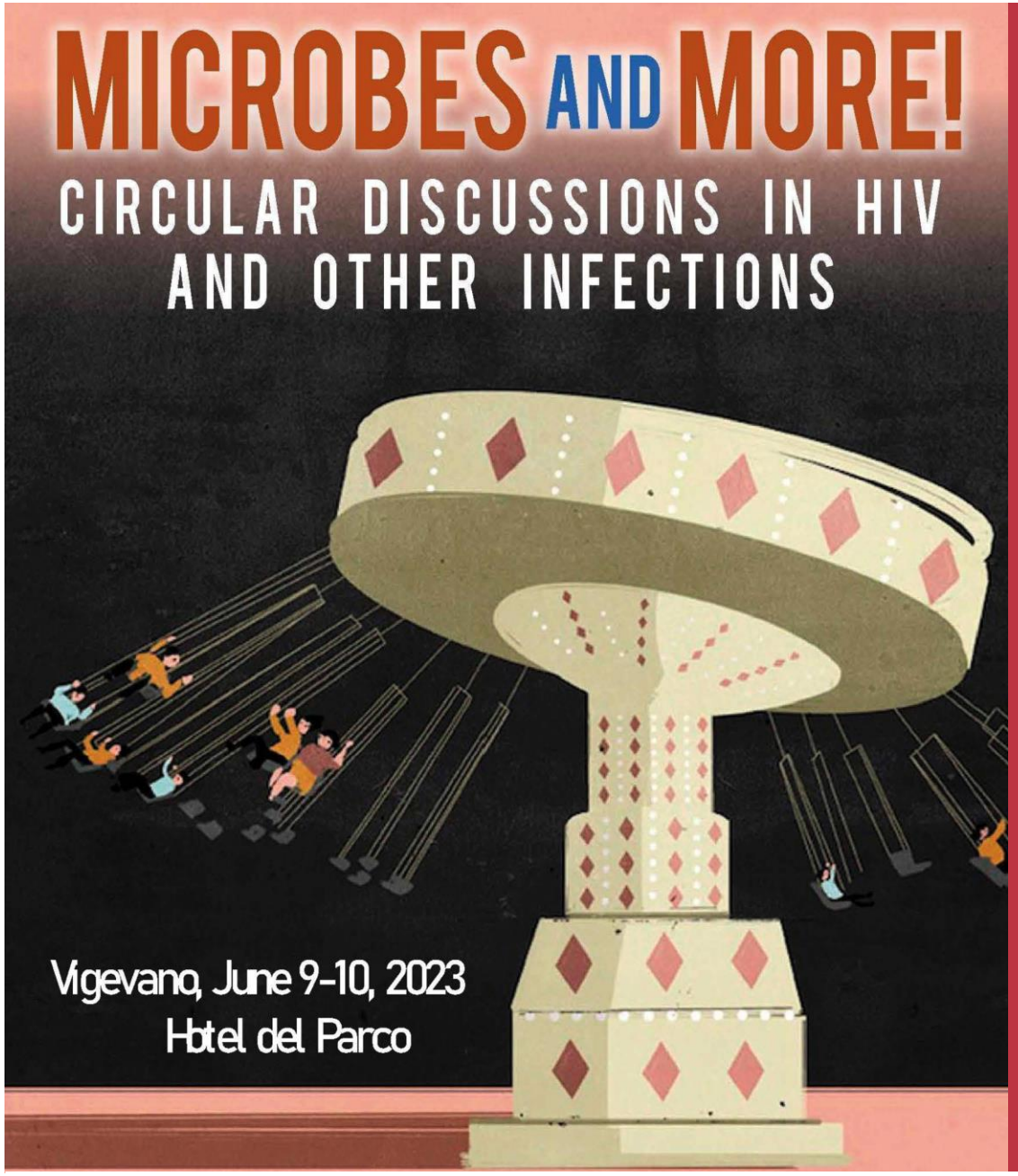

Immune responses to SARS-CoV-2 natural infection and vaccination in people living with HIV

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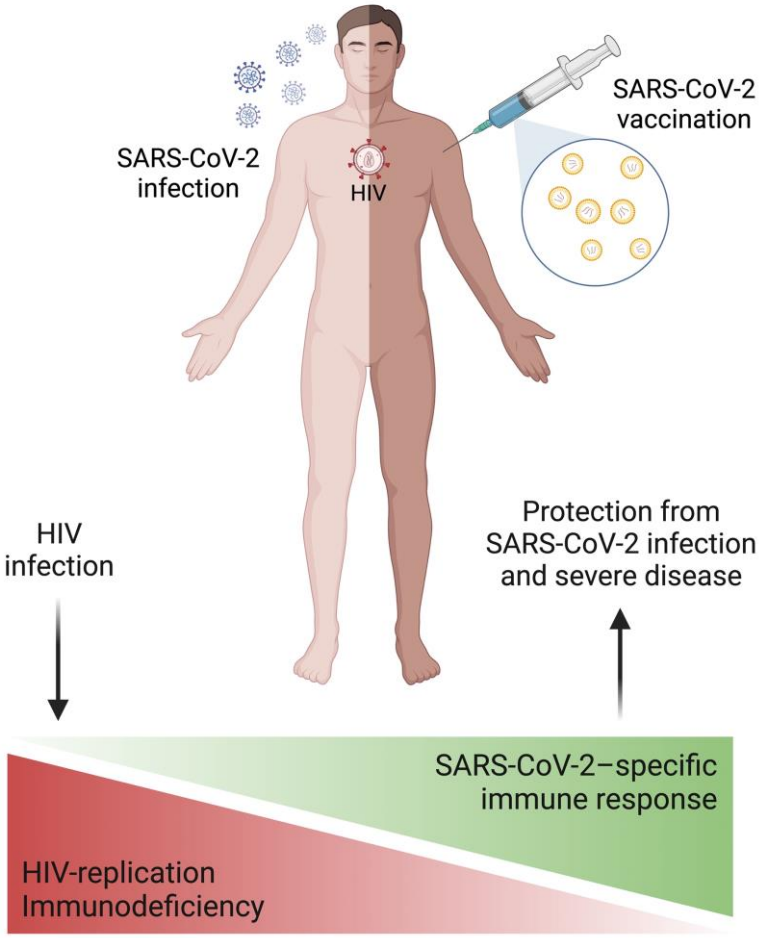
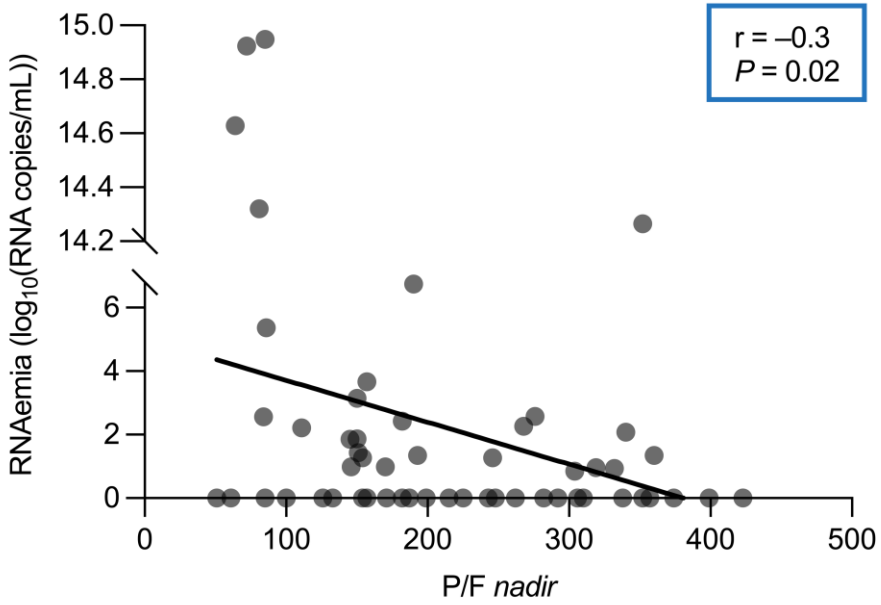
Background

