T-Cell Responses Induced by HTI Vaccines and Vesatolimod Correlate With Improved Control of HIV Rebound

Abstract 05957

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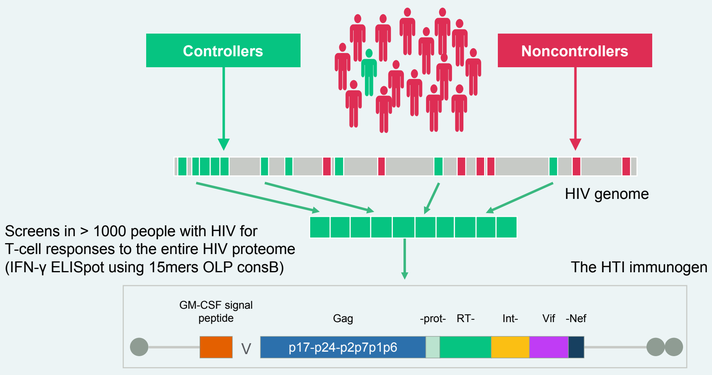
Background

- Vaccination with HIV-specific T-cell immunogens is a key component of a potential HIV cure strategy
- The HIVACAT T-cell immunogen (HTI) redirects cellular immune responses to HIV targets associated with viral control[1,2] (Figure 1)

Figure 1. Identification of beneficial T-cell targets that confer protection in HIV-controllers



Protective ratio was calculated as the ratio of the median viral loads between OLP non-responders and OLP responders.
ELISpot, enzyme-linked immunospot; GM-CSF, granulocyte-macrophage colony-stimulating factor; HTI, HIVACAT T-cell immunogen; OLP, overlapping peptide.

- HTI is a 529 aa immunogen that includes regions of Gag, Pol, Vif, and Nef covering 26 beneficial overlapping peptides (OLP) identified with a protective ratio > 1 and linked by triple alanine sequences (AAA). Post-vaccination responses to regions covered by HTI in the HVTN 502 (STEP) trial exhibited higher in vitro virus replication inhibition capacity and were associated with lower viral set points in breakthrough infections[3]
- Vesatolimod (VES), a toll-like receptor-7 agonist, activates immune responses, potentially leading to improved HIV control. VES induced a modest delay in HIV rebound in HIV controllers who stopped antiretroviral therapy (ART). The combination of VES with Ad26/MVA vaccination improved virologic control and delayed viral rebound after ART discontinuation[4-6]

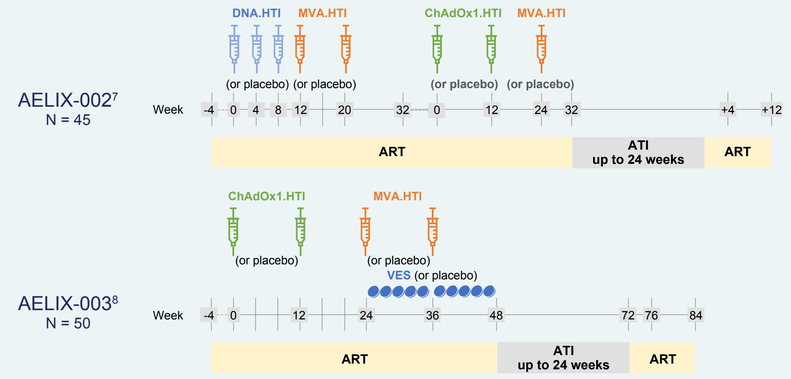
Objectives

- To report AELIX-003 final immunogenicity results, and AELIX-002/AELIX-003 pooled analyses of immune correlates of virological outcomes after a 24-week analytical treatment interruption (ATI)

Methods

- AELIX-002 (NCT03204617) and AELIX-003 (NCT04364035) were randomized, placebo-controlled studies in early-treated people with HIV of HTI vaccines given alone or in combination with VES, respectively (Figure 2)[7-8]
- Populations, ATI design, and ART resumption criteria were the same in both trials

