Oral Abstract Session-06

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144 - T-Cell Responses Induced by GS-1966+GS-1144 Vaccines in Virally Suppressed People With HIV

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Disclosure: Dr SenGupta has Self: is an employee of Gilead Sciences, Inc., and may own stock in Gilead Sciences, Inc.

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Presentation # 144

T-Cell Responses Induced by GS-1966+GS-1144 Vaccines in Virally Suppressed People With HIV

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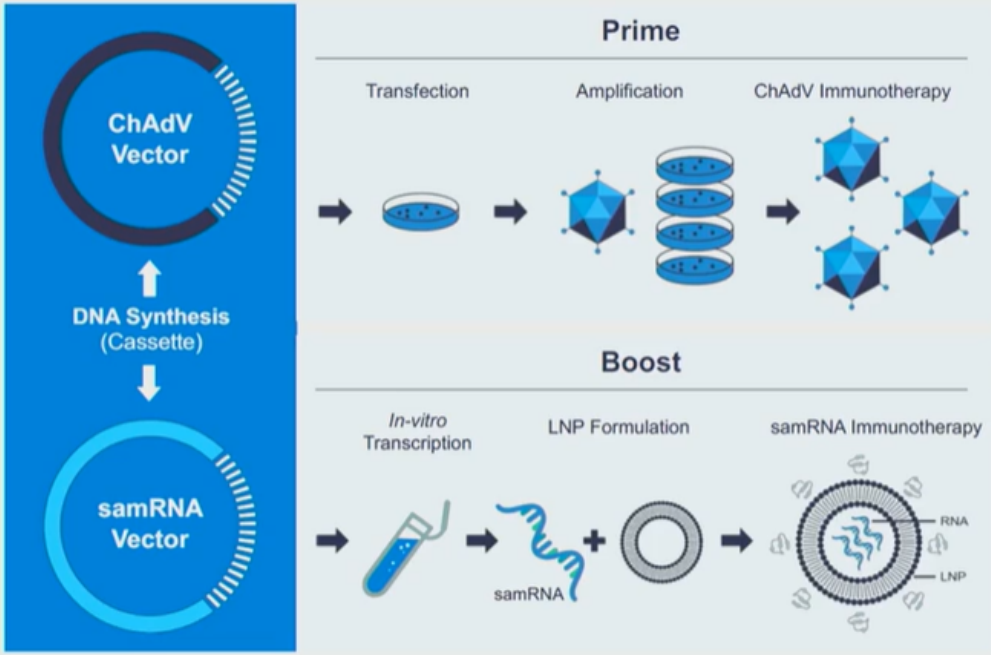
GS-1966 + GS-1144: A Novel Heterologous Therapeutic Vaccine Regimen for HIV

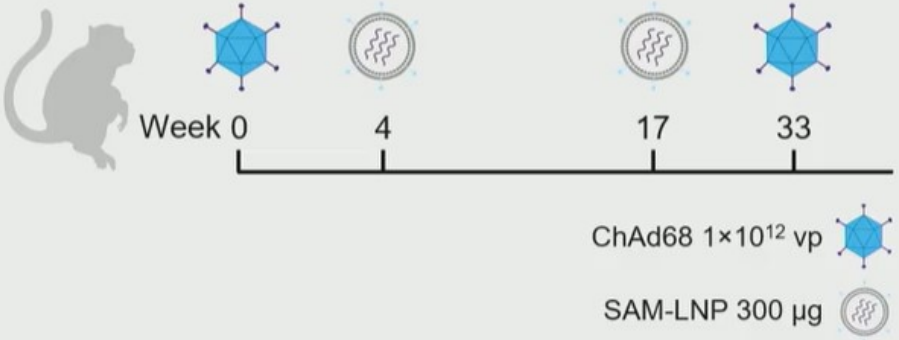
- Therapeutic vaccination to enhance HIV-specific T-cell immunity may be a key component of HIV cure strategies
- Gritstone's chimpanzee adenovirus vector (ChAd) + self-amplifying mRNA (samRNA) platform was shown to be safe and immunogenic in phase 1/2 oncology studies[1]
- **GS-1966:** ChAd
- **GS-1144:** samRNA packaged in lipid nanoparticles (LNPs)
- Both vectors encode a novel conserved HIV-1 immunogen that spans Gag, Pol, and Nef

