CD4 T cell depletion, and not age, drives reconstitution within CD4 cell compartments in HIV-infected children initiating ART in Uganda

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ABSTRACT

Background: The naïve CD4 T cell pool is maintained by new thymic emigrants, proliferation within the naïve pool and cell loss through death or differentiation to memory cells. Drivers influencing these homeostatic mechanisms in HIV-infected children are not fully understood, particularly in resource-limited settings.

Methods: 199 ART-naïve Ugandan children (45 girls, 5-10 years) in the ARROW trial underwent CD4 immunophenotyping at ART initiation, and at 4, 12, 24, 36 and 48 weeks. CD4 subsets were identified by expression of CD45RA, CD31, HLA-DR and Ki67 by flow cytometry. We estimated trends over time using linear mixed models for log cell %.

Results Over 48 weeks on ART there was a marked shift from memory to naïve phenotypes (Table), most substantial in those initiating ART with lowest CD4 (<0.5). Adjusting for pre-ART CD4%, there was no independent effect of age on changes in Recent Thymic Emigrants (RTE), CD45RA+CD31+ (p=0.27), Central Naïve (CD45RA-CD31-) (p=0.45) or Memory (Δ, CD45RA-CD31-) (p=0.72) compartments. At ART initiation, HLA-DR and Ki67 expression were lowest in RTEs, intermediate in CD4%, and highest in H compartments (all p-values <0.02). Over 48 weeks on ART, 104+CD4 T cells declined profoundly in all compartments and across all pre-ART CD4%. In contrast, declines in HLA-DRs were smaller and had mostly occurred by week 4, thereafter remaining similar.

 Geometric Mean cell % (95% CI) (Δ)

Table: CD4 cell subpopulations at ART initiation and 48 weeks on ART.

METHODS

-1207 ART-naïve children meeting WHO criteria for ART in Uganda/Zimbabwe were eligible and entered into the ARROW trial (pre-ART sampling) and started combination ART.

RESULTS - pre-ART CD4 depletion is a better predictor than age

• The shift from memory to naïve phenotypes was most substantial in those initiating ART with lowest CD4 (<0.5).
• Although the median age varied slightly across pre-ART CD4 groups, there was a good spread of ages in each group.
• Adjusting for pre-ART CD4, there was no independent effect of age on changes in Recent Thymic Emigrants (RTE), CD45RA+CD31+ (p=0.27), Central Naïve (CD45RA-CD31-) (p=0.45) or Memory (Δ, CD45RA-CD31-) (p=0.72) compartments.

SUMMARY

I HIV-infected children with most profound immunosuppression had highest pre-ART proliferation and activation and greatest shift from memory to naïve phenotypes after ART.

- Although young children have an active thymus, we did not find any evidence to support an independent contribution of age, over and above CD4 depletion, and not age per se, drives CD4 reconstitution.

- This may be because profound CD4 depletion is a marker for failure of the thymus to keep pace with CD4 loss through proliferation and expansion, regardless of age.

- Older and younger children can reconstitute CD4 cells well, providing they have not experienced profound immunocompromise.

- A sustained and dramatic effect on CD4 proliferation but only a modest impact on activation, occurring shortly after ART initiation, suggesting that non-viral drivers sustain ongoing immune activation despite ART.

- This will be investigated in future studies.

REFERENCES