Safety, Immunogenicity, and Effect on Viral Rebound of T/B-Cell Vaccines in Chronic ART-Treated PWH

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BACKGROUND

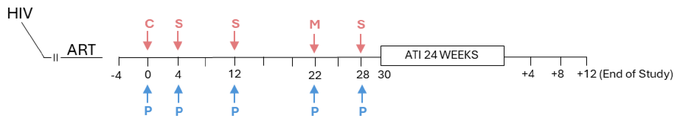
Vaccine-induced HTI-specific T-cell responses have been associated with extended time off-ART in **early-treated PWH (etPWH)** in 2 independent clinical trials, but did not prevent viral rebound when ART was interrupted[1,2,3]

We **hypothesized** that efficacy of **T-cell vaccines** could be **improved** with the support of humoral responses by adding a **B-cell immunogen** into the vaccine regimen.

METHODS

BCN03 (NCT05208125) was a randomized (2:1), placebo-controlled trial testing the safety and immunogenicity of ChAdOx1.HTI (**C**), MVA.HTI (**M**) and ConM.SOSIP.v7 (**S**) vaccines in 30 ART-suppressed cis-gender men who initiated ART during **chronic stages of infection (ctPWH).**

HTI- and S-specific T-cells were evaluated by **IFNγ-ELISpot**, S-specific IgG by **ELISA**, and **neutralization** of 7 Tier1/2 pseudoviruses (one expressing S) by a **TZM-bl assay**. Immunophenotype was done by **flow cytometry**. Near full-genome **intact proviruses** were amplified from CD4+ T-cells to address **vaccine coverage**. Two weeks after last S vaccination, participants entered a **24-week ATI**, and ART was resumed earlier if pVL >100,000 copies/mL once or >10,000 for 8 consecutive weeks.



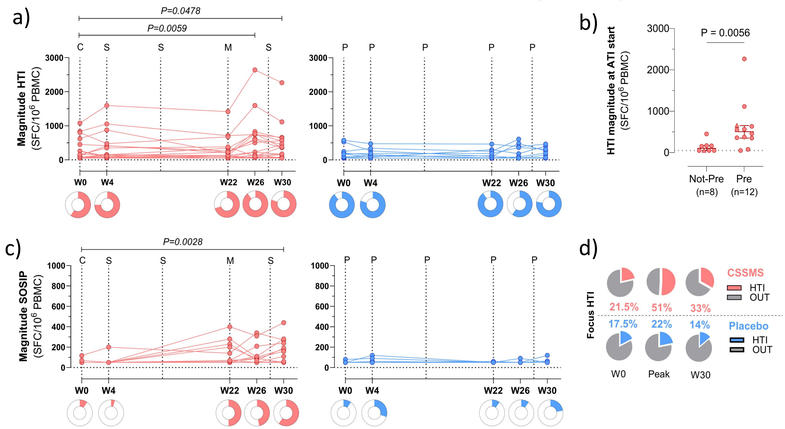
Overview of the intervention visits, showed in weeks, throughout the study.

CSSMS vaccine regimen was **safe** and **well tolerated**.
Related **AEs** were mostly **mild** (G1 and G2) and **transient (<72h)**.

Characteristic	CSSMS n=20	Placebo n=10	ITT population n=30
Age, years, median (range)	42 (22 – 56)	38 (23 – 52)	40 (22 – 56)
BMI, kg/m², median (range)	25.7 (23.7 – 27.5)	25.1 (18.1 – 27.9)	25.3 (18.1 – 27.9)
Sex, male (%)	20 (100)	10 (100)	30 (100)
Nadir CD4 count, cell/mm³	472 (357 – 800)	484 (384 – 727)	482 (357 – 800)
Time from first ART start, years	7.6 (2.2 – 13.1)	6.8 (2.7 – 15)	6.8 (2.2 – 15)
CD4 absolute cell count, cells/mm³	780 (603 – 1,261)	817 (433 – 1,137)	780 (433 – 1,261)
CD4/CD8 ratio	1.1 (0.7 – 1.6)	1.3 (0.6 – 1.7)	1.1 (0.6 – 1.7)
Presence of HLA genotype associated with natural HIV control			
Yes, n (%)	2 (10)	1 (10)	3 (10)
No, n (%)	18 (90)	9 (90)	27 (90)