People living with HIV (PLWH) may display an increased risk of **severe COVID-19 outcomes** as well as **lower immune responses to SARS-CoV-2 infection and vaccination**, especially those with *low CD4 T-cell counts* and/or *uncontrolled HIV viremia*.

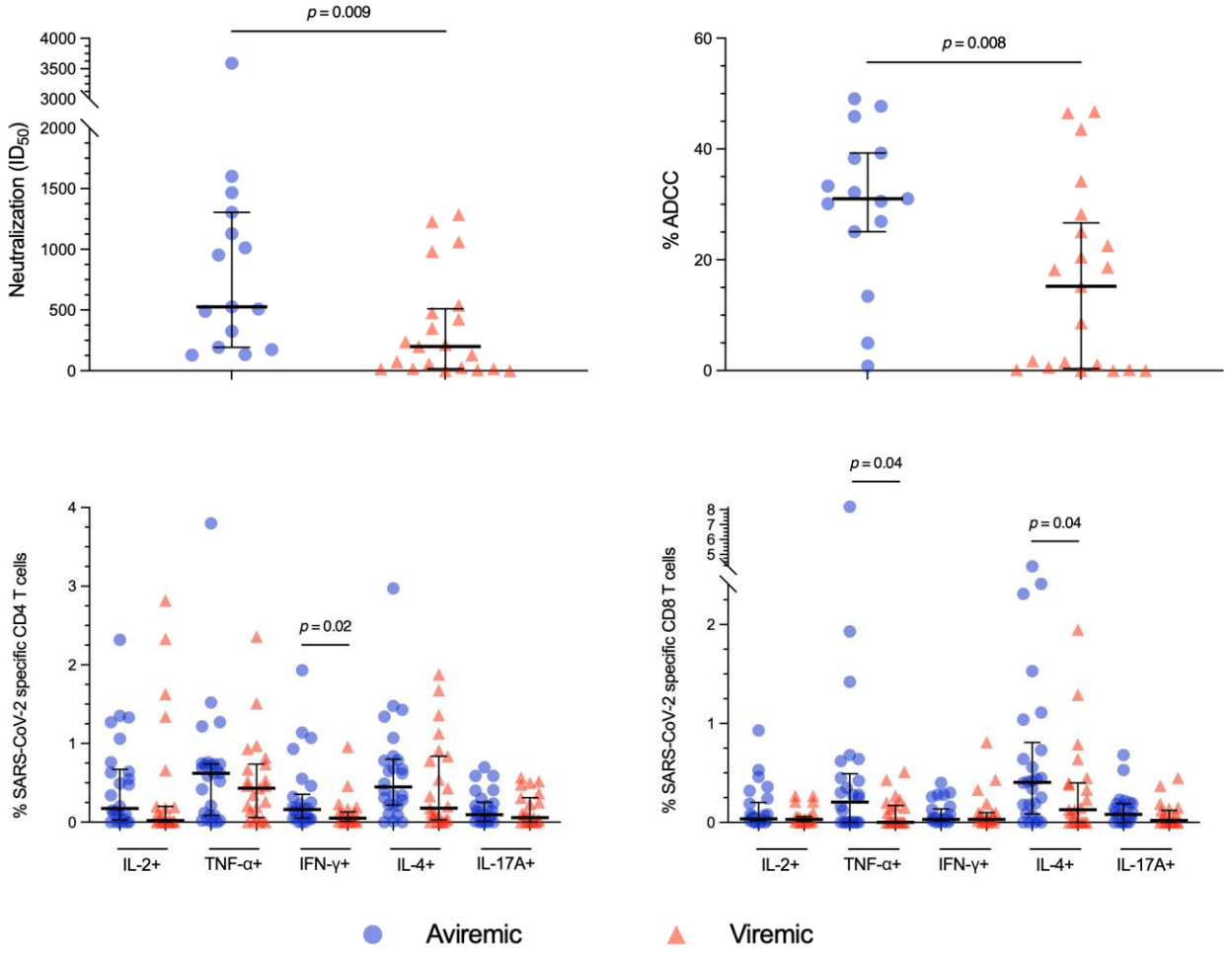


Augello M, et al. *Curr HIV/AIDS Rep*. 2023.

Background



High **SARS-CoV-2 RNAemia** has emerged as a **hallmark of severe COVID-19** linked to a profound **immune dysregulation**.

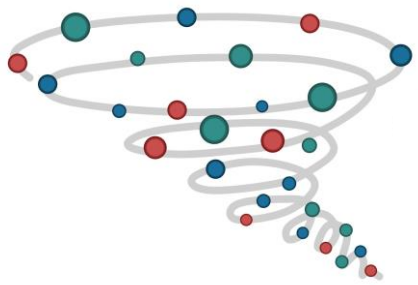


Rovito R, et al. *Sci Rep*. 2022.
Fajnzylber J, et al. *Nat Commun*. 2020.
Jacobs JL, et al. *Clin Infect Dis*. 2021.

