HIV-SPECIFIC T CELL FREQUENCIES AND FUNCTION AFTER ART DURING ACUTE OR EARLY HIV

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BACKGROUND

•Antiretroviral therapy (ART) started during acute or early HIV infection (AEHI) has multiple benefits, but its immunologic effects are not well defined.

•We hypothesized that early ART would limit antigen exposure and reduce T cell immune responses in a multinational, prospective, open-label study.

METHODS

•ACTG 5354 enrolled and rapidly initiated ART in adults with Fiebig stages I-V of AEHI at 30 sites in Americas, Africa, and Southeast Asia (Table 1). Fiebig stage at start of ART was assigned retrospectively by centralized testing. A secondary endpoint of A5354 was to assess if timing of ART during AEHI influenced HIV-specific T cells after 48 weeks of ART. Comparisons were between pre-specified study Groups: Group I (G1: Fiebig I/II [n=49]); Group 2 (G2: Fiebig III/IV [n=79]) and Group 3 (G3: Fiebig V [n=60]).

• PBMC were stimulated (6 h) with PTE peptide pools (NIH HIV Reagent Program) consisting of *env, gag, nef* or *pol* peptides. Some cells were incubated with SEB (positive control) or were incubated without stimulation (negative control). Brefeldin A and CD107a antibody (for staining) were added during the 6 h incubation.

• Cells were stained for expression of CD3, CD4 and CD8 and intracellular for expression of CD40L, Mip1b, IFN-g, TNF-a, CD107a and analyzed by flow cytometry excluding debris, doublets and dead.

Table 1. Participant baseline characteristics

	Group 1 (Fiebig I-II) (n=49)	Group 2 (Fiebig III-IV) (n=79)	Group 3 (Fiebig V) (n=60)
Age, median years (IQR)	26 (22-35)	30 (24-40)	26 (23-38)
Male	92%	85%	82%
Cisgender	96%	92%	100%
Race			
Black/African American	42%	49%	70%
White	31%	50%	28%
Asian	27%	1%	2%
Initial ART Regimen			
EVG/COBI/FTC/TAF	63%	82%	83%
DTG/3TC/TDF	37%	13%	13%
CD4, median cells/mm^3 (IQR)	348 (211-493)	383 (264-538)	490 (366-652)
HIV RNA, median $\log_{10}$ cp/mL (IQR)	6.4 (5.3-7.0)	6.5 (6.0-7.0)	5.4 (5.0-6.4)

ART initiation in the earliest Fiebig stages (I/II) may result in reduced frequencies, but not polyfunctionality, of HIV-specific T cells.

Fig. 1. Frequencies of T cells that expressed any one of the possible activation markers tended to be diminished in Fiebig I/II (Group 1) participants compared to other groups

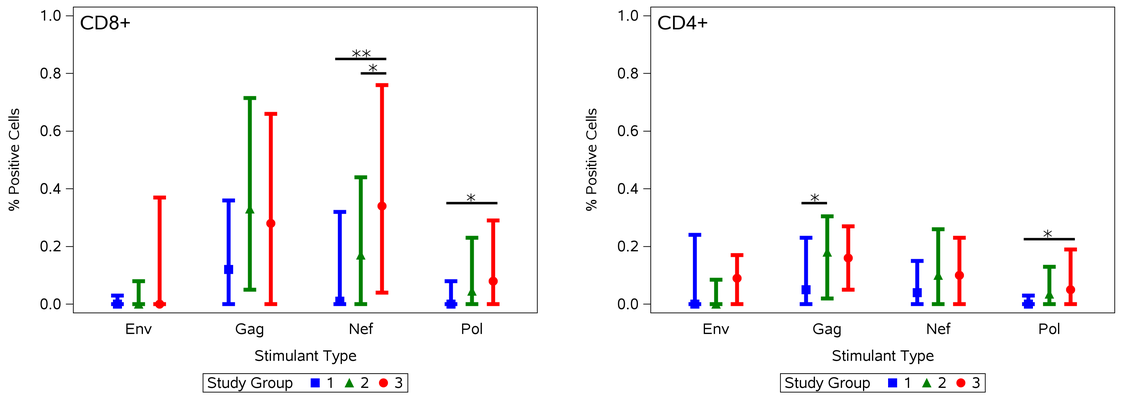

Fig. 1 . Percentage of CD8+ or CD4+ T cells responding to peptide pools plotted (y-axis) as median (symbol) and interquartile range (whiskers) . Significant differences between groups are indicated (*p<0.05; **p<0.01; Wilcoxon test).

