Reduction in HIV Reservoir Markers with Gag/Pol/IL-12 DNA Therapeutic Vaccination

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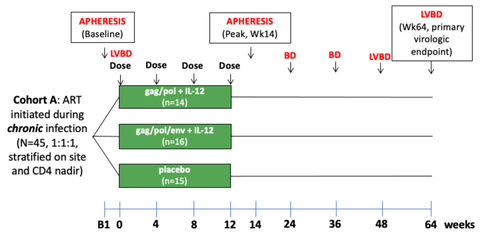
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BACKGROUND AND OBJECTIVES

- T cell-based therapeutic vaccination is a potential approach to achieving durable control of HIV
- We previously reported that HIV gag/pol/IL-12 DNA therapeutic vaccination significantly boosted total Gag-specific vaccine-matched T cell responses compared to placebo by IFN-γ ELISPOT in participants on chronic suppressive antiretroviral therapy (ART) (Chew et al, CROI 2022, Poster 00284). Gag responses were both greater in magnitude and broader, with new Gag peptide responses elicited that were not present at baseline. Gag/pol/env/IL-12 DNA vaccination led to numerically increased but smaller Gag-specific responses, not significantly increased from placebo.
- **We evaluated the effects of gag/pol and gag/pol/env DNA vaccination on markers of HIV persistence in the PENNVAX trial**

METHODS

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



Vaccine/Placebo: 1) multiclade (A, B, C, D) consensus gag/pol 2 mg + IL-12 1 mg (**Gag/Pol/IL-12 [G/P]**), 2) gag/pol 2 mg + env (clades A, C) 6 mg + IL-12 1 mg (**Gag/Pol/Env/IL-12 [G/P/E]**) or 3) **placebo** (**PBO**, sterile water for injection) by intramuscular injection and electroporation

Key Eligibility Criteria: Adults 18-65 years, CD4+ T cell count ≥350 cells/mm^3, ART initiated during chronic 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, no recent immunomodulatory or immunosuppressive therapy

Virologic outcomes:

- Total and defective proviruses by intact proviral DNA assay (IPDA)
- Total HIV-1 DNA (LTRgag) and cell-associated RNA (LTRgag RNA [caRNA]) (isolated CD4+ T cells from PBMCs)
- Plasma HIV-1 RNA (vRNA) by automated single-copy assay (SCA)

Statistical analyses: All analyses by treatment received

- Two participants with known ART interruptions excluded from analyses
- Change from baseline to week 64 analyzed using repeated measures generalized estimating equations (GEE)
- Percentage of participants with undetectable plasma vRNA by SCA at each time point reported with 95% confidence intervals by Clopper-Pearson and compared between arms by Fisher exact tests.
- Values below the limit of detection (LOD) were assigned half the LOD.

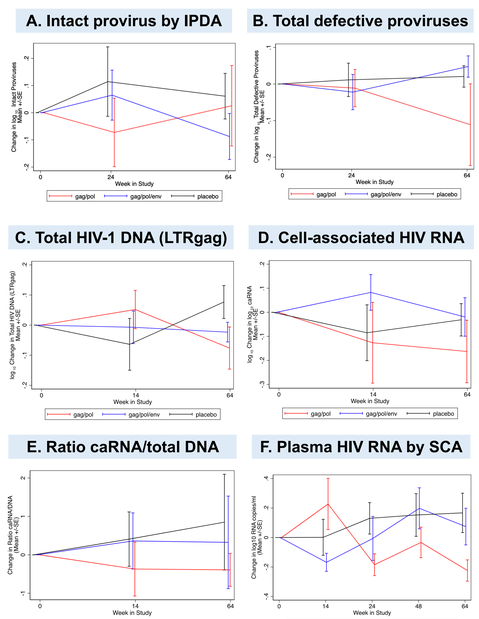
A trend in reduction in detectable plasma HIV-1 viral RNA by single copy assay was observed with HIV-1 consensus gag/pol/IL-12 DNA therapeutic vaccination—the same arm that had significantly boosted and broadened HIV-1 Gag-specific T cell responses—in the PENNVAX trial of participants with HIV on long-term suppressive ART.