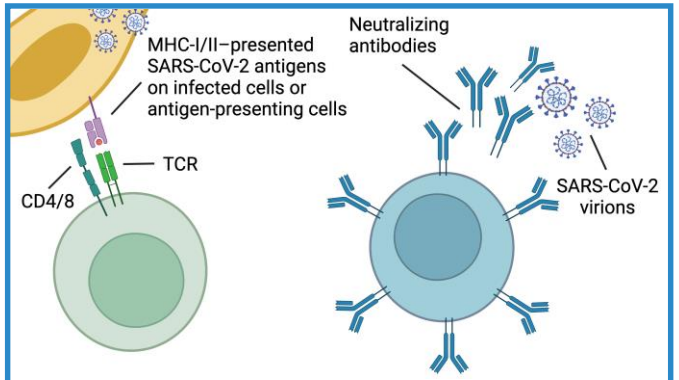
Study aim

Whether *SARS-CoV-2 RNAemia* and *dysregulated SARS-CoV-2–specific immune responses* may play a role in the pathogenesis of COVID-19 in PLWH is unclear.

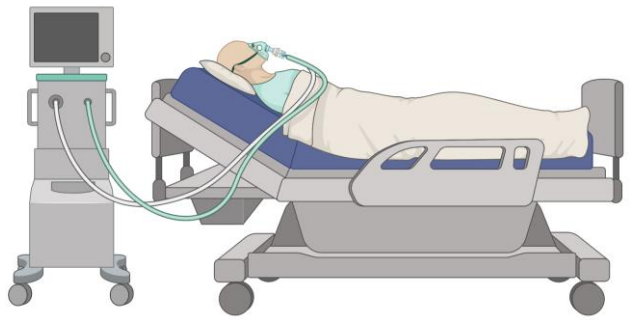
The aim of the study was to measure **SARS-CoV-2 RNAemia** in PLWH and explore its association with:



Systemic inflammation



T-cell and humoral responses



Clinical severity

Methods

- **Study population**: unvaccinated *PLWH* and *age/sex-matched people living without HIV (PLWOH)* hospitalized for *COVID-19 pneumonia* at a median of *10 days from symptoms onset* (March 2020 – January 2021)
- **SARS-CoV-2 RNAemia**: plasma → *RT-qPCR (N gene)*
- **Plasma cytokines**: plasma → *cytometric bead array*
- **T-cell activation** (HLA-DR+CD-38+), **cytotoxic T-cells** (GRZB+PRF+), **GRZB/PRF production** (MFI) **by cytotoxic T-cells**: PBMCs → *flow cytometry*
- **SARS-CoV-2–specific T-cells**: PBMCs (stimulation with wild type SARS-CoV-2 S+N+M peptides) → *flow cytometry*
- **Anti-RBD antibodies**: plasma → *ELISA*
- **Spike-ACE2 binding inhibition activity**: plasma → *receptor binding inhibition assay*
- **Statistics**: *Mann-Whitney test* and *Spearman's correlation*

Results

Demographic and clinical characteristics of study participants

	PLWH (*n*=18)	PLWOH (*n*=18)	*P* value*
Age, years [median (IQR)]	60 (49–67)	60 (47–66)	0.7843
Sex [*n* (%)]			>0.9999
Male	14 (77.8)	14 (77.8)	
Female	4 (22.2)	4 (22.2)	
Ethnicity [*n* (%)]			0.0903
Caucasian	15 (83.3)	13 (72.2)	
Latin-American	1 (5.6)	5 (27.8)	
African	2 (11.1)	0 (0)	
Comorbidities [*n* (%)]			
Hypertension	9 (50)	5 (27.8)	0.3053
Chronic heart disease	4 (22.2)	5 (27.8)	>0.9999
Chronic pulmonary disease	1 (5.6)	1 (5.6)	>0.9999
Chronic kidney disease	3 (75)	1 (25)	0.6026
Liver disease	5 (27.8)	1 (5.6)	0.1774
Diabetes	2 (11.1)	6 (33.3)	0.2285
Neurologic disease	4 (22.2)	1 (5.6)	0.3377
History of cancer	5 (27.8)	2 (11.1)	0.4018
P_aO_2/F_iO_2 *nadir* [median (IQR)]	140 (122–151.5)	207 (156.3–309.3)	**0.0005**
Maximum oxygen therapy [*n* (%)]			0.1756
Low-flow systems	10 (55.6)	5 (27.8)	
CPAP/NIV/OTI	8 (44.4)	13 (72.2)	
Outcome [*n* (%)]			>0.9999
Death	1 (5.6)	0 (0)	
Dismissal	17 (94.4)	18 (100)	

IQR: interquartile range; P_aO_2: arterial partial pressure of oxygen; F_iO_2: fraction of inspired oxygen; CPAP: continuous positive airway pressure; NIV: noninvasive ventilation; OTI: orotracheal intubation. *Statistical analyses: Mann-Whitney *U* test, Fisher exact test, Chi-square test.

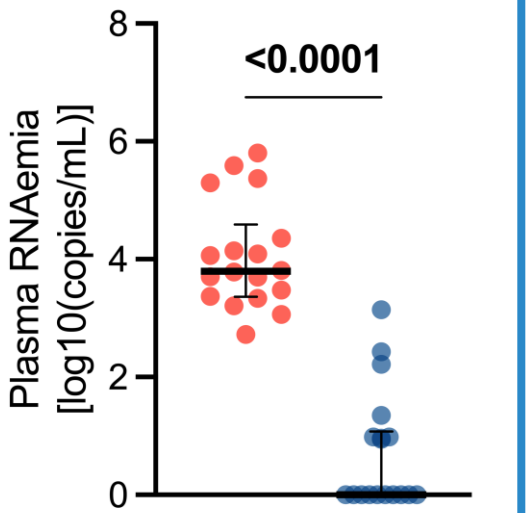
Results

HIV-related characteristics of PLWH

Immunologic parameters [median (IQR)]	
CD4 T-cell count *nadir*, cells/µL	59 (12.5–331.3)
Current CD4 T-cell count, cells/µL	361.5 (210.3–653.5)
Current CD4/CD8 ratio	0.4 (0.11–1.1)
Current CD4 T-cell count [*n* (%)]	
<200 cells/µL	4 (22.2)
200–500 cells/µL	7 (38.9)
>500 cells/µL	7 (38.9)
Current plasma HIV-RNA [*n* (%)]	
Undetectable (<50 copies/mL)	15 (83.3)
Previous AIDS diagnosis [*n* (%)]	5 (27.8)
Time from HIV diagnosis, years [median (IQR)]	18 (6.25–34.5)
Current cART regimen [*n* (%)]	
INSTI-based	9 (50)
PI-based	3 (16.7)
INSTI+PI-based	1 (5.6)
NNRTI-based	3 (16.7)
None (cART-naïve)	2 (11)

