A Placebo-Controlled Randomized Trial of the HTI Immunogen Vaccine and Vesatolimod

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Background

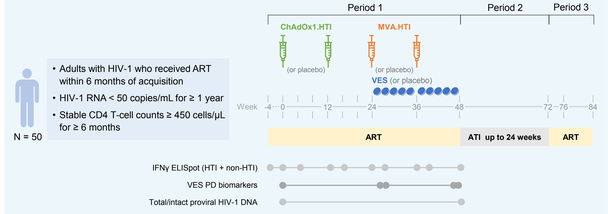
- Therapeutic vaccines designed to enhance HIV-specific T-cell immunity have been postulated to be a key component of any HIV cure strategy
- HIVACAT T-cell immunogen (HTI) is a novel HIV vaccine immunogen designed to elicit cellular immune responses to HIV regions within group-specific antigen (Gag), polymerase (Pol), viral infectivity factor (Vif), and negative regulatory factor (Nef) proteins that are associated with viral control in humans[1]
- In people with HIV (PWH) treated early with antiretroviral therapy (ART), the HIV-specific T cell response induced by a combination of DNA.HTI (D), MVA.HTI (M), and ChAdOx1.HTI (C) vaccines was associated with longer time off ART during analytical treatment interruption (ATI)[2]
- Vesatolimod (VES) is a toll-like receptor 7 (TLR7) agonist under investigation as part of an HIV cure strategy; TLR7 agonists activate immune responses and potentially lead to improved HIV control in combination with other agents[3-5]
- We conducted a Phase 2a study (AELIX-003 [NCT04364035]) of ChAdOx1.HTI and MVA.HTI vaccines (referenced collectively as CCMM) with VES in adults who received ART within the first 6 months of HIV acquisition

Objectives

- To evaluate the safety, immunogenicity, and efficacy of CCMM in combination with the TLR7 agonist VES in early-treated PWH

Methods

Figure 1. AELIX-003 Study Design



ELISpot = enzyme-linked immunosorbent spot; HLA = human leukocyte antigen; IFNγ = interferon-γ; PD = pharmacodynamics.

- Double-blind, randomized (2:1) trial conducted at 9 sites in Spain **(Figure 1)**
- Participants were randomized 2:1 to receive CCMM and oral VES 6 mg or placebo while continuing ART
  - Criteria for ART resumption during ATI: plasma viral load (pVL) > 100,000 copies/mL, pVL > 10,000 copies/mL for 8 consecutive weeks, or CD4 < 350 cells/µL
- Randomization was stratified based on HLA type with potential for superior viral control (HLA-B27 [any subtype], HLA-B57 [any subtype], HLA-B58:01, HLA-B15:16, and/or HLA-B15:17)

Endpoints

Primary: proportion of participants developing solicited Grade 3 or 4 local or systemics reactions in the 7 days after receiving CCMM + VES, or developing treatment-emergent serious adverse events during Period 1

Secondary and Exploratory:

- Proportion of participants with T-cell responses, including breadth and magnitude, to HTI-encoded regions as determined by IFNγ ELISpot (Period 1)
- Changes from baseline (BL) in serum/plasma cytokines, gene expression (including IFN-stimulated genes), and immune cell phenotype/activation in peripheral blood
- Change from BL in peripheral viral reservoir at Week 48
- Proportion of participants with pVL < 50 or < 2000 copies/mL at 12 and 24 weeks after ATI start; proportion who remain off ART at 12 and 24 weeks after start of ATI; time to pVL ≥ 50 or ≥ 10,000 copies/mL during ATI; and time to ART resumption (Period 2)

Results

Study Participant Disposition, Demographics, and Baseline Characteristics (Table 1)

- A total of 50 participants were randomized; 47 (placebo: n = 17; CCMM + VES: n = 30) entered the ATI phase and restarted ART
- Of these 47 participants, 46 (placebo: n = 17; CCMM + VES: n = 30) completed the study
  - 1 in the placebo group discontinued (personal decision)

