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MAJOR ARTICLE

SARS-CoV-2 Humoral and Cellular Immune Responses of Patients With HIV After Vaccination With BNT162b2 mRNA COVID-19 Vaccine in the Tel-Aviv Medical Center

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Background. Little is known about vaccine efficacy and sustainability among people with HIV (PWH). We estimated humoral and cellular immune responses postvaccination with BNT162b2 mRNA coronavirus disease 2019 (COVID-19) vaccine among PWH in Tel-Aviv Medical Center.

Methods. The vaccine humoral response was evaluated by measuring immunoglobulin G (IgG) titers of antispike receptor-binding domain antibodies (anti-RBD IgG). Cellular response was assessed by stimulating donor peripheral blood mononuclear cells with pooled complete S-peptide mix.

Results. One hundred thirty-six PWH who completed 2 doses of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine were tested for anti-RBD IgG and compared with 61 vaccinated health care workers (HCWs). The antibody titers were similar between the groups (median, 118 BAU/mL for PWH and 101.4 BAU/mL for HCWs; $P = .231$), although the mean time from second vaccine was 4.5 months in PWH and 6.7 months in HCWs ($P < .0001$). Longer time from second vaccine dose was associated with decreased antibody level, as were CD4 counts <300 cells/μL compared with higher CD4 counts (25.1 BAU/mL vs 119.3 BAU/mL, respectively; $P = .047$). There was no difference in cellular immune response between vaccinated PWH, convalescent unvaccinated PWH, and vaccinated HCWs.

Conclusions. The humoral immune response of PWH was comparable to that of HCWs after BNT162b2 mRNA vaccination. Cellular immune response did not differ between vaccinated PWH, convalescent PWH, and vaccinated HCWs. PWH with CD4 counts <300 cells/μL (n = 9) had lower antibody titers compared with patients with counts >300 cells/μL (n = 127).

Keywords. cellular vaccine response; COVID-19; HIV; humoral vaccine response.

In December 2019, the first cases of coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were reported from Wuhan, Hubei province, in China. In March 2020, the World Health Organization declared COVID-19 a global pandemic, with >239 million cases worldwide and >5 million deaths as of November 2021 [1]. According to the Joint United Nations Programme on HIV/AIDS 2020 data, there are 37.7 million people with HIV (PWH) throughout the world [2]. An increasing body of evidence indicates that PWH who acquire SARS-CoV-2 are at heightened risk for hospitalization and progression to severe disease. Data from clinical studies in the United States, United Kingdom, and Spain have shown that advanced HIV disease and the presence of the comorbidities common among the aging HIV population present risk factors for severe disease [3–5]. According to those studies, the prevalence of SARS-CoV-2, as confirmed by positive polymerase chain reaction (PCR) testing, was not higher among PWH compared with the general population. However, due to the wide spectrum of clinical presentations of SARS-CoV-2, ranging from asymptomatic to life-threatening disease, the real prevalence might be underestimated when determined solely by PCR testing.

The SARS-CoV-2 mRNA-based vaccine became available in Israel in December 2020. Immunocompromised patients, including PWH, were prioritized to receive the vaccine, along with the elderly population and health care workers (HCWs). It is known that PWH might have a reduced humoral response following several vaccinations, as described for hepatitis B and A vaccines, especially in PWH with low CD4 counts and

Received 15 November 2021; editorial decision 14 February 2022; accepted 20 February 2022; published online 23 February 2022.

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Open Forum Infectious Diseases®2022

https://doi.org/10.1093/ofid/ofac089

uncontrolled viral replication [6–9]. A recent study from Israel [10] and a smaller study from the United States [11] showed a robust serologic response among PWH that was observed 2–3 weeks after the second dose of the BNT162b2 mRNA vaccine. That response was not inferior to the serologic response of HIV-negative patients. In another study, the cellular immune response to the BNT162b2 vaccine was measured by ELISpot in 12 patients, and it, too, did not differ from the cellular response of HIV-negative controls [12]. However, little is known about the level and durability of the humoral and cellular responses among PWH after COVID-19 recovery or after SARS-CoV-2 mRNA-based vaccination.

