<td>+0.6% (-3.6%, +4.9%) P=0.76</td>
<td>+0.7% (-1.9%, +3.4%) P=0.57</td>
<td>+0.0% (-4.3%, +4.3%) P=1.00</td>
</tr>
</tbody>
</table>

Multivariable modelling showed that the relationship with age was the result of lower CD4 for age in older children.
Conclusions

• In all age groups, the cell populations in the 3 CD4 compartments were lower than have been reported in healthy Caucasian children (Huenecke S et al, 2008)

• Total CD4 count may be an important driver or consequence of lower Recent Thymic Emigrants and higher central naïve/ memory populations, with a far stronger association than age alone
Conclusions 2

• In children surviving without ART, there may be a shift to maintain the CD4 cell pool through the relative expansion of central naïve and memory pools at the expense of Recent Thymic Emigrants.

• This may indicate that with time the capacity of the thymus to keep pace with CD4 cell loss is diminished.

• The long term consequences of this trend for subsequent ART response are under investigation in ARROW.
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  – MRC/UVRI Entebbe, Uganda
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