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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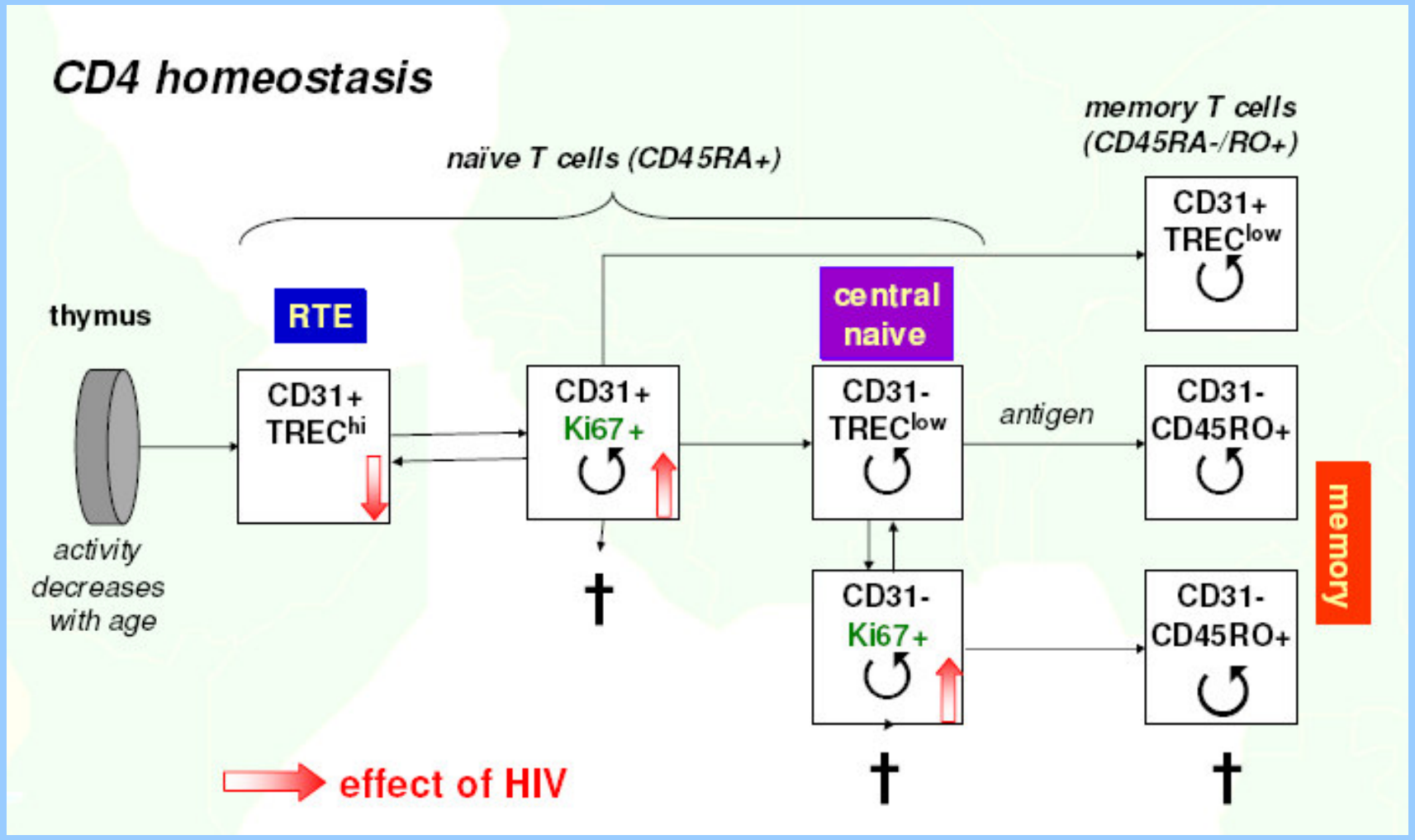
Background