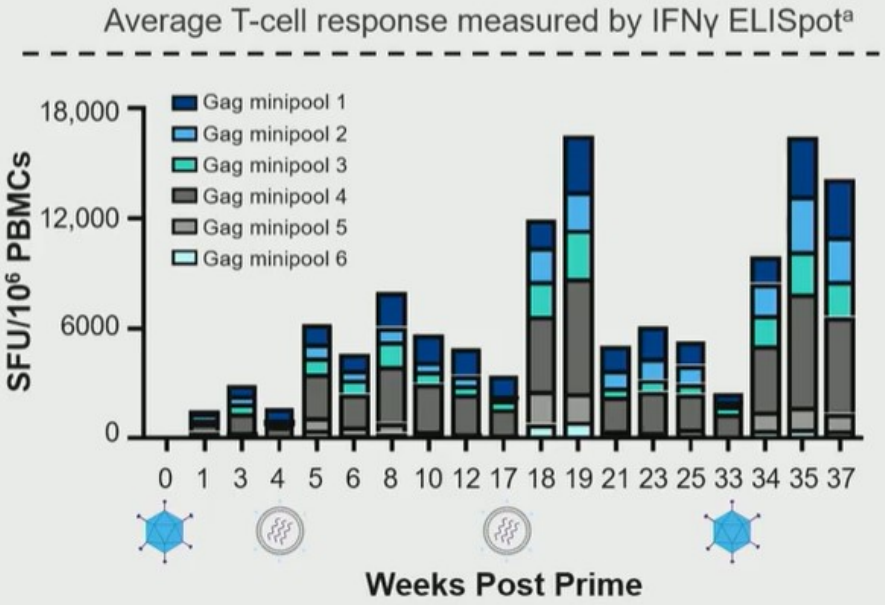


1. Palmer CD, et al. *Nat Med*. 2022;28:1619-1629.

Gritstone Vaccine Platform Elicited Strong & Broad T-Cell Responses in Non-Human Primates

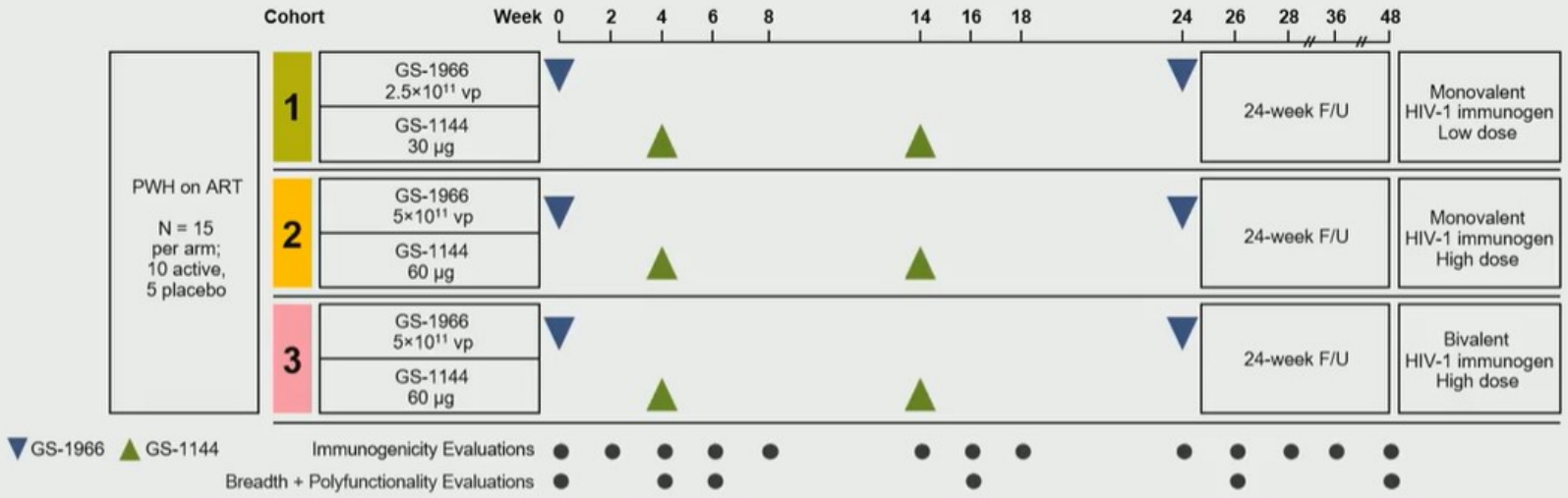
- Naïve rhesus macaques vaccinated with ChAd + samRNA expressing full-length SIV Gag immunogen
- Strong and broad T-cell responses were elicited to multiple Gag peptide pools





