Prior COVID-19 Alters Antibody Function In ART-Suppressed PWH Receiving SARS- CoV2 Vaccination

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INTRODUCTION

Anti-SARS-Cov-2 vaccine-induced neutralizing antibodies are crucial to protection; however, other immune system components like T cell- and Fc-mediated responses also play a role in fighting COVID-19.

Newer SARS-Cov-2 variants show reduced sensitivity to the antibodies elicited by vaccination or administered therapeutically, and bi-specific booster vaccines targeting specific Omicron variants are currently recommended.

Most people with HIV (PWH) who receive suppressive ART develop vaccine-driven immune responses (anti-RBD antibodies, RBD/ACE binding competition and neutralization) that are comparable with those of healthy controls.

However, PWH with low CD4 count, other health conditions, African American ethnicity, and age over 65 have higher risk of severe COVID-19 and death. In PWH booster vaccine doses (i.e. administered after the initial 2-dose schedule) increase antibody response in PWH, but not T-cell response.

In this report we analyze the immune response to anti-SARS-Cov-2 vaccination in PWH with or without a diagnosis of COVID-19 prior to vaccination.

METHODS

Study participants were enrolled at the Philadelphia FIGHT Jonathan Lax Treatment Center, Philadelphia, PA under a protocol approved by the Philadelphia FIGHT IRB.

Sampling: blood was collected prior to COVID-19 first and second vaccination, and after 3 and 6 months.

Homogenous time resolved fluorescence (HTRF) assays was used to measure the ability of plasma to block the interaction of SARS-Cov-2 with ACE2

Serum antibody binding assays were performed using an ELISA method.

Integrated HIV proviral DNA was assessed using Alu-gag RT-PCR on CD4+ T cells. Time to viremia: days to first VL > 50 copies/ml off ART.

Cell viability protection assays were performed with VERO-E6 cells and serial dilutions of USA-WA1/2020 SARS-CoV-2

Titers of N-, S1-, and RBD-specific antibodies were measured using the MSD V-PLEX multiplex assay.

ADCD: ACE-2 CHO pulsed with biotinylated SARS-CoV-2 S1 or RBD protein were treated with purified IgG, followed by guinea pig complement, and stained with goat anti-guinea pig C3-FITC

ADCP: Purified plasma IgG antibodies were analyzed for their ability to mediate phagocytosis of S1 and RBD antigen-coated fluorescent beads by THP1 cells.

ADCC: NK cell degranulation (CD107) and intracellular cytokine production (IFN-g and TNF-a) were measured after exposure to S1- and RBD-pulsed (ACE2)-CHO cells using flow cytometry

T cell responses to SARS-Cov-2 peptide pools (12-17-mer, 10 AA overlap) derived from spike (5 pools), nucleocapsid (2 pools), membrane (1 pool), and envelope (1 pool) proteins were measured using IFN-g ELISPOT

SARS-CoV-2 Pseudovirus neutralization assay was performed testing the ability of participants' sera to neutralize the infection of CHO-ACE2 cells with Luc-tagged SARS-CoV-2 pseudovirus (IgE-SARS-CoV-2 S-BA.1 and IgE-SARS-CoV-2 S-BA.2) using a using britelite plus luminescence reporter gene assay

Statistical analysis: changes from baseline and between visits were assessed using the Wilcoxon signed rank test; p values were adjusted for multiple testing (Benjamini Hochberg FDR)

1. Study population

Baseline characteristics

		GROUP	
		HIV^{POS} COVID^{NEG}	HIV^{POS} COVID^{POS}
Sex (n)	Female	8	9
	Male	12	15
Race (n)	Black/African American	13	18
	White	7	6
Ethnicity (n)	Hispanic/Latinx	3	4
	Non-Hispanic/Latinx	17	20
Other	CD4 count (mean; SD)	811; 368	750; 307
	AGE (mean; SD)	50.75; 9.6	50.2; 12.3
Vaccination ** Only contributed baseline measures*	Moderna (2x)	14	22
	Pfizer (2x)	4	1
	Other/incomplete record*	2	1

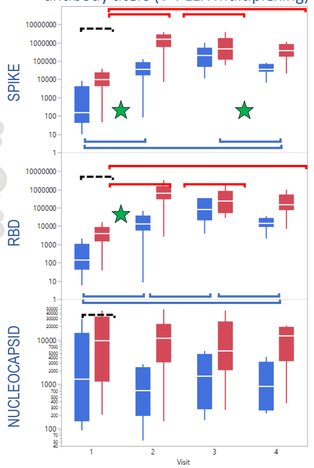
Sampling timeline

VISIT 1 • Before 1st dose → VISIT 2 • Before 2nd dose → VISIT 3 • 3 months → VISIT 4 • 6 months

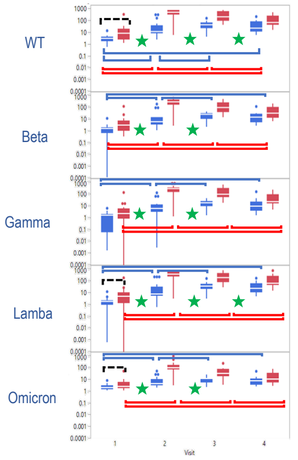
2.Antibody response to anti-SARS-Cov-2 vaccination.

