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Humoral and Cellular Immune Response Elicited by mRNA Vaccination Against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in People Living With Human Immunodeficiency Virus Receiving Antiretroviral Therapy Based on Current CD4 T-Lymphocyte Count

Andrea Antinori,[1] Stefania Cicalini,[1] Silvia Meschi,[2] Veronica Bordoni,[3] Patrizia Lorenzini,[1] Alessandra Vergori,[1,©] Simone Lanini,[1] Lidya De Pascale,[1] Giulia Matusali,[2] Davide Mariotti,[3] Alessandro Cozzi Lepri,[4] Paola Gallì,[5] Carmela Pinnetti,[1] Roberta Gagliardini,[1] Valentina Mazzotta,[1] Ilaria Mastrorosa,[1] Susanna Grisetti,[1] Francesca Colavita,[2] Eleonora Cimini,[3] Elisabetta Grilli,[1] Rita Bellagamba,[1] Daniele Lapa,[2] Alessandra Sacchi,[3] Alessandra Marani,[5] Carlo Cerini,[1] Caterina Candela,[1] Marisa Fusto,[1] Vincenzo Puro,[6] Concetta Castilletti,[2,©] Chiara Agrati,[3,©] Enrico Girardi,[7,©] and Francesco Vaia[5]; for the HIV-VAC Study Group[a]

[1]Clinical Department, HIV/AIDS Unit, National Institute for Infectious Diseases Lazzaro Spallanzani Istituto di Ricovero e Cura a Carattere Scientifico, Roma, Italy; [2]Laboratory of Virology, National Institute for Infectious Diseases Lazzaro Spallanzani IRCCS, Roma, Italy; [3]Laboratory of Cellular Immunology and Clinical Pharmacology, National Institute for Infectious Diseases Lazzaro Spallanzani IRCCS, Roma, Italy; [4]Centre for Clinical Research, Epidemiology, Modelling and Evaluation, Institute for Global Health, University College of London, London, United Kingdom; [5]Health Direction, National Institute for Infectious Diseases Lazzaro Spallanzani IRCCS, Roma, Italy; [6]Risk Management, National Institute for Infectious Diseases Lazzaro Spallanzani IRCCS, Roma, Italy; and [7]Clinical Epidemiology, National Institute for Infectious Diseases Lazzaro Spallanzani IRCCS, Roma, Italy

Background. Data on SARS-CoV-2 vaccine immunogenicity in PLWH are currently limited. Aim of the study was to investigate immunogenicity according to current CD4 T-cell count.

Methods. PLWH on ART attending a SARS-CoV-2 vaccination program, were included in a prospective immunogenicity evaluation after receiving BNT162b2 or mRNA-1273. Participants were stratified by current CD4 T-cell count (poor CD4 recovery, PCDR: <200/mm^3; intermediate CD4 recovery, ICDR: 200–500/mm^3; high CD4 recovery, HCDR: >500/mm^3). RBD-binding IgG, SARS-CoV-2 neutralizing antibodies (nAbs) and IFN-γ release were measured. As control group, HIV-negative healthcare workers (HCWs) were used.

Findings. Among 166 PLWH, after 1 month from the booster dose, detectable RBD-binding IgG were elicited in 86.7% of PCDR, 100% of ICDR, 98.7% of HCDR, and a neutralizing titre ≥1:10 elicited in 70.0%, 88.2%, and 93.1%, respectively. Compared to HCDR, all immune response parameters were significantly lower in PCDR. After adjusting for confounders, current CD4 T-cell <200/mm^3 significantly predicted a poor magnitude of anti-RDB, nAbs and IFN-γ response. As compared with HCWs, PCDR elicited a consistently reduced immunogenicity for all parameters, ICDR only a reduced RBD-binding antibody response, whereas HCDR elicited a comparable immune response for all parameters.

Conclusion. Humoral and cell-mediated immune response against SARS-CoV-2 were elicited in most of PLWH, albeit significantly poorer in those with CD4 T-cell <200/mm^3 versus those with >500 cell/mm^3 and HIV-negative controls. A lower RBD-binding antibody response than HCWs was also observed in PLWH with CD4 T-cell 200–500/mm^3, whereas immune response elicited in PLWH with a CD4 T-cell >500/mm^3 was comparable to HIV-negative population.

Keywords. HIV; AIDS; anti–SARS-CoV-2 vaccine; immunogenicity.

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[a]Members of the IV-VAC Study Group are listed in the Acknowledgments section.

Correspondence: Andrea Antinori, Clinical Department of Infectious Diseases and Research, HIV/AIDS Unit, National Institute for Infectious Diseases Lazzaro Spallanzani IRCCS, Via Portuense 292, 00149 Roma, Italy (andrea.antinori@inmi.it).

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An effective vaccination strategy currently represents the main control measure of the coronavirus disease 2019 (COVID-19) pandemic [1], particularly in highly vulnerable people at high risk of severe COVID-19 [2].

People living with human immunodeficiency virus (PLWH), despite the beneficial effects of early antiretroviral therapy (ART) [3], may persistently experience a chronic immune dysregulation [4], leading to incomplete restoration of immune health [5].

Observational studies have suggested that COVID-19 may have a worse prognosis in PLWH compared with the

HIV-negative population, with an increased risk of mortality [6, 7]. Recent data suggest that a higher risk of severe COVID-19 in PLWH may be associated with poor neutralizing antibody (nAb) titers, and this might reflect a diminished antibody response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) natural infection [8]. These data are consistent with the observation that HIV infection may favor a poor serological response to vaccines for viral agents, such as influenza [9] and hepatitis B [10].

At present, few data have been published on the immunogenicity of SARS-CoV-2 vaccination in PLWH. Preliminary data in PLWH from a single-arm, open-label study from a large, controlled, phase 2/3 randomized trial in the United Kingdom showed that ChAdOx1-nCoV-19 vaccine, given as prime-boost dosing 4–6 weeks apart, was safe and produced consistent immune responses in PLWH on ART and with CD4 T-cell counts >350 cells/mm^3 [11]. Similarly, the interim results from a randomized, double-blind, placebo-controlled phase 1b/2 trial on the safety and immunogenicity of the same adenovirus-vectored vaccine in South Africa showed comparable safety and immunogenicity between PLWH with a median CD4 count of 695 cells/mm^3 and HIV-negative people [12].

Three observational studies have been published on mRNA vaccines in PLWH. In the first study, 98% of PLWH enrolled in a prospective evaluation of the BNT162b2 vaccine had a mean CD4 T-cell count of 700 cells/mm^3. The study showed a detectable receptor-binding domain (RBD)–binding immunoglobulin G (IgG) response at a median of 18 days after the second dose [13]. In a small prospective study of PLWHs with a median CD4 T-cell count of 913 cells/mm^3 receiving BNT162b2, a robust humoral and cellular immune response that was comparable to that observed in healthy donors was observed [14]. Finally, in another small size prospective study, PLWH and receiving BNT162b2 or mRNA-1273, 86% had a CD4 T-cell count >200 cells/mm^3 and developed high titers of anti-RBD antibodies [15]. Nonetheless, in these studies, information about the immunogenicity of SARS-CoV-2 vaccination in PLWH with a low current CD4 T-cell count is lacking, and the value of this marker in predicting vaccine response in PLWH has not yet been estimated.

Our aim in this study was to evaluate the immunogenicity of SARS-CoV-2 vaccination with an mRNA vaccine (BNT1622b or mRNA-1273) in PLWH based on the current CD4 T-cell count and to estimate this variable as a predictor of immune response to vaccination.

METHODS

Study Design and Population

On 24 March 2021, as part of the nationwide mass vaccination program in Italy, the National Institute for Infectious Diseases Lazzaro Spallanzani in Rome started a vaccination campaign against SARS-CoV-2 in PLWH, according to the Ministry of Health recommendations. The campaign was primarily targeted to fragile individuals, for example, those with previous AIDS, a current CD4 T-cell count <200 cells/mm^3, or comorbidities. In the following months, the vaccination campaign was extended to all PLWH.

