Baseline Viral Load Impacts Premature Aging in Infants With Perinatally Acquired HIV in EARTH Cohort

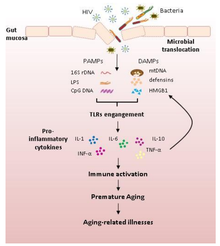
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BACKGROUND

In the natural course of HIV infection, the virus primarily infects CD4 cells, leading to their severe depletion. This depletion compromises gut mucosa integrity, increasing intestinal permeability and resulting in the translocation of microbial products, such as pathogen-associated molecular patterns (PAMPs), and damage-associated molecular patterns (DAMPs). This translocation triggers the production of proinflammatory cytokines, which promote immune activation, a hallmark of HIV infection that may contribute to premature aging.

Aim: This study aims to evaluate the impact of baseline viral load on the premature aging profile in infants ART-naïve with perinatally acquired HIV (PHIV), enrolled in the Early Anti-Retroviral Treatment in HIV children (EARTH) cohort.



STUDY POPULATION

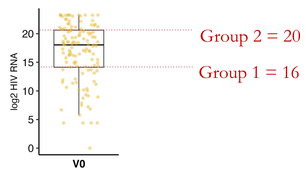
Thirty-six PHIV infants, ART-naïve at enrolment, with a median age of 1.6 (1.3-2.5) years, were studied. Infants were stratified in two groups according to plasmaviremia: Group 1 with low viremia (<25 percentile Log2 HIV-RNA) and Group 2 with high viremia (>75 percentile of Log 2 HIV-RNA)

EARTH cohort
N= 215 enrolled kids



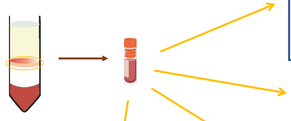
Baseline Viremia substudy
N= 36 enrolled PHIV infants, ART-naive at enrolment
Median age 1.6 (1.3-2.5) years

Study design
Group 1 (<25 percentile of Log2 HIV RNA)
Group 2 (>75 percentile of Log2 HIV RNA)



METHODS

Immune activated, senescent and exhausted CD4 and CD8 T cells were studied by flow cytometry. Relative telomere length, T-cell receptor excision circles (TREC), and HIV-DNA in peripheral blood mononuclear cells (PBMC) were measured by multiplex real-time PCR, real-time PCR and ddPCR, respectively.



Relative telomere length (RTL)
by Multiplex Real Time PCR



T-cell rearrangment excision circles (TREC)
by Real Time PCR

HIV reservoir
HIV-DNA by digital droplet PCR



in the QX200™ Droplet Generator (Bio-Rad).
Levels of HIV-DNA were normalized against TERT and expressed as copies/10^6 PBMC

Immunophenotype by Fortessa X20

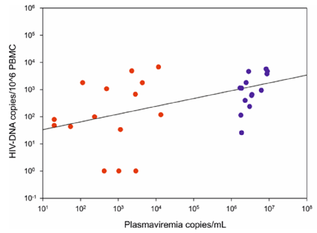
CD3+ CD4 + and CD8+ T cells
- CD45±CD27±CCR7± → naive/memory
- CD38+ HLA-DR + → activation
- CD28-CD57+ → senescence
- PD-1+ and TIGIT+ → exhaustion

Statistical analyses were performed using SigmaPlot software.

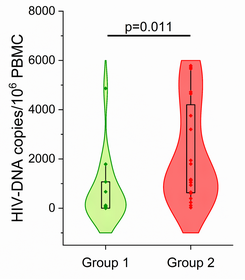
From early in life, higher levels of plasmaviremia may increase the HIV reservoir, contributing to initiate the premature aging process.
Early ART is essential to limit aging-related processes and associated comorbidities.

RESULTS

1. The HIV reservoir size is correlated with plasmaviremia in PHIV infants.

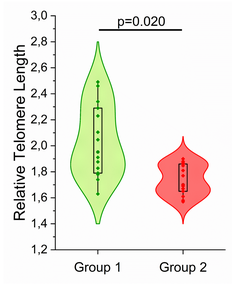


Overall, plasmaviremia significantly correlated with HIV-DNA in PBMC (r=0.525, p=0.003).