- 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

Murray JM et al, 2003

- 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



Study objective

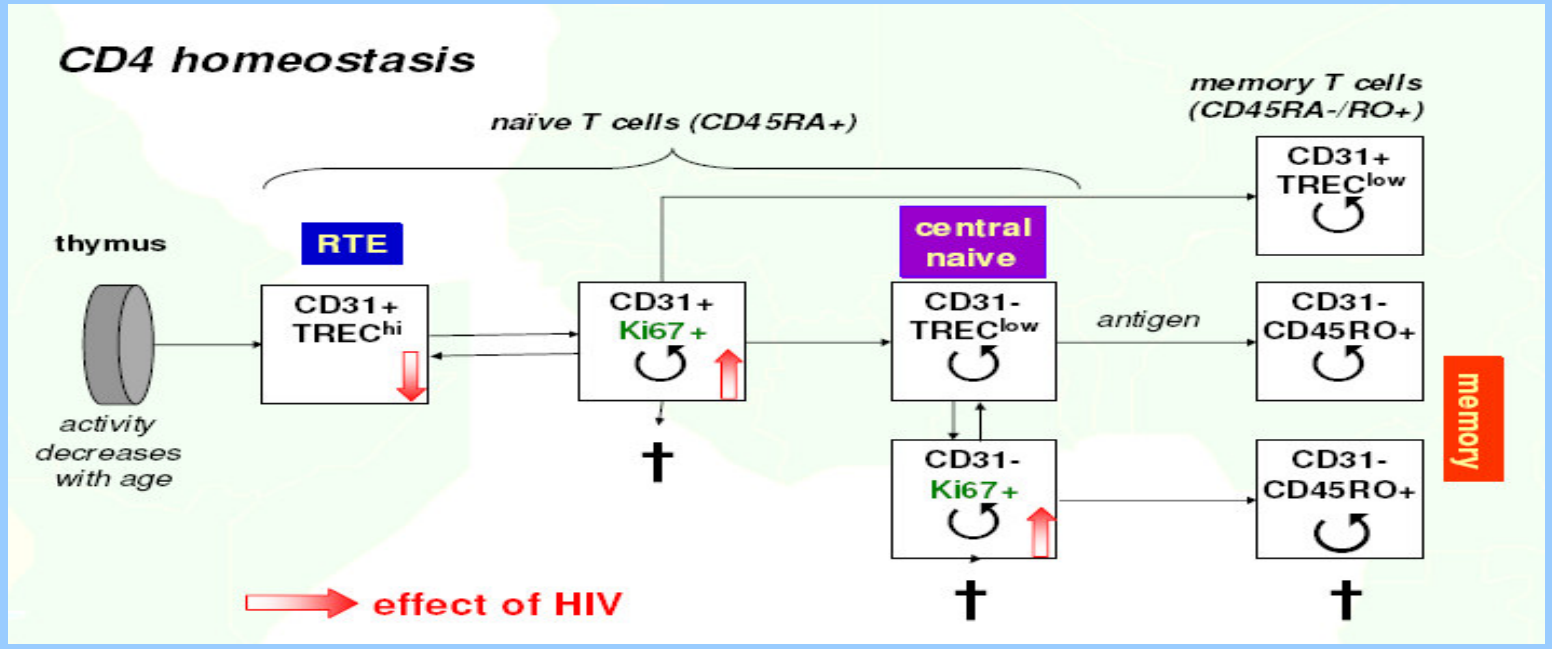
- To determine the CD4 T-cell populations in HIV infected Ugandan children initiating antiretroviral therapy

