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MULTIFACETED PREMATURE AGING IN ADOLESCENT/YOUNG ADULT WITH PERINATAL ACQUIRED HIV

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BACKGROUND

HIV infection has become a chronic condition due to advances in antiretroviral treatment (ART). However, people living with HIV appear to have higher rates of aging-associated illnesses (frailty, metabolic, cardiovascular, bone and neurodegenerative disorders, and cancer), compared to general population.

ART is not able to eradicate the virus which, likely through the damage of gut mucosa and the release of PAMPs and DAMPs into circulation, induces an inflammatory/immune activated status, that causes biological and immunological senescence, and increases vulnerability for age-linked comorbidities.

Studies on children (0-5 years) with perinatal acquired HIV infection showed that these patients exhibit premature aging and accelerated immune senescence compared to healthy children [1]. Moreover, the timing of ART initiation appears important for consequences on the immune and biological aging profile of children with perinatal acquired HIV [2,3].

Few data are available on adolescent/young adult with perinatal acquired HIV; thus, the assessment of aging biomarkers and their relation with the HIV reservoir becomes a priority to characterize and monitor adolescent/young adult with perinatal acquired HIV (PHIV).

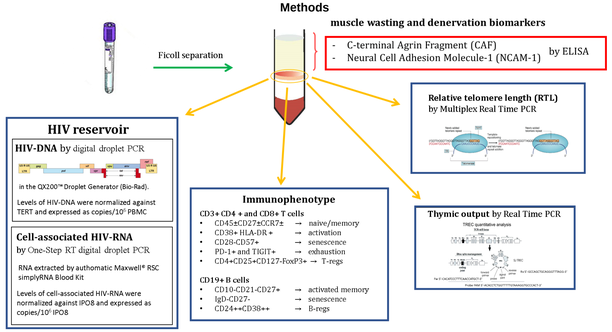
PATIENTS and METHODS

Forty-one PHIV adolescents/young adults (PHIVYA) (age 16 - 30 years) under antiretroviral therapy and with undetectable viremia for at least 10 years, and 23 aged-matched healthy controls were enrolled in this study. The immune aging profile (activated, senescent, exhausted and regulatory T and B cells) was studied by flow cytometry [4]. HIV-DNA and cell-associated HIV-RNA in PBMC were measured by ddPCR and One-Step ddPCR, respectively [3]. Levels of T-cell receptor excision circle (TREC) and relative telomere length (RTL) were quantified by multiplex real-time PCR [3]. Circulating muscle wasting and denervation biomarkers NCAM1 (neural cell adhesion molecule 1) and CAF (C-terminal Agrin Fragment), associated with aging and sarcopenia, were assessed by ELISA. Statistical analyses were performed using RStudio software and data were adjusted by age.

Characteristics of studied cohorts

Characteristics Median [IQR]	PHIVYA (n. 41)	Healthy controls (n. 23)
Age (years)	23 [19-26]	19 [18-27]
Age at ART initiation (years)	3.5 [0.8-6.3]	-
Time on ART (years)	20.8 [16.9-22.7]	-
Comorbidities	18/41	-

Methods



HIV reservoir correlates with **multifaceted profile of premature aging** (immune and cellular senescence and functional biomarkers) in adolescent/young adult with perinatal acquired HIV.

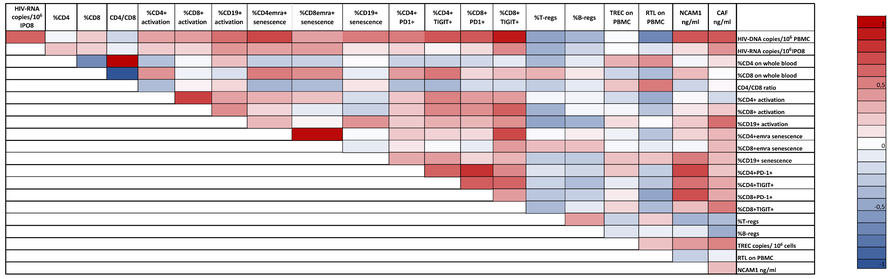
RESULTS

1. Comparison of immune profile between PHIV adolescent/young adult and healthy controls.

Compared to healthy controls, PHIVYA have higher levels of immune aging profile (CD4/CD8 ratio, activation, senescence, exhaustion and regulatory T and B cells), cellular aging markers (TREC and RTL), and functional muscle wasting and denervation biomarkers (NCAM1 and CAF).