Table 1. Baseline Characteristics

Category		Placebo n = 17	CCMM + VES n = 33	Total N = 50
Age, years		37 (21-59)	38 (24-55)	36 (21-59)
Male at birth, n (%)		17 (100)	33 (100)	50 (100)
BMI, kg/m²		23.7 (19-33)	23 (16-44)	23.3 (16-44)
Time from HIV transmission to ART initiation, days		86 (16-167)	61 (7-170)	67 (7-170)
Fiebig stage at ART initiation, n (%)[6]	I	0	2 (6.1)	2 (4.0)
	II	1 (5.9)	3 (9.1)	4 (8.0)
	III	0	3 (9.1)	3 (6.0)
	IV	3 (17.6)	3 (9.1)	6 (12)
	V	6 (35.3)	12 (36.4)	18 (36.0)
	VI	5 (29.4)	7 (21.2)	12 (24.0)
	Missing	2 (11.8)	3 (9.1)	5 (10.0)
Pre-ART pVL, log copies/mL		4.9 (1.9-7)	5.2 (2.5-7)	5.2 (1.9-7)
Current ART, n (%)	BIC/TAF/FTC	10 (58.8)	15 (45.5)	25 (50.0)
	DTG/ABC/3TC	5 (29.4)	13 (39.4)	18 (36.0)
	DTG + TDF or TAF/FTC	1 (5.9)	5 (15.1)	6 (12)
	RPV/TAF/FTC	1 (5.9)	0	1 (2)
Time on ART, months		43 (17-116)	41 (16-132)	42 (16-132)
Absolute CD4, cells/µL		831 (534-1,333)	882 (451-1,600)	872 (451-1,600)
CD4/CD8 ratio		1.2 (1-2)	1.2 (1-2)	1.2 (1-2)
Beneficial HLA alleles, n (%)[a]		4 (23.5)	6 (18.2)	10 (20)

Data are median (minimum-maximum) except where specified. [a]HLA-B27 (any subtype), HLA-B57 (any subtype), HLA-B58:01, and HLA-B15:16 and/or HLA-B15:17. 3TC = lamivudine; ABC = abacavir; BIC = bictegravir; BMI = body mass index; DTG = dolutegravir; FTC = emtricitabine; ITT = intention to treat; RPV = rilpivirine; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate.

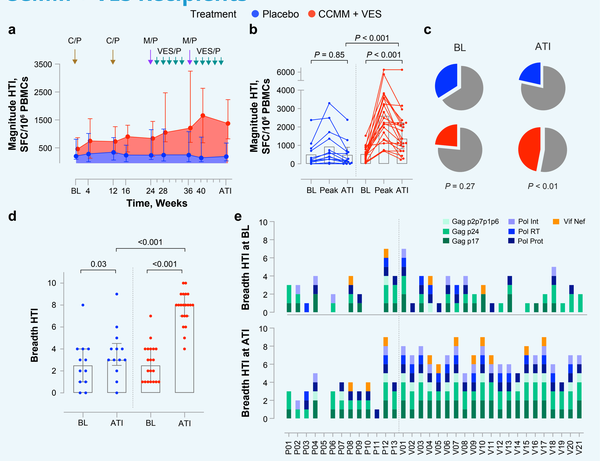
Safety of CCMM + VES 6 mg x 10 Doses

- 1 participant experienced a serious adverse event (acute cholangitis) at Week 46 that was considered by the investigator to be unrelated to study drugs
- There were no cases of cytokine-release syndrome
- Safety of the ATI:
  - There were no cases of clinically relevant acute retroviral syndrome prompting early ART resumption
  - 8 participants had mild COVID-19 infection, which did not trigger early ART resumption
  - 1 participant resumed ART at Week 18 of ATI due to an acute hepatitis B infection
- All participants achieved pVL < 50 copies/mL after ART resumption

HTI Vaccine Immunogenicity (Preliminary Data: n = 13 placebo and n = 21 CCMM + VES; Figure 2)

- Participants receiving CCMM + VES showed broad and strong HTI-specific responses
- At ATI, close to 50% of all HIV T cells were specific to HTI targets, with no specific patterns of immunodominance across the HIV subproteins covered by the HTI immunogen