Figure 2. AELIX-002 and AELIX-003 study designs



- Adults with HIV-1 who received ART within 6 months of acquisition
- HIV RNA < 50 copies/mL for ≥ 1 year
- Stable CD4 counts ≥ 450 cells/mm^3 for ≥ 6 months

ART restart criteria during ATI
- Clinical: ≥ grade 3 acute retroviral syndrome (ARS)
- Virological
  - pVL > 100,000 copies/mL
  - pVL > 10,000 copies/mL for 8 weeks
- Immunological: 2 consecutive CD4 < 350 cells/mm^3

ART, antiretroviral therapy; ATI, analytical treatment interruption; ELISpot, enzyme-linked immunospot; HLA, human leukocyte antigen; HTI, HIVACAT T-cell immunogen; IFN-γ, interferon gamma; pVL, plasma viral load; VES, vesatolimod.

Analyses

- Longitudinal changes in HTI-specific T-cell responses were measured by IFN-γ enzyme-linked immunospot (ELISpot) up to the start of ATI, and magnitude, breadth, and focus of the responses at ATI start were compared between studies
- Longitudinal changes in total and intact proviral HIV-1 DNA and levels at ATI start were compared
- Viral rebound dynamics were compared between studies
- Correlations between efficacy and clinical and immune parameters were investigated
- Pooled survival analysis of efficacy outcomes was undertaken using the Gehan–Breslow–Wilcoxon test stratifying the trial participants by HTI responses reached in the active and placebo arms

Results

Baseline characteristics (Table 1)

- Study populations were comparable between AELIX-002 and AELIX-003
- ART was initiated after a median (range) of 63 (6-140) and 67 (7-170) days after the estimated date of HIV-1 acquisition in the AELIX-002 and AELIX-003 studies, respectively
- Ten (22.2%) and 10 (20%) vaccine recipients expressed at least 1 beneficial human leukocyte antigen (HLA) class I allele(s) in the AELIX-002 and AELIX-003 studies, respectively

Table 1. Baseline characteristics

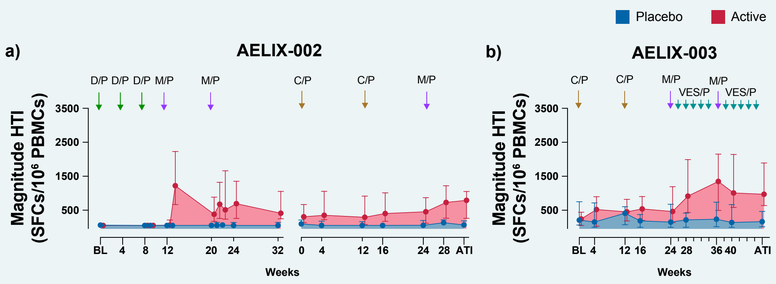
Baseline characteristics	AELIX-002 (n = 45)	AELIX-003 (n = 50)	*P*-value
Age, years	36 (20, 57)	38 (21, 59)	.6707
Sex, male, n (%)	44 (97.8)	50 (100)	.4737
Time from estimated HIV transmission to ART initiation, days	63 (6, 140)	67 (7, 170)	.4634
Fiebig stage at ART initiation, n (%)[9]			
I	2 (4.4)	2 (4)	.2022
II	2 (4.4)	4 (8)	
III	2 (4.4)	3 (6)	
IV	2 (4.4)	6 (12)	
V	24 (53.3)	18 (36)	
VI	13 (28.9)	12 (24)	
Missing	0	5 (10)	
pVL at ART initiation, $\log_{10}$ copies/mL	4.7 (2.9, 7)	5.2 (2, 7)	.1144
Absolute CD4, cells/mm^3	745 (457, 2156)	872 (451, 1600)	.1246
CD4/CD8 ratio	1 (0.5, 3.3)	1.22 (0.54, 2.14)	.0516
Beneficial HLA alleles, n (%)			
Any	10 (22.2)	10 (20)	.9792
B*27:05	5 (11.1)	6 (12)	
B*57:01	3 (6.7)	4 (8)	
B*15:17	1 (2.2)	1 (2)	
B*15:03	1 (2.2)	0	
B*58:01	0	1 (2)	
Months on ART before study entry	28 (13, 60)	42 (16, 132)	**< .0001**
Months on ART at ATI start	49 (34, 79)	55 (29, 143)	.3326

Data are median (minimum, maximum) except where specified.
ART, antiretroviral therapy; ATI, analytical treatment interruption; HLA, human leukocyte antigen; pVL, plasma viral load.