RESULTS

• Frequencies of T cells that expressed any one of the possible activation markers tended to be diminished in Group 1 participants (Fiebig I/II) compared to other groups (Fig. 1).

• Polyfunction of CD8+ T cells was similar between groups. Polyfunctional responses to *gag* peptide pool is shown for G1, G2 and G3 participants (Fig. 2).

• Modest, but significant differences were noted comparing Group 1 vs Group 2 for percentages of CD4+ T cells expressing two functions after stimulated with *env* (median [IQR]: 11.25 [8.55-13.66] vs 9.13 [6.52-11.87], p=0.016; *nef* (10.38 [8.64-12.77] vs 8.87 [6.25-11.09], p=0.012 or *pol* (10.74 [8.39-13.82] vs. 8.62 [6.84-11.72], p=0.014).

• HIV cell-associated (CA) DNA (Pol or Gag) measured in PBMC at week 48 generally did not correlate with frequencies of HIV-reactive T cells (Table 2).

Fig. 2. Similar polyfunctional responses between Groups for gag-specific CD8+ T cells

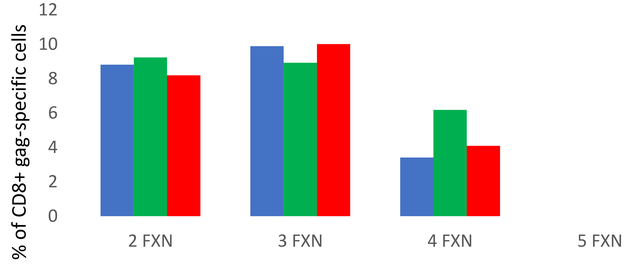

Fig. 2. Median percentages of gag-specific CD8+ T cells (y-axis) expressing 2 or more functions (FXN; x-axis) for Group 1(blue), Group 2 (green) and Group 3 (red) participants are shown.

Table 2. Spearman correlations between CA-DNA and HIV-specific T cell response (Total+)

		Week 48 CA-DNA			
		Pol		Gag	
Immunology Response	Controlling for study Group	Correlation	P-value	Correlation	P-value
CD4+/Total+ (%): Env		0.03	0.77	0.03	0.77
CD4+/Total+ (%): Env	Y	-0.00	0.97	-0.01	0.95
CD4+/Total+ (%): Gag		0.08	0.36	0.04	0.62
CD4+/Total+ (%): Gag	Y	0.04	0.67	-0.00	0.96
CD4+/Total+ (%): Nef		-0.01	0.91	0.06	0.44
CD4+/Total+ (%): Nef	Y	-0.05	0.56	0.03	0.74
CD4+/Total+ (%): Pol		0.10	0.23	0.05	0.53
CD4+/Total+ (%): Pol	Y	0.05	0.59	-0.01	0.90
CD8+/Total+ (%): Env		0.07	0.38	0.07	0.41
CD8+/Total+ (%): Env	Y	0.04	0.68	0.03	0.74
CD8+/Total+ (%): Gag		0.05	0.52	0.07	0.42
CD8+/Total+ (%): Gag	Y	0.03	0.72	0.04	0.61
CD8+/Total+ (%): Nef		0.07	0.40	0.12	0.14
CD8+/Total+ (%): Nef	Y	-0.01	0.91	0.04	0.60
CD8+/Total+ (%): Pol		0.19	0.025	0.02	0.82
CD8+/Total+ (%): Pol	Y	0.14	0.092	-0.04	0.60

CONCLUSIONS

- Compared to later Fiebig stages, ART intervention in the earliest Fiebig I/II stages can lead to diminished frequencies, but not polyfunctional responses of HIV-reactive T cells measured at a later time point (week 48). The effect of ART on HIV-specific T cell frequencies may reflect an impact of intervention during a period overlapping with the early T cell expansion phase characteristic of acute HIV infection.
- Frequencies of HIV-infected cells that persist on ART do not appear to drive HIV-reactive T cells in adults treated during acute or early HIV infections (AEHI).
- Overall, despite some immunologic differences related to timing, administration of ART during AEHI does not preclude the detection of HIV-reactive cells at later time points.

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