HIV-specific T cell dynamics in Acute-Treated, Chronic-Treated, and Elite Controller People With HIV

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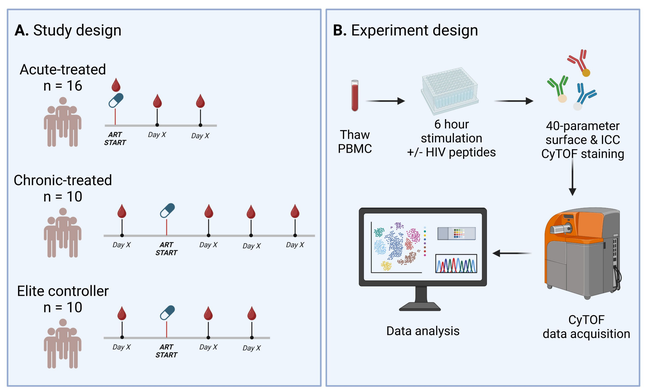
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BACKGROUND

Early initiation of antiretroviral therapy (ART) can preserve immune function and is associated with increased incidence of post-treatment control of HIV, yet differences in HIV-specific immune responses between people with HIV (PWH) who initiated ART during acute vs. chronic infection are poorly defined. **The extent to which immune responses in early- and late-treated PWH differ from those of elite controllers (ECs)–who exhibit ART-free control of HIV–has also not been fully evaluated.** We used CyTOF to compare the frequencies, phenotypes, and effector functions of HIV-specific CD8+ T cells in blood specimens from PWH who began ART during acute or chronic HIV and from ECs.

METHODS

PBMC collected prior to ART and up to 4 timepoints after ART initiation were obtained from the UCSF SCOPE cohort (n = 16 acute, n = 10 chronic, n = 10 ECs). Cells were analyzed using a 40-parameter CyTOF panel following a 6-hour stimulation with peptides spanning the HIV proteins Gag, Pol, Env, Tat, and Nef. HIV-specific T cells were assessed using a combination of 12 effector cytokines/chemokines and cytolytic/degranulation markers.



CyTOF panel for deep phenotyping and functional characterization of T cells in viremic and ART-suppressed PWH

Cell Type Identifier	Differentiation State	Activation State	Homing/Cell Adhesion	Effector Functions
CD3	CD27	CD25	CCR5	IFN-γ
CD4	CD45RO	CD28	CCR6	IL-2
CD8	CD45RA	CD38	CCR7	IL-4
CD19	CD57	CD69	CD29	IL-6
	CD95/FAS	CTLA-4	CXCR4	IL-10
	CD127	HLA-DR	CXCR5	IL-17
	Ki67	ICOS		TNF-α
		Ox40		MIP-1β
		PD-1		CXCL13
		TIGIT		Perforin
				Granzyme B
				CD107a/LAMP1

HIV-specific CD8+ T cells from elite controllers have distinguishing phenotypic and functional characteristics that may explain their ability to mediate ART-free HIV control.

RESULTS

Figure 1. Elite controllers (ECs) exhibit significantly higher frequencies of total and effector memory HIV-specific CD8+ T cells compared to acute and chronic-treated groups before ART initiation.

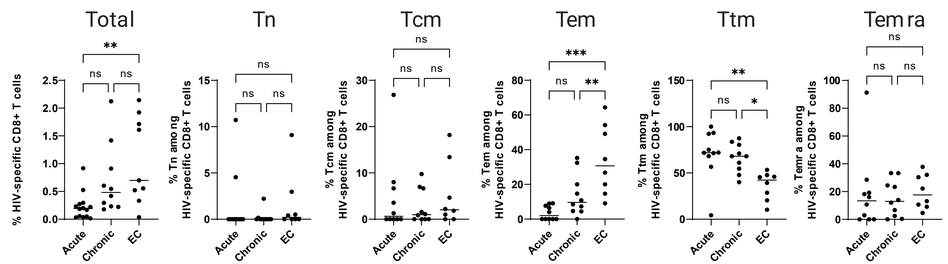


Figure 2. Before ART, HIV-specific CD8+ T cells from ECs differentially express markers of differentiation (CD27) and activation states (CD38, CD69, CTLA4) as compared to the other groups.