Immunogenicity

- HTI vaccine alone (AELIX-002) or in combination with VES (AELIX-003) induced strong and focused HTI-specific T-cell responses, which were boosted with repeat doses (Figure 3)

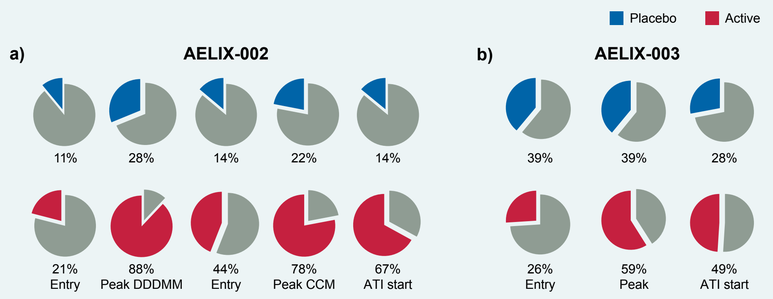
Figure 3. Magnitude of HTI-specific responses



Total HTI-specific T cells were assessed by IFN-γ-detecting ELISpot assay, using 10 peptide pools covering HTI. Median (interquartile range) magnitude of response (sum of SFCs / 10^6 PBMCs for 10 HTI pools) is shown in placebo (blue) and active (red) arms over the AELIX-002 (a) and AELIX-003 (b) studies.
BL, baseline; C, ChAdOx1.HTI; D, DNA.HTI; ELISpot, enzyme-linked immunospot; HTI, HIVACAT T-cell immunogen; M, MVA.HTI; P, placebo; PBMC, peripheral blood mononuclear cell; SFC, spot-forming cell; VES, vesatolimod.

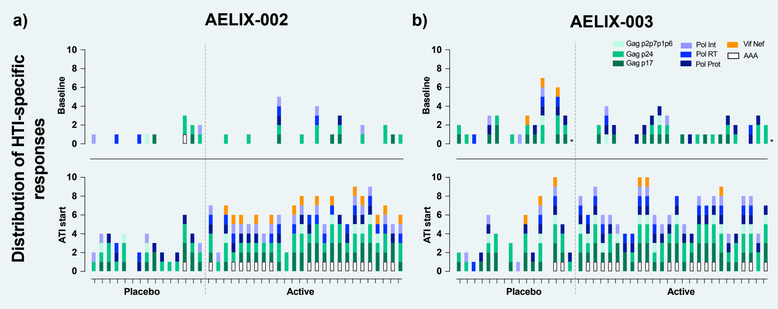
- At the time of ATI start, the median (range) of the total anti-HIV-1 T-cell response that was HTI-specific was 14% (0-50) and 28% (0-82) in placebo versus 67% (0-100) and 49% (0-100) in vaccine and vaccine + VES recipients, respectively (Figure 4)

Figure 4. Focus of HTI-specific responses



Average distribution of total HIV-1 T cells according to their specificity at the indicated timepoints. HTI-specific responses are shown for placebo (blue) and active (red) arms. The other non-HTI HIV-1–specific responses are shown in gray.
ATI, analytical treatment interruption; C, ChAdOx1.HTI; D, DNA.HTI; HTI, HIVACAT T-cell immunogen; M, MVA.HTI.