[a]Assay: IFNγ ELISpot, 6 overlapping Gag peptide pools, 20 peptides each; mean for each pool across animals shown (n = 6).
ELISpot, enzyme-linked immunosorbent spot; **IFN**, interferon; **PBMC**, peripheral blood mononuclear cell; **SEM**, standard error of mean; **SFU**, spot-forming unit; **VP**, virus particle.

Phase 1b Study Design: First in People With HIV on ART



Study Design

- Randomized, blinded, placebo-controlled
- 49 participants were enrolled: PWH virally suppressed on ART
  - 45 males and 4 females
  - Median age (Q1, Q3): 40 (33, 51) years
  - Median years since HIV diagnosis (Q1, Q3): 10 (6, 17) years
  - Plasma HIV-1 RNA levels < 50 copies/mL, CD4+ T-cell count > 350 cells/µL

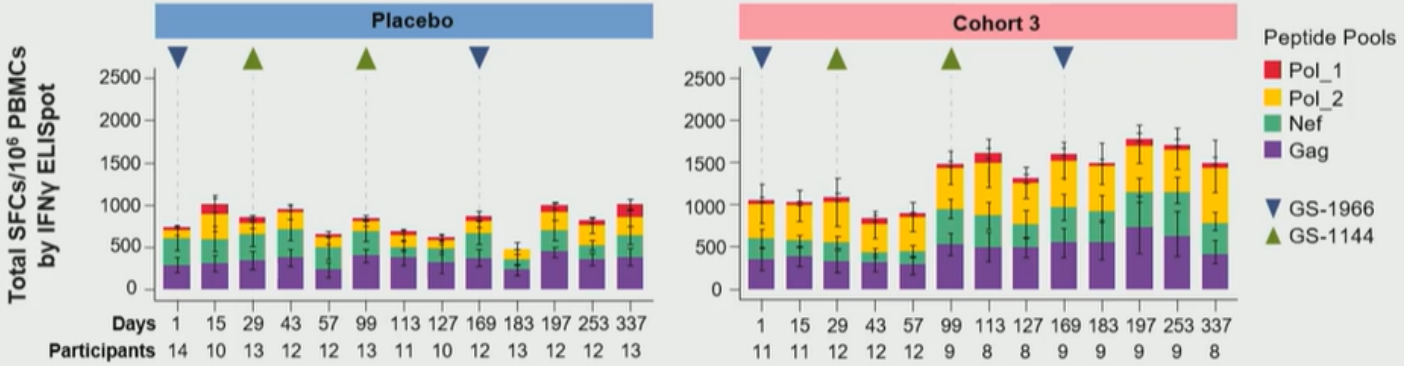
Objectives

- *Primary*: Safety and tolerability
- *Secondary*: Immunogenicity by IFNγ ELISpot
- *Exploratory*: Breadth and polyfunctionality of vaccine-specific T-cell response

ART, antiretroviral therapy; **ELISpot,** enzyme-linked immunosorbent spot; **F/U**, follow-up; **IFN,** interferon; **PWH**, people living with HIV; **Q**, quartile; **vp**, virus particles.

GS-1966 + GS-1144 Was Safe, Well Tolerated, and Induced Modest Vaccine-Specific T-Cell Responses

- GS-1966 + GS-1144 was safe and well tolerated
- Most common TEAEs included mild to moderate ISRs and transient flu-like symptoms
- Cohort 3 had the numerically largest change from baseline to peak T-cell response



Mean ± standard error of mean.