The HIV-VAC study is an observational study on the outcomes of SARS-CoV-2 vaccination in PLWH. According to the protocol, demographic, epidemiologic, clinical, and laboratory characteristics of PLWH being vaccinated were collected. The main study outcomes are the prevalence and magnitude of anti-spike RBD-binding antibody response after vaccination and the prevalence and magnitude of neutralizing activity and cell-mediated immune response after vaccination (only in a subgroup of participants). By protocol, following written informed consent, blood samples were collected for all PLWH enrolled at the time of first dose (baseline, T0), before the second dose (T1), and 1 month after the second dose (T2); the study will continue with further evaluation time points after the second dose. The Scientific Committee of the Italian Drug Agency and the Ethical Committee of the Lazzaro Spallanzani Institute, as the national review board for the COVID-19 pandemic in Italy, approved the study.

Here, we present results on immunogenicity (humoral, neutralizing, and cell-mediated response) at T1 and T2 of follow-up. The study population consisted of PLWH who completed the 2-dose schedule with the BNT162b2 or mRNA-1273 vaccine up to 20 July 2021 and were consecutively enrolled in the immunogenicity substudy. Individuals with a SARS-CoV-2 infection diagnosis, defined by a reverse-transcription polymerase chain reaction–positive result on nasopharyngeal swab, or positivity to anti-N and/or to anti-spike RBD (anti-S/RBD) antibodies at T0 or to anti-N at T1 or T2 were excluded from the present analysis. An unmatched control group of healthcare workers (HCWs) vaccinated with BNT162b2 who underwent the same schedule of blood sample collection enrolled in another surveillance study [16] were included as external controls.

Laboratory Procedures

Two commercial chemiluminescence microparticle antibody assays, the SARS-CoV-2–specific anti-N and the anti-S/RBD tests (ARCHITECT SARS-CoV-2 IgG and ARCHITECT SARS-CoV-2 IgG II Quantitative; Abbott Laboratories, Wiesbaden, Germany, respectively), were performed on the ARCHITECT i2000sr (Abbott Diagnostics, Chicago, IL) and used according to the manufacturer's instruction; an index >1.4 and binding antibody units (BAU)/mL ≥7.1 are considered positive, respectively.

A microneutralization assay (MNA) was performed, as previously described, using SARS-CoV-2/Human/ITA/PAVIA10734/2020 as the challenging virus [17]. Briefly, serum samples were heat-inactivated at 56°C for 30 minutes and titrated in duplicate in 7 two-fold serial dilutions (starting

dilution 1:10). Equal volumes (50 μL) of serum and medium containing 100 median tissue culture infective dose$_{50}$ (TCID50) SARS-CoV-2 were mixed and incubated at 37°C for 30 minutes. Serum–virus mixtures were then added to subconfluent Vero E6 cell monolayers and incubated at 37°C with 5% CO_2. After 48 hours, microplates were observed for the presence of cytopathic effect using a light microscope. To standardize interassay procedures, positive control samples that showed high (1:160) and low (1:40) neutralizing activity were included in each assay session. Serum from the National Institute for Biological Standards and Control (United Kingdom; NIBSC) with known neutralization titer (research reagent for anti–SARS-CoV-2 Ab NIBSC code 20/130) was used as the reference in MNA.

We studied interferon-gamma (IFN-γ) and interleukin-2 (IL-2) production in response to spike stimulation as a surrogate of specific T-cell function. Briefly, whole blood was stimulated in vitro at 37°C (5% CO_2) with a pool of peptides covering the sequence of the SARS-CoV-2 spike protein (SARS-CoV-2 PepTivator Prot_S1, Prot_S, and Prot_S+; Miltenyi Biotec, Germany). After 16–20 hours of incubation, plasma was harvested and stored at −80°C until use. IFN-γ levels were measured using an automatic enzyme-linked immunosorbent assay (Next Gen ELISAs, Automated Immunoassay [ELLA], protein simple), and the IFN-γ values obtained from the stimulated samples were subtracted from the unstimulated control value. Staphylococcal enterotoxin B was used as the positive control. The detection limit of these assays was 0.17 pg/mL and 0.54 pg/mL for IFN-γ and IL-2, respectively.

Statistical Analyses

PLWH included in the present analysis were stratified into the following 3 groups according to the degree of immune recovery: patients with current CD4 T-cell count <200 cells/mm^3 (poor CD4 recovery [PCDR]), patients with current CD4 T-cell count between 200 and 500 cells/mm^3 (intermediate CD4 recovery [ICDR]), and patients with current CD4 T-cell count >500 cells/mm^3 (high CD4 recovery [HCDR]). Descriptive statistics were presented as median with interquartile range (IQR) for continuous variables and frequency with proportion for categorical variables. For the comparison over time within each group, parameters at T1 and T2 were compared with the baseline level using the paired Wilcoxon sign-rank test, and paired proportions were compared using the McNemar test. The overall responses at times T1 and T2 were also compared by gender. For the comparison between groups, the Kruskal-Wallis test was performed to determine if groups were significantly different on all continuous variables considered. Specifically, the Dunn test with Bonferroni correction was used for pairwise multiple comparisons of each parameter between any pairs. The χ^2 test was used for comparison of proportions. Moreover, a multivariable linear regression model was fitted to evaluate the association between current CD4 T-cell count or CD4/CD8 ratio and the magnitude of immune response after adjustment for main confounders such as age, years living with HIV, CD4 nadir, level of HIV-RNA (<50 vs >50 copies/mL), type of mRNA vaccination, and presence of previous or current malignancy. Further, a different multivariable linear regression model, adjusted for gender and age, was fitted to control the association between the magnitude of immune response (anti-S/RBD, nAb titers, and IFN-γ) and PLWH groups and HCWs. Since the distribution of data was positively skewed, a logarithmic transformation was performed for RBD-binding IgG, nAb titers, IFN-γ, and IL-2 in order to make the data conform more closely to the normal distribution and to improve the model fit. Finally, linear regression was used to investigate the correlation between the CD4 count and CD4/CD8 ratio at T0 and the level of each parameter at T2. A 2-sided P value < .05 was considered statistically significant. Analyses were performed using STATA v15.1.

RESULTS

Study Population

A total of 166 PLWH were included in the analysis (PCDR = 32, ICDR = 56, HCDR = 78). The main characteristics of participants living with HIV according to current CD4 T-cell count at vaccination are listed in Table 1. The 3 groups significantly differed for years of living with HIV, previous AIDS diagnosis, current or previous malignancy, CD4 nadir, and CD4/CD8 ratio. All HIV patients were on ART at the time of SARS-CoV-2 vaccination, and the 3 groups significantly differed for duration of ART exposure. The proportion of PLWH with HIV-RNA <50 copies/mL was 68.8% in PCDR, 92.9% in ICDR, and 100% in HCDR (P < .001). No significant difference was observed for main noninfectious comorbidities in the 3 groups. At vaccination, 93 (57%) received BNT162b2 and 70 (43%) received mRNA-1273. For the control group, 169 unmatched HCWs were included; 71.6% were female with a median age of 42 years (IQR, 32–53). All HCWs received the BNT162b2 vaccine.