Figure 5. HTI breadth



Cumulative breadth of vaccine-elicited responses toward 10 peptide pools covering the HTI immunogen, color coded by the different HIV-1 subproteins included in the HTI immunogen study entry (top) and after completion of the last series of vaccinations / vaccinations + vesatolimod (bottom) for each placebo and active arm participant in both trials. *Participants with no available ELISpot data are shown.
AAA, peptide pool covering AAA-linker regions; ATI, analytical treatment interruption; ELISpot, enzyme-linked immunospot; HTI, HIVACAT T-cell immunogen.

- No significant differences in breadth (ie, number of reactive pools) of induced responses were detected between trials, or in immunodominance patterns across the HIV subproteins covered by the HTI immunogen (Figure 5)
- Overall, both trials showed comparable strong, focused, and broad HTI-specific responses at ATI start (Table 2)

Table 2. HTI-specific responses at ATI start

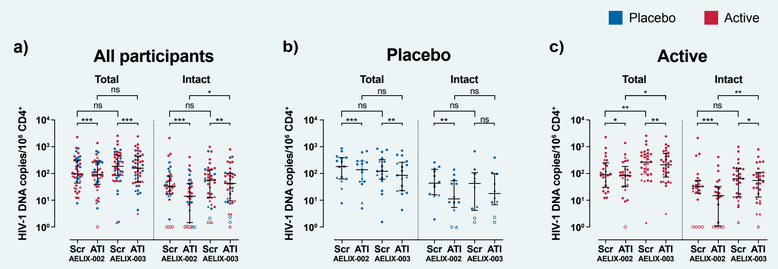
	Placebo			Active		
Immune parameter	AELIX-002 (n = 15)	AELIX-003 (n = 16)	*P*	AELIX-002 (n = 26)	AELIX-003 (n = 26)	*P*
HTI magnitude	65 (50, 520)	165 (50, 1155)	.1441	790 (50, 2655)	970 (115, 3780)	.0662
HTI focus	14 (0, 50)	25 (0, 82)	.0742	71 (0, 100)	48 (24, 76)	.0075
HTI breadth	1 (0, 3)	1 (0, 8)	.1442	3 (0, 6)	4 (1, 7)	.2353
Cumulative HTI breadth	2 (0, 6)	2 (0, 10)	.6107	6 (2, 9)	6 (4, 10)	.5302

Data are median (minimum, maximum).
ATI, analytical treatment interruption; HTI, HIVACAT T-cell immunogen; HTI breadth, number of reactive peptide pools covering the HTI sequence; HTI focus, % of HTI-specific T-cell frequencies / total HIV-1 proteome–specific T-cell frequencies; HTI magnitude, SFCs / 10^6 PBMCs; PBMC, peripheral blood mononuclear cell; SFC, spot-forming cell.

Viral reservoir

- Participants in AELIX-002 tended to have lower levels of reservoir in comparison with participants in AELIX-003 at study entry, with statistically significant differences observed at ATI start (Figure 6)

Figure 6. Viral reservoir

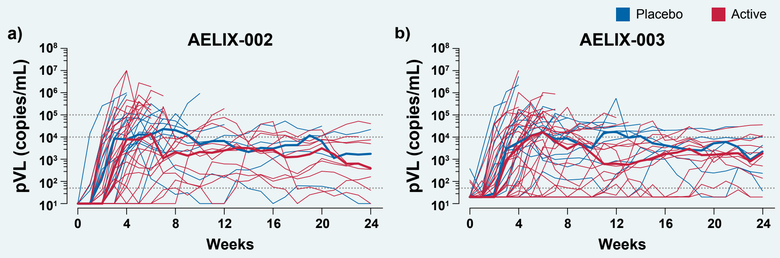


Comparison between levels of total and intact proviral HIV-1 DNA at screening and ATI start in both trials for a) all participants, b) placebo arms, and c) active arms. Participants with beneficial HLA alleles are shown in triangles. Participants with undetectable reservoir levels are shown in open circles/triangles. Median and interquartile ranges are presented. Mann–Whitney and Wilcoxon tests were used for comparisons between clinical trials and between 2 different timepoints within same participant, respectively.
*P < .05; **P < .01; ***P < .001.
ATI, analytical treatment interruption; HLA, human leukocyte antigen; ns, not significant; Scr, screening.