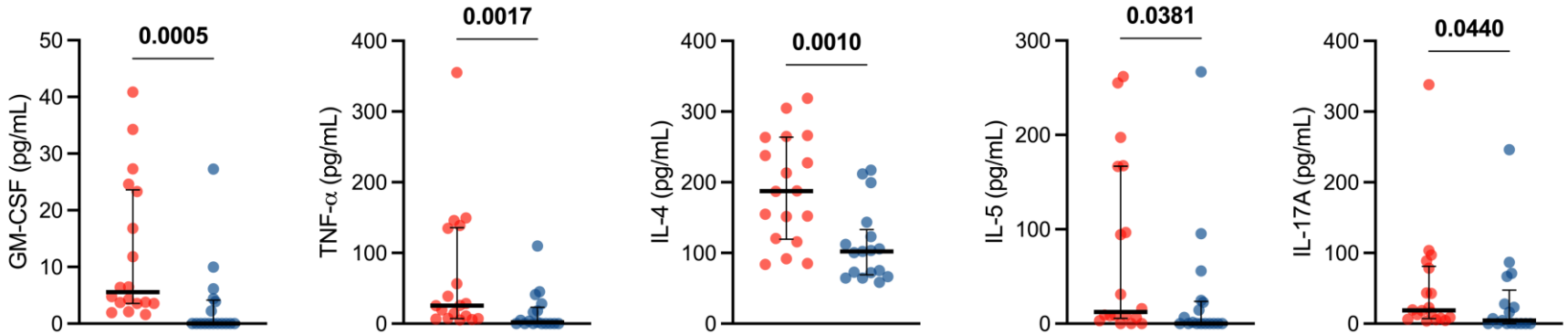
Results

Higher SARS-CoV-2 RNAemia in PLWH

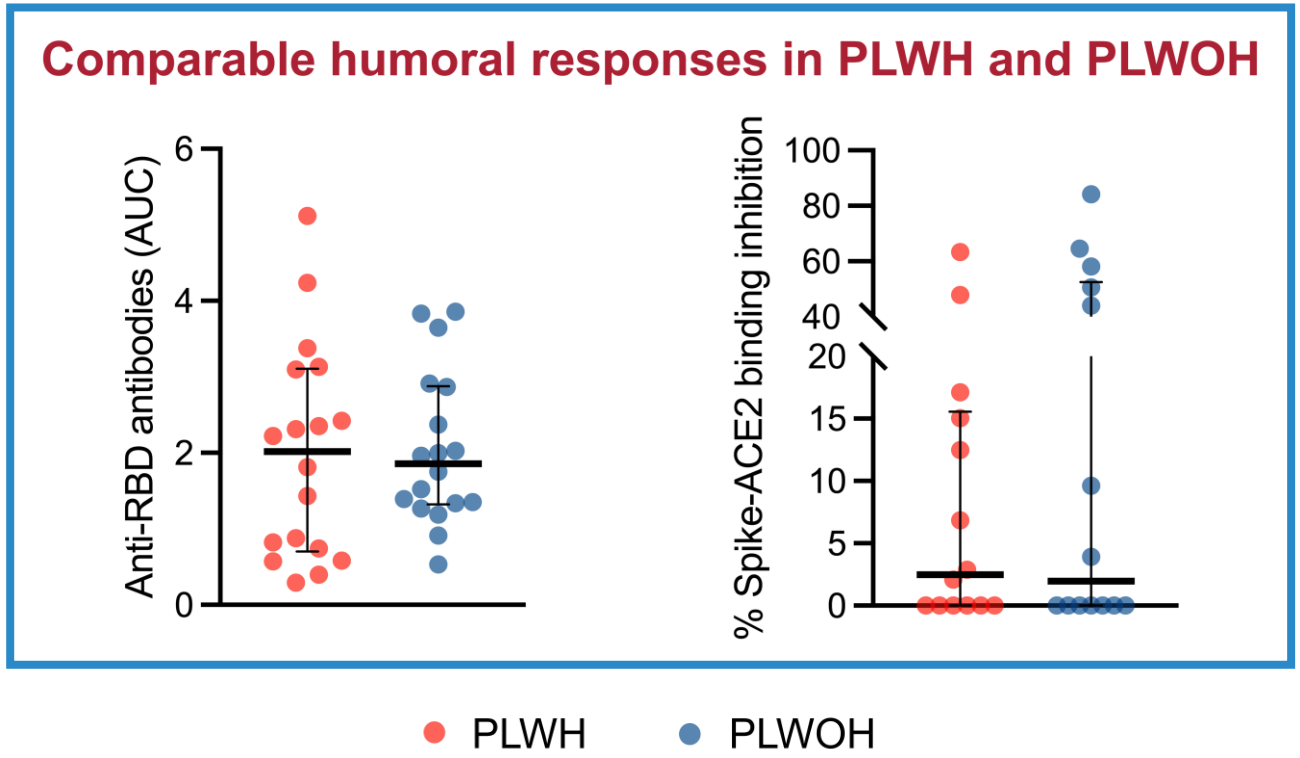


PLWH PLWOH

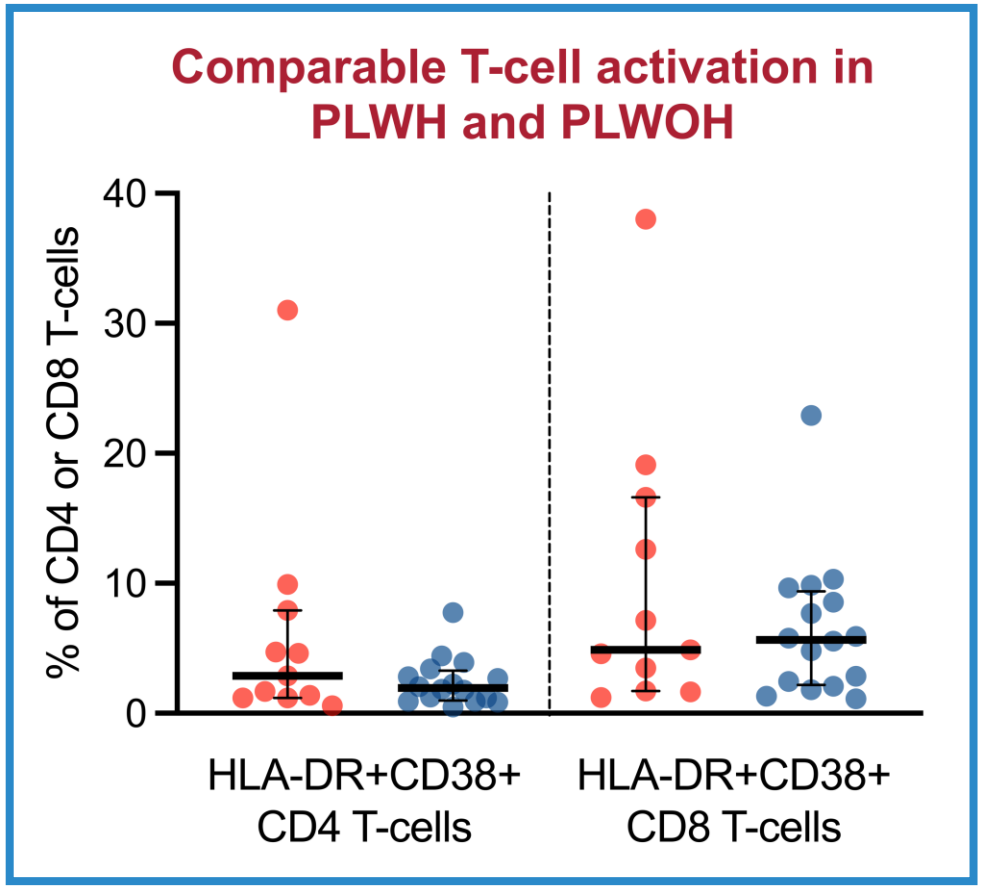
Higher systemic inflammation in PLWH