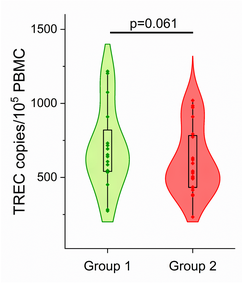


Baseline levels of HIV-DNA in PBMC were significantly higher in Group 2 than in Group 1 (1159 [617-4426] vs 89 [9-1607] copies/106 PBMC, p=0.011).

2. High plasmaviremia impacts relative telomere lengths and thymic output in PHIV infants.



Relative telomere lengths were significantly shorter in Group 2 than in Group 1 (1.82 [1.68-1.90] vs 1.93 [1.78-2.26], p=0.020).



TREC levels were lower in Group 2 than in Group 1 (518 [426-666] vs 647 [538-865], p=0.061).

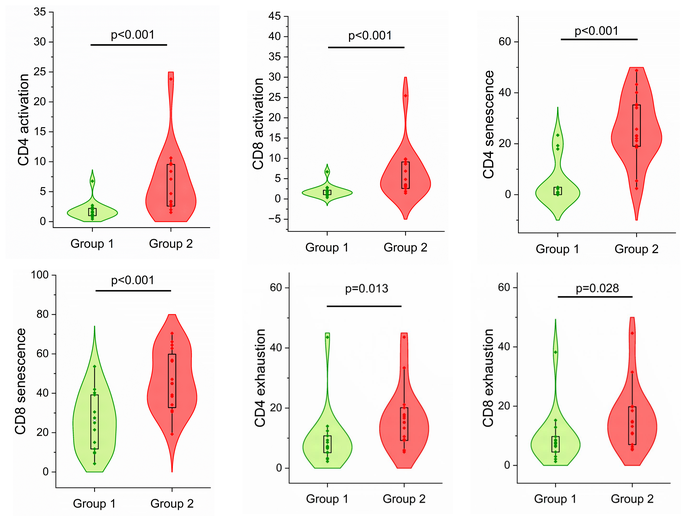
RESULTS

3. High plasmaviremia impacts immune activation, senescence and exhaustion in PHIV infants.

Group 2 had higher percentages of activated, senescent and exhausted CD4 and CD8 T cells than Group 1 (Table and Figure).

Table. Comparison of immune activated, senescent and exhausted CD4 and CD8 cells between PHIV infants with low (Group 1) and high (Group 2) plasmaviremia.

Parameters Median [IQR]	Group 1 (n=16)	Group 2 (n=20)	p-value
CD4 activation (%CD4+CD38+HLA-DR+)	1.56 [1.0-2.21]	3.36 [2.60-9.55]	**<0.001**
CD8 activation (%CD8+CD38+HLA-DR+)	1.75 [1.06-2.15]	3.51 [2.59-9.13]	**<0.001**
CD4 senescence (%CD4+EMRA+CD28-CD57+)	2.33 [0.53-18.60]	23.13 [18.79-35.33]	**<0.001**
CD8 senescence (%CD8+EMRA+CD28-CD57+)	44.97 [31.96-61.32]	26.22 [11.29-39.45]	**<0.001**
CD4 exhaustion (%CD4+PD-1+)	7.04 [5.17-10.77]	15.25 [9.23-20.11]	**0.013**
CD8exhaustion (%CD8+PD-1+)	7.54 [4.52-9.75]	14.66 [7.04-19.80]	**0.028**



CONCLUSIONS

Higher levels of viral load are strongly correlated with HIV-DNA and are associated with increased immune activation and senescence, suggesting that baseline levels of plasmaviremia may accelerate the aging process in PHIV infants from a very early age. These finding support the early initiation of ART to reduce viremia and potentially mitigate premature aging process.

ACKNOWLEDGMENT

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References

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2. Dalzini A et al. Size of HIV-1 reservoir is associated with telomere shortening and immunosenescence in early-treated European children with perinatally acquired HIV-1. J Int AIDS Soc. 2021; 24(11): e25847.
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