ATI outcomes

- Viral outcomes during ATI (time to first detectable, time to reach plasma viral load [pVL] > 10,000, peak pVL reached, last pVL before ART resumption, time off ART) were comparable between participants in the 2 studies (Figure 7 and Table 3)

Figure 7. HIV-1 pVL during ATI



Individual and median HIV-1 pVL during the 24 weeks of ATI in both trials, for all placebo (blue) and active (red) arms. Lines are interrupted at week of ART resumption. Dotted lines represent limit of HIV-1 pVL detection and the 10,000 and 100,000 virologic thresholds for ART resumption.
ATI, analytical treatment interruption; ART, antiretroviral therapy; pVL, plasma viral load.

Table 3. Viral rebound parameters during ATI

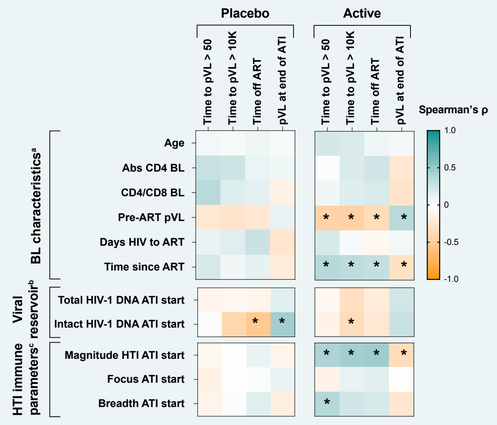
ATI	Placebo			Active		
Viral rebound	AELIX-002 (n = 15)	AELIX-003 (n = 17)	*P*	AELIX-002 (n = 26)	AELIX-003 (n = 30)	*P*
Time to pVL > 50, weeks	2.71 (1.14, 6.29)	3 (1, 14.10)	.7146*	3.14 (1, 10.14)	3.14 (1.14, 21.14)	.6963*
Time to pVL > 10,000, weeks	4.86 (1.57, 24.29)	5 (2.14, 24.10†)	.7341*	5.07 (2.86, 24.14†)	5.14 (2.14, 25†)	.6373*
Time off ART, weeks	9.14 (3.29, 24.29)	12.7 (3, 24.10†)	.5312*	7.43 (3.86, 24.14†)	10.14 (4.14, 25†)	.6577*
pVL at end of ATI, HIV-1 RNA copies/mL	82,359 (1771, 980,171)	37,200 (38, 5,370,000)	.2297	64,866 (20, 10,000,000)	38,700 (20, 10,000,000)	.6451

Data are median (minimum, maximum) . †Censored at this time point, did not reach the event; *Gehan–Breslow–Wilcoxon test; pVL < 20 and > 10,000,000 are shown as 20 and 10,000,000.
ART, antiretroviral therapy; ATI, analytical treatment interruption; pVL, plasma viral load.

Pooled analyses of immune correlates of viral control

- Both trials showed similar types of correlations between ATI outcomes and baseline characteristics, viral reservoir, and immune parameters
- Lower pre-ART pVL was associated with delayed rebound, increased time off ART, and lower plasma viral load at the end of ATI
- Both breadth and total magnitude of HTI-specific responses were associated with delayed rebound, increased time off ART, and lower pVL at the end of the ATI (Figure 8)
- The same correlates were identified by Cox proportional hazards models and logistic regression using ART resumption ≤ 12 weeks and > 12 weeks as dichotomic response

