Rectal Microbiome Associations with HIV Vaccine-Induced Binding Antibody Responses in RV306

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BACKGROUND

The RV306 trial[1] tested late boosts of the RV144 vaccine regimen, the first and only large HIV vaccine clinical trial to show a modest protective effect to HIV-1 acquisition (~31%)[2]. Immune-correlates analyses of RV144 identified plasma IgG antibodies binding to the V1V2 region of HIV-1 envelope as inversely correlated to infection risk[3].

The rectal mucosa is a major portal for HIV-1 entry and harbors a microbial community that plays a critical role in shaping local immune homeostasis[4].

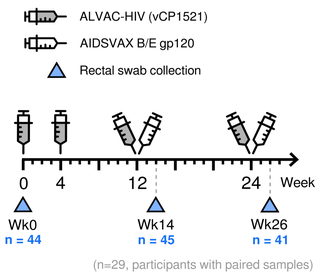
We investigated interactions between the rectal microbiome and vaccine-induced binding antibody (bAb) responses in the RV144 vaccine series of the RV306 study design.

METHODS

Rectal swabs were collected from male participants in the RV306 active arm and analyzed using shotgun metagenomic sequencing (***Figs. 1 and 2***).

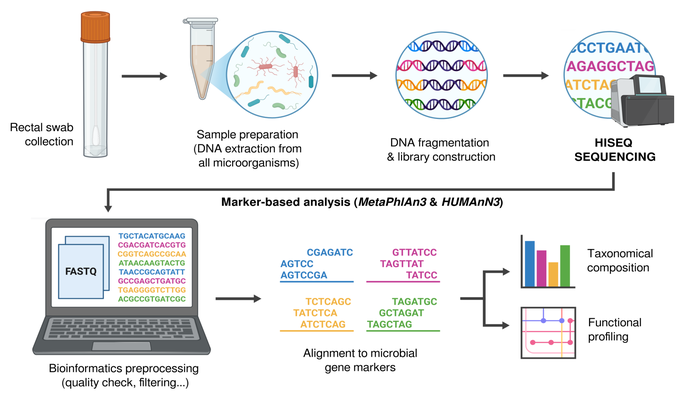
Participants were classified as high and low responders based on bAb levels at Wk26.

Figure 1. Study design and rectal sample collection among RV306 participants



MaAsLin2 was used for differential abundance (DA) analyses.

Figure 2. Shotgun metagenomic sequencing overview



Gut bacteria are linked to higher bAb levels induced by a preventive HIV vaccine, suggesting a potential role in modulating vaccine-induced immunity.

RESULTS

- Distinct core bacterial taxa discriminated high and low responders for each plasma IgG bAb at Wk26 (***Fig. 3***).
- No significant differences were detected between high and low responders at Wk0.
- Consistently high responders across all four bAbs compared were enriched in *Mediterraneibacter gnavus* (ex *Ruminococcus gnavus*) and depleted in *Dorea formicigenerans* and *Anaerobutyricum hallii* (ex *Eubacterium hallii*) (***Fig. 4***).
- Despite weak, non-significant correlations, taxa enriched in high responders positively associated with neutrophil levels and negatively with lymphocyte levels. In contrast, depleted taxa showed the opposite correlation trend (***Fig. 5***).

Figure 3. Differentially abundant bacterial species at Wk26

Bacteroides caccae	▲	***Anaerobutyricum hallii***	▼▼
Bacteroides finegoldii	▲▲	*Bacteroides eggerthii*	▼
Bifidobacterium longum	▲	*Dialister pneumosintes*	▼
Blautia hansenii	▲	***Dorea formicigenerans***	▼▼▼
Blautia sp. CAG:257	▲▲	*Eubacterium ramulus*	▼
Clostridium innocuum	▲	*Eubacterium siraeum*	▼▼
Flavonifractor plautii	▲	*Mediterraneibacter lactaris*	▼
Mediterraneibacter gnavus	▲▲▲▲	*Mediterraneibacter torques*	▼▼
Phocaeicola coprocola	▲	*Oscillibacter sp. 57_20*	▼
Phocaeicola coprophilus	▲	*Prevotella sp. CAG:520*	▼
Phocaeicola dorei	▲	*Pseudocoprococcus catus*	▼▼
Phocaeicola plebeius	▲		

