

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 rising to a constant age-corrected level after a period of time. Using non-linear mixed-effects models for log(CD4/expected CD4 in uninfected child of the same age), we investigated the effects of pre-ART age, sex, WHO stage and weight-for-age z-score on pre-ART and long-term CD4-for-age.

Results: 1206 children were enrolled (51% girls; ages 0.4-17.6 years) and followed for median (IQR) 2.8 (2.5,3.2) years. Our model identified two groups of children. Group 1: 930 (77%) children had asymptotic CD4 reconstitution (median (IQR) age 5.8 (2.4,9.0) years; pre-ART CD4 344 (158,634) cells/μl, estimated CD4 after 2.8 years of follow-up 693 (645,866) cells/μl). The two key findings were: 1) a strong correlation between their pre-ART and long-term CD4 (r=0.37; p<0.0001), ie children who started ART with lower CD4 achieved lower CD4 in the long-term and 2) an association of older age at ART initiation with lower long-term CD4 reconstitution (p<0.0001). Lower pre-ART CD4-for-age was also associated with older age and lower weight-for-age z-score at ART initiation (both p<0.0001) and lower long-term CD4-for-age with male sex (p=0.002). Group 2: The 276 children for whom asymptotic CD4 reconstitution did not fit were older (7.2 (2.4,10.7) years; p=0.005), with higher pre-ART CD4 (469 (191,908) cells/μl) and CD4-for-age (-1.1 (-1.7,-0.6); both p<0.0001). We used linear regression to identify four types of CD4-for-age trajectory within this sub-population.

Conclusions: Our data suggest that CD4 and age at ART initiation may both drive different long-term profiles of immune reconstitution. These drivers appear to act in both a continuous and a stepwise manner to separate qualitatively different responses to ART in the long term. In the context of increasing availability of ART, our results highlight the importance of considering long-term immunological health, as well as short-term disease progression, in formulating future guidelines for ART initiation.

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 18, 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 timepoint was available in children participating in a sub-study).

Study outcome : CD4-for-age reconstitution

CD4-for-age = log(CD4/expected CD4 in uninfected child of the same age)¹

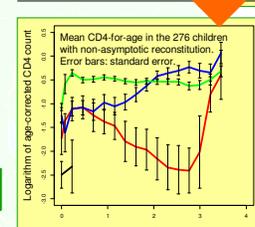
A value of zero (a ratio of 1) thus corresponds to the CD4 count expected in a healthy child of the same age.

We thank all the patients and staff from all the centres participating in the ARROW trial. Joint Clinical Research Centre, Kampala, Uganda; P Mugenyi, V Musime, VD Afayo, E Bagurukira, J Bwomezi, J Byaruhanga, P Erimu, C Karungi, H Kizito, M Mutumba, WS Namala, J Namusanje, R Nandugwa, TK Najjuko, E Natukunda, M Ndigendawani, SO Nsiyona, F Odongo, K Robinah, M Ssenyonga, D Sseremba, J Teziyabirri, CS Tumusiime, MRC/UVRI Uganda Research Unit on AIDS, Entebbe, Uganda; P Munderi, P Nahirya-Ntege, M Aber, FN Kagawa, P Kaleebu, R Katuramu, JH Kyalimpa, J Lutaakome, L Matama, M Musunguzi, G Nabulime, A Ruberantwari, R Sebuku, IM Ssekamatte, G Tushabe, D Wangi. Baylor-Uganda, Paediatric Infectious Disease Centre, Mulago Hospital, Uganda; A Kekitiinwa, P Musoke, S Bakeera-Kitaka, R Namuddu, P Kasirye, JK Balungi, A Babirye, J Asele, S Nakakanzi, NC Ssemambo, J Nakafero, JN Kairu, EK George, G Musoba, J Ssanyu, S Ssenyonga. University of Zimbabwe, Harare, Zimbabwe; KJ Nathoo, MP Bwakura-Dangarembizi, F Mapeing, T Mhute, T Vhembo, R Mandidwa, D Nyoni, C Kalanda, GC Tinago, J Bhiri, D Muchabwa, S Mudzingwa, MM Chipiti, M Phiri, J Steamer, CC Marozva, SJ Maturure, L Matanhike, S Tsikirayi, L Munetsi. Medical Research Council Clinical Trials Unit, London, UK; DM Gibb, MJ Thomson, AD Cook, A Prendergast, AA Fenier, B Naidoo, MJ Spyer, AS Walker, LK Kendall. Independent DART Trial Monitors: R Nantuka. Trial Steering Committee: I Walter (Chair), E Luyirika, H Lyall, E Malunga, C Mwansambwa, M Nyathi, A Wapashabulo, DM Gibb, A Kekitiinwa, P Mugenyi, P Munderi, KJ Nathoo; Observers S Kinn, M MacNeil, M Roberts, W Snowden. Data and Safety Monitoring Committee: A Breckenridge (Chair), C Hill, J Matenga, A Pozniak, J Tumwine. Endpoint Review Committee: G Tudor-Williams (Chair), H Barigye, HA Mujuru, G Ndeezi. Funding: ARROW is funded by the UK Medical Research Council and the UK Department for International Development (DfID). Drugs are provided by GlaxoSmithKline.

