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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ABSTRACT

The naïve CD4 T cell pool is maintained by thymic production of new cells, proliferation within the naïve pool and 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 when ART is often initiated with advanced immunodeficiency.

METHODS

1210 ART-naïve children meeting WHO criteria for ART in Uganda/Zimbabwe were enrolled into the ARROW trial and started combination ART. 199 children in Uganda (54% girls, aged 5 months-18 years) underwent CD4 immunophenotyping at ART initiation using a combination of CD4, CD45RA and CD31.

RESULTS

As expected, CD4 and CD4-for-age a score varied significantly with age at ART initiation (see tables), as did the percentage of CD4 cells in the ‘Recent Thymic Emigrant’ (RTE, CD4+/CD31+), ‘Central Naive’ (CN, CD4+/CD31-) and memory (M, CD4+/CD31-) compartments (p<0.001, p<0.01, p<0.001 respectively). However, multivariable modelling showed this relationship with age was predominantly the result of the lower CD4-for-age in older children (after adjusting for CD4-for-age, p=0.13, 0.40, 0.70 respectively). Every 1 unit lower CD4-for-age was associated with 4.4% smaller RTE, 2.15 larger CN and 3.65 greater M subpopulations at ART initiation (p<0.001). There was no impact of sex on the CD4 subpopulations (p>0.5), but there was a trend towards children with lower weight-for-age having greater CN subpopulations (0.75 greater for every 1 unit lower weight-for-age, adjusted p=0.12).

However, multivariable modelling showed this relationship with age was predominantly the result of the lower CD4-for-age in older children.

REFERENCES


SUMMARY

In all agegroups, the cell proportions in these 3 CD4 compartments were lower than have been reported in healthy Caucasian children.

- this was largely due to a reduction in the RTE and increase in CN+ memory cells (data not shown)

Total CD4 count seems to be an important driver or consequence of lower RTE and higher CN+ memory naive/memory populations, with a far stronger association than age alone.

Children surviving without ART, there may be a shift to maintaining the CD4 cell pool through the relative expansion of central naive and memory pools at the expense of RTE at some child-specific timepoint. This may indicate that with time, the capacity of the thymus to keep pace with CD4 loss is diminished.

- the long-term consequences for subsequent ART response are unclear but will be investigated in this ongoing study.