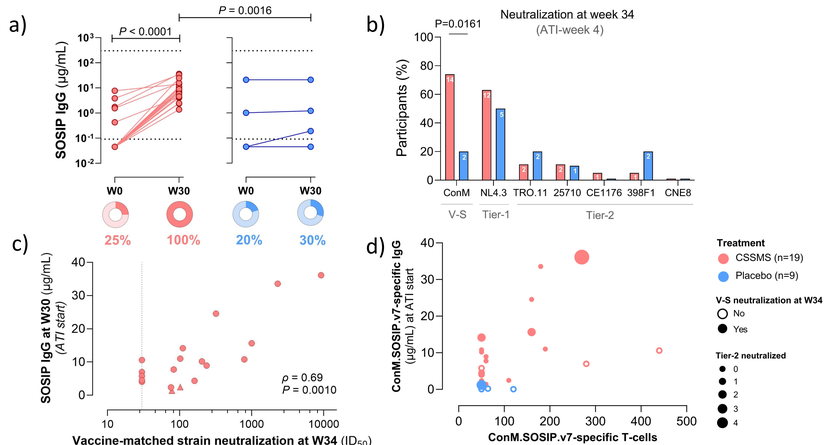
Summary of demographic and clinical characteristics of study participants at baseline. Median (range) is reported, unless stated otherwise.

RESULTS 1: T-cell immunogenicity



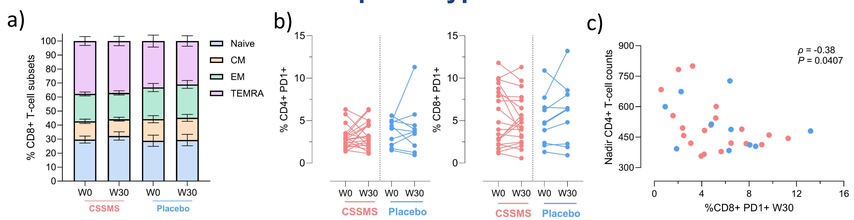
HTI- (a) and SOSIP-specific (b) T-cell magnitude in CSSMS (red) and placebo recipients (blue). c) HTI-specific T-cell magnitude at week 30 between people without or with pre-existing responses at baseline, compared by Mann-Whitney test. d) T-cell focus towards HTI over the total HIV proteome. Friedman test with Dunn's correction was used for longitudinal analyses.

RESULTS 2: Humoral immunogenicity



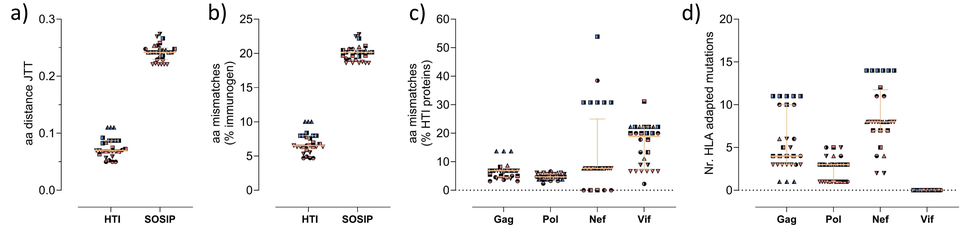
a) Anti-SOSIP IgG levels between CSSMS (red) and placebo recipients (blue). Two-way ANOVA corrected by Tukey was used for analyses. b) Percentage of participants with neutralization against 7 pseudoviruses (including a vaccine-matched strain; "V-S") at 4 weeks upon ATI. Fisher's exact test was used. c) Spearman's correlation between anti-SOSIP IgG levels and V-S neutralization. d) 5-parameter graphical representation indicating the correlation between anti-ConM.SOSIP.v7 IgG levels and ConM.SOSIP.v7-specific T-cell magnitude at ATI start

