Including Env in an HIV therapeutic vaccine blunts Gag/Pol-specific T cell responses

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BACKGROUND

- T cell-based therapeutic vaccination is a potential approach to achieving durable control of HIV.
- It is assumed, but has not been thoroughly evaluated, that inclusion of Env antigens in a therapeutic vaccine may blunt immunologic responses to conserved Gag and Pol targets.
- **We evaluated the impact of including Env antigen on Gag- and Pol-specific T cell responses in an HIV-1 DNA therapeutic vaccine trial.**

METHODS

Study Design: Two-site (Los Angeles and San Francisco) randomized, blinded, placebo-controlled clinical trial, "PENNVAX"

Study Intervention/Schema

- Randomization 1:1:1 to DNA vaccination with 1) multiclade consensus gag/pol (clades A, B, C, D) 2 mg + IL-12 1 mg (**Gag/Pol/IL-12**), 2) gag/pol 2 mg + env (clades A, C) 6 mg + IL-12 1 mg (**Gag/Pol/Env/IL-12**) or 3) **placebo** (sterile water for injection)
- Randomization stratified on 1) site of enrollment and 2) CD4 nadir (<200 vs ≥200 cells/mm^3)
- Vaccine/placebo administered by intramuscular injection and electroporation (CELLECTRA® 2000) at Weeks 0 (W0), 4, 8, and 12

Key Inclusion Criteria: Adults 18-65 years, screening CD4$^+$ T cell count ≥350 cells/mm^3, initiated antiretroviral therapy (ART) during chronic infection (e.g. ≥6 months after initial HIV infection) creatinine clearance >60 mL/min, HIV-1 RNA <50 copies/mL for ≥24 months (isolated blips up to 200 allowed), continuous ART for ≥ 24 months

Key Exclusion Criteria: Receipt of immunomodulatory or immunosuppressive therapy within 4 weeks prior to enrollment, active malignancy or recent serious illness, active (untreated) HBV or HCV, pregnancy or breastfeeding

Primary Outcomes: 1) safety and 2) magnitude and breadth of T cell responses by IFN-γ ELISpot

- T cells in peripheral blood mononuclear cells (PBMCs) reactive to vaccine-matched and potential T cell epitope (PTE) Gag, Pol, and Env peptide pools were measured pre- (B1 and W0) and post-vaccination (W14) (Wistar Institute)
- Gag matrix mapping followed by individual Gag peptide mapping and Short Term Cell Line (STCL) assay used to interrogate individual Gag peptide responses (Wistar Institute)

Other Outcomes:

- T cell responses measured by IFN-γ ELISpot using peptide pools spanning highly conserved regions of Gag and Pol (tHIVconsvX immunogens M3 and M4) at B1 and W14 (Goonetilleke Lab, UNC)
- Inducible HIV reservoir measured by differentiation quantitative viral outgrowth assay (dQVOA) at B1 and W14 (Southern Research)

Analysis population and statistical analyses: All participants who initiated study intervention, by treatment received (one participant received a different treatment from assigned due to site error), with assay results from samples collected per protocol. Fold change from baseline to Week 14 was compared between arms using Wilcoxon tests.

RESULTS: SAFETY THROUGH 64 WEEKS

Adverse Events (AEs)	Number (%) of participants experiencing event by treatment arm			
	Gag/Pol/IL-12 n (%) (N=14)	Gag/Pol/Env/IL-12 n (%) (N=16)	Placebo n (%) (N=15)	Overall p-value (Fisher's exact test)
Grade 3+ AEs	3 (21%)	2 (12%)	4 (27%)	0.65
All related AEs	3 (21%)	7 (44%)	6 (40%)	0.46
Serious AEs	2 (14%)	0 (0%)	1 (7%)	0.19

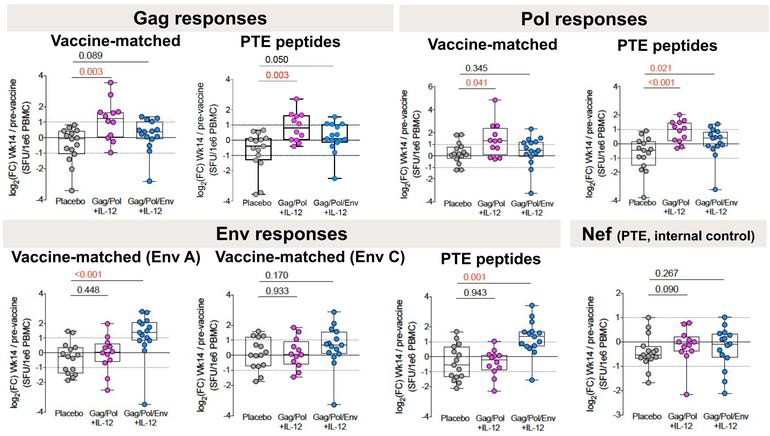
No significant between-arm differences in proportion with AEs comparing each active arm to placebo

Vaccination with consensus HIV-1 *gag/pol/IL-12* and *gag/pol/env/IL-12* DNA elicited *de novo* Gag-specific T cell responses and boosted Gag-, Pol-, and Env-specific responses in a randomized controlled trial of people with HIV who initiated ART during chronic infection.

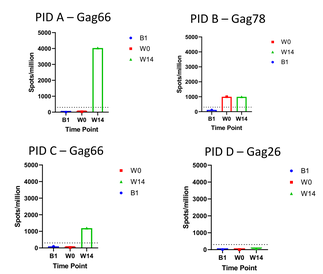
Inclusion of Env antigen in the vaccine limited the induction of Gag and Pol-specific T cell responses.

