Hybrid Immunity in People With HIV Is Shaped by Inflammasome-Driven Innate and Adaptive Responses

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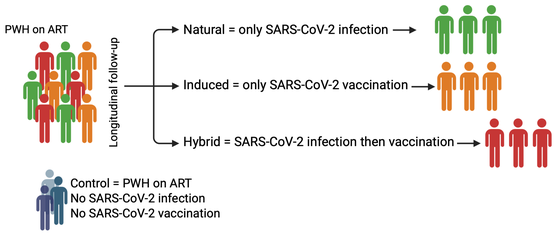
BACKGROUND

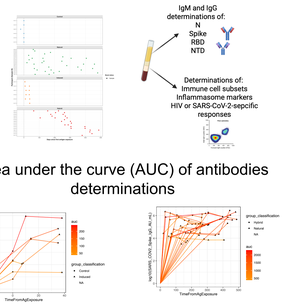
The immune responses generated by vaccination, natural infection, or a combination of both ("hybrid immunity") are central to protection against viral pathogens. Understanding the magnitude, quality, and durability of these responses in people with HIV (PWH) is critical for informing prevention strategies and guiding immunization policies for this population.

SARS-CoV-2 infection in PWH preferentially enhanced inflammasome activation, whereas vaccination primarily strengthened adaptive immunity, promoting effector/memory programs and antigen-specific CD4⁺ T cell responses.
Hybrid immunity integrates innate and adaptive arms, promoting durable T cell memory and higher Spike/RBD antibody titers than infection or vaccination alone.

METHODS

Antiretroviral (ART)-treated PWH were recruited at the Grady Ponce Center in Atlanta (n=36) in 2021





Area under the curve (AUC) of antibodies determinations

The intercept and slope of 1161 plasma cytokines and flow cytometry parameters were calculated using a linear mixed-effects models (LMMs) to test both slope and intercept differences between groups

RESULTS

SARS-CoV-2 infection markedly enhanced inflammasome activity, with T, B, and innate cells showing increased ASC formation and active Caspase-1. Vaccination strengthened adaptive immunity through transcriptional programs supporting effector and memory T cell function. Hybrid immunization, where infection primed innate responses and vaccination reinforced adaptive immunity, elicited superior outcomes across both arms. This included sustained elevations of plasma IFN-γ and IL-15, and enhanced T cell effector functions yielding robust long-term memory (CD4 TCM/TSCM and CD8 TCM/TEM). Moreover, hybrid immunity generated significantly higher antibody titers against SARS-CoV-2 Spike and RBD compared with infection or vaccination alone.

Distinct Immune Signatures Associated with Natural SARS-CoV-2 Infection, Vaccine-Induced Immunity, and Hybrid Immunity

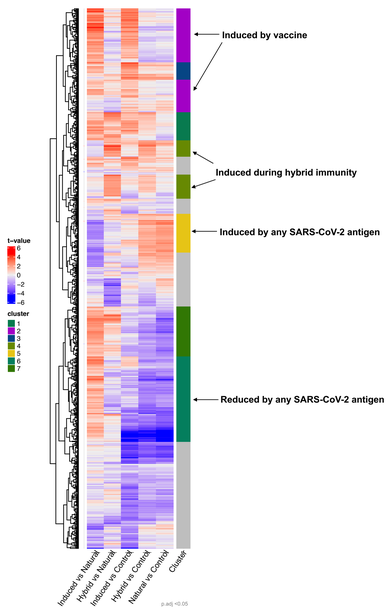


Figure 1. Immune clusters linked to infection, vaccination, or hybrid immunity. Heatmap of t-values from linear mixed-effects models of 1,161 plasma cytokine and antibodies plus flow cytometry parameters (intercept differences between groups; FDR < 0.05). Red = higher, blue = lower. Rows are clustered; Columns indicate groups comparisons, side bar indicates cluster IDs.

SARS-CoV-2 Infection Enhances MCP-3 Production and Inflammasome Activation Across T, B, and Innate Cells

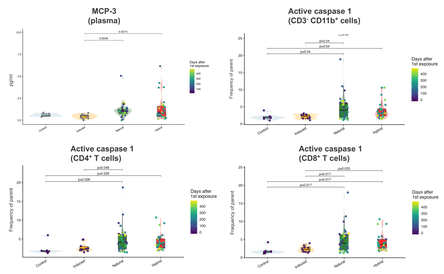


Figure 2. Representative plots (4 of 69 parameters induced by SARS-CoV-2 infection only) showing plasma MCP-3 (pg/ml) and frequency of active caspase-1⁺ cells in CD3⁻CD11b⁺ myeloid cells, CD4⁺ T cells, and CD8⁺ T cells across Control, Vaccine (Induced), Natural infection, and Hybrid groups. Violin plots with overlaid individual data points; colors of dots indicate days after first exposure. p values denote pairwise group comparisons from linear mixed model.

Vaccine-Induced Immunity Is Characterized by increased Stem-Like CD8⁺ T Cell–Associated Activation programs and NLRP3 Inflammasome Activation

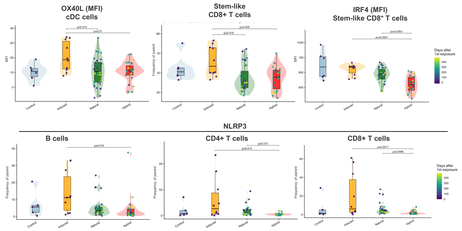


Figure 3. Representative plots of vaccine-induced immune parameters. Increased OX40L (MFI) in cDCs, frequency of and expression of IRF4 instem-like CD8⁺ T cells, Bottom plots: NLRP3 expression in B, CD4⁺ and CD8⁺ T cells across Control, Induced (Vaccine), Natural, and Hybrid groups. Violin plots display distributions with individual data points overlaid color-coded by days after first antigen exposure. p values represent pairwise group comparisons derived from linear mixed-effects models.