Prior COVID-19 results in enhanced Ab response to vaccination

Anti-Spike S-1, RBD, and nucleocapside antibody titers (V-PLEX multiplexing)



Inhibition of ACE-Spike variants interaction by plasma antibodies (HTRF)



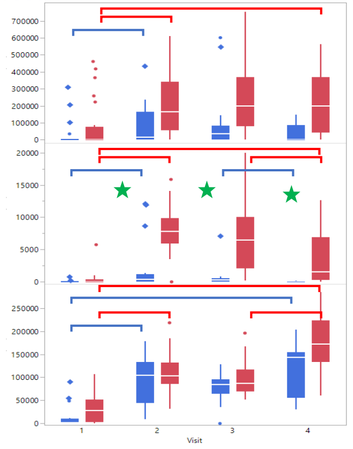
3. Functional characterization.

Prior COVID-19 results in enhanced ADCD and neutralizing activity after vaccination

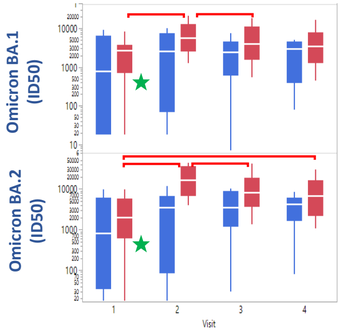
Antibody-Dependent Cell-mediated Cytotoxicity (ADCC)

Antibody-Dependent Complement Deposition (ADCC)

Antibody-Dependent Cell Phagocytosis (ADCP)



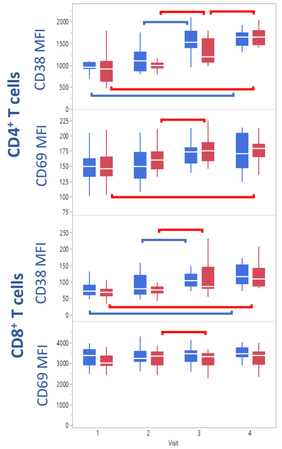
Pseudovirus neutralization assay



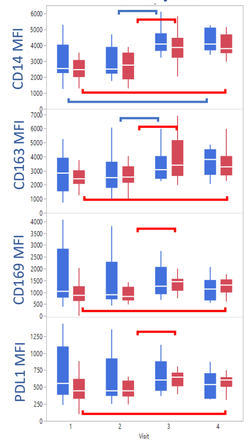
4. Immune activation and T-cell responses to SARS-Cov-2 and HIV.

Evidence for increased leukocyte immune activation was noted after second dose in both groups with higher persisting activation in those with prior COVID-19. T-cell responses to SARS-Cov-2 spike rose in both groups after vacconation, while anti-HIV responses were not affected.

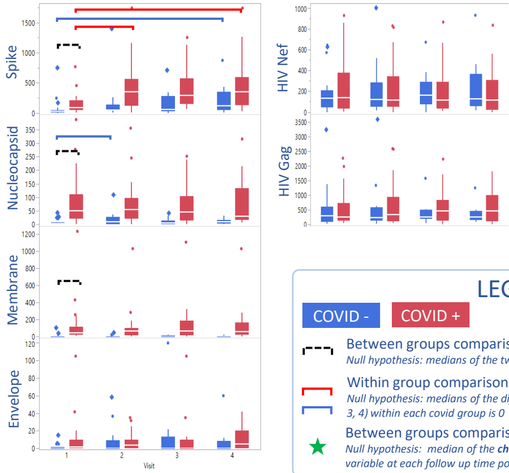
T cells



Monocytes



T-cell ELISPOT (IFN-γ)



LEGEND

COVID - COVID +

Between groups comparisons at the same time point, P<0.05.
Null hypothesis: medians of the two groups at V1 are equal

Within group comparisons between time points, P<0.05.
Null hypothesis: medians of the difference from baseline after vaccination (at visit 2, 3, 4) within each covid group is 0

Between groups comparison of change over time, P<0.05.
*Null hypothesis: median of the **change (difference) from baseline (visit 1)** of each variable at each follow up time point **(visit 2, 3, and 4)** for the two groups are equal*

CONCLUSIONS

- In HIV-infected, ART-suppressed individuals, prior COVID-19 infection results in an enhanced antibody and T-cell responses to RNA-based vaccines, particularly after the first vaccine dose.
- In both groups, vaccination induced production of anti-spike antibodies that reacted with all variants tested.
- Vaccination resulted in increased non-neutralizing functional responses (ADCC, ADCD, and ADCP) in both COVID-19-exposed and naïve individuals.
- The vaccine-induced ADCD was greater in COVID-exposed individuals at all time points
- Neutralizing activity towards later strains (Omicron BA.1 and BA.2) was also greater in COVID-19-exposed individuals.
- We observe significant difference in vaccine-induced cellular activation after second dose with higher retention of activation in COVID-19-exposed a
- Vaccination resulted in increased anti-Spike T-cell-mediated responses, but not in anti-HIV Gag or Nef responses (no LRA effect).