RV546: ALFQ Adjuvant Improves T Cell Immune Responses to Late Boosting at Fractional Doses in Previously Vaccinated Volunteers

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Abstract

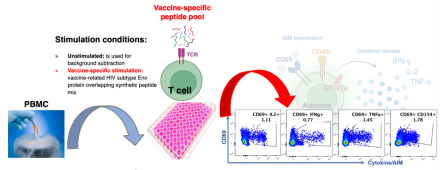
Background:
RV546 was designed to evaluate late boost strategies for people living without HIV who participated in the RV306 study administering RV144 vaccines with a late vaccine boost. Participants were enrolled into RV546 6-8 years post last vaccination for a single heterologous vaccine boost, with or without, the Army Liposomal Formulation with QS21 (ALFQ) adjuvant with full or fractional dosing.

Methods:
Eighty-one participants without HIV who had previously received a late boost of AIDSVAX®B/E (contains A244d11 gp120) with or without ALVAC (contains 92TH023 envelop and Gag Lai sequences) were enrolled to receive IHV01 (gp120-CD4 chimera subunit HIV-1 in aluminum phosphate) and A244d11 gp120 at full or fractional (one-fifth) dose with or without ALFQ or placebo. T cell immunogenicity was evaluated by flow cytometry-based AIM/ICS assay as CD69 co-expression with IFN-gamma, TNF-alpha, IL-2, or CD154 in the CD4 memory subpopulation at weeks 0, 2, 24, and 48 post-immunization. Polyfunctional score was calculated using the COMPASS R package. Total magnitude of immune response was calculated using the SPICE software. Placebo recipients were excluded from this analysis.

Results:
Significant durable T cell memory responses were observed to A244d11 gp120 and 92TH023 but not to Gag (Lai) components of AIDVAX-B/E and ALVAC-HIV vaccines 6-8 years post-final immunization in RV306 prior to late boosting in RV546. CD4 T cells responded to both IHV01 chimera protein and A244 gp120 env vaccine components. Most of cytokine responses, especially IFN-gamma, and polyfunctional scores significantly increased in CD4 memory T cells relative to pre-vaccination. These responses peaked at week 2, IFN-gamma and polyfunctional scores were maintained through week 48 for all study groups. While ALFQ did not increase T cell responses in full dose groups, ALFQ significantly improved fractional dose performance for IFN-gamma, TNF-alpha, and IL-2 production and for total magnitude of immune response. ALFQ significantly improved durability of the responses to A244d11 envelop but not IHV01 chimera protein in fractional dose groups. We also observed significantly better IFN-gamma responses post-fractional dose with ALFQ compared to full dose plus ALFQ at peak response.

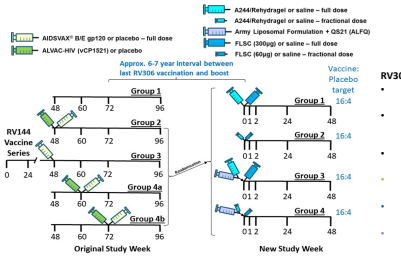
Conclusions:
In vaccine-experienced participants, inclusion of ALFQ with the protein boost improves the magnitude of T cell responses when fractional vaccine doses are administered.

Methods



Primary measurements for CD4 T cells:
AIM: Activation Induced Marker (measured by flow cytometry)
ICS: Intracellular Cytokine Staining (measured by flow cytometry)
CD69 co-expression with IFN-γ, TNF-α, IL-2, or CD154 (CD40L) in CD4 memory (all but naïve) subpopulation
Polyfunctional Score: COMPASS calculated from flow cytometry data
is a measure of quality of immune response and reflects what proportion of activated cells express more than one activation parameter. As more parameters are expressed as higher the Score (max Score is 1).