▲ Enriched in High responders
▼ Depleted in High responders

- IgG gp70-V1V2 CaseA2
- IgG gp70-V1V2 92TH023
- IgG gp120 MNgD-D11
- IgG1 gp120 A244gD-D11
- Consistent response among bAbs

Figure 4. Abundance boxplots of species in the subset with consistent responses among bAbs

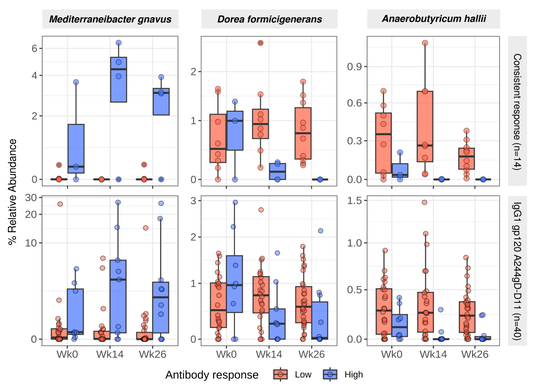


Figure 5. Correlations of discriminant bacteria with neutrophil and lymphocyte percentage at Wk0 and Wk26

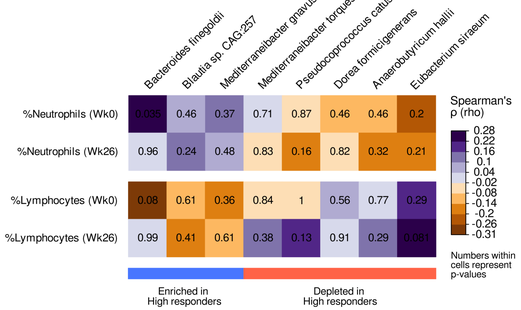
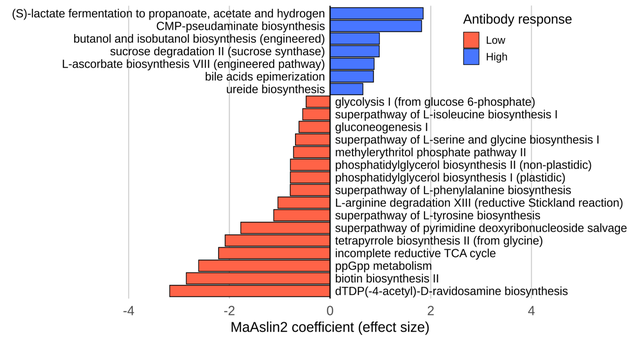


Figure 6. Discriminant microbial metabolic pathways at Wk26



- At community-level, consistently high responders positively associated with pathways involved in short chain fatty acids (SCFAs) and bile acids production. In comparison, low responders showed a more general functional capacity (***Fig. 6***).
- Linked to inflammatory bowel diseases, *M. gnavus* has shown the potential to modify bile acids in the gut[5] and to produce pro-inflammatory polysaccharides[6]. However, marked strain-level diversity may explain inconsistent results across vaccine studies[7,8].
- *D. formicigenerans* and *A. hallii*, similarly to *M. gnavus*, are members of the *Lachnospiraceae* family known for being SCFA-producing bacteria and potential modulators of vaccine-induced immune responses[9].

CONCLUSIONS

Results suggest that a transient shift from an SCFA-dominated gut environment toward a more immune-stimulatory microbiome may support higher HIV-specific bAb levels induced by the RV144 prime/boost vaccine regimen.

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ADDITIONAL KEY INFORMATION

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