RESULTS 3: Immunophenotype and T-cell exhaustion



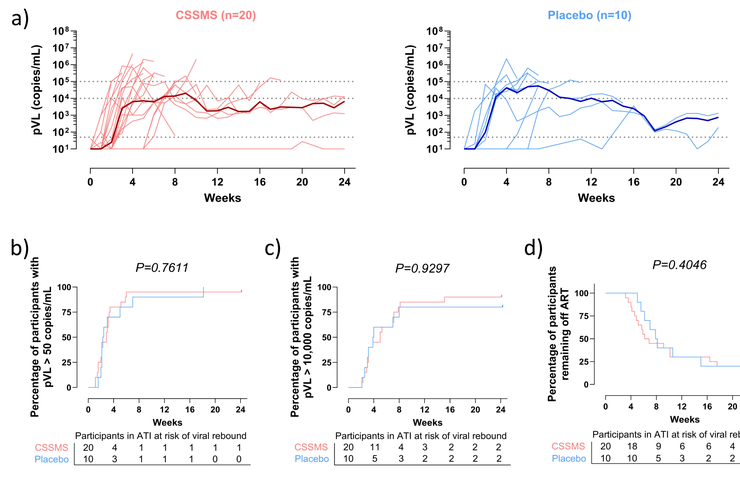
a) Memory CD8+ T-cell populations classified by CD45RA and CCR7 expression (central memory (CM; CCR7+CD45RA-), effector memory (EM; CCR7-CD45RA-), naïve (CCR7+CD45RA+), and terminally differentiated effector memory re-expressing RA (TEMRA; CCR7-CD45RA+). b) T-cell exhaustion measured by PD1 expression in both CD4 and CD8 T-cells. Wilcoxon test was used. c) Spearman's correlation of Nadir CD4 T-cell counts and PD1 expression on CD8 T-cells at W30.

RESULTS 4 : Vaccine coverage of proviral intact viruses



From the 28 intact provirus sequences recovered from 12 participants at week 0, the amino-acid (aa) distance (a), as well as the percentage of mismatches (b), between each of the vaccine immunogens (HTI and SOSIP) were calculated using Jones–Taylor–Thornton (JTT) amino-acid substitution model. The percentage of aa mismatches (c) and the number of HLA-adapted polymorphisms (d) was calculated for the different HIV-1 proteins included in the HTI immunogen based on [3,4]. Recovered proviruses from each participant are represented by the same symbol shape, with CSSMS and placebo recipients depicted in red and blue, respectively.

RESULTS 5 : No impact on viral rebound kinetics



a) Weekly measurements of HIV-1 pVL for all CSSMS (left) and placebo (right) recipients from ATI start to their respective end of ATI. Time to reach >50 copies/ml (b), or > 10,000 copies/ml (c), and time off treatment (d) for all CSSMS (red) and placebo (blue) recipients. The Gehan-Breslow-Wilcoxon test was used, and P-values are shown

CONCLUSIONS

- **Combined T/B-cell vaccination (CSSMS)** in ART-suppressed **ctPWH** was **safe** and induced coordinated **cellular and humoral** responses, with dominant vaccine-matched virus neutralization.
- Greater **CD8 T-cell exhaustion** and a higher proportion of **escape variants** in reservoir proviruses of ctPWH *vs.* etPWH may have contributed to **reduced HTI immunogenicity** and **limited** post-intervention virological control during ATI, unlike previous AELIX trials with more complex regimens[1, 2, 3].
- Whether dominant ConM.SOSIP.v7-induced responses may have exerted a ***functional 'veto' effect*** to generate HTI-specific T-cells warrants **further investigation** and supports exploring combination of T-cell vaccine with bNAbs, as alternative approaches.

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