Safety and Antiviral Response Monitoring Post Infusion of Autologous HIV-Specific T Cells Targeting Conserved Epitopes in Individuals with HIV on Antiretroviral Therapy: A Phase I Clinical Trial (NCT03485963)

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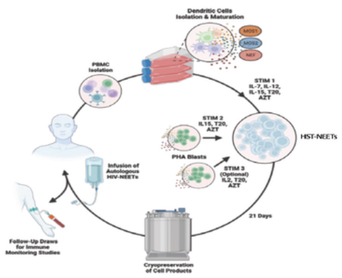
Introduction

The advent of antiretroviral therapy (ART) has improved clinical outcomes for people living with HIV (PLWH), however latent HIV reservoirs in CD4+ T cells is a limitation in HIV eradication. While T cell immune responses have shown to be critical in HIV control, viral immune escape mutations limit T cell mediated anti-HIV immunity. Thus, T cell therapy targeting non-escaped HIV epitopes is a promising treatment strategy for PLWH. In a phase I clinical trial, we evaluated the safety, immunologic and virologic responses of a novel HIV-1 multi-antigen specific T cell therapy (HST-NEET) targeting HIV Nef and conserved epitopes of Gag and Pol (Mos 1 and Mos2) in people with HIV suppressed on ART.

Hypothesis

We hypothesized that T cells targeting conserved HIV epitopes would expand and persist in HIV+ individuals following autologous T cell infusions and elicit antiviral effects.

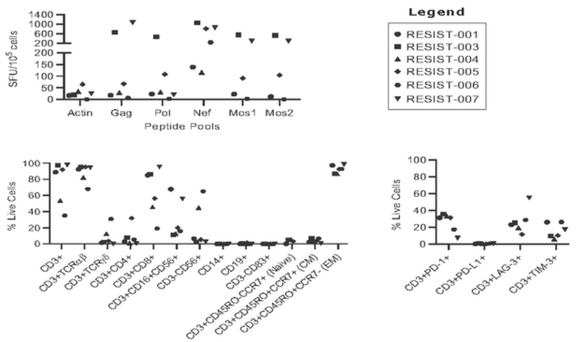
Methods



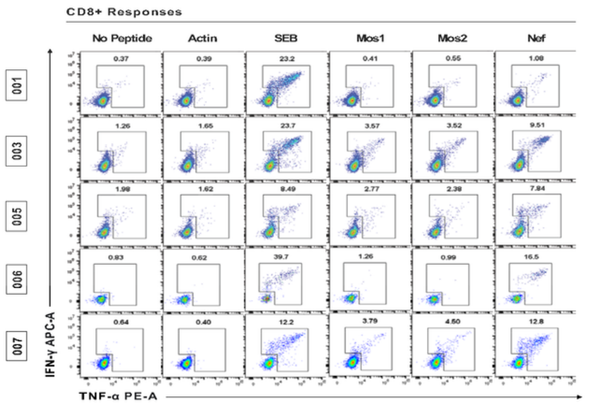
HST-NEETs manufacturing procedure. HST-NEETs infusion products were ex vivo expanded over the course of two to three stimulations with antigen-presenting cells pulsed with HIV antigens. Participants received two infusions ($2x10^7$ cells/m^2 BSA/dose) of HST-NEETs without prescribed lymphodepletion. Image created in BioRender.

Results

HST-NEET infusion products met clinical dose requirements with specificity for 1-3 viral antigens comprising predominantly $CD3^+CD8^+$ effector memory populations



HST-NEET infusion products elicited polyfunctional and polyclonal responses to HIV antigens



CD8-restricted HIV epitopes were identified in HST-NEET infusion products

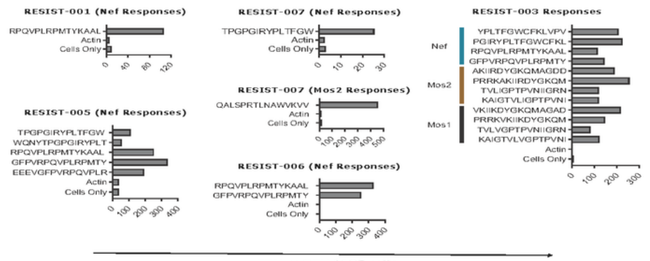
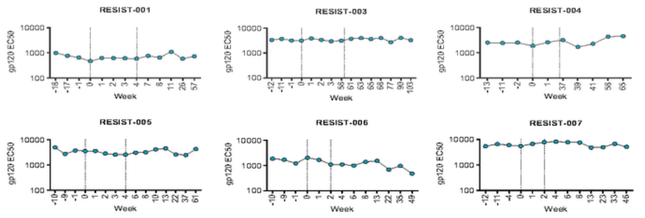