Figure 8. Immune correlates of viral control

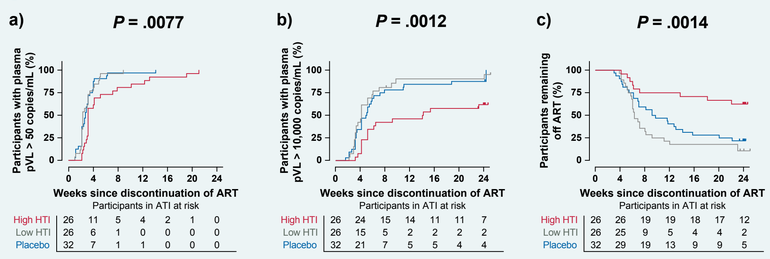


[a]Placebo = 32, active = 56. [b]For total HIV-1 DNA, placebo = 32, active = 56, for intact HIV-1 DNA, placebo = 22, active = 51. [c]Placebo = 30, active = 52. Spearman's ρ is used for correlations. All tests are 2-sided, unadjusted for multiple comparisons, with 5% error rate. Significant correlations are shown by * when P < .05.
BL, baseline; ART, antiretroviral therapy; ATI, analytical treatment interruption; HTI, HIVACAT T-cell immunogen; pVL, plasma viral load.

Pooled analyses of ATI outcomes stratified by above/below median HTI response at ATI start

- In the survival analysis, participants with HTI-specific responses above the median magnitude of the pooled populations (n = 84; 32 placebo and 52 active) at ATI start had a significantly delayed (time to pVL > 50 copies/mL) and slower (time to pVL > 10,000 copies/mL) viral rebound, and an increased time off ART versus individuals with below the median responses (P < .05 for all) (Figure 9)

Figure 9. ATI outcomes



a) Time to pVL > 50 copies/mL, defined as time (days) to the first of 2 consecutive determinations above 50 copies/mL. b) Time to pVL > 10,000 copies/mL, defined as time (days) to the first of 2 consecutive determinations above 10,000 copies/mL. c) time to ART resumption since ATI start in all participants from AELIX-002 and AELIX-003 according to the threshold of the corresponding median of HTI magnitude (SFCs / 10^6 PBMCs) at ATI start in active participants.
Gehan–Breslow–Wilcoxon test was used to compare groups, significant when P < .05.
ART, antiretroviral therapy; ATI, analytical treatment interruption; HTI, HIVACAT T-cell immunogen; PBMC, peripheral blood mononuclear cell; pVL, plasma viral load.

Conclusions

- HTI vaccination alone or in combination with VES induced equally strong and broad HTI responses and did not impact the viral reservoir
- HTI responses at ATI start in the AELIX-003 trial were similar to those induced by the more complex AELIX-002 vaccine regimen
- The magnitude of HTI T-cell responses correlated with better viral control during ATI
- Participants with HTI-specific responses above 835 spot-forming cells / 10^6 peripheral blood mononuclear cells—corresponding to the median magnitude of the pooled active participants at ATI start—had a significantly delayed and slower viral rebound, and an increased time off ART versus individuals with below the median responses
- The magnitude of HTI T-cell response as a potential correlate of improved viral control during ATI needs to be confirmed in future trials

References: **1.** Mothe B, et al. *J Transl Med*. 2011;9:208. **2.** Mothe B, et al. *J Transl Med*. 2015;13:60. **3.** Hancock G, et al. *PLoS Pathog*. 2015;11:e1004658. **4.** Borducchi E, et al. *Nature*. 2016;540:284-287. **5.** Riddler SA, et al. *Clin Infect Dis*. 2021;72:e815-24. **6.** SenGupta D, et al. *Sci Transl Med*. 2021;13:eabg3071. **7.** Bailon L, et al. *Nature Med*. 2022;28:2611-2621. **8.** Mothe B, et al. Poster 433 presented at CROI 2023, 19-23 February 2023, Seattle, WA, USA. **9.** Fiebig E, et al. *AIDS*. 2003;17:1871-1879.

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Disclosures: **C.B.** and **B.M.** are co-inventors of the HTI immunogen (patent application PCT/EP2013/051596). **C.B.**, **B.M.**, and **I.M.** are co-inventors of US patent application no. 62/935,519 and US patent application no. 62/851,546, which have relevance to the vaccine regimen used in this study. **B.M.** reports consultancy personal fees from AELIX Therapeutics SL, as well as speakers' fees from Gilead, Janssen, and ViiV Healthcare, outside the submitted work.

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