The Tel-Aviv Crusaid Kobbler AIDS Center is one of the largest HIV centers in Israel, with ~2100 PWH being followed regularly. The goals of the current study were to estimate humoral and cellular immune responses 3–6 months after the second vaccine dose in patients vaccinated with the BNT162b2 mRNA vaccine.

METHODS

Study Population and Study Design

The study patients were recruited during their routine follow-up at the Crusaid Kobbler AIDS Center, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel.

We conducted a prospective study of humoral and cellular immune responses 3–6 months after the second vaccine dose (between April 28, 2021, and August 28, 2021) among PWH without evidence of previous infection with SARS-CoV-2 (based on patient-reported history).

Humoral Immune Response

With the introduction of the BNT162b2 vaccine in Israel in December 2020, PWH were prioritized to receive a 2-dose schedule along with the general elderly population, immunocompromised individuals, and HCWs. The majority of our patients were vaccinated between January and March 2021. All patients who arrived for a routine follow-up in our clinic and met the inclusion criteria of being vaccinated with 2 doses of BNT162b2 Pfizer mRNA vaccine were invited to participate in this study. Humoral immune response was compared with a group of HIV-negative HCWs who received 2 doses of BNT162b2 vaccine and provided a blood sample for serological testing before receiving a third vaccine dose (a booster).

Cellular Immune Response

In addition to testing of their humoral immune response (anti–receptor-binding domain immunoglobulin G [anti-RBD IgG]), the first 30 vaccinated PWH as well as first 9 COVID-19 convalescent PWH were asked to provide a blood sample for evaluation of cellular immunity 3–6 months after the second vaccine dose or recovery from COVID-19. Their results were compared with the 8 vaccinated HCWs who provided a blood sample for evaluation of cellular immune response 4 months after completing the vaccine schedule.

Demographic and clinical data, including antiretroviral therapy (ART), comorbidities, CD4 count, and HIV viral load, were extracted from medical files.

Evaluation of Antibodies Against SARS-CoV-2

A commercial automated SARS-CoV-2 IgG assay was used for the evaluation of antibody response among individuals who had received the BNT162b2 vaccine. The chemiluminescent microparticle immunoassay provided qualitative and quantitative determination of anti-SARS-CoV-2 spike protein RBD IgG antibody levels (SARS-CoV-2 IgG II Quant, Cat #6S60, Abbott, Ireland). The result was provided as arbitrary units (AU) per milliliter, as defined by the manufacturer, ranging between 0 and 40 000 AU/mL for anti-RBD IgG (a level of >150 AU/mL was considered positive). Conversion of AU/mL to World Health Organization binding antibody units (BAU/mL) was conducted using the manufacturer's instructions.