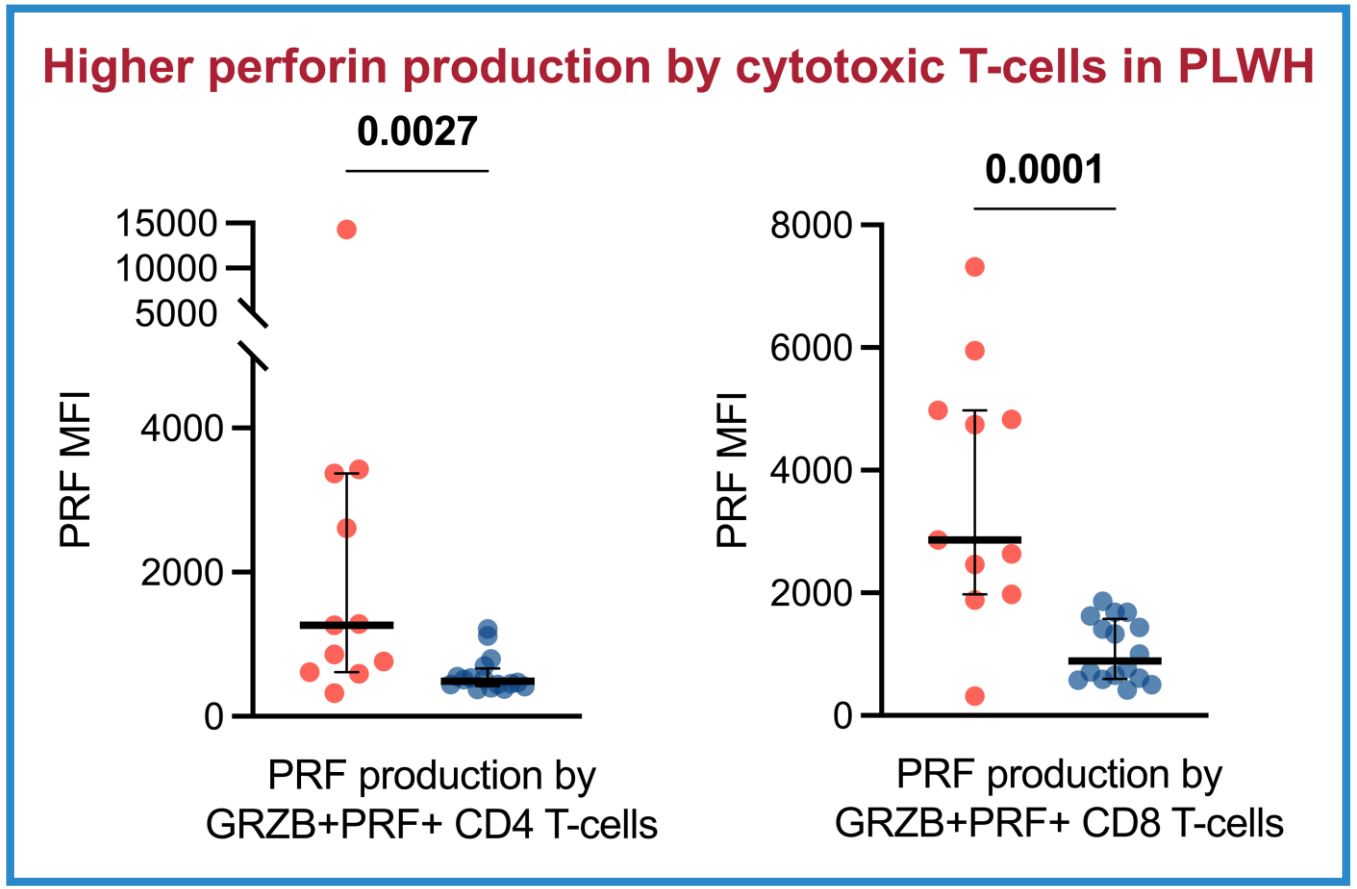


Results


Comparable humoral responses in PLWH and PLWOH
Anti-RBD antibodies (AUC)
6
4
2
0
% Spike-ACE2 binding inhibition
100
80
60
40
20
15
10
5
0
PLWH
PLWOH