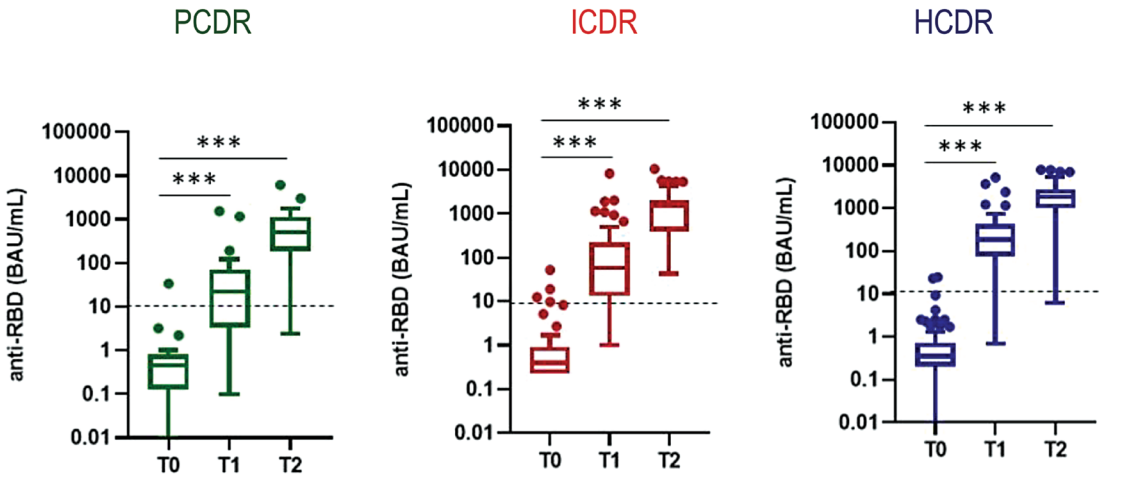
RBD-Binding IgG Response and nAb Response After Vaccination in PLWH

First, we compared RBD-binding IgG responses by gender and found no evidence for an association. Median changes (IQR) at T1 were 98.4 (20.6–254.5) in males vs 86.7 (20.6–4010.3) in females (P = .97; Supplementary Table 1). The corresponding figures at T2 were 1360.5 (521.9–2357.7) vs 1142.9 (736.0–1923.2; P = .78). A significant increase in the magnitude of RBD-binding IgG response from time of priming dose (T0) to time of the second dose (T1) and at 1 month after the second dose (T2) was observed for all PLWH groups (Figure 1). After the priming dose of vaccine (T1), immunogenicity measured by RBD-binding IgG response was significantly lower in PCDR than in ICDR (P = .011) and HCDR (P < .001) and was lower

Table 1. Main Characteristics of People Living With Human Immunodeficiency Virus (n = 166) at Time of the Priming Dose of Severe Acute Respiratory Syndrome Coronavirus 2 Vaccine According with Current CD4 T-Cell Count (cells/mm^3)

Characteristic	PLWH With Current CD4 <200 Cells/mm^3 N = 32	PLWH With Current CD4 200–500 Cells/mm^3 N = 56	PLWH With Current CD4 >500 Cells/mm^3 N = 78	*P* Value
Gender, Female, n (%)	8 (25.0)	9 (16.1)	10 (12.8)	.290
Age, median (IQR), years	57 (52–60)	54 (46–59)	54 (46–59)	.105
Years living with HIV, median (IQR)	22.2 (2.9–30.8)	9.2 (1.8–25.7)	11.0 (5.8–24.8)	.033
Previous AIDS diagnosis, n (%)	12 (37.5)	26 (46.4)	37 (47.4)	<.001
Current or previous malignancy, n (%)	2 (6.3)	14 (25.0)	9 (11.5)	.030
Hepatitis C virus-antibody positivity, n (%)	12 (37.5)	18 (32.1)	17 (21.8)	<.021
HIV-RNA <50 copies/mL, n (%)	22 (68.8)	52 (92.9)	78 (100.0)	<.001
Nadir CD4 T cells/mm^3, median (IQR)	49 (23–122)	63 (29–150)	174 (68–280)	<.001
Current CD4 T cells/mm^3, median (IQR)	140 (100–163)	335 (245–441)	727 (585–856)	<.001
Current CD8 T cells/mm^3, median (IQR)	671 (503–1030)	694 (505–1196)	859 (640–1139)	.112
CD4/CD8 T-cell ratio, median (IQR)	0.16(0.12–0.26)	0.44 (0.28–0.69)	0.90 (0.67–1.17)	<.001
At least 1 comorbidity, n (%)	11 (34.4)	16 (30.2)	23 (15.4)	.876
Cardiovascular	6 (18.8)	14 (25.0)	12 (19.4)	.378
Neurologic	2 (6.3)	3 (5.4)	6 (7.7)	.862
Renal	1 (3.1)	1 (1.8)	1 (1.3)	.805
Diabetes	2 (6.3)	1 (1.8)	1 (1.3)	.283
Chronic obstructive pulmonary disease/ asthma	3 (9.4)	3 (5.5)	11 (14.1)	.254
Liver cirrhosis	4 (12.5)	18 (32.1)	13 (16.7)	.040
Current antiretroviral therapy, n (%)	32 (100)	56 (100)	78 (100)	1.000
Years of HIV therapy, median (IQR)	13.7 (1.4–21.7)	6.4 (1.8–14.7)	10.1 (5.0–14.0)	.190
Type of vaccine administered, n(%)				
BNT162b2	22 (68.8)	38 (67.9)	35 (44.9)	.010
mRNA-1273	10 (31.3)	18 (32.1)	43 (55.1)	

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range; PLWH, people living with human immunodeficiency virus; PCDR, poor CD4 recovery (CD4 count <200 cells/mm^3); ICDR, intermediate CD4 recovery (CD4 count 200-500 cells/mm^3); HCDR, high CD4 recovery (CD4 count >500 cells/mm^3).



	PCDR			ICDR			HCDR		
Median	0.5	21.9	507	0.4	59	1477	0.4	183	1782
IQR	0.2; 0.8	3.7; 68.5	212; 1143	0.3; 0.9	15; 214	471; 2056	0.2; 0.7	77; 421	989; 2769

***p<0.001 by paired Wilcoxon test

Abbreviations: PCDR, poor CD4 recovery:current CD4 T cell count <200 cell/mm^3; ICDR: intermediate CD4 recovery: current CD4 T cell count 200-500 cell/mm^3; HCDR, high CD4 recovery: current CD4 T cell count >500 cell/mm^3

Figure 1. Change in RBD-binding immunoglobulin G response (BAU/mL) in people living with human immunodeficiency virus from time of priming dose, to time of second dose, and at 1 month after the second dose. Abbreviations: BAU, binding antibody unit; HCDR, high CD4 recovery; HCWs, healthcare workers; ICDR, intermediate CD4 recovery; IQR, interquartile range; PCDR, poor CD4 recovery; RBD, receptor binding domain.

Table 2. Proportion of Participants Anti–Receptor-Binding Domain and Neutralization Responder to BNT162b2 or mRNA-1273 Vaccination

	Anti-RBD Response		Neutralization (nAb) Response	
CD4 count	Detectable RBD-Binding IgG (%)[a]	Median (IQR) Binding Antibody Units per Milliliter of RBD-Binding IgG[b]	nAB ≥10 (Reciprocal Dilution Values at MNA) (%)[c]	Median (IQR) Reciprocal Dilution Values at MNA[d]
PCDR	26/30 (86.7)	507 (212–1143)	21/30 (70.0)	30 (5–80)
ICDR	53/53 (100)	1477 (471–2056)	45/51 (88.2)	40 (10–160)
HCDR	76/77 (98.7)	1782 (989–2769)	67/72 (93.1)	80 (40–160)
HCWs	168/168 (100)	2353 (1378–3758)	72/73 (98.6)	80 (40–160)

Responder was defined as having a detectable RBD-binding IgG response and with nAb titers at MNA ≥1:10, respectively) at 1 month after the second dose in the 3 PLWH groups and in HCWs.

Abbreviations: HCDR, high CD4 recovery; HCW, healthcare worker; ICDR, intermediate CD4 recovery; IgG, immunoglobulin G; IQR, interquartile range; MNA, microneutralization assay; nAb, neutralizing antibody; PCDR, poor CD4 recovery; RBD, receptor-binding domain.

