The size of HIV reservoir is associated with telomere shortening and immunosenescence in early ART-treated HIV-infected children

BACKGROUND

- Despite suppressive antiretroviral treatment, HIV reservoir persists in the host cells.
- Identifying factors which contribute to the size of HIV reservoir is critical for studies aimed at inducing ART-free HIV remission.
- HIV infection is linked to premature senescence, with increased risk of aging-associated illnesses.
- Early ART has been associated with a reduced HIV reservoir in HIV-perinatally infected children, but its impact on the senescence process is an open question.

AIM

To define the relationship between the HIV reservoir and the biological and immunosenescence in perinatally HIV-infected children who started early ART.
STUDY POPULATION

CARMA STUDY

Child and Adolescent Reservoir Measurements on early suppressive ART
Multicenter cross-sectional study of HIV-perinatally infected children and adolescents

Aim: Identify virological and immunological factors associated with limited HIV proviral reservoir size

37 HIV-perinatally infected children enrolled in 7 European centers (median age 12 [7;15] years old)

Criteria of inclusion:
- ART initiation before 24 months of life
- Viral suppression in the first 12 months after ART initiation
- Viral suppression for ≥ 5 years
- Viral blips 50 to <400 c/mL returning to <50c/ml on repeat sampling and single annual viral load between 400 and 1000 c/mL returning to <50c/ml on repeat sampling were permitted
METHODS

HIV-DNA RESERVOIR

CD4 cells
*Droplet Digital PCR*

IMMUNOPHENOTYPE

CD4 and CD8 cells
*Flow cytometry*
- Immune senescence
- Immune activation

BIOLOGICAL AGING

CD4 and CD8 cells
*Real Time PCR*
- Telomere length
- Thymic output
RESULT -- HIV-DNA CORRELATES

HIV-DNA in CD4 cells correlates with:

- ↑ HIV-DNA in PBMC
- ↑ Activation of CD8 cells
- ↑ Activation of CD4 cells
- ↓ Telomere length in CD4 cells

Age at ART initiation correlates with:

- ↓ % CD4 cells at baseline
- ↑ % CD8 cells at baseline
- ↑ HIV-DNA in PBMC
- ↑ HIV-DNA in CD4 cells

Univariate analysis: Spearman correlations
RESULTS – HIV-DNA RESERVOIR ASSOCIATIONS

The association of HIV reservoir in CD4 cells with studied parameters has been evaluated by multivariable Poisson regression (adjusted for baseline %CD4, plasmaviremia, age at reservoir measurement and age at ART initiation as interaction term).
RESULTS – HIV-DNA RESERVOIR ASSOCIATIONS

HIV-DNA in CD4 cells

↑ senescent CD4 cells
↓ telomere length in CD4 cells

↑ activated CD8 cells
↑ thymic output in CD8 cells

These associations decrease by 1%, 10%, 6% and 6% for each month ART is delayed
RESULTS – EARLY TREATMENT

Early treated children (ART initiation <6 months of age) display significantly lower HIV-DNA and CD4 senescent cells than late treated ones.

- **HIV DNA on CD4**: Early treated children show a significantly lower HIV-DNA concentration compared to late treated children, with a p-value of 0.003.

- **% CD4 immune senescent cells**: Similarly, early treated children exhibit a lower percentage of CD4 immune senescent cells, with a p-value of 0.045.
CONCLUSIONS

This is the first demonstration that HIV reservoir is directly associated with telomere shortening and immunosenescence in CD4 cells.

HIV reservoir is directly associated with CD8 activation and thymic output

The earlier ART is initiated, the stronger are these associations

Early ART initiation restricts the viral reservoir and prevents premature aging in perinatally HIV-infected children
Thanks for your attention