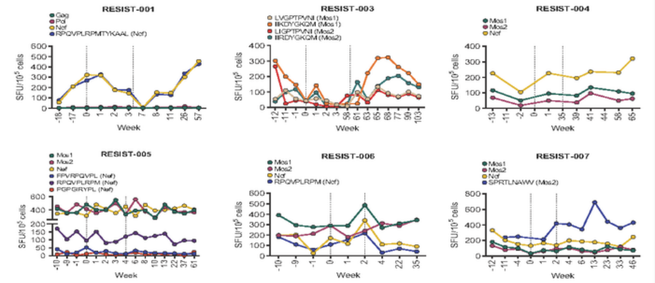
Table 2. $CD8^+$ Epitope Specificities in HST-NEET Infusion Products

Study ID	HLA Class I	Epitopes	HXB2 Location	Predicted HLA Restrictions
RESIST-001	A34, B45, B58, C06, C16	NEF-QVPLRPMTYK	71-85	A34
RESIST-003	A02, B42, B53, C04, C17	POL-LVGPTPVNI	132-140	A02, C17
		POL-IIKDYGKQM	982-990	B42
		POL-LIGPTPVNI	132-140	A02, C17
		POL-IIRDYGKQM	982-990	B42
		NEF-FPVRPQVPL	68-76	B42, B53, C04
		NEF-RPQVPLRPM	71-79	B42, C04
		NEF-RYPLTFGW	134-142	A02
		NEF-RYPLTFGWCF	135-143	A02
RESIST-004	A30, A34, B15, B42, C14, C17	Products Unavailable		
RESIST-005	A02, A03, B07, B44, C05, C07	NEF-FPVRPQVPL	68-76	B07
		NEF-RPQVPLRPM	71-79	B07
		NEF-PGPGIRYPL	129-137	B07
RESIST-006	A02, A29, B07, B44, C15, C05	NEF-RPQVPLRPM	71-79	B07
RESIST-007	A23, A68, B07, B53, C06, C07	GAG-SPRTLNAWV	148-156	B07, B53
		NEF-TPGPGIRYPL	128-141	B07

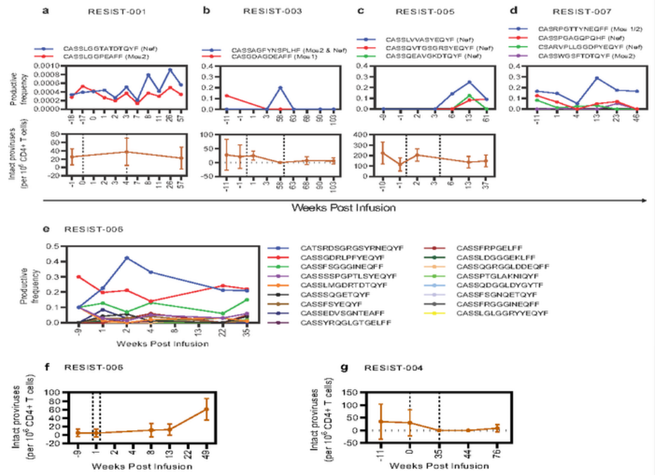
Env-specific antibody levels did not significantly change in patients post HST-NEET infusions



HIV-specific responses increased post-infusion in some participants



Expansion and persistence of HIV-reactive T cell clones associated with marked decrease in HIV reservoir size in some participants



Clinical Characteristics and Outcomes

Study ID	Age (Years)	Sex	Race/Ethnicity	HIV Subtype	CD4 at Study Entry	CD4 Nadir	Years on ART	Total Weeks in Study	Weeks Between Infusions	Severe Adverse Events	Best IPDA Responses (HIV provirus/10^6 CD4+ T cells)
RESIST-001	33	M	African American	B	696	303	7.8	57	4	No	Stable
RESIST-003	47	M	African American	B	676	2	Not Known	103	59	No	Decreased 21 → 0 (59w)
RESIST-004	33	M	African	C	367	250	2.3	76	35	No	Decreased 30 → 0 (35w)
RESIST-005	57	F	African American	Not Known	1537	152	Not Known	51	4	No	Stable
RESIST-006	48	M	Caucasian	B	746	563	9.6	49	2	No	Increased
RESIST-007	54	F	African	A	843	155	13.2	46	2	No	Pending

Conclusions

Autologous HST-NEETS were safe and well tolerated without severe infusion-related toxicities.

Epitope mapping of the products identified multiple CD8-restricted epitopes, including 3 repeated Nef epitopes associated with the HLA-B07 supertype.

Expansion and persistence of HIV-specific T cell populations post-infusion was observed even without prescribed lymphodepletion.

HST-NEETs infusions may be associated with durable decreases in the HIV reservoir as measured by IPDA.

Future Directions

Autologous transplantation followed by administration of HST-NEETs for treatment of HIV associated lymphoma, a phase II clinical trial (NCT04975698)

Evaluate safety of HST-NEETs therapy following allogeneic bone marrow transplantation (alloBMT), a phase I clinical trial (NCT04248192)

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