Figure 2. HTI Immunogenicity Profile in Placebo and CCMM + VES Recipients

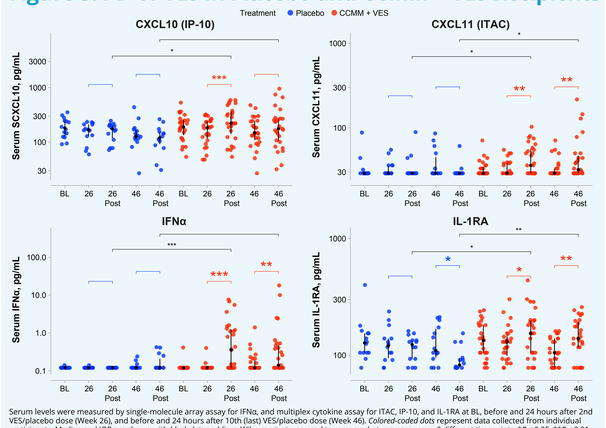


Total HIV-1- and HTI-specific T cells were assessed by IFN-γ-detecting ELISpot assay, using 10 peptide pools covering HTI. **(a)** Median (interquartile range [IQR]) magnitude of response (sum of spot-forming cells [SFCs]/10⁶ peripheral blood mononuclear cells (PBMCs) for 10 HTI pools). **(b)** Individual and median magnitudes of response (sum of SFCs/10⁶ PBMCs for HTI pool) for placebo (blue) and CCMM + VES (red) recipients at BL, peak immunogenicity time point, and Week 48 (ATI start). **(c)** Average distribution of total HIV-1 T cells according to specificity. HTI-specific responses for placebo *(blue)* and CCMM + VES *(red)* recipients and non-HTI HIV-1 specific responses *(gray)* are shown. **(d)** Cumulative breadth (median and IQR) of vaccine-elicited responses. **(e)** Cumulative distribution of HTI-specific responses within the different HIV-1 subproteins at BL and start of ATI for each placebo (P01-P13) and CCMM + VES (V01-V21) recipient. Mann-Whitney and Wilcoxon test was used to compare between groups and between 2 different time points within same participant, respectively. Int = integrase; Prot = protease; RT = reverse transcriptase.

VES Pharmacodynamic Biomarkers (Figure 3)

- VES consistently increased the production of acute phase cytokines (IFNα and interleukin-1 receptor antagonist [IL-1RA]) and chemokines (IFNγ-inducible protein-10 [IP-10] and IFN-inducible T-cell-α chemoattractant [ITAC]) 24 hours postdosing in CCMM + VES recipients

Figure 3. PD of VES in Placebo and CCMM + VES Recipients

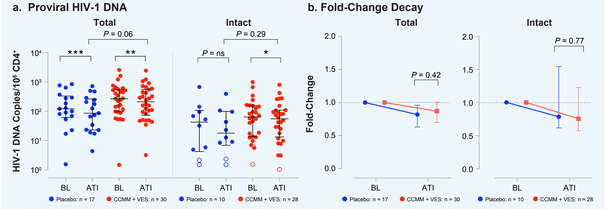


Serum levels were measured by single-molecule array assay for IFNα, and multiplex cytokine assay for ITAC, IP-10, and IL-1RA at BL, before and 24 hours after 2nd VES/placebo dose (Week 26), and before and 24 hours after 10th (last) VES/placebo dose (Week 46). *Colored-coded dots* represent data collected from individual participants. Median and IQR are shown with *black dots* and *lines*. Wilcoxon test was used to compare between groups or 2 different timepoints. *$P \le 0.05$, **$P \le 0.01$, ***$P \le 0.001$. CXCL = C-X-C motif chemokine ligand.

Viral Reservoir (Figure 4)

- No differences in the reduction of total (integrated) or intact (replication competent) proviral HIV-1 DNA were observed between arms **(Figure 4)**

Figure 4. HIV-1 Reservoir Decay in Placebo and CCMM + VES Recipients

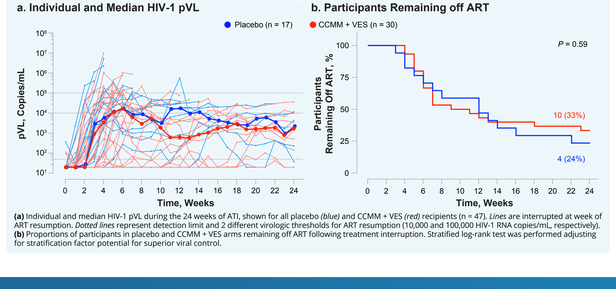


(a) Comparison between levels of total and intact proviral HIV-1 DNA at BL and ATI in placebo *(blue)* and CCMM + VES *(red)* recipients. Participants with undetectable reservoir are shown in *open circles*. **(b)** Fold-change decay for total and intact proviral HIV-1 DNA by treatment group from BL to ATI start. Median and IQR are represented. Mann-Whitney and Wilcoxon tests were used to compare between groups and between 2 different time points within same participant, respectively. ns = not significant. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

ATI Period (Figure 5)