Immunogenicity, SFCs/10⁶ PMBCs	Placebo	Cohort 1	Cohort 2	Cohort 3	*P* value[a]
Peak, median (min, max)	1846 (605, 3172)	1169 (4, 8484)	1254 (175, 5672)	1860 (404, 5920)	0.53
Change from baseline to peak, median (min, max)	740 (86, 2848)	647 (0, 1612)	526 (0, 2888)	986 (400, 2490)	0.49

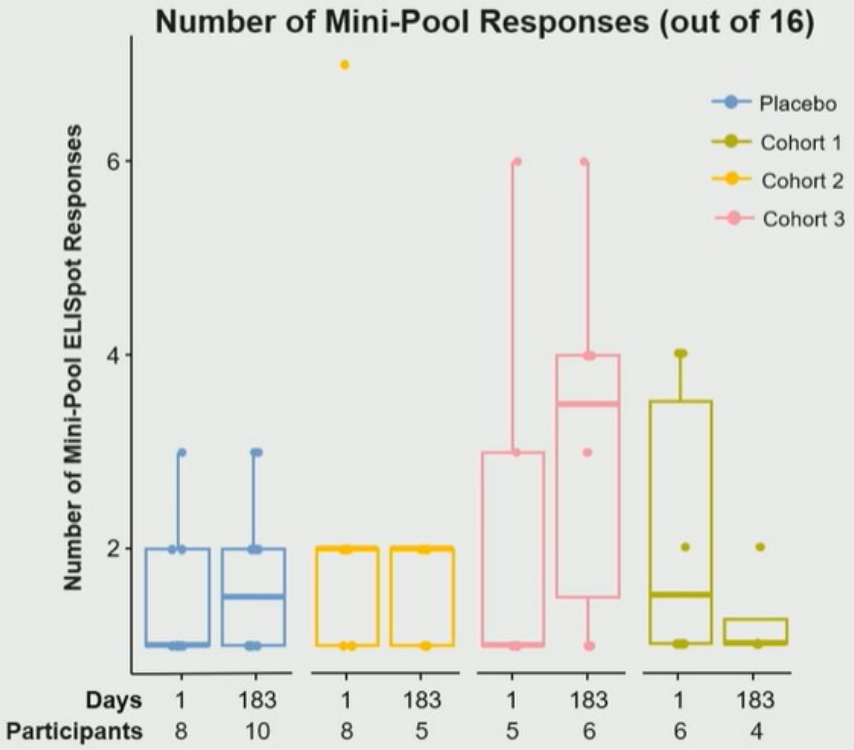
Validated IFNγ ELISpot using 4 peptide pools spanning vaccine insert; only participants with data for all 4 peptide pools are reported. Samples collected predose at vaccination timepoints.
IFNγ ELISpot, interferon-gamma enzyme-linked ImmunoSpot; **ISR**, injection-site reaction; **PBMC**, peripheral blood mononuclear cell; **SFC**, spot-forming cells; **TEAE**, treatment-emergent adverse event.
Benson CA, et al. Poster presented at: HIV Drug Therapy Glasgow; November 10-13, 2024; Glasgow, UK. Poster P211.

GS-1966 + GS-1144: Breadth of Vaccine-Specific T-Cell Response

- No significant differences in median number of mini-pool ELISpot responses over time or between cohorts
- Cohort 3 had the numerically highest number of mini-pool responses at end of vaccination (day 183)

