T CELL EXPRESSING MULTIPLE INHIBITORY RECEPTORS PERSIST ON LONG-TERM ART

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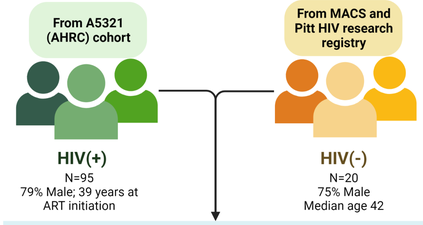
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BACKGROUND

- Persistent antigen stimulation during chronic viral infection accompanied by the increased expression of inhibitory receptors (IR) or checkpoint inhibitors such as PD-1 and CTLA-4. Expression of these inhibitory receptors is associated with loss of T cell effector function
- In people living with HIV (PWH), expression of these IRs is still observed despite suppression of plasma viremia on ART.
- We obtained serial samples from participants on ACTG A5321 to assess longitudinal changes in frequencies of T cells expressing multiple IRs and compare these with age-matched individuals without HIV.

METHODS



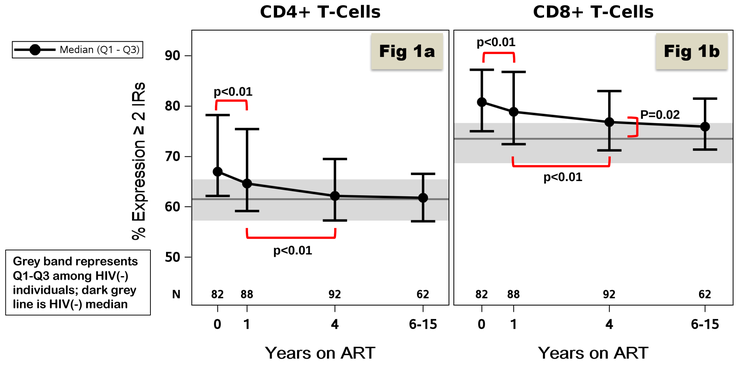
- Cryopreserved PBMC from the HIV(+) participants obtained pre-ART and at year 1, 4, and 6-15 on ART and from HIV(-) individuals obtained at a single timepoint were used for these flow assays.
- Frequencies of T cells expressing the different IR combinations were evaluated using Boolean analysis in FlowJo. Frequencies were then compared between the A5321 participants at year 4 on ART and the 20 HIV(-) individuals.

STUDY POPULATION DEMOGRAPHICS (N=95)

Age at initiation of ART, median (Q1, Q3), years	39 (31, 47)
Age at A5321 entry, median (Q1, Q3) years	48 (38, 53)
Sex at birth – female	20 (21%)
Race/Ethnicity:	
White Non-Hispanic	49 (52%)
Black Non-Hispanic	18 (19%)
Hispanic (Regardless of Race)	26 (27%)
American Indian, Alaskan Native	2 (2%)
Pre-ART plasma HIV-1 RNA, median (Q1-Q3), log_{10} copies/mL	4.6 (4.3-5.0)
A5321 entry plasma HIV-1 RNA, copies/mL	<40 (99%)
Pre-ART CD4+ T-cell count, median (Q1-Q3), cells/mm^3	290 (159, 384)
A5321 entry CD4+ T-cell count, median (Q1-Q3), cells/mm^3	665 (505, 839)
Years on therapy at A5321 entry, median (Q1-Q3)	6.8 (4.4, 7.6)

Despite sustained suppression of HIV-1 viremia on ART, CD8+ T cells continue to express multiple inhibitory receptors at frequencies higher than age-matched individuals without HIV. These frequencies are strongly correlated with frequencies prior to ART initiation.

MULTIPLE IR EXPRESSION ON T CELLS



- Frequencies of CD4+ (Figure 1a) and CD8+ (Figure 1b) T cells expressing ≥2 IR decreased from pre-ART to year 1 on ART and from year 1 to year 4 on ART (p<0.01)
- At year 4 on ART, frequencies of CD4+ T cells expressing 2 or more IR were similar between ART-suppressed PWH and HIV(-) individuals (Fig 1a).
- Meanwhile, frequencies of CD8+ T cells expressing 2 or more IR were higher in PWH (median 76.9% vs 73.5%; Fig 1b).

CORRELATION BETWEEN PRE- AND ON-ART FREQUENCIES

Frequencies of T cells that express multiple IR prior to ART initiation (pre-ART) strongly correlated with frequencies on ART. For example, the frequencies CD4+ T cells expressing 2 IR (CTLA4 and PDL1; Figure 2) and CD8+ T cells expressing 3 IR (CTLA4, PD1, and TIM3; Figure 3) pre-ART continue to be strongly correlated with frequencies at 4, and 6-15 years on ART (r=0.65 to 0.76; p<0.001).

Fig 2 %CTLA4+ and PDL1+ CD4+ Cells

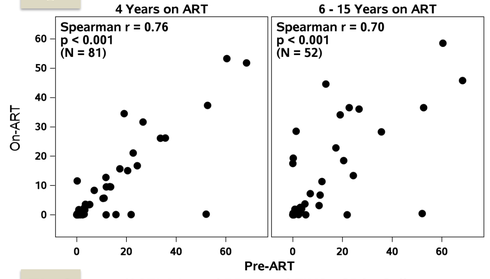
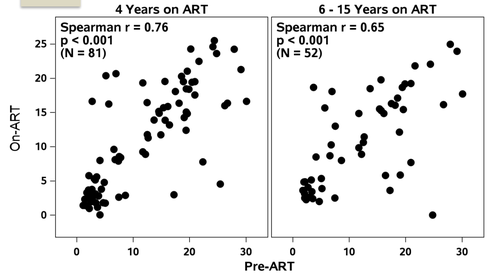


Fig 3 %CTLA4+ and PD1+ and TIM3+ CD8+ Cells



CONCLUSIONS & IMPLICATIONS

- T cells among PWH who are virally suppressed on ART for several years continue to express multiple inhibitory receptors.
- Frequencies of CD8+ T cells with multiple IR are higher compared to age-matched HIV(-) individuals
- Frequencies prior to ART initiation correlate with those on ART suggesting an immune dysregulation legacy effect.
- Safe and effective strategies aimed at reversing T cell immune exhaustion in HIV should consider continued expression of multiple inhibitory receptors despite years of antiretroviral therapy.

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