IMPACT OF GUT MICROBIOTA ON IMMUNOGENICITY TO COVID-19 VACCINES IN PLWH

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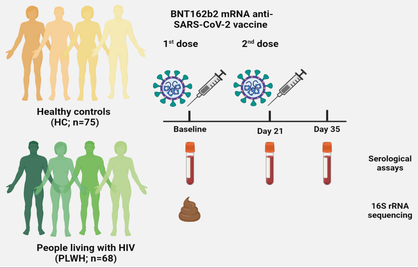
BACKGROUND

Although mRNA SARS-CoV-2 vaccines are generally safe and effective, in certain immunocompromised individuals they can elicit poor immunogenic responses. Among these individuals, **people living with HIV (PLWH) have poor immunogenicity** to several oral and parenteral vaccines. As the **gut microbiome is known to affect vaccine immunogenicity**, we investigated whether baseline gut microbiota predicts immune responses to the BNT162b2 mRNA SARS-CoV-2 vaccine in healthy controls (HC) and PLWH after two doses of BNT162b2. Here, we showed for the. first time that the gut microbial composition influences the response to BNT162b2 in PLWH.

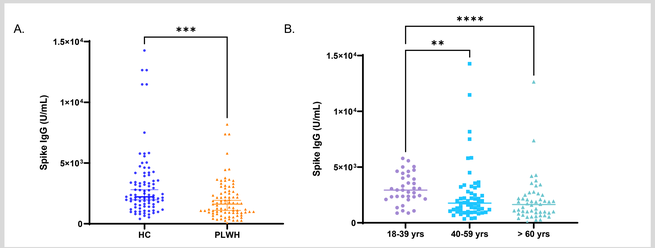
STUDY DESIGN

16S rRNA sequencing was performed on DNA extracted from fecal samples collected from PLWH (n=68) and HC (n=75) prior to vaccination. Humoral and cellular responses to the SARS-CoV-2 vaccine were evaluated on day 35 after the first dose. Specialized bioinformatic tools were used for predicting bacterial communities. Associations between gut microbiota and SARS-CoV-2 spike IgG antibody levels, spike CD4⁺ T-cell responses, total baseline IgG, and clinical parameters such as age, gender, and body mass index (BMI) were analyzed.



RESULTS

PLWH and elderly individuals displayed less immunogenicity to the BNT162b2 vaccine

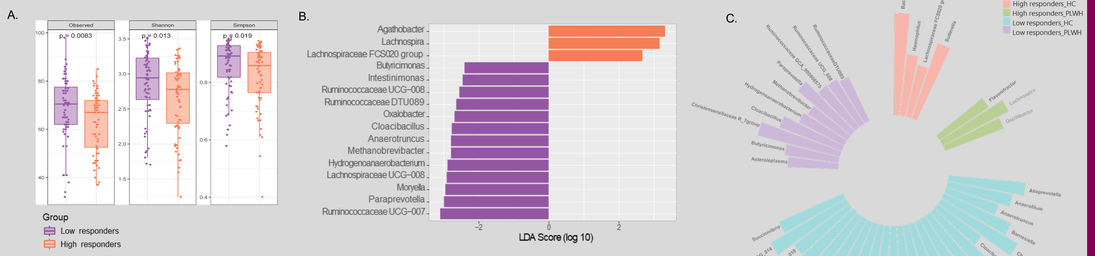


Changes in the spike IgG levels between **(A)** Healthy controls (HC) and people living with HIV (PLWH), **(B)** Individuals in different age groups, 18-39, 40-59 and >60 years.

HIGHLIGHTS

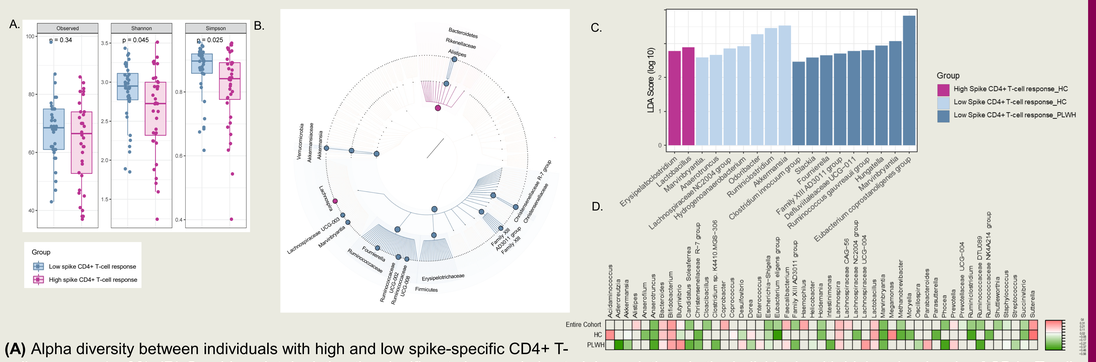
- We showed for the first time that the gut microbial diversity strongly correlates with responses to the BNT162b2 vaccine in PLWH.
- HC developed significantly higher spike IgG titers than PLWH.
- Individuals with high spike IgG titers and high spike-specific CD4+ T-cell responses against SARS-CoV-2 showed lower α-diversity in the gut, both in the whole cohort and within the subgroups of HC and PLWH.
- *Bifidobacterium* and *Faecalibacterium* were the microbial markers of individuals with higher spike IgG levels.
- Immunomodulatory bacteria such as *Agathobacter*, *Lactobacillus, Bacteroides*, and *Lachnospira* correlated positively with both spike IgG levels and spike-specific CD4⁺ T-cell responses.
- Overall, we found a significant association of bacterial abundance (Shannon p=0.02, Simpson p=0.019) with spike IgG levels, independent of age.