Day 183 Breadth Metrics

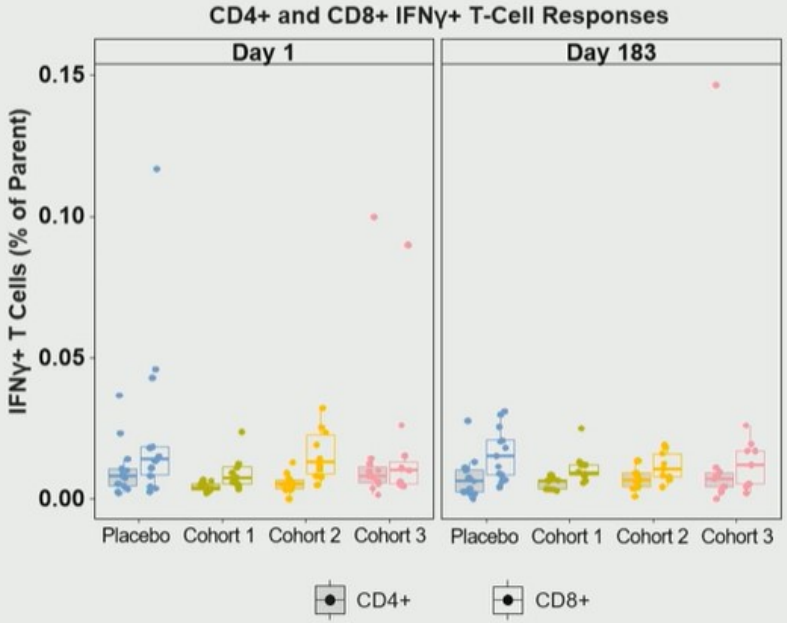
	Placebo	Cohort 1	Cohort 2	Cohort 3
Median No. Mini-Pool ELISpot Responses	1.5	1.0	2.0	3.0
Participants With ≥ 1 Gag Response, %	54%	38%	56%	62%



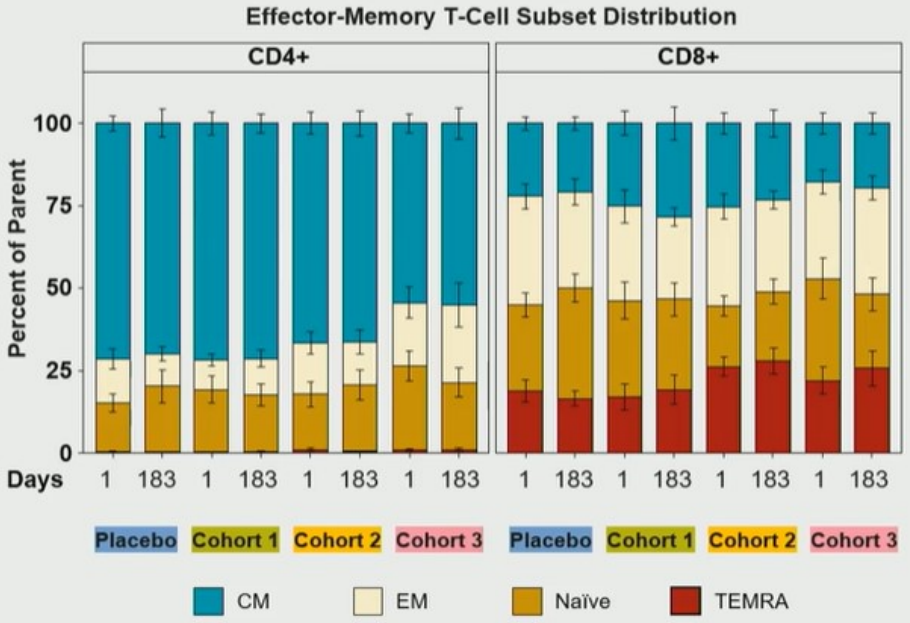
Only participants with data reported for all 16 peptide pools are included. Participants with responses below LOD for all 16 peptide pools were excluded.
Quantitative limit of detection = 1; cell viability > 70%.

GS-1966 + GS-1144 Induced Both CD4+ and CD8+ T-Cell Responses

- Vaccine-specific T-cell responses were CD8+ T-cell dominant, but CD4+ T-cell responses were also generated
- No changes in the frequency of effector-memory subsets were observed for CD4+ or CD8+ T cells