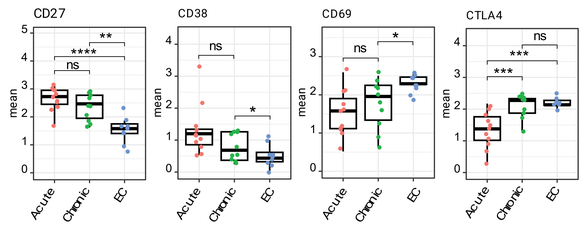


Figure 3. Expression of the follicle-homing receptor, CXCR5, is uniquely elevated on HIV-specific CD8+ T cells in ECs compared to acute and chronic groups before ART.

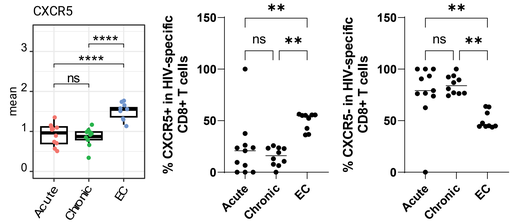


Figure 4. CXCR5-expressing HIV-specific CD8+ T cells in ECs before ART exhibit high levels of CD69 and low levels of CD38, suggesting a T resident memory rather than an activated state.

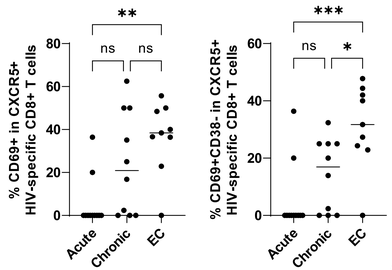
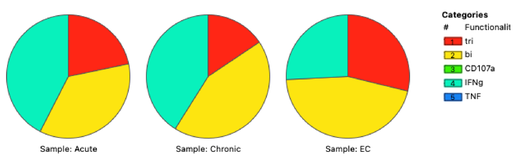


Figure 5. CXCR5-expressing HIV-specific CD8+ T cells tend to be more polyfunctional in ECs compared to the other groups before ART.



RESULTS

Figure 6. Frequencies of total HIV-specific CD8+ T cells significantly declined after ART in ECs but not in other groups.

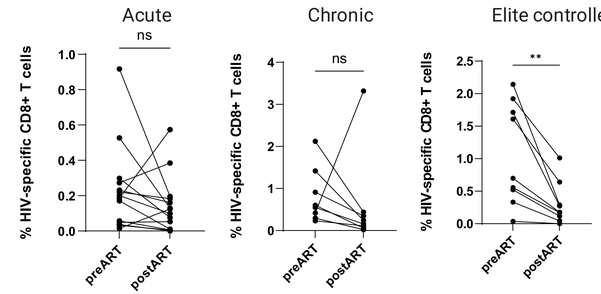
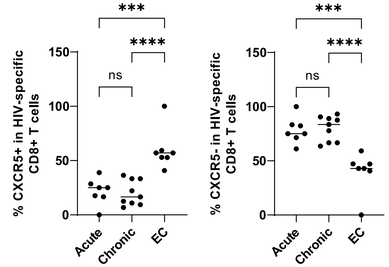


Figure 7. Frequencies of CXCR5-expressing HIV-specific CD8+ T cells remained significantly elevated in ECs even after ART initiation.



CONCLUSIONS

Our data demonstrate that ECs have higher frequencies of HIV-specific CD8+ T cells before ART compared to acute and chronic-treated PWH. These HIV-specific cells, like those from the chronic-treated group, expressed activation/exhaustion marker CTLA4, possibly due to chronic antigen stimulation. However, HIV-specific CD8+ T cells from ECs uniquely express high levels of CXCR5, which may help direct these effector cells to lymphoid follicles, a primary site of HIV persistence. CXCR5-expressing HIV-specific CD8+ T cells exhibited a tissue-resident phenotype, lower signs of chronic activation, and tended to be more polyfunctional than their CXCR5+ counterparts in the other groups. After ART initiation, frequencies of HIV-specific CD8+ T cells significantly declined in ECs; however; frequencies of CXCR5+ cells remained higher in ECs as compared to the acute- and chronic-treated groups. Together, our findings suggest that HIV-specific CD8+ T cells in ECs have distinguishing phenotypic and functional features that may explain their ability to mediate ART-free HIV control.

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