[a]Comparisons between human immunodeficiency virus (HIV) groups using the χ^2 test: PCDR vs ICDR, $P = .014$; PCDR vs HCDR, $P = .021$; ICDR vs HCDR, $P = 1.0$. Comparisons of people living with human immunodeficiency virus (PLWH) with HCWs using the Fisher exact test: PCDR vs HCWs, $P < .001$; ICDR vs HCWs, $P = 1.0$; HCDR vs HCWs, $P = .313$.

[b]Comparisons between HIV groups using the Kruskal-Wallis test $P < .001$; using the Dunn test with Bonferroni adjustment for multiple comparisons: PCDR vs ICDR, $P = .029$; PCDR vs HCDR, $P < .001$; ICDR vs HCDR, $P = .184$. Comparisons of PLWHs with HCWs using the Kruskal-Wallis test $P < .001$; using the Dunn test with Bonferroni adjustment: PCDR vs HCWs, $P < .001$; ICDR vs HCWs, $P < .001$; HCDR vs HCWs, $P = .031$.

[c]Comparisons between HIV groups using the χ^2 test: PCDR vs ICDR, $P = .041$; PCDR vs HCDR, $P = .002$; ICDR vs HCDR, $P = .356$. Comparisons of PLWHs with HCWs using the Fisher exact test: PCDR vs HCWs, $P < .001$; ICDR vs HCWs, $P = .019$; HCDR vs HCWs, $P = .116$.

[d]Comparisons between HIV groups using the Kruskal-Wallis test $P < .001$; using the Dunn test with Bonferroni adjustment for multiple comparisons: PCDR vs ICDR, $P = .150$; PCDR vs HCDR, $P = .001$; ICDR vs HCDR, $P = .239$. Comparisons of PLWHs with HCWs using the Kruskal-Wallis test $P < .001$; using the Dunn test with Bonferroni adjustment: PCDR vs HCWs, $P < .001$; ICDR vs HCWs, $P = .05$; HCDR vs HCWs, $P = 1.0$.

in ICDR than in HCDR ($P = .004$; Supplementary Figure 1a). One month after the second dose (T2), a detectable RBD-binding IgG response was elicited in 86.7% of PCDR, 100% of ICDR, and 98.7% of HCDR (PCDR vs ICDR, $P = .014$; PCDR vs HCDR, $P = .021$; ICDR vs HCDR, $P = 1.0$; Table 2). The level of RBD-binding IgG (BAU/mL) response at T2 was lower in PCDR than ICDR ($P = .029$) and HCDR ($P < .001$) but not different between ICDR and HCDR ($P = .184$; Figure 2A). At T2, nAb titer response against SARS-CoV-2 (defined as a titer >1:10) was elicited in 70.0% of PCDR, 90.8% of ICDR, and 90.9% of HCDR (PCDR vs ICDR, $P = .041$; PCDR vs HCDR, $P = .002$; ICDR vs HCDR, $P = .356$; Table 2). The magnitude of nAb titers (MNA reciprocal of dilution) was lower in PCDR than HCDR ($P = .001$) but not in PCDR compared with ICDR ($P = .150$) and in ICDR compared with HCDR ($P = .239$; Figure 2B). A significant correlation between RBD-binding IgG at time T2 and nAb titers was found using the nonparametric Spearman correlation coefficient (r = 0.85, $P < .001$; Supplementary Figure 2a).

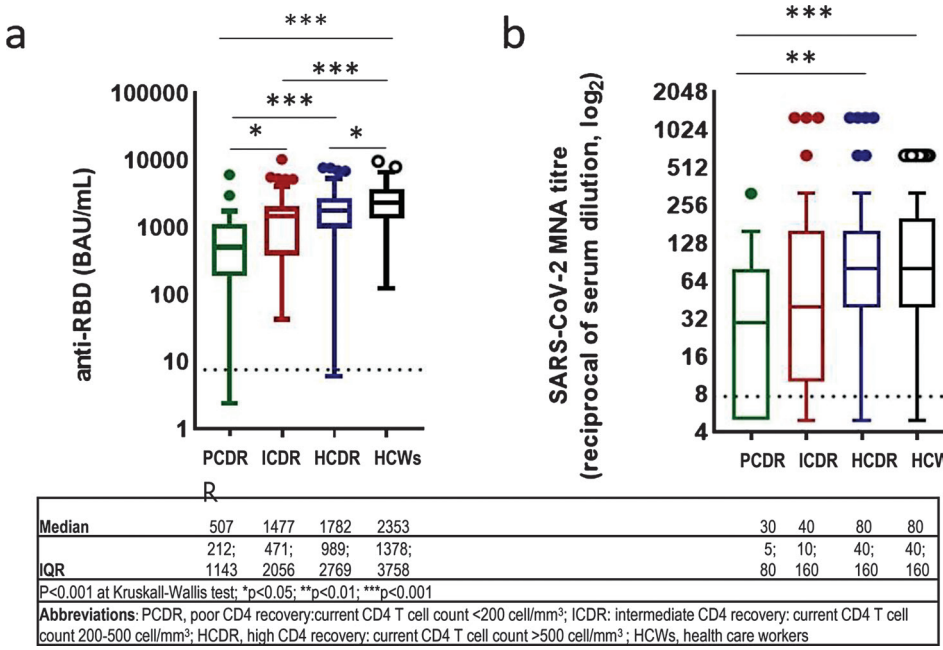


Figure 2. Humoral response in people living with human immunodeficiency virus and HCWs after the priming dose and the second dose of BNT162b2 or mRNA-1273 vaccine. Abbreviations: BAU, binding antibody unit; HCDR, high CD4 recovery; HCWs, healthcare workers; ICDR, intermediate CD4 recovery; IQR, interquartile range; MNA, microneutralization assay; PCDR, poor CD4 recovery; RBD, receptor binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Spike-Specific T-Cell Response After Vaccination in PLWH

First, we compared T-cell responses by gender and found no evidence for an association. Median changes at T1 were 24.3 (0.01–159.6) in males vs 49.8 (4.3–116.1) in females (P = .42; Supplementary Table 1). The corresponding figures at T2 were 220.7 (51.2–441.6) vs 122.7 (76.4–358.8; P = .51). In contrast, the data carried some evidence that the IL-2 response was greater in females vs males. Median changes at T1 were 54.5 (4.2–151.8) vs 159.6 (25.3–235.6; P = .03) and 150.8 (61.5–353.5) vs 215.2 (99.5–523.4) at T2 (P = .17). A significant increase in the specific T-cell response (IFN-γ and IL-2 production after spike peptide stimulation) from time of the priming dose (T0) to time of the second dose (T1) and at 1 month after the second dose (T2) was observed for all PLWH groups (Figure 3), except for IFN-γ production at T1, which was not different from baseline in PCDR. One month after the second dose (T2), IFN-γ release after stimulation was significantly lower in PCDR than ICDR (P = .007) and