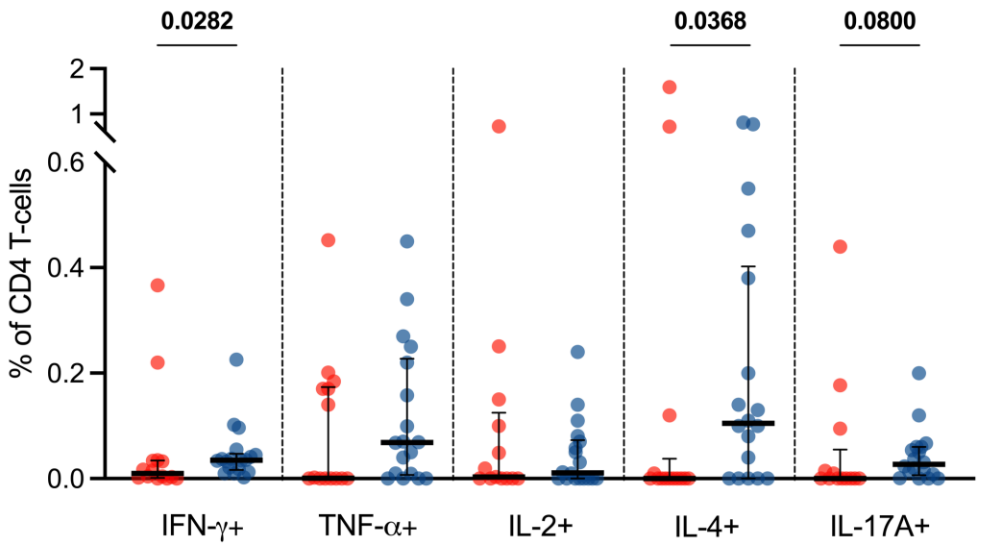
Results

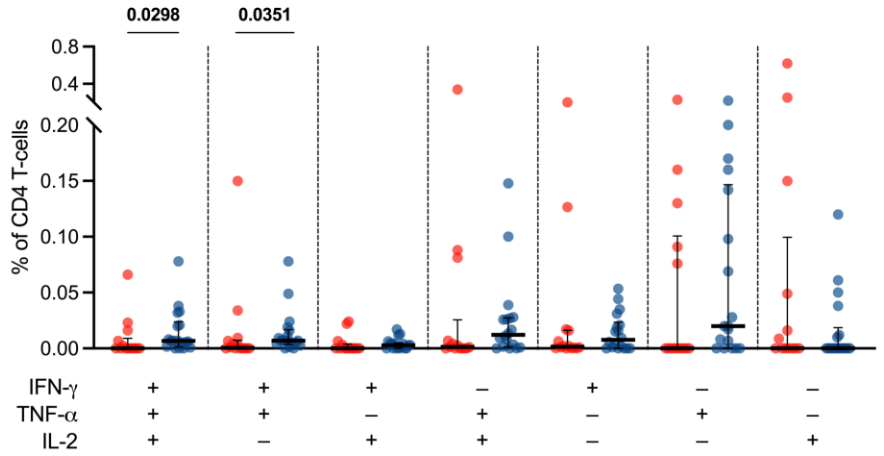

Comparable T-cell activation in PLWH and PLWOH
% of CD4 or CD8 T-cells
40
30
20
10
0
HLA-DR+CD38+ CD4 T-cells
HLA-DR+CD38+ CD8 T-cells
PLWH
PLWOH

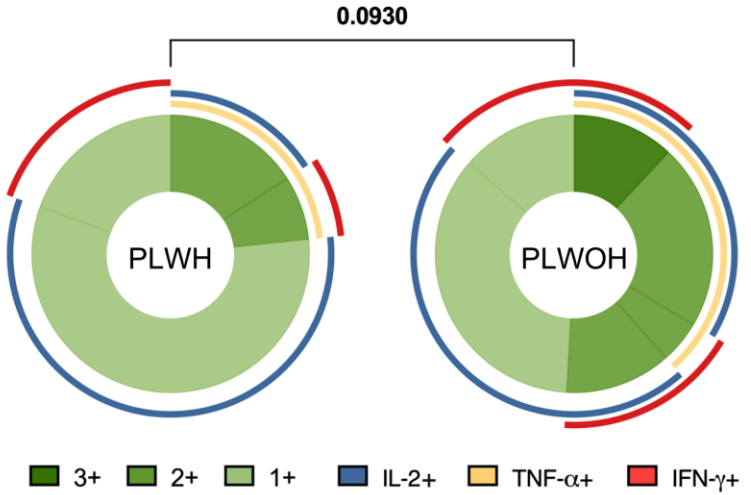

Higher perforin production by cytotoxic T-cells in PLWH
0.0027
0.0001
PRF MFI
15000
10000
5000
4000
2000
0
PRF production by GRZB+PRF+ CD4 T-cells
8000
6000
4000
2000
0
PRF production by GRZB+PRF+ CD8 T-cells

Results

Fewer and less polyfunctional SARS-CoV-2–specific cytokine-producing CD4 T-cells in PLWH