Median ± IQR; dot = mean; no statistical significance by Kruskal-Wallis test

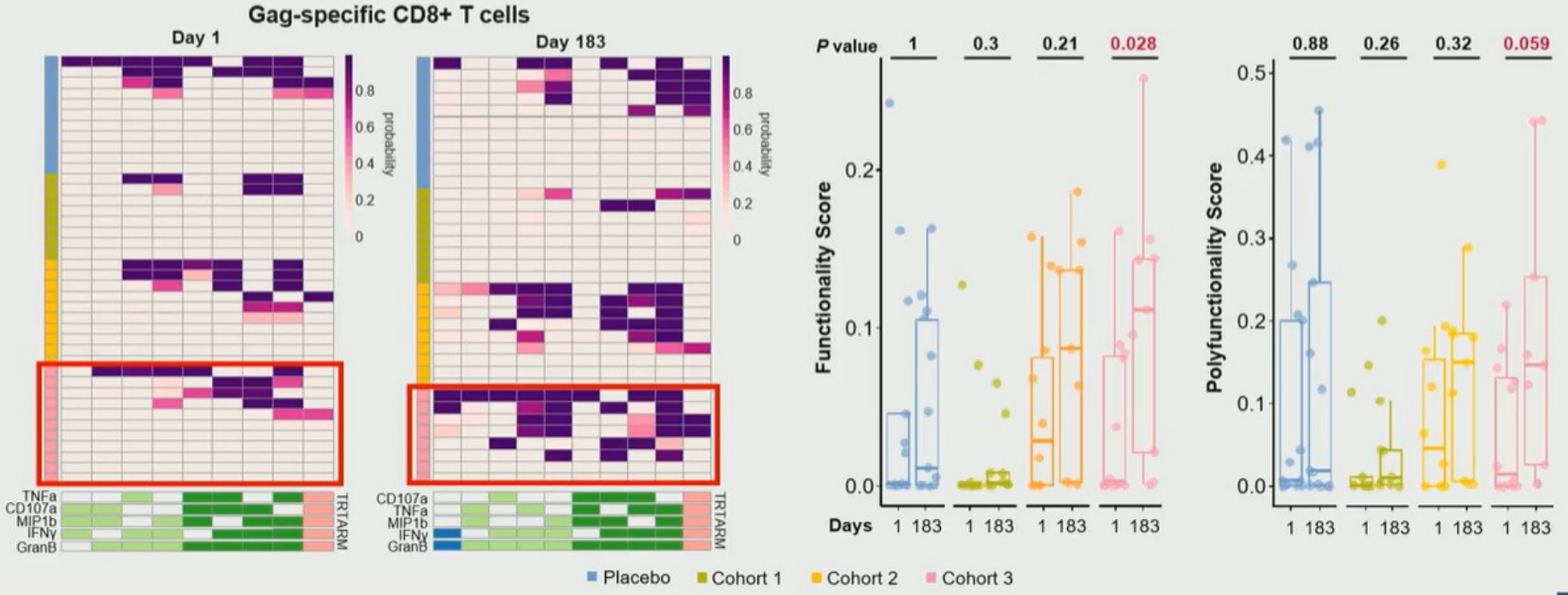


Mean across 4 vaccine peptide pools +/- SEM; no statistical significance by Kruskal-Wallis test

CM, central memory; **EM**, effector memory; **ICS**, intracellular cytokine staining; **IQR**, interquartile range; **SEM**, standard error of the mean; **TEMRA**, effector memory cells re-expressing CD45RA.

GS-1966 + GS-1144 Increased Polyfunctionality of Gag-Specific T Cells

- Increased polyfunctionality of Gag-specific CD8+ T cells observed in Cohort 3 at end of vaccination by COMPASS analysis



Assay: qualified intracellular cytokine staining (4 peptide pools).
Adjusted *P* values shown.

Conclusions

- In this phase 1b study in PWH on ART, GS-1966+GS-1144 administered at the highest dose with a bivalent immunogen (cohort 3) induced modest vaccine-specific T-cell responses
- Breadth of the vaccine-specific T-cell response was not significantly different over time or between cohorts
- Significant increases in Gag-specific T-cell polyfunctionality by COMPASS analysis were noted for both CD4+ and CD8+ T-cell in cohort 3
- Future studies are needed to optimize therapeutic vaccine strategies for HIV cure. Combination approaches will likely be needed to both reduce viral reservoir and enhance vaccine responses through immune modulation

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