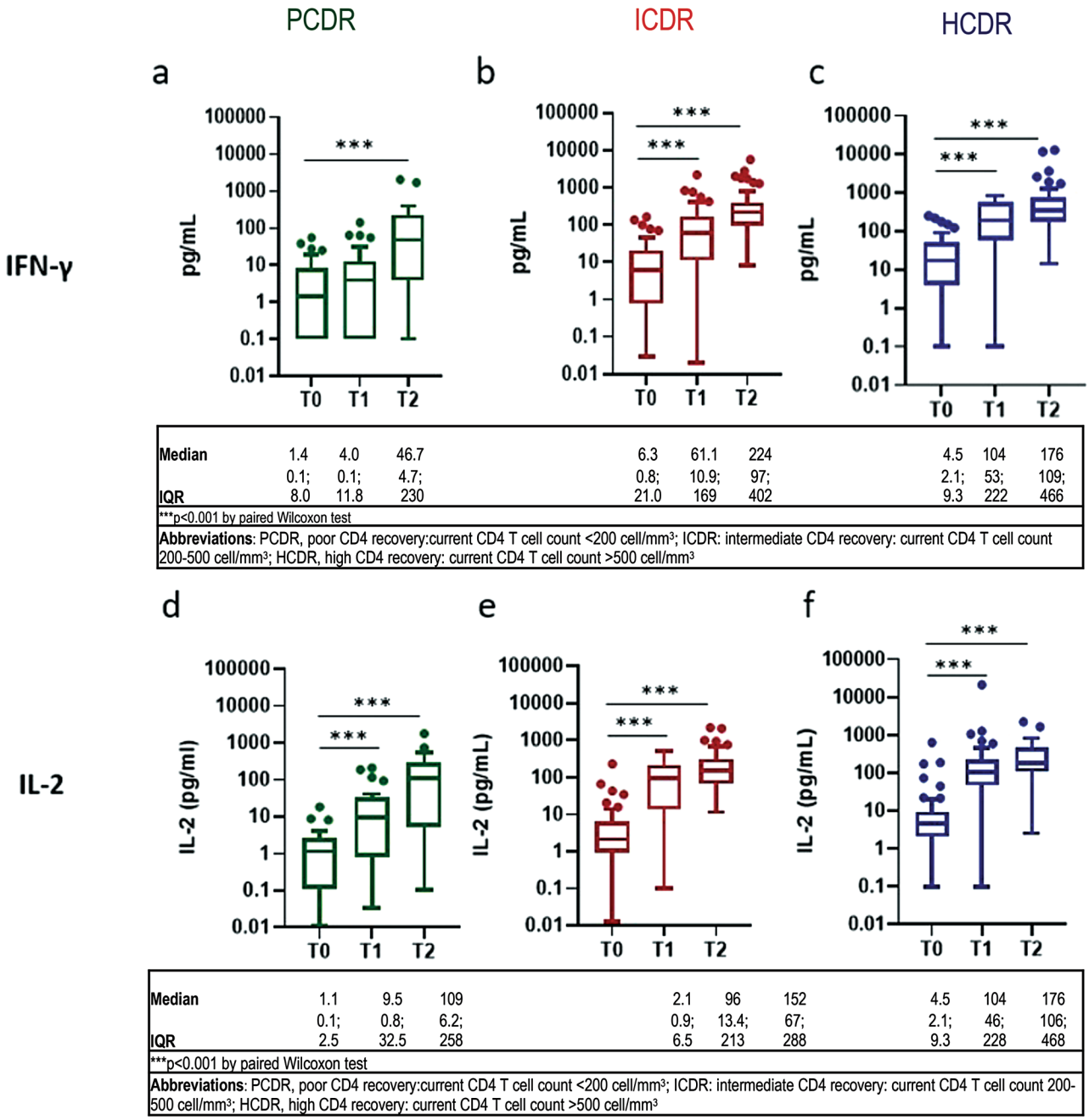


Figure 3. Increase in cell-mediated immunogenicity in people living with human immunodeficiency virus from T0 to T2, expressed as picograms per milliliter of IFN-γ or IL-2 release at the time of priming dose, at time of the second dose, and at 1 month after the second dose. Abbreviations: HCDR, high CD4 recovery; ICDR, intermediate CD4 recovery; IFN-γ, interferon-gamma; IL-2, interleukin-2; IQR, interquartile range; PCDR, poor CD4 recovery.

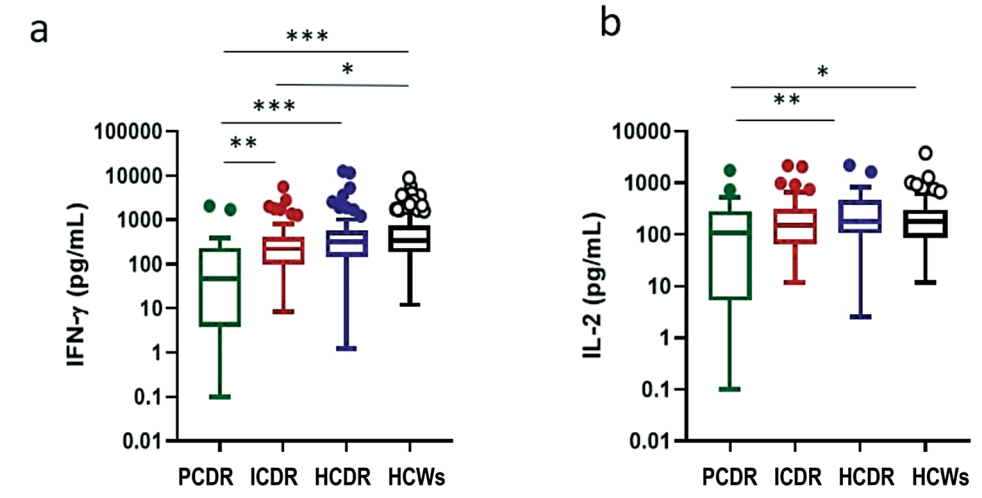
HCDR ($P < .001$) but not different between ICDR and HCDR ($P = .557$; Figure 4A). Median (IQR) values of IL-2 release after stimulation were lower in PCDR than HCDR ($P = .006$) but not between PCDR and ICDR ($P = .171$) or between ICDR and HCDR ($P = .570$; Figure 4B). A positive correlation between IFN-γ and IL-2 was observed (Pearson r = 0.428, $P < .0001$), suggesting a coordinated response (Figure 5A); this correlation was confirmed as significant in PCDR and ICDR but only as marginal in HCDR (Figure 5B–5D). A significant correlation between RBD-binding IgG BAU/mL at time T2 and IFN-γ pg/mL was also found using the nonparametric Spearman correlation coefficient (r = 0.16, $P = .004$; Supplementary Figure 2b).

Role of Current CD4 T-Cell Count and CD4/CD8 Ratio in Predicting Immunogenicity

In PLWHs, a significant correlation between CD4 T cells/mm^3 and magnitude of RBD-binding IgG (Figure 6A), nAb titers (Figure 6B), and IFN-γ release (Figure 6C) was observed using simple linear regression. Having magnitude of RBD-binding IgG production, nAb titer, and IFN-γ release as dependent covariates, a current CD4 count <200 cells/mm^3 was associated with a significantly lower magnitude of immune response, after adjusting for the main identified confounders (age, years of living with HIV, CD4 nadir, HIV-RNA <50 vs >50 copies/mL, type of mRNA vaccine, and previous or current malignancy; Table 3). The CD4/CD8 ratio was associated only with increasing magnitude of RBD-binding IgG production after multivariable adjustment (Table 3).