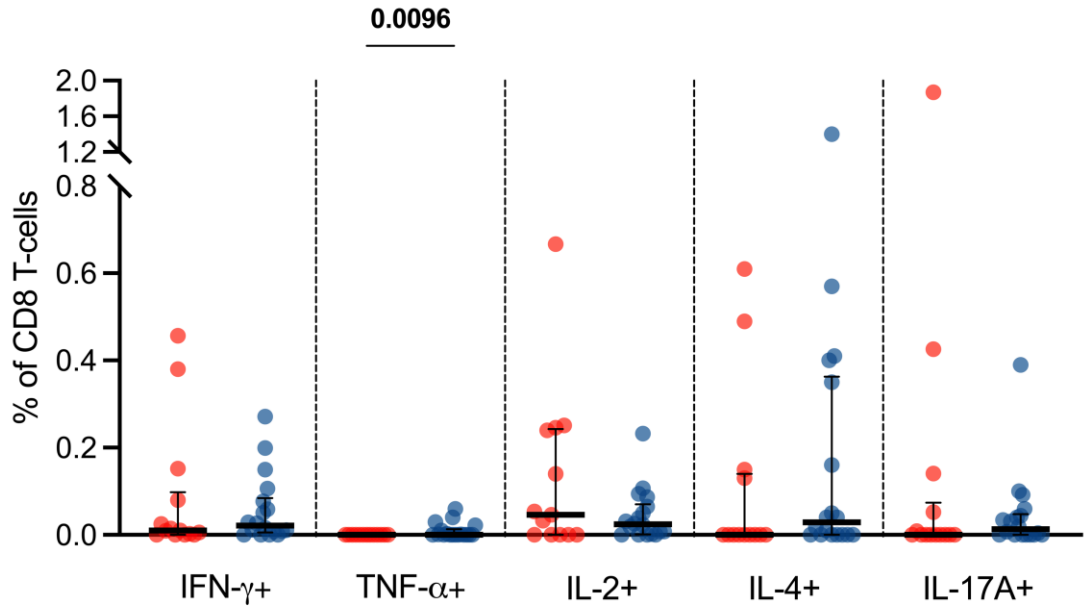




● PLWH ● PLWOH

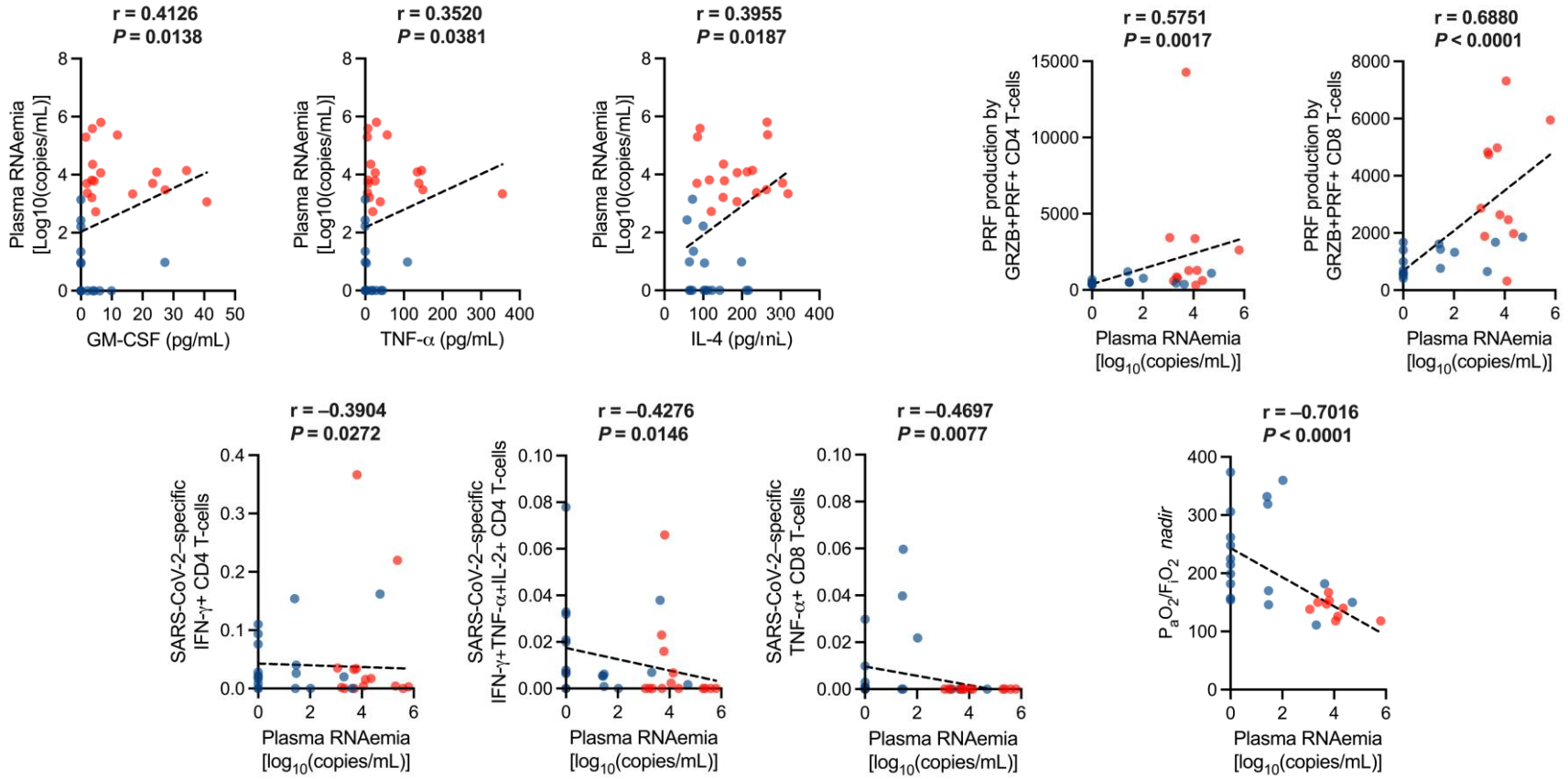
Results

Fewer SARS-CoV-2–specific cytokine-producing CD8 T-cells in PLWH



Results

SARS-CoV-2 RNAemia correlates positively with plasma inflammatory cytokines and perforin production by cytotoxic T-cells, and negatively with SARS-CoV-2–specific T-cells and P_aO_2/F_iO_2 *nadir*



● PLWH ● PLWOH

Conclusions

PLWH hospitalized for COVID-19 pneumonia feature *high SARS-CoV-2 RNAemia* which is linked to *elevated plasma cytokines*, *skewed T-cell responses* and *worse parameters of respiratory function*.

These data suggest a link between *HIV-related T-cell dysfunction* and *poor control over circulating SARS-CoV-2* that may in turn fuel *systemic inflammation* and influence *COVID-19 severity* in PLWH.

Presented at *CROI 2023, 19–22 February 2023, Seattle (WA) – #P344*
Presented at *ECCMID 2023, 15–18 April 2023, Copenhagen (DK) – #P2667*
Under review on *iScience*

Immune responses to SARS-CoV-2 vaccination in PLWH

Six-month immune responses to mRNA-1273 Vaccine in combination antiretroviral therapy-treated late presenter people with HIV according to previous SARS-CoV-2 Infection

Matteo Augello, Valeria Bono, Roberta Rovito, Camilla Tincati, Antonella D'arminio Monforte and Giulia Marchetti

Objective: Immune responses to SARS-CoV-2 mRNA vaccines in people with HIV (PWH) with a history of late presentation (LP) and their durability have not been fully characterized.

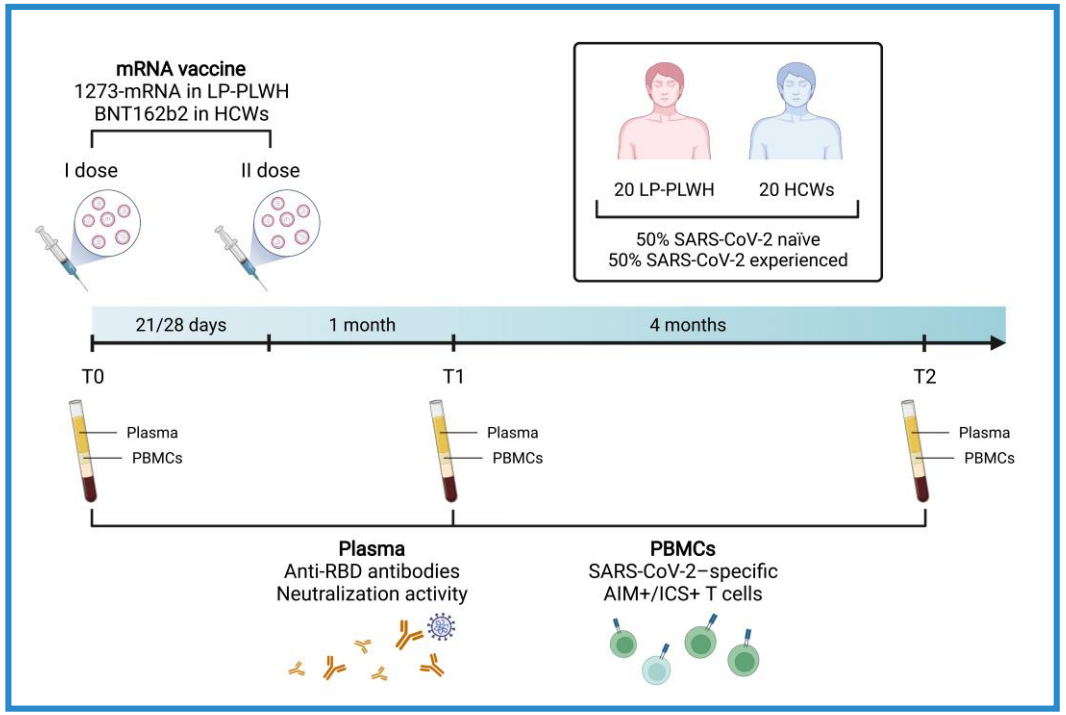
Design: In this prospective, longitudinal study, we sought to assess T-cell and humoral responses to SARS-CoV-2 mRNA vaccination up to 6 months in LP-PWH on effective combination antiretroviral therapy (cART) as compared to HIV-negative healthcare workers (HCWs), and to evaluate whether previous SARS-CoV-2 infection modulates immune responses to vaccine.