These findings suggest consensus Gag/Pol vaccination may facilitate clearance of productively infected cells during ART.

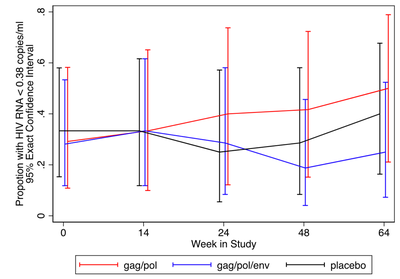
CHANGE FROM BASELINE TO WEEK 64 IN MEASURES OF HIV PERSISTENCE

Fig	Assay	Change from baseline to Week 64: G/P total n=12	G/P/E total n=16	PBO total n=15	Between-arm p-value: G/P vs PBO	G/P/E vs PBO	G/P vs G/P/E
A	**Intact provirus**, mean (SE) log10 change count/10^6 CD4	0.03 (0.15)	-0.09 (0.08)	0.06 (0.08)	0.84	0.22	0.51
B	**Total (3'+5') defective provirus**, mean (SE) log10 change count/10^6 CD4	-0.11 (0.11)	0.05 (0.03)	0.02 (0.03)	0.26	0.11	0.18
	3' defective provirus, mean (SE) log10 change count/10^6 CD4	-0.14 (0.11)	-0.02 (0.06)	-0.01 (0.03)	0.25	0.84	0.34
	5' defective provirus, mean (SE) log10 change count/10^6 CD4	-0.06 (0.10)	0.19 (0.12)	0.05 (0.04)	0.35	0.26	0.12
C	**Total HIV-1 DNA**, mean (SE) log10 change copies/10^6 CD4	-0.08 (0.07)	-0.02 (0.03)	0.08 (0.05)	0.09	0.12	0.50
D	**caRNA**, mean (SE) log10 change copies/10^6 CD4	-0.16 (0.13)	-0.02 (0.08)	-0.03 (0.07)	0.37	0.91	0.58
E	**caRNA/total DNA**, mean (SE) change	-0.39 (0.43)	0.32 (1.20)	0.85 (1.25)	0.35	0.76	0.58
F	**Plasma SCA**, mean change (SE) log10 copies/mL	-0.22 (0.07)	0.07 (0.12)	0.17 (0.13)	**0.01**	0.61	**0.04**

SE = standard error; statistically significant p-values in bold.



CHANGE FROM BASELINE TO WEEK 64 IN PROPORTION WITH UNDETECTABLE PLASMA vRNA BY SINGLE COPY ASSAY



Study Week	Percentage (95% CI) with undetectable plasma vRNA on SCA by treatment arm and week: G/P (n=12)	G/P/E (n=16)	PBO (n=15)	Between-arm p-value: G/P vs PBO	G/P/E vs PBO
Wk 0	29 (11-58)	28 (12-53)	33 (15-58)	0.78	0.72
Wk 14	33 (10-65)	33 (12-62)	33 (12-62)	1.00	1.00
Wk 24	40 (12-74)	29 (8-58)	25 (5-57)	0.65	1.00
Wk 48	42 (15-72)	19 (4-46)	29 (8-58)	0.68	0.68
Wk 64	50 (21-79)	25 (7-52)	40 (16-68)	0.71	0.46

CONCLUSIONS

- Decay in residual viremia with G/P vaccination suggests the vaccine may facilitate clearance of productively infected cells during ART
- Also observed were non-significant and modest but consistent signals of reductions in other markers of HIV persistence, particularly 3' defective provirus, total HIV-1 DNA and caRNA with G/P vaccination, suggesting true biologic effect of G/P vaccination
- Additional work is needed to characterize vaccine-induced immune responses and correlates of favorable virologic responses

ADDITIONAL INFORMATION

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