Comparisons of Immunogenicity of Vaccine Between PLWH and HCWs

Compared with HCWs, the proportion of a detectable RBD-binding IgG response 1 month after the second dose was lower in PCDR ($P < .001$) but comparable in ICDR ($P = 1.0$) and in HCDR ($P = .313$; Table 2), and the median values of RBD-binding IgG response 1 month after the second dose of mRNA vaccine were significantly lower for all PLWHs groups (HCWs vs PCDR, $P < .001$; HCW vs ICDR, $P < .001$; HCWs vs HCDR, $P = .031$; Figure 2A). Comparing the nAbs of PLWHs with that of HCWs, the proportion of nAb vaccine responders was significantly lower in PCDR ($P < .001$) and in ICDR ($P = .019$) but not in HCDR ($P = .116$; Table 2), and the magnitude of nAb response was significantly lower in PCDR ($P < .001$), only marginally lower in ICDR ($P = .050$), and not different in HCDR ($P = 1.000$; Figure 2B). Compared with HCWs, the median (IQR) value of IFN-γ release after stimulation was lower in PCDR ($P < .001$) and in ICDR ($P = .020$) but not in HCDR ($P = .528$; Figure 4A), and the median (IQR) value of IL-2 release after stimulation was lower in PCDR ($P = .024$) but not in ICDR ($P = 1.000$) or in HCDR ($P = .932$; Figure 4B). Using



Median	46.7	223.6	315	343	109	152	176	177
IQR	4.7; 230	97.2; 402.2	148.5; 552.9	188; 715	6.2; 258	67; 288	109; 466	87; 304
P<0.001 at Kruskall-Wallis test;					p=0.019 at Kruskall-Wallis test;			
*p<0.05; **p<0.01; ***p<0.001								

Abbreviations: PCDR, poor CD4 recovery:current CD4 T cell count <200 cell/mm^3; ICDR: intermediate CD4 recovery: current CD4 T cell count 200-500 cell/mm^3; HCDR, high CD4 recovery: current CD4 T cell count >500 cell/mm^3 ; HCWs, health care workers

Figure 4. Cell-mediated immunogenicity in people living with human immunodeficiency virus and HCWs at 1 month after the second dose. Immune response is expressed as median (IQR) release of IFN- γ and IL-2 (pg/mL) after severe acute respiratory syndrome coronavirus 2 spike peptide stimulation. Abbreviations: HCDR, high CD4 recovery; HCWs, healthcare workers; ICDR, intermediate CD4 recovery; IFN-γ, interferon-gamma; IL-2, interleukin-2; IQR, interquartile range; PCDR, poor CD4 recovery.

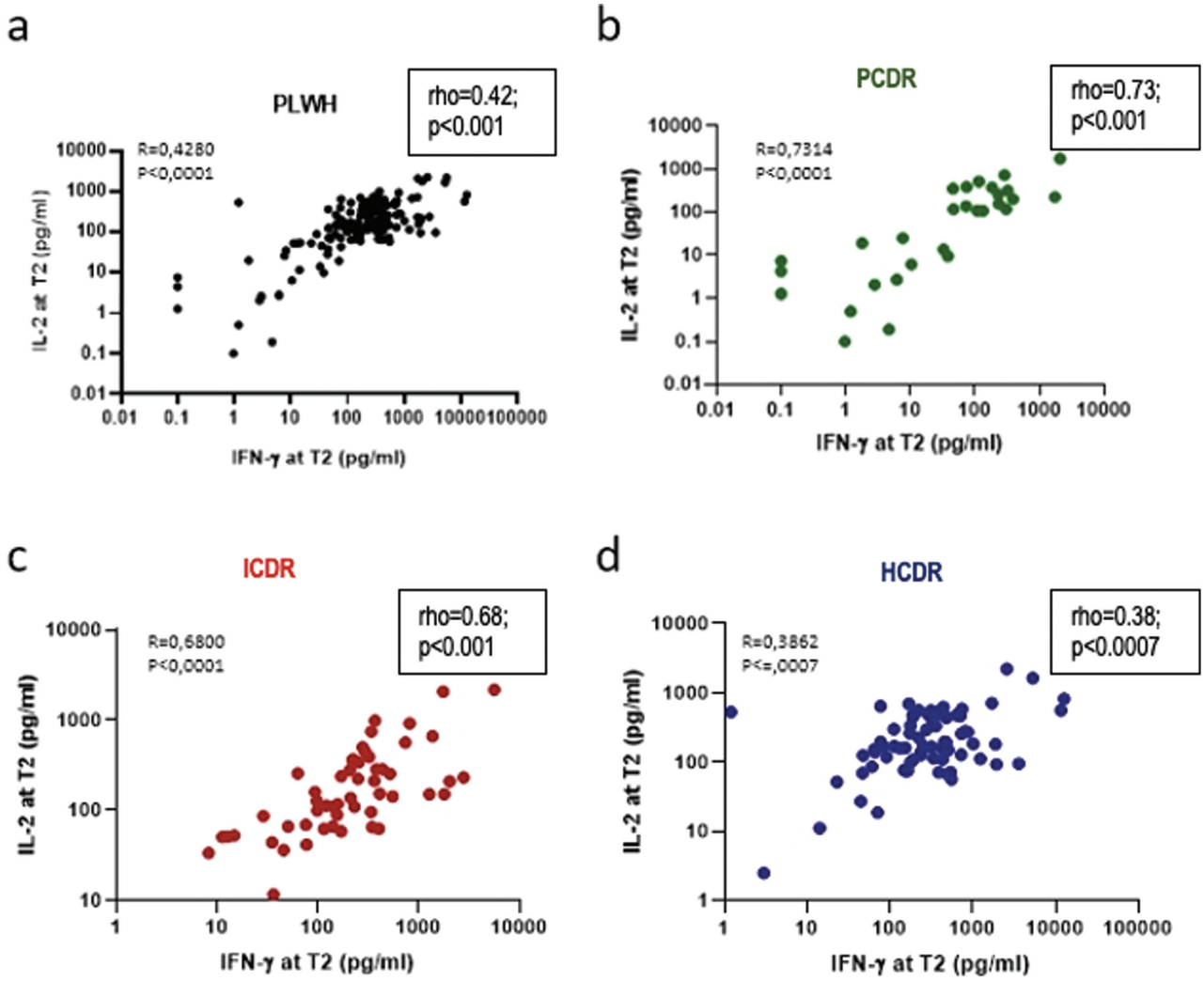


Figure 5. Scatter plots of the association between IFN-γ (pg/mL) and IL-2 (pg/mL) production in blood samples of PLWH collected 1 month after the second dose of severe acute respiratory syndrome coronavirus 2 mRNA vaccine. IFN-γ and IL-2 production in overall PLWH population (Pearson, r = 0.427 $P < .001$). *A*, IFN- γ and IL-2 production in PLWH with SID (Pearson, r = 0.80; $P < .001$). *B*, IFN-γ and IL-2 production in PLWH with MID (Pearson, r = 0.71; $P < .001$). *C*, IFN- γ and IL-2 production in PLWH with NID (Pearson, r = 0.48; $P < .001$). *D*, All *P* values were calculated using linear regression (r, Pearson correlation coefficient). Abbreviations: IFN-γ, interferon-gamma; IL-2, HCDR, high CD4 recovery; ICDR, intermediate CD4 recovery; PCDR, poor CD4 recovery.

HCWs as the reference, after adjustment for gender and age by multivariable linear regression, a significant association between PCDR and reduction in the magnitude of the immune response was found for all 3 parameters (MNA, $P < .001$; RBD-binding IgG, $P < .001$; IFN-γ, $P < .001$). ICDR was associated only with a significant reduction of RBD-binding antibodies, whereas no significant association was observed for HCDR after multivariable adjustment (Table 4).

DISCUSSION

According to these findings, SARS-CoV-2 vaccination with an mRNA vaccine induced a robust humoral and cell-mediated immune response in most PLWH receiving ART. Notably, this immunogenicity was strongly related to CD4 T-cell count at the time of vaccination. Thus, in PLWH with a current CD4 T-cell count >500 cells/mm^3, the immune response after the second dose was comparable for humoral and cell-mediated immunity to that found in HCWs. These results are consistent with previously published data on immunogenicity after adenovirus-vectored [11, 12] or mRNA vaccines [13–15] in PLWH on ART and with high CD4 T-cell counts. In contrast, we found no evidence for an association with gender, with the exception of IL-2 responses, which appeared to be larger in females vs males. A well-integrated immune response represents the main goal of vaccination strategies, and we showed that mRNA vaccination of PLWH with high CD4 T-cell counts was able to induce a coordinated immune response, seen in recovered patients after natural SARS-CoV-2 infection [18] and as described in HCWs [16].