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, 3.2) years). Our model identified two distinct groups according to whether CD4 reconstitution could be fitted using the asymptotic model (see Modelling Section):

At ART initiation	276 (23%) children did not have asymptotic CD4 reconstitution	930 (77%) children had asymptotic CD4 reconstitution
Girls, n (%)	125 (45%)	485 (52%)
Age (years)	7.1 (2.4, 10.7)	5.8 (2.4, 9.0)
WHO stage 4, n (%)	39 (14%)	131 (14%)
CD4 count (cells/μl) ¹	469 (191, 908)	344 (158, 634)
CD4-for-age	-1.1 (-1.7, -0.6)	-1.4 (-2.1, -0.9)
Weight for age-z-score	-2.0 (-3.2, -1.0)	-2.2 (-3.3, -1.3)



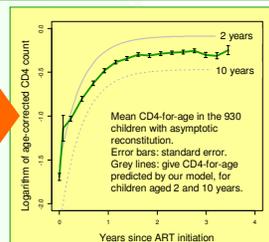
Among these 276 children, we used linear models to identify 4 subgroups: those with significantly (p<0.05) continuously increasing or decreasing CD4-for-age with time; those with no significant change in CD4, and those without enough measurements to identify a slope with confidence interval.

- 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 reconstitution 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 2nd-line treatment.

• 37 children (13%) had ≤2 CD4 measurements. Of these, 32 died, and the other 5 were lost to follow-up, early in the trial.

Median (IQR) values given	Age (years)	CD4 count (cells/μl)	CD4-for-age
Significant, increasing CD4-for-age	5.0 (1.7, 9.1)	552 (256, 882)	-1.1 (-1.5, -0.6)
No significant CD4-for-age change	7.4 (2.4, 10.9)	522 (262, 979)	-1.0 (-1.4, -0.4)
Significant, decreasing CD4-for-age	10.0 (7.3, 11.9)	200 (95, 451)	-1.5 (-2.3, -0.8)
Early death/loss to follow-up	5.4 (1.8, 9.1)	130 (22, 671)	-2.1 (-4.2, -1.1)

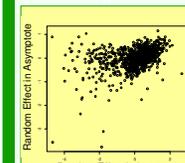


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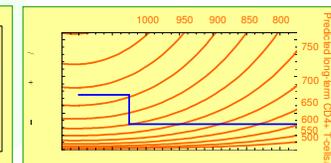
- On ART, CD4-for-age showed an initially steep increase, slowing as it approached a long-term plateau.
- The time for half the ultimate increase in CD4-for-age, ln(2)/c, was ~16 weeks (c = 0.043/weeks).
- Using a model-building procedure based on the Akaike Information Criterion, we found significant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

Parameters fitted in the model were as follows:

pre-ART CD4-for-age (intercept):	Estimate (95% CI)	p-value
Change per year older at ART initiation	-1.64 (-1.72, -1.57)	<0.0001
Change per unit higher weight-for-age	0.17 (0.13, 0.22)	<0.0001
long-term CD4-for-age (asymptote):	-0.19 (-0.23, -0.14)	<0.0001
Change per year older at ART initiation	-0.05 (-0.06, -0.04)	<0.0001
Change in boys (vs. girls)	-0.09 (-0.15, -0.03)	0.0021



We found a strong correlation between random effects (which represent inter-individual variability) in pre-ART and long-term CD4-for-age (r=0.37; p<0.0001)

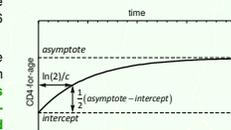


Our models allow us to predict long-term CD4 count, based on pre-ART age and count. The figure shows long-term expected CD4 count (orange contours), given pre-ART age and CD4. Current WHO CD4 guidance thresholds (blue line) result in a higher long-term count for younger than for older children.

MODELLING

Mathematical model: Based on previous work in European children², we assumed an asymptotic CD4-for-age reconstitution over time on ART, with CD4 count rising from a low starting value (intercept) to a nearer-normal level for age (asymptote) in the long term:

$$CD4\text{-for-age} = \text{asymptote} - (\text{asymptote} - \text{intercept}) e^{-ct}$$



Statistical model: Linear and non-linear least-squares fits separated children with qualitatively different CD4-for-age trajectories. In children showing asymptotic reconstitution, non-linear mixed-effects models were used to account for inter-individual variability, and examine effects of pre-ART age, sex, WHO staging and weight-for-age on pre-ART (intercept) and long-term (asymptote) CD4-for-age, and proportional recovery rate (c).

SUMMARY

CD4 count and age both drive response to ART and long-term profiles of immune reconstitution in resource-limited settings

- CD4 reconstitution after ART initiation was better in the long term if the pre-ART CD4 count had been high.
- CD4-for-age was higher before ART, and also reached a better long-term level, in children initiating ART at younger ages; the age effect acting in a continuous manner on pre-ART and long-term CD4 counts.
- Children showing non-asymptotic reconstitution had a number of different recovery profiles, which demand further investigation.

In the context of increasing ART availability, our results highlight the importance of considering long-term immune reconstitution, as well as short-term disease progression, in formulating guidelines for ART initiation in children

In order to ensure immune competence in adulthood, universal ART may be warranted in vertically-infected children still ART-naïve at ages older than 10 years, regardless of CD4 count.

References:
¹Huensecke S et al. Eur J Haematol 2008;80:532-9; ²Lewis J et al. J Infect Dis 2012;205:548-556