Methods

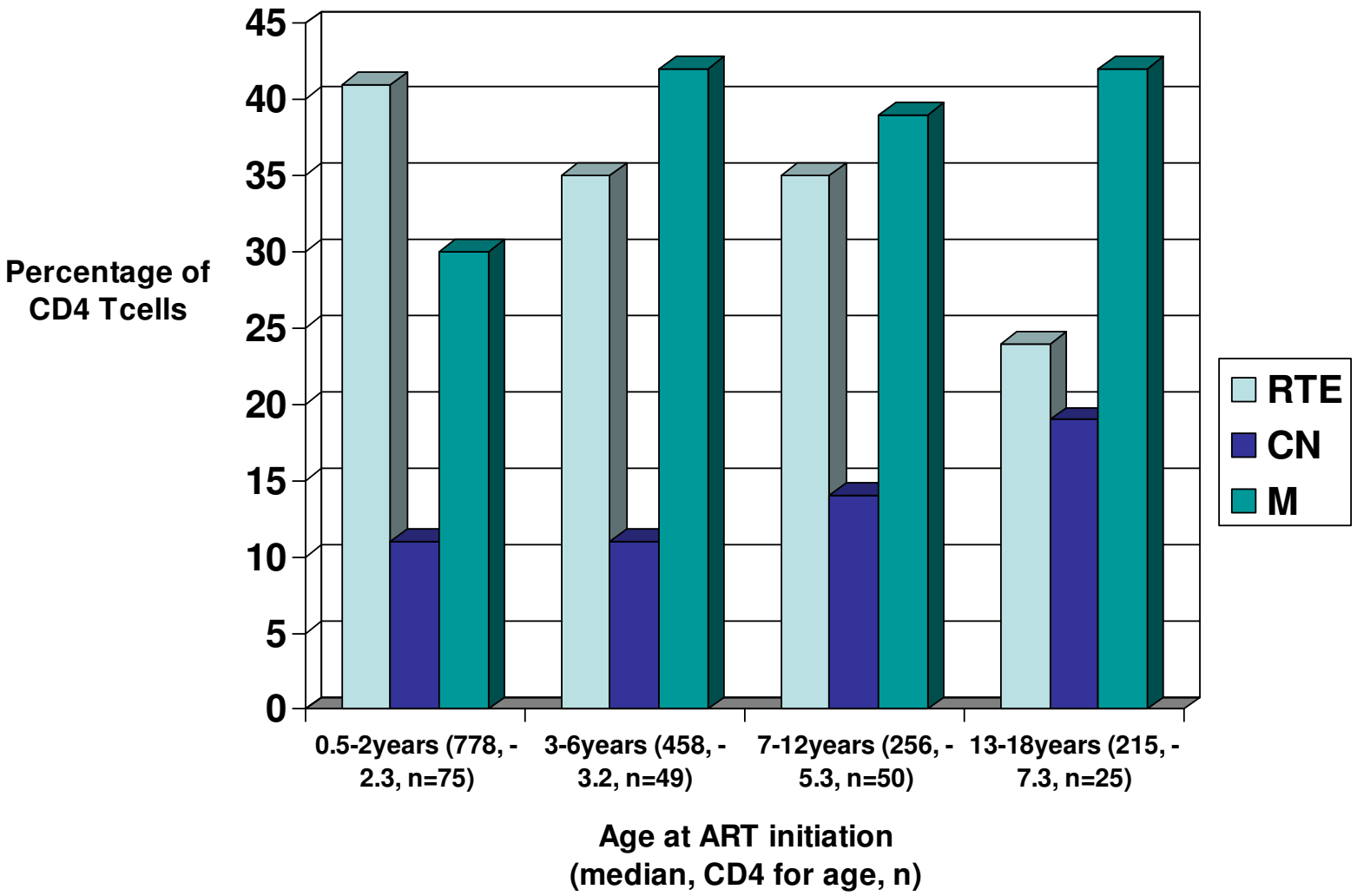
- 1207 ART-naive children meeting WHO criteria for ART in Uganda/Zimbabwe were enrolled into the ARROW clinical trial and started on ART
- 199 children in Uganda underwent CD4 immunophenotyping at ART initiation using a combination of CD4, CD45RA and CD31 antibodies
- Study participants were:
  - 54% girls
  - Aged 5months to 18yrs

Methods 2

- 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



Results: Pre ART CD4 depletion Versus Age as a predictor of CD4 sub populations

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

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

Acknowledgments

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