- 10 of 30 participants (33%) in the active arm remained off ART for 24 weeks compared with 4 of 17 placebo recipients (24%)
- Reasons for resuming ART before 24 weeks of ATI were pVL ≥ 100,000 copies/mL (16 CCMM + VES; 8 placebo) and pVL ≥ 10,000-100,000 copies/mL for 8 consecutive weeks (2 CCMM + VES; 5 placebo)
  - 1 CCMM + VES participant voluntarily resumed ART at Week 23 of ATI and 1 CCMM + VES participant at Week 18 due to hepatitis B infection

Figure 5. HIV-1 pVL and Percentage of Participants Remaining ART-Free During 24-Week ATI

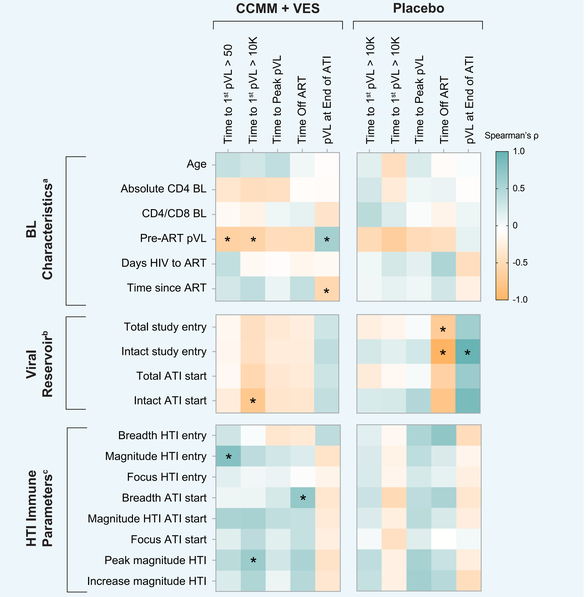


(a) Individual and median HIV-1 pVL during the 24 weeks of ATI, shown for all placebo *(blue)* and CCMM + VES *(red)* recipients (n = 47). *Lines* are interrupted at week of ART resumption. *Dotted lines* represent detection limit and 2 different virologic thresholds for ART resumption (10,000 and 100,000 HIV-1 RNA copies/mL, respectively). **(b)** Proportion of participants in placebo and CCMM + VES arms remaining off ART following treatment interruption. Stratified log-rank test was performed adjusting for stratification factor potential for superior viral control.

Preliminary Correlate Analyses (Figure 6)

- In the CCMM + VES group, higher pre-ART pVL correlated with worse viral outcomes (shorter time to viral rebound > 50 and > 10,000 copies/mL, and higher pVL at the end of ATI)
- In the placebo group, lower pre-intervention viral reservoir size was associated with better viral outcomes (longer time off ART and lower pVL at the end of ATI)
- In the CCMM + VES group, higher magnitude and breadth of vaccine response correlated with better viral outcomes (longer time to viral rebound > 50 or > 10,000 copies/mL, and longer time off ART, respectively)

Figure 6. Subgroup Analysis of Correlates Associated With Viral Kinetics During ART (Interim Analysis)



[a]Placebo: n = 17; CCMM + VES: n = 33; [b]For total HIV-1 DNA: placebo: n = 17, and CCMM + VES: n = 30; for intact HIV-1 DNA: placebo: n = 10, and CCMM + VES: n = 28; [c]Placebo: n = 13; CCMM + VES: n = 21. 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 $P < 0.05$.

Conclusions

- The combination of the HTI vaccine and VES as part of an HIV cure strategy in early-treated PWH was safe and well tolerated
- Preliminary immune data suggest that HTI vaccines given in combination with VES induce high levels of HTI-specific T-cell responses; VES consistently induced PD response over multiple doses in combination therapy with HTI vaccine
- A lower pre-intervention reservoir was associated with better viral outcomes during the ATI, but only in the placebo group
- The magnitude and breadth of vaccine response correlated with better viral outcomes
- The impact of VES on antiviral activity of HTI-specific T cells and virus control remains to be investigated

References: 1. Mothe B, et al. J Transl Med 2015;13;60. **2.** Bailón L, et al. Nat Med 2022;28:2611-21. **3.** Borducchi E, et al. Nature 2016;540:284-7. **4.** Riddler SA, et al. Clin Infect Dis 2021;72:e815-24. **5.** SenGupta D, et al. Sci Transl Med 2021;13:eabg3071. **6.** Fiebig E, et al. AIDS 2003;17:1871-9.

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