Nevertheless, in PLWH with poor CD4 recovery, we observed a significantly reduced response to SARS-CoV-2 vaccination

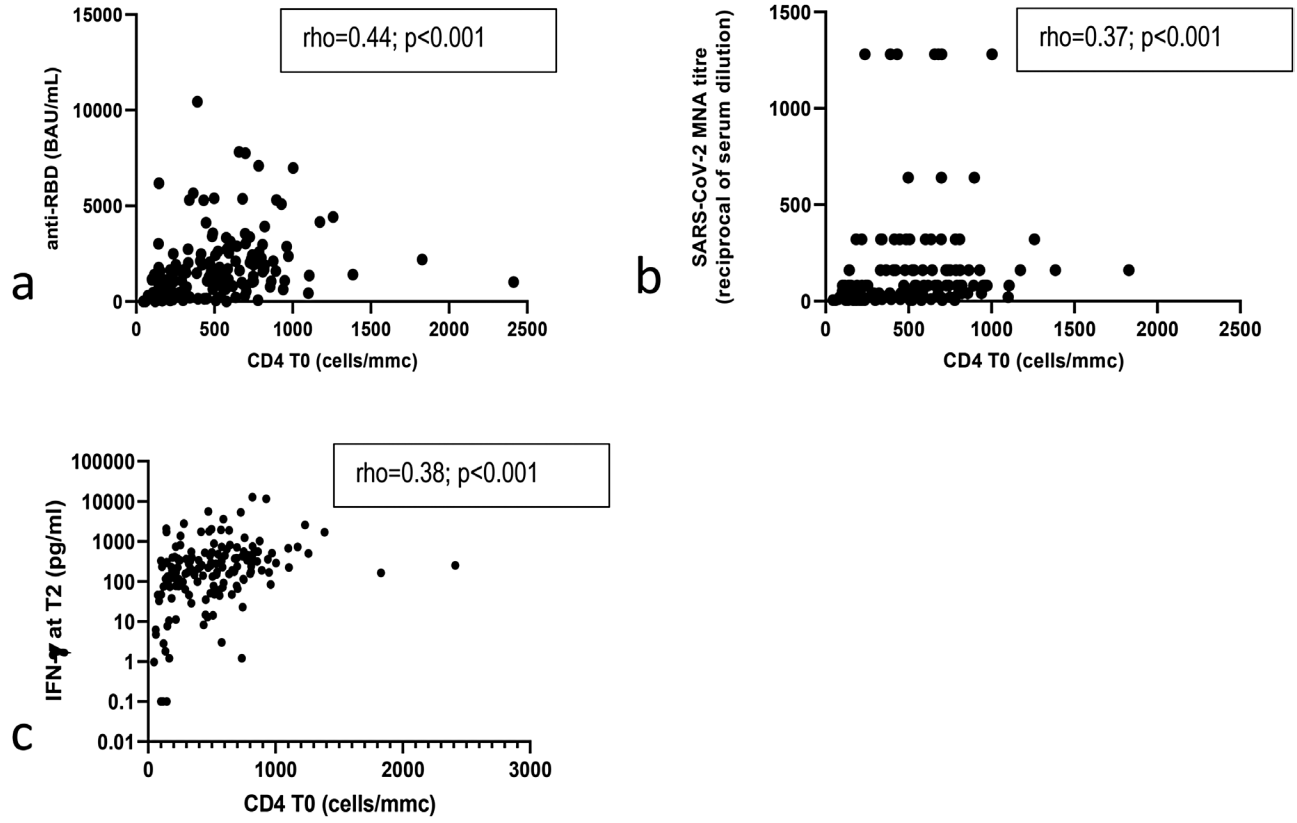


Figure 6. Scatter plots of the association between CD4 T-cell count (per mm^3) at the time of priming dose of mRNA vaccine and RBD-binding immunoglobulin G (IgG) response, neutralizing antibody response, and IFN- γ production at T2 in people living with human immunodeficiency virus. CD4 T-cell count was performed at T0, and blood samples were collected for immunologic response 1 month after the dose of SARS-CoV-2 mRNA vaccine. RBD-binding IgG response (BAU/mL) at T2 and current CD4 T-cell count at T0 (rho = 0.44; $P < .001$). *A,* Neutralizing antibody MNA reciprocal dilution at T2 and current CD4 T-cell count at T0 (rho = 0.37; $P < .001$). *B,* Interferon gamma release after S-peptide stimulation (pg/mL) at T2 and current CD4 T-cell count at T0 (rho = 0.38; $P < .001$). *C,* rho, Spearman rank correlation coefficient. Abbreviations: BAU/mL, binding antibody units per milliliter; IFN-γ, interferon-gamma; MNA, microneutralization assay; RBD, receptor-binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

compared with both immunologically restored PLWH and HIV-negative controls. In PLWH with a current CD4 T-cell count <200 cells/mm^3, a neutralizing activity was detectable in only 70%. This proportion might be remarkable in light of severe and persistent immunologic dysregulation, although substantially lower than that observed in PLWH with a high CD4 T-cell count and in HIV-negative controls.

Correlates of protection by vaccines against COVID-19 are currently unclear [19], as studies evaluating the impact of an impaired immunological response to vaccines on the risk of SARS-CoV-2 infection and symptomatic COVID-19 are lacking. To our knowledge, the present study is the first to characterize the immune response to SARS-CoV-2 vaccination in advanced PLWH and may provide useful information for answering the question of what vaccine strategy is feasible in this vulnerable population.

A low CD4/CD8 ratio was also suggested as a factor associated with increased innate and adaptive immune activation and immune-senescent phenotype [20] and also to a poor magnitude of SARS-CoV-2–specific responses [21]. In our analysis, the CD4/CD8 ratio was independently associated with only RBD-binding production after vaccination and not to neutralizing or cell-mediated response, although we cannot exclude a residual effect.

Our data highlight that PLWH seem to display a better immune response after SARS-CoV-2 vaccination than observed for other immunosuppressed populations, such as solid organ transplant recipients [22]. It was found that 35% of renal transplant recipients developed nAbs after BNT162b2 vaccination [23], and similar results were observed in those who received rituximab [24]. These are poorer rates than the 70% observed in PLWH with current, very low CD4 T-cell counts. A reasonable explanation for this discrepancy may be the different mechanisms of immunosuppression in the 2 populations. Transplant recipients and patients receiving anti-CD20 therapy experience a strong active pharmacological immunosuppression due to the ongoing treatment. In contrast, effective ART that is able to suppress HIV replication can allow a partial restoration of functional immune response in patients with existing low CD4 T-cell counts.

Table 3. Analysis of Current CD4 T-Cell Count and CD4/CD8 Ratio Strata as Independent Predictors of Magnitude of Immune Response to Vaccination Among People Living With Human Immunodeficiency Virus

	Crude			Adjusted		
	Beta	95% CI	*P* Value	Beta	95% CI	*P* Value
Dependent variable: receptor-binding domain–binding immunoglobulin G (binding antibody unit per milliliter)						
Current CD4 T-cell count (cells/mm^3)[a]						
<200	**–0.66**	**–.92 to .41**	**<.001**	**–0.64**	**–.94 to .34**	**<.001**
200–500	–0.19	–.41 to .03	.092	–0.16	–.39 to .07	.182
>500	ref			ref		
CD4/CD8 ratio, per 0.5 increase[b]	**0.24**	**.13 to .34**	**<.001**	**0.16**	**.01 to .30**	**.033**
Dependent variable: neutralizing antibody titer (reciprocal dilution at microneutralization assay)						
Current CD4 T-cell count (cells/mm^3)[a]						
<200	**–0.52**	**–.78 to .25**	**<.001**	**–0.41**	**–.70 to .12**	**.006**
200–500	–0.20	–.43 to .02	.076	–0.08	–.31 to .15	.497
>500	ref			ref		
CD4/CD8 ratio, per 0.5 increase[b]	0.17	.05 to .28	.002	0.06	–.09 to .20	.426
Dependent variable: interferon gamma (pg/mL)						
Current CD4 T-cell count (cells/mm^3)[a]						
<200	**–1.03**	**–1.36 to .69**	**<.0001**	**–0.74**	**–1.13 to .34**	**<.001**
200–500	–0.14	–.42 to .14	.335	–0.03	–.28 to .34	.850
>500	ref			ref		
CD4/CD8 ratio, per 0.5 increase[b]	0.15	.02 to .28	.020	–0.05	–.19 to .10	.544

All analyses are based on logarithmic units. Significant associations are in bold.

