Vaccination with consensus HIV-1 gag/pol/IL-12 and gag/pol/IL-12 DNA 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

<table>
<thead>
<tr>
<th>Gag responses</th>
<th>Pol responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine-matched</td>
<td>PTE peptides</td>
</tr>
</tbody>
</table>

- 6 participants with at least one new response to an individual Gag peptide at Wt 14 following Env/match regimen.
- 5 of 6 participants (4 gag/pol recipients, 1 gag/pol/env recipient) had confirmed de novo vaccine-induced Gag peptide responses (representative from STCL assay below, position of defined 330 SFU/M cells [dotted line]).

METHODS

Study Design: Two-site (Los Angeles and San Francisco) randomized, blinded, placebo-controlled clinical trial, "PENNvAX" Study Intervention/Schema: Randomization to 1:1:1:1 DNA vaccination with 1 multiclade consensus gag/pol (clades A, B, C, D) 2 mg + IL-12 1 mg (Gag/Pol/IL-12), 2 mg + IL-2 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/mm³).

Vaccine/placebo administered by intramuscular injection and electroporation (CELLECTRA®-2000) at Week 0 (W0), 4, 8, and 12.

Key Inclusion Criteria: Adults 18-65 years, screening CD4+ T cell count ≥350 cells/mm³, initiated antiretroviral therapy (ART) during chronic infection (≥6 months after initial HIV infection) creatinine clearance ≥60 mL/min, HIV-1 RNA≤50 copies/ml, ≥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.

Other Outcomes:

- T cell responses measured by IFN-γ ELISPOT using peptide pools spanning highly conserved regions of Gag and Pol (HIVconsx 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

<table>
<thead>
<tr>
<th>Grade 1 &amp; 2 AEs (%)</th>
<th>Grade 3 &amp; 4 AEs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 (21%)</td>
<td>7 (44%)</td>
</tr>
<tr>
<td>2 (12%)</td>
<td>6 (40%)</td>
</tr>
</tbody>
</table>

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

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.

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.

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

M3 Gag Pol pools M3 Gag Pol pools M3 Env Pol pools

RESULTS: PRE- AND POST-VACCINATION dQVOA

Pre-vaccination baseline IUPM from baseline, by treatment arm

Additional Key Information

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