Methods: SARS-CoV-2 spike (S)-specific T-cell responses were determined by two complementary flow cytometry methodologies, i.e. activation-induced marker (AIM) assay and intracellular cytokine staining (ICS), whereas humoral responses were measured by ELISA (anti-RBD antibodies) and receptor-binding inhibition assay (spike-ACE2 binding inhibition activity), before vaccination (T0), 1 month (T1) and 5 months (T2) after the second dose.

Results: LP-PWH showed at T1 and T2 significant increase of: S-specific memory and circulating T follicular helper (cTfh) $CD4^+$ T-cells; polyfunctional Th1-cytokine (IFN-γ, TNF-α, IL-2)- and Th2-cytokine (IL-4)-producing S-specific $CD4^+$ T-cells; anti-RBD antibodies and spike-ACE2 binding inhibition activity. Immune responses to vaccine in LP-PWH were not inferior to HCWs overall, yet S-specific $CD8^+$ T-cells and spike-ACE2 binding inhibition activity correlated negatively with markers of immune recovery on cART. Interestingly, natural SARS-CoV-2 infection, while able to sustain S-specific antibody response, seems less efficacious in inducing a T-cell memory and in boosting immune responses to vaccine, possibly reflecting an enduring partial immunodeficiency.

Conclusions: Altogether, these findings support the need for additional vaccine doses in PWH with a history of advanced immune depression and poor immune recovery on effective cART.

AIDS 2023, **37**:000–000



- *Comparable T-cell and humoral responses* to primary SARS-CoV-2 vaccine cycle *in cART-treated late presenter (LP) PLWH* and people without HIV
- *Negative correlation* between *vaccine-elicited immune responses* and *markers of immune recovery on cART*
- *Comparable humoral* but *lower T-cell memory* in *LP-PLWH with previous SARS-CoV-2 infection*

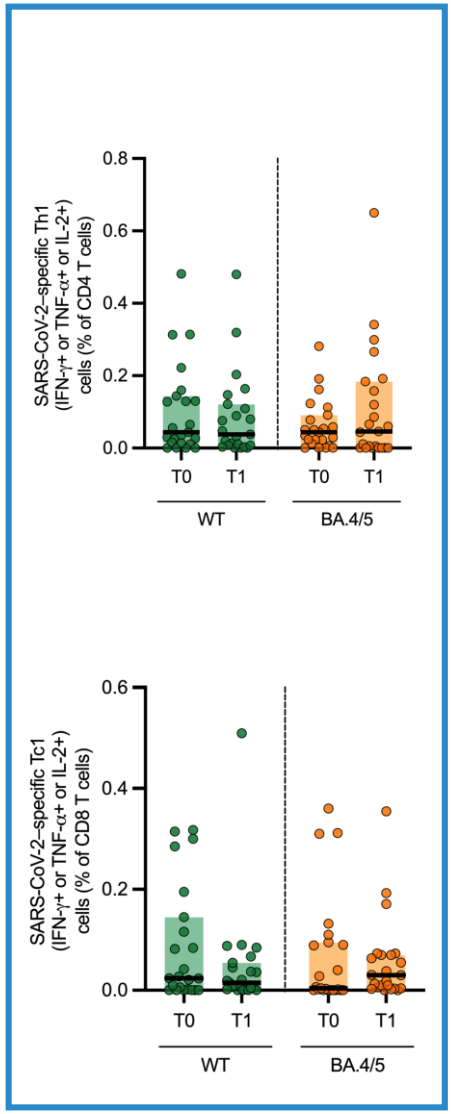
Immune responses to SARS-CoV-2 vaccination in PLWH

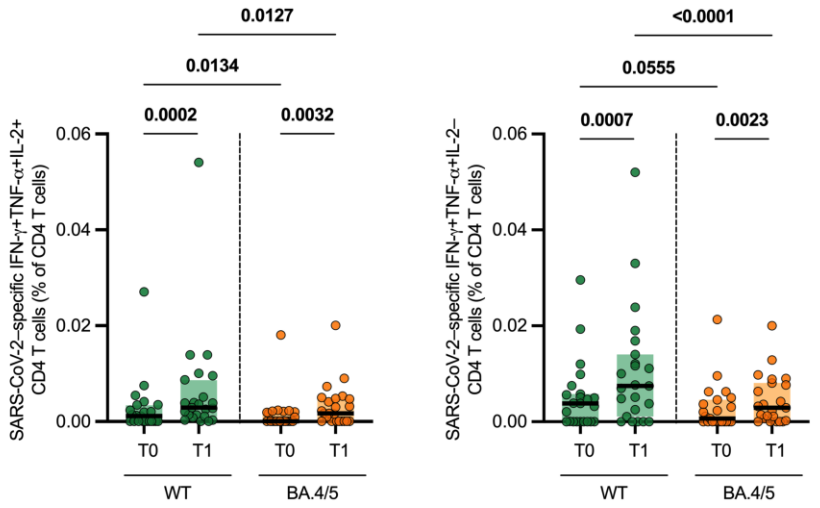
SARS-CoV-2–specific immune responses against *wild type (WT) virus* and *BA.4/5 variant* induced by a bivalent mRNA booster given as a 4th dose (*n*=30)

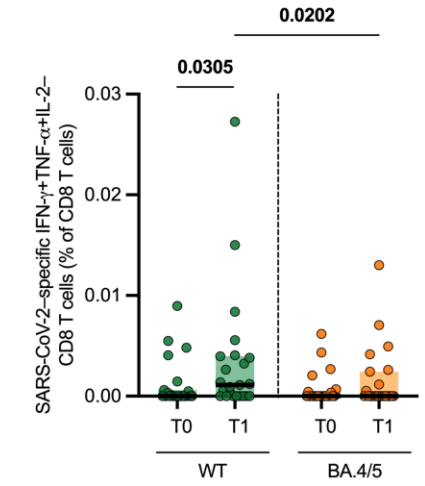
- SARS-CoV-2–specific T-cells
- SARS-CoV-2–specific B-cells
- Anti-RBD total antibodies
- Spike-ACE2 binding inhibition activity
- Antibody avidity and Fc-mediated effector functions (ADCC)?
- Time-points: T0 (before 4th dose), T1 (1 month → *peak*), T2 (6–8 months → *durability*)

Preliminary results

- **No increase in frequencies** of SARS-CoV-2–specific CD4 and CD8 T-cells
- **Increase in polyfunctionality** of SARS-CoV-2–specific cytokine-producing T-cells







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All clinical staff
Patients

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