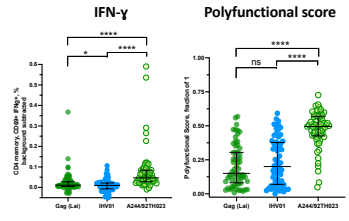
Trial Background



RV306-RV546 Vaccine products cross-talk:
- RV306 AIDVAX-B/E has the same A244 Env as RV546 A244.
- RV306 ALVAC-HIV contains **92TH023** env that is CRF01-AE as is **A244** and two env **are identical in V2 region**.
- RV306 AIDVAX-B/E contains Subtype B MN env and IHV01 contains Subtype B Bal env.
- ALVAC-HIV contains Gag (Lai, subtype B) which is unique for RV306.
- IHV01 contains human CD4-D1D2 which is unique for RV546.
- ALFQ is unique for RV546.

Group1: Full Dose, no ALFQ
Group2: Fractional Dose, no ALFQ
Group3: Full Dose, with ALFQ
Group4: Fractional Dose, with ALFQ

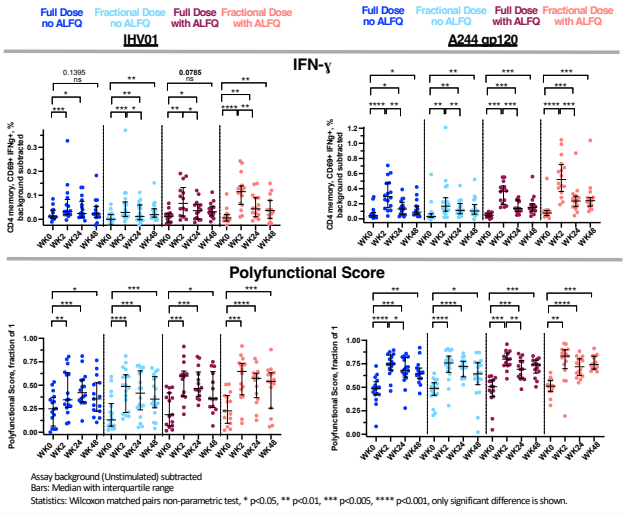
Results, Part I
Pre-existing T cell Memory Responses



RV546 Week 0, 6-7 years after RV306

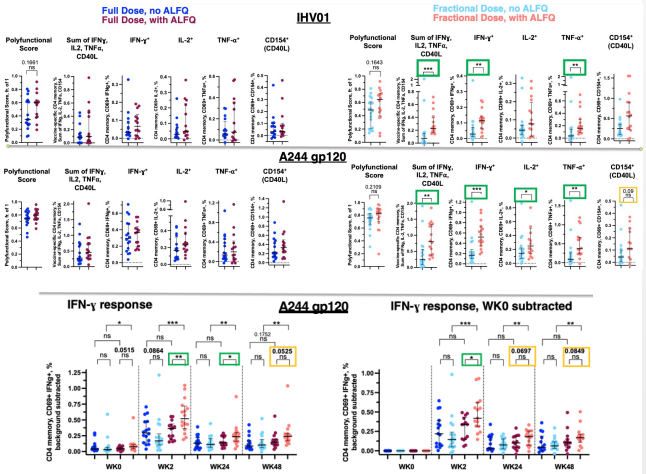
RV546 groups combined
Assay background (Unstimulated) subtracted
Bars: Median with interquartile range
Statistics: Wilcoxon matched pairs non-parametric test, * p<0.05, **** p<0.001, ns non-significant.

Results, Part II
Responses Increase Post-Vaccination



Assay background (Unstimulated) subtracted
Bars: Median with interquartile range
Statistics: Wilcoxon matched pairs non-parametric test, * p<0.05, ** p<0.01, *** p<0.005, **** p<0.001, only significant difference is shown.

Results, Part III: ALFQ Improves CD4 T cell Responses post-Fractional Dosage (Week 2, peak)



Assay background (Unstimulated) subtracted. Bars: Median with interquartile range
Statistics: Mann-Whiney unpaired non-parametric test, * p<0.05, ** p<0.01, *** p<0.005, only significant difference is shown.

Conclusions

- **A244/92TH023 specific CD4 T cells detected 6~7 years after last immunization in RV306.**
- **CD4 T cells responded to both RV546 vaccine components, peaking at week 2, and maintained at week 48.**
- **ALFQ increased the magnitude and durability and CD4 T cell responses when using fractional dosage.**

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