Bacterial diversity is lower in individuals with higher spike IgG titers



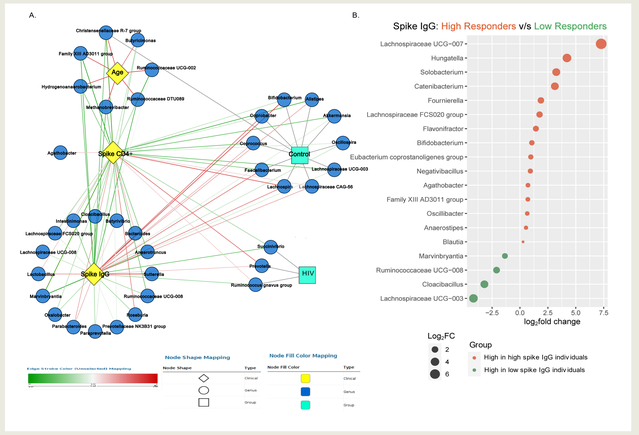
(A) Alpha diversity decreased significantly in individuals with high spike IgG titers in the entire cohort (n=143). **(B)** Differentially abundant bacterial genus between individuals with high and low spike IgG as detected by LEfSe . **(C)** Circular plot depicting the significant microbial biomarkers abundant in either the high responders or low responders in both the HC and PLWH group via LEfSe analysis.

Spike-specific CD4+ T-cell response shows negative association with α-diversity



(A) Alpha diversity between individuals with high and low spike-specific CD4+ T-cell response (n=90). **(B)** Graphlan plot depicting the significant changes in bacterial populations in the individuals with high or low levels of CD4+ T-cell response. **(C)** Differences in the richness of bacterial genus between the people with high and low CD4+ T-cell responses to spike protein within the HC and PLWH group via LEfSe analysis. **(D)** Spearman correlation for associating the CD4+ T-cell responses-specific microbiome with antibody levels.

Gut microbiota α-diversity and composition are associated with spike IgG levels irrespective of age



	p value	Beta Coefficient
Observed	0.05	-0.16
Shannon	0.01	-0.20
Simpson	0.01	-0.20
Age	0.03	-0.17
Gender	0.73	0.02
Total IgG	0.09	-0.14
BMI	0.78	-0.02
Observed, Age	0.04	-0.76
Shannon, Age	0.02	-0.04
Simpson, Age	0.01	0.22

Table: Univariate and multivariate regression analysis for analyzing the linear relationship between baseline characteristics and Spike IgG response among individuals.

(A) Network analysis of linking different bacterial genus to clinical factors such as spike IgG levels on day 35, age, and spike-specific CD4⁺ T-cell responses. **(B)** DESeq2 analysis to compensate and normalize different clinical parameters, such as age, gender, disease group, to further determine the differential abundance of different microbes associated with spike IgG.

CONCLUSION

In this entire cohort, gender, BMI, and baseline total IgG levels did not affect the spike IgG titers but **age showed negative correlation with spike IgG** (p=0.04). HC showed significantly higher spike IgG titers as compared to the PLWH (p=0.0001). Within the PLWH group, *Flavonifractor*, *Lachnospira*, and *Oscillibacter* were markers of indivdiuals with high spike IgG levels. Bacterial diversity was observed to be lower in individuals with higher spike IgG titers and higher spike-specific CD4⁺ T-cell response. In summary, microbial abundance was observed to be independent of age and influenced spike IgG levels. This study will, therefore, stimulate further search for microbiome predictors of poor vaccine response as well as identify novel microbiome-based therapies to improve the vaccine immunogenicity.

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