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus.

[a]Adjusted for age, years living with HIV, CD4 nadir, HIV-RNA undetectable (<50 vs >50 copies/mL), type of mRNA vaccine (BNT162n2 or mRNA-1273), previous or current malignancy.

[b]Adjusted for age, years living with HIV, CD4 nadir, current CD4 T-cell count, HIV-RNA undetectable (<50 vs >50 copies/mL), type of mRNA vaccine (BNT162n2 or mRNA-1273), previous or current malignancy.

The main limitation of our study was the observational, nonrandomized nature of the design, thus, the lack of a matched HIV-negative control group. However, the comparisons with HCWs were controlled for gender and age. Moreover, despite the short duration of current follow-up, we were still unable to generate appropriate information on waning of a protective immune response after SARS-CoV-2 vaccination in PLWH. Although females were underrepresented in our sample, we were able to detect significant differences in IL-2 responses when we compared males with females.

Table 4. Multivariable Linear Regression Models of Factors Associated With Magnitude of Receptor-Binding Domain–Binding Immunoglobulin G Response, Neutralizing Antibody Response at Microneutralization Assay, and Interferon-Gamma Release After S-Peptide Stimulation With Different Groups

CD4 count	Beta	95% Confidence Interval		*P* Value
Dependent variable: receptor-binding domain–binding immunoglobulin G (binding antibody units per milliliter)[a] at 1 month after the second dose				
PCDR	–0.69	–0.89	–0.49	<.001
ICDR	–0.23	–0.40	–0.06	.008
HCDR	–0.05	–0.21	0.10	.485
HCWs	ref			
Dependent variable: microneutralization assay (reciprocal of dilution, $\log_2$) [a] at 1 month after second dose				
PCDR	–0.43	–0.71	–0.16	.002
ICDR	–0.14	–0.39	0.11	.261
HCDR	0.05	–0.18	0.27	.695
HCWs	ref			
Dependent variable: interferon-gamma (pg/mL) [a] at 1 month after second dose				
PCDR	–1.05	–1.33	–0.78	<.001
ICDR	–0.20	–0.43	0.02	.077
HCDR	0.08	–0.29	0.13	.446
HCWs	ref			

Results were adjusted for gender and age by means of 3 separate multivariable linear regression models.

Abbreviations: HCDR, high CD4 recovery; HCWs, healthcare workers; ICDR, intermediate CD4 recovery; PCDR, poor CD4 recovery.

[a]All values are expressed as $\log_{10}$.

Despite these limitations, the results of the present study may assist the select subpopulation of PLWH who respond poorly to SARS-CoV-2 vaccination with additional dosing strategies, as recently recommended in those with low CD4 counts [25] and currently investigated in other immunosuppressed people [26]. In the context of the current debate on the benefits and risks of a booster dose, it was suggested that an additional dose could be delivered to immunocompromised individuals without an adequate immune response to the standard schedule [27]. Our data support that PLWH with current CD4 T-cell counts <200 cells/mm^3 should receive an additional dose. This dose could also be offered to PLWH with a CD4 count between 200 and 500 cells/mm^3, taking into account both dysregulation and poor immune response compared with HIV-negative controls.

In conclusion, the present study supports the hypothesis that mRNA vaccination would be able to elicit robust humoral and cellular immune responses against SARS-CoV-2 in most PLWH receiving ART, particularly in those with full immune recovery after suppressive therapy. Nevertheless, this immune response to vaccination is significantly poorer in those with a current CD4 T-cell count <200 cells/mm^3, suggesting that chronic, persistent dysregulation in the ART-treated population may affect the effector immune response to this vaccination. The implications of these findings as correlates of protection of SARS-CoV-2 vaccination in PLWH should be further investigated.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Authors contributions. A. A., S. L., and A. V. conceptualized and designed the study and wrote the protocol. A. A., S. C., C. A., and C. Castilletti wrote the first draft of the manuscript and referred to appropriate literature. A. A., F. V., E. G., C. A., C. C., and V. P. conceived of and supervised the study and contributed to data interpretation. P. L. and A. C. L. were the main authors responsible for formal data analysis and also contributed to drafting of the manuscript. M. F. and L. D. P. were responsible for data curation. A. V., C. P., V. M., R. G., and I. M. revised the manuscript content and reviewed and edited the manuscript. S. M., G. M., F. C., and D .L. performed all of the serology tests and neutralization assays. V. B., D. M., E. C., and A. S. performed all T-cell function tests. L. D. P., C. Cerini, and C. Candela performed and supervised the anti–severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination campaign at Istituto Nazionale Malattie Infettive (INMI) for individuals living with human immunodeficiency virus and enrolled participants. S. G., E. G., and R. B. enrolled participants and reviewed the manuscript. All authors agreed with and approved the final version of the manuscript.

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Data Sharing. Anonymized participant data will be made available upon reasonable requests directed to the corresponding author. Proposals will be reviewed and approved by the investigator and collaborators on the basis of scientific merit. After approval of a proposal, data can be shared through a secure online platform after signing a data access agreement.

Potential conflicts of interest. Outside of this submitted work: A. A. has served as a paid consultant to Gilead Sciences, Janssen-Cilag, Merck, GlaxoSmithKline, Astra Zeneca, Roche, and ViiV Healthcare; received research institutional grants from Gilead Sciences, Janssen-Cilag, and ViiV Healthcare; received payment or honoraria from Gilead Science and ViiV Healthcare; and received support for attending meetings and/or travel from ViiV Healthcare and AbbVie. A. V. received an institutional grant from Gilead Sciences, speakers' honoraria/educational activities from Merck Sharp & Dohme and Janssen-Cilag, and served an advisor for Janssen-Cilag. E. G. received institutional grants for Gilead Sciences, the Italian Ministry of Health, and Mylan; personal fees from Gilead Sciences and ViiV; and consulting fees from Mylan. R. G. reports payments to their institution from Gilead; consulting fees from MSD, Gilead, Janssen, ViiV, and Thera Technologies; speakers' honoraria/educational activities from ViiV Healthcare, Merck Sharp & Dohme, and Gilead Sciences; and served as an advisor for ViiV Healthcare and Janssen-Cilag. C. P. received a personal fee from Gilead-Sciences for a case presentation, received a travel grant from Gilead, and served on an advisory board for Janssen-Cilag. S. C. reports consulting fees paid to self from ViiV, Janssen-Cilag, MSD, and Gilead; payment or honoraria from ViiV, Janssen-Cilag, MSD, and Gilead; support for attending meetings and/or travel from ViiV, Janssen-Cilag, MSD, and Gilead; and participation on a data safety monitoring board or advisory board for ViiV, Janssen-Cilag, MSD, and Gilead. R. B. reports consulting fees from ViiV, Gilead, and MSD; payment or honoraria from Gilead, MSD, and ViiV; support for attending meetings and/or travel from Gilead and Janssen-Cilag; and participation on a data safety monitoring board or advisory board for ViiV, Gilead, Janssen-Cilag, and Merck Sharp & Dohme (MSD). A. C.-L. reports grants or contracts paid to University College of London (UCL) from the Icona Foundation Study and from the EuCARE project funded by the EU under the HORIZON Europe Programme (grant agreement 6944397) and consulting fees from Fondazione GlaxoSmithKline. All remaining authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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