Characteristics Median [IQR]	PHIVYA (N=41)	HEALTHY CONTROLS (N=23)	P-value adjusted by age
%CD4	37.0 [29.8-39.7]	36.6 [34.7-40.2]	0.481
%CD8	30.3 [24.7-36.8]	21.1 [18.0-25.3]	**0.000**
CD4/CD8	1.2 [0.9-1.7]	1.8 [1.4-2.2]	**0.000**
CD4 activation (%CD3+CD4+CD38+HLA-DR+)	1.2 [1.0-2.1]	0.5 [0.4-0.6]	**0.000**
CD8 activation (%CD3+CD8+CD38+HLA-DR+)	1.2 [0.7-1.8]	0.4 [0.3-0.6]	**0.000**
CD19 activation (%CD19+CD10-CD21lowCD27+)	7.6 [6.0-10.4]	3.4 [2.6-5.4]	**0.000**
CD4 emra senescence (%CD4+CD45RA+CD27-CD28-CD57+)	8.1 [5.3-18.2]	3.7 [2.2-4.9]	**0.000**
CD8 emra senescence (%CD4+CD45RA+CD27-CD28-CD57+)	6.9 [4.0-12.5]	3.4 [2.4-6.2]	**0.003**
CD19 senescence (%CD19+CD27-IgD-)	10.5 [8.4-14.6]	9.2 [4.8-11.8]	**0.051**
%CD4+PD-1+	11.4 [7.8-13.6]	6.6 [5.6-9.5]	**0.000**
%CD4+TIGIT+	3.7 [2.0-6.9]	2.2 [1.0-3.9]	**0.005**
%CD8+PD-1+	11.9 [8.2-13.8]	6.8 [4.5-7.4]	**0.000**
%CD8+TIGIT+	15.6 [11.9-20.5]	5.1 [3.9-7.6]	**0.000**
T-regs (%CD4+CD25+CD127-FoxP3+)	12.2 [9.5-19.8]	4.2 [2.2-6.1]	**0.000**
B-regs (%CD19+CD24++CD38++)	3.3 [2.5-4.7]	1.9 [0.9-2.9]	**0.001**
TREC copies/10⁵ PBMC	425 [289-809]	750 [568-1506]	**0.025**
RTL on PBMC	1.20 [1.10-1.30]	1.30 [1.20-1.40]	**0.013**
NCAM1 ng/mL	365 [285-575]	283 [241-374]	**0.007**
CAF pg/mL	2283 [1990-2866]	2120 [1663-2357]	**0.047**

2. Spearman correlation plot of HIV reservoir with immune, biological and functional markers of aging.



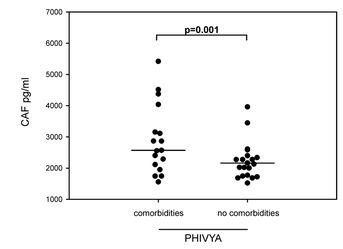
Color scale represents Spearman's correlation coefficient. Red and blue correspond to positive and negative coefficient, respectively.

HIV reservoir positively correlates with immune senescent, activated and exhausted T and B cells, inversely correlates with regulatory T and B cells, TREC and RTL, and positively correlates with NCAM1 and CAF.

3.Comparison of levels of functional muscle wasting and denervation markers of aging between PHIV adolescent/young adult with or without comorbidities.

PHIVYA with comorbidities have significantly higher circulating levels of CAF than PHIVYA without.

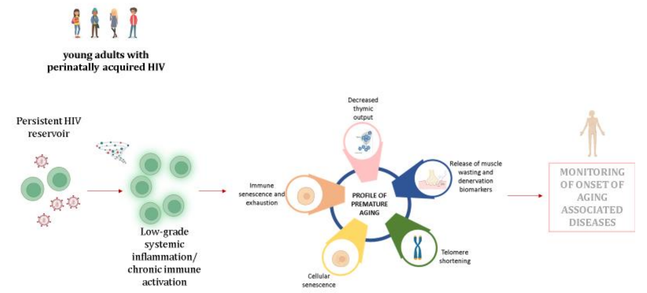
No difference was found in immunological and cellular biomarkers of aging.



CONCLUSIONS

Our findings provide evidence that PHIV adolescent/young adult experiences premature aging, and reinforce the relationship between the HIV reservoir and immune senescence.

In addition, our findings demonstrate for the first time that the HIV reservoir positively correlates with circulating denervation biomarkers, thus adding new tools for minimally invasive monitoring of biological aging in this population over time.



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