Long-term Profiles of CD4 Reconstitution in HIV-infected Children Initiating Antiretroviral Therapy in Uganda and Zimbabwe

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ABSTRACT

Background: Studies of long-term immune reconstitution after antiretroviral therapy (ART) initiation are scarce in HIV-infected children in resource-limited settings.

Methods: HIV-infected ART-naïve children meeting WHO criteria for ART in Uganda and Zimbabwe were enrolled in the ARROW trial between 2007 and 2008. CD4 counts were measured by flow cytometry at ART initiation and every 12 weeks subsequently. Based on our previous work in European children, we assumed an asymptotic CD4 reconstitution over time on ART with CD4 regain to a constant age-corrected level after a period of time. Using non-linear mixed-effects models for log(CD4)/log(CD4c) in uninfected child of the same age), we investigated the effects of pre-ART age, sex, WHO stage and weight-for-age on pre-ART and long-term CD4-for-age.

Results: 1206 HIV-infected ART-naïve children were enrolled and started combination ART (51% girls, 0.4 to 17.6 years old, median (IQR) follow-up: 2.8 (2.5, 3.3) years). Our model identified two distinct groups according to whether CD4 reconstitution could be fitted using the asymptotic model (see Modelling Section)...

RESULTS

276 (23%) children did not have asymptotic CD4 reconstitution

930 (77%) children had asymptotic CD4 reconstitution

Among these 276 children, we used linear models to identify 4 subgroups: those with significantly (p<0.05) continuously increasing or decreasing CD4-for-age with time; those with no significant change in CD4, and those without enough measurements to identify a slope with confidence intervals.

- 43 children (16%) increased CD4 for-age continuously over the long term.
- 179 children (65%) had a small, fast initial CD4 recovery, but no further improvement to the levels seen in the asymptotic group (non-significant change in CD4-for-age).
- 17 children (6%) had decreasing CD4-for-age.

This group probably represents non-response or treatment failure, followed by CD4 recovery on follow-up treatment.

- 37 children (13%) had zCD2 measurements. Of these, 32 died, and the other 5 were lost to follow-up, early in the trial.

METHODS

Participants: HIV-infected ART-naïve children meeting WHO criteria for ART in Uganda/Zimbabwe were enrolled into the ARROW trial between March 15, 2007, and November 28, 2008, and started combination ART.

- Pre-ART age, sex, WHO staging and weight were recorded.
- Clinical markers and CD4 counts were recorded at ART initiation, and then every 12 weeks. (A week 4 tropin test was available in children participating in a sub-study).

- Study endpoints: CD4-for-age reconstitution (CD4-for-age = log(CD4)/log(34CD4c) in uninfected child of the same age).

A value of zero (a ratio of 1) thus corresponds to the CD4 count expected in a healthy child of the same age (CD4c).

Lack of a significant change in CD4-for-age over time is termed as ‘asymptotic’ CD4 reconstitution.

No significant CD4-for-age change

Significant, increasing CD4-for-age change

Significant, decreasing CD4-for-age change

Early death/loss to follow-up

<table>
<thead>
<tr>
<th>CD4 count (cells/µl)</th>
<th>CD4-for-age</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial CD4 count</td>
<td>Age (years)</td>
<td>Change</td>
</tr>
<tr>
<td>550 (462, 642)</td>
<td>0.14 (0.07, 0.20)</td>
<td>0.05</td>
</tr>
<tr>
<td>650 (744, 744)</td>
<td>0.20 (0.12, 0.28)</td>
<td>0.05</td>
</tr>
<tr>
<td>750 (842, 842)</td>
<td>0.26 (0.18, 0.34)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

In this group:

- On ART, CD4-for-age showed an initially steep increase, slowing as it approached a long-term plateau.
- The time for half the ultimate increase in CD4-for-age, ln(2)/c, was ~16 weeks (1 = 0.043 weeks).
- Using a model-building procedure based on the Akaike Information Criterion, we found signs and effects of age and weight-for-age on pre-ART CD4-for-age, and of age and sex on long-term CD4-for-age...