These findings support the potential of T-cell based therapeutic vaccination, without Env-targeting immunogens, in approaches for ART-free HIV remission.

RESULTS: T CELL RESPONSES (VACCINE-MATCHED AND PTE) BY IFN-γ ELISPOT



- 6 participants with at least one "new" response to an individual Gag peptide at Wk14 following matrix mapping.
- **5 of 6 participants (4 *gag/pol* recipients, 1 *gag/pol/env* recipient) had confirmed *de novo* vaccine-induced Gag peptide responses** (representative results from STCL assay below, positive response defined ≥300 SFU/M cells [dotted line])



7/12 (58%) *gag/pol* vs 4/15 (27%) *gag/pol/env* vs 0/15 (0%) placebo recipients had at least 2-fold increase in Gag-specific T cell responses (p<0.001 for gag/pol vs placebo and p=0.100 for gag/pol/env vs placebo, Fisher exact test)

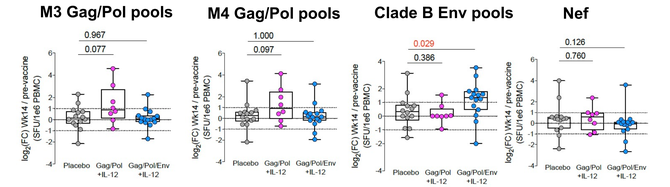
RESULTS: BASELINE CHARACTERISTICS

Variable	Gag/Pol/IL-12 (N=14)	Gag/Pol/Env/IL-12 (N=16)	Placebo (N=15)	Total (N=45)
Age, median (interquartile range, IQR) years	55 (50-58)	56 (52-60)	55 (44-57)	55 (48-58)
Gender				
Cis-gender male	13 (92.9%)	15 (93.8%)	12 (80.0%)	40 (88.9%)
Cis-gender female	1 (7.1%)	0 (0.0%)	1 (6.7%)	2 (4.4%)
Non-binary	0 (0.0%)	1 (6.2%)	1 (6.7%)	2 (4.4%)
Transgender female	0 (0.0%)	0 (0.0%)	1 (6.7%)	1 (2.2%)
Ethnicity				
Hispanic or Latino	2 (14.3%)	2 (15.4%)	6 (40.0%)	10 (23.8%)
Non-Hispanic or Latino	12 (85.7%)	11 (84.6%)	9 (60.0%)	32 (76.2%)
Race				
White	7 (50.0%)	10 (62.5%)	7 (46.7%)	24 (53.3%)
African American or Black	4 (28.6%)	2 (12.5%)	0 (0.0%)	6 (13.3%)
Other specified race (including mixed race)	3 (21.4%)	3 (18.9%)	7 (46.7%)	13 (28.9%)
Number of years since first HIV+, median (IQR)	18.3 (10.1-28.8)	21.0 (17.0-29.1)	14.7 (10.6-24.7)	19.9 (11.6-27.1)
Months HIV suppressed prior to study entry, median (IQR)	101 (72-123)	90 (53-148)	121 (71-143)	101 (65-141)
Screening CD4+ T cell count (cells/mm^3), median (IQR)	707 (471-753)	490 (424-761)	576 (370-814)	525 (426-753)
CD4 nadir <200 cells/mm^3	6 (42.9%)	8 (50.0%)	7 (46.7%)	21 (46.7%)
CD4+ T cell count nadir (cells/mm^3), median (IQR)	242 (174-331)	190 (86-335)	223 (75-299)	221 (100-331)

CONCLUSIONS

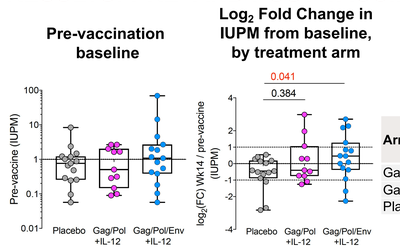
- HIV-specific T cell responses, including responses to highly conserved Gag and Pol regions, were boosted with consensus sequence gag/pol and gag/pol/env + IL-12 DNA vaccination
- Inclusion of env immunogen hampered T cell responses to Gag and Pol, possibly due to antigenic competition, immunodominance of Env epitopes, and/or higher env plasmid dose received
- Provides evidence that a therapeutic vaccine can broaden Gag-specific T cell responses and induce *de novo* responses in participants with chronic treated HIV on long term ART
- Apparent increase in inducible reservoir in env-vaccinated participants - additional reservoir work will confirm dQVOA findings
- Detailed analyses to further characterize vaccine responders may reveal correlates of Gag or Pol response for future therapeutic vaccine design
- Vaccination with gag/pol/IL-12 +/- env DNA in persons with treated HIV is safe

RESULTS: VACCINE-INDUCED T CELL RESPONSES TO HIGHLY CONSERVED GAG/POL REGIONS



Consistent relationship observed as with vaccine-matched peptide stimulation, with trend towards boosting of T cell responses to highly conserved Gag/Pol regions, and loss of this response but boosting of Env-specific responses with env-inclusive vaccination

RESULTS: PRE- AND POST-VACCINATION dQVOA



Arm	Ratio of IUPM at Week 14/Baseline Median (IQR)
Gag/pol (n=11)	0.76 (0.59-2.09)
Gag/pol/env (n=15)	1.38 (0.77-2.42)
Placebo (n=15)	0.73 (0.54-1.13)

Significant increase in IUPM (infectious units per million resting CD4+ T cells) in env-vaccinated participants compared to placebo

ADDITIONAL KEY INFORMATION

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