Hybrid Immunity Is Associated with Enhanced T Cell Effector Function and Durable Memory Differentiation

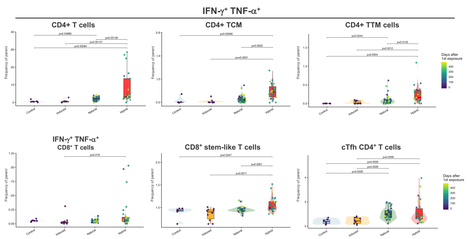
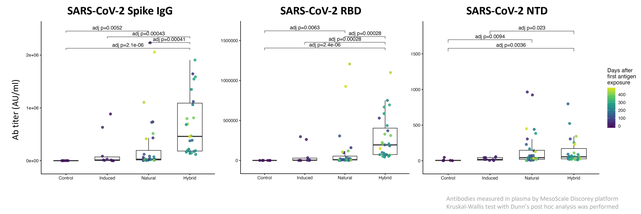


Figure 4. Representative plots showing immune parameters enriched in hybrid immunity. Frequencies of IFN-γ⁺TNF-α⁺ CD4⁺ and CD8⁺ T cells, cytokine-producing CD4⁺ TCM and TEM subsets, stem-like CD8⁺ T cells, and circulating Tfh (cTfh) CD4⁺ T cells across Control, Vaccine (Induced), Natural, and Hybrid groups. Violin plots display distributions with overlaid individual data points; colors indicate days after first exposure. P values derive from pairwise group comparisons using linear mixed-effects models.

Hybrid immunity induced higher levels of Spike, RBD, and NTD IgG antibodies



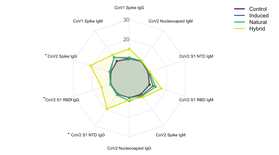


Figure 5. Plasma antibodies measured by MesoScale Discovery platform across Control, Vaccine (Induced), Natural, and Hybrid groups. Top panels show antigen-specific Ig levels with individual points color-coded by days after first antigen exposure; adjusted *p* values from Kruskal–Wallis with Dunn's post hoc are shown. Bottom radar plot summarizes relative IgG/IgM breadth across Spike/RBD/NTD/Nucleocapsid, highlighting enhanced responses in hybrid immunity.

Hybrid Immunity Balances Innate and Adaptive Immune Programs Associated with SARS-CoV-2 Antibody Responses

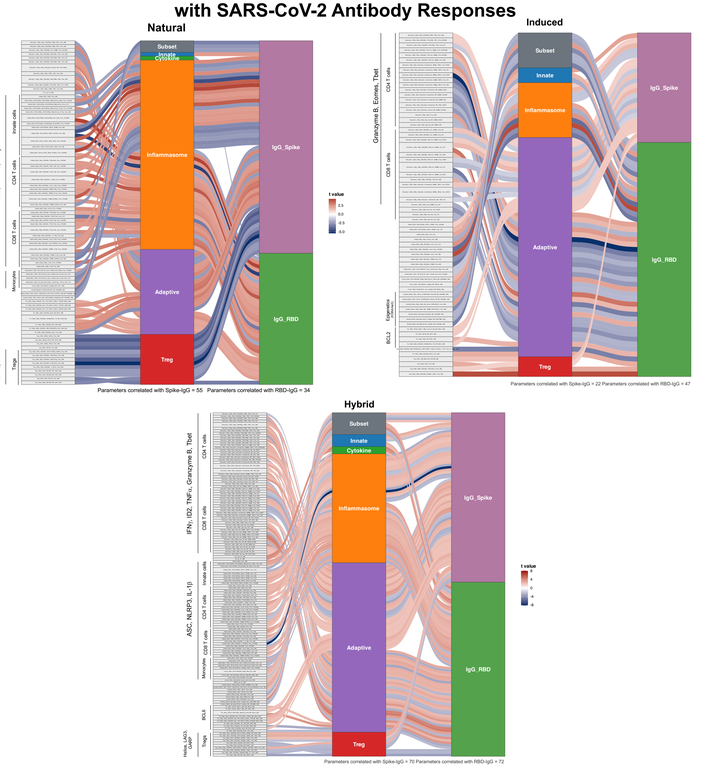


Figure 6. Sankey plots showing immune parameters significantly associated with Spike and RBD antibody AUC. Individual parameters (left) are grouped by immune compartment or functional category (middle: Subset, Innate, Cytokine, Inflammasome, Adaptive, Treg) and linked to antigen-specific IgG responses (right: IgG Spike or IgG RBD). Ribbon color indicates direction and magnitude of association (t value; red = positive, blue = negative). Numbers below panels indicate the total parameters correlated with each antibody specificity.

CONCLUSION

Hybrid immunity generated the most robust and durable immune profile by combining infection-primed innate activation with vaccine-enhanced adaptive effector and memory responses, resulting in superior T cell function and higher Spike/RBD antibody titers. Vaccines designed for long-term protection may need to recapitulate key features of hybrid immunity.

PLAIN LANGUAGE SUMMARY

In people with HIV on ART, COVID-19 infection strongly activates early immune alarm systems, increasing inflammation signals in several types of immune cells. Vaccination, in contrast, mainly strengthens the body's long-term defenses by improving T cell function and immune memory. People who were infected and later vaccinated developed the strongest protection, showing better immune responses, longer-lasting immune memory, and higher levels of protective antibodies.

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Schematic figures created in https://BioRender.com

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