Peripheral Blood Mononuclear Cell Isolation and Stimulation

Peripheral blood mononuclear cells (PBMCs) were isolated from whole blood by Ficoll gradient centrifugation. Following isolation, the cells were stored in liquid nitrogen for later use. T-cell response was assessed by stimulating donor PBMCs with a pooled complete S-peptide mix in the presence of a protein transport inhibitor (Brefeldin A), followed by staining for an activation marker (CD40L) and intracellular cytokines (tumor necrosis factor alpha [TNFα] and interferon gamma [IFNγ]). The complete S-peptide mix used for stimulation is a pool of lyophilized peptides, consisting mainly of 15-mer sequences with overlap of 11 amino acids, covering the complete protein coding sequence (aa 5–1273) of the SARS-CoV-2 spike glycoprotein (GenBank MN908947.3, Protein QHD43416.1; Cat #130-127-951, Miltenyi Biotec, Germany). Briefly, donor PBMCs were plated in a 96-well plate at a concentration of 0.5–1 × 10^6 PBMCs/μL and incubated at 37°C and 5% CO_2 with 2 μL of either complete pooled S-peptide mix, CytoStim for positive control, or 10% dimethyl sulfoxide (DMSO) in sterile water as negative control. After 2 hours, Brefeldin A was added to each well, and the cells were incubated for an additional 4 hours. The cells were then stained with viability dye, followed by fixation, permeabilization, and staining for surface markers (CD3, CD20, CD14, CD4, CD8, and CD154) and for TNFα and INFγ. Following staining, samples were acquired by BD FASCCanto II, and 20 000 $CD4^+$ events were collected for each sample. The analysis was performed on gated $CD4^+$ T cells, and the absolute number of activated $INF\gamma^+$ and $TNF\alpha^+$ cells was recorded and normalized for 1 × 10^6 $CD4^+$ T cells (Supplementary Figure 1). In order to calculate the actual response rate, the absolute number of positive events in the unstimulated negative control was deducted from the absolute

number of events in the S-stimulated samples, as shown in the following formula:

$$\left(\frac{1 \times 10^6\,(\#Stimulated\ cytokine + CD4s)}{\#Total\ recorded\ CD4s} - \frac{1 \times 10^6\,(\#\ Unstimulated\ cytokine + \ CD4s)}{\#Total\ recorded\ CD4s}\right)$$

HIV-Related Tests

HIV viral load was determined with Cepheid Xpert HIV-1 Viral Load, and a result of <40 copies/mL was considered undetectable. $CD4^+$ and $CD8^+$ T-cell counts were determined by flow cytometry analysis of freshly collected peripheral blood (within 4–6 hours after blood sampling).

Statistical Analysis

Continuous variables were first tested for normal distribution by means of the Kolmogorov-Smirnov test and Q-Q pilots, were summarized, and are displayed as mean (SD) for normally distributed variables and as median (interquartile range [IQR]) for non–normally distributed variables. Continuous variables were compared by a *t* test if normally distributed or by Kruskal-Wallis/Mann-Whitney test if not normally distributed. Correlation between 2 continuous parameters was calculated by Spearman analysis. $P < .05$ was considered statistically significant for all analyses. Multivariable linear regression analysis was performed to control for demographic characteristics (age and gender) and time from second vaccine dose. IBM SPSS Statistics for Windows, version 27 (IBM Corp.), was used for all statistical analyses.

RESULTS

Study Population

The majority of the PWH were males (79.6%), with MSM comprising the predominant HIV risk group (69.8%) (Table 1). Almost one-half of the patients reported being current smokers (44.8%). The mean CD4 count (SD) was 756 (314) cells/μL, and viral load was undetectable for most of the patients (95.6%). There were 9 patients with CD4 counts <300 cells/μL, 3 of them with CD4 count <200 cells/μL. Most of the patients (94%) were treated with an integrase inhibitor–based ART regimen.

The majority of the patients did not have any comorbidities, while 9.2% had hypertension and 7% were obese. The median time from HIV diagnosis to study participation was 9 years.

The HCWs were significantly older than the HIV-positive patients, with a median age (IQR) of 49 (42–63) years vs 44 (37–52) years ($P = .002$). There were more male patients in PWH group (79.6%) compared with 52% in the HCW group ($P = .0001$).

All patients who arrived for a routine follow-up visit 3–6 months after completing a 2-dose vaccination with the BNT162b2 mRNA COVID-19 vaccine were invited to be enrolled in this study. Levels of IgG antibodies against the SARS-CoV-2 spike protein receptor-binding domain were checked. A total of 136 HIV-positive individuals were included in the study and provided blood samples for serology testing. Their results were compared with a group of 61 HIV-negative vaccinated HCWs who received 2 doses of BNT162b2 mRNA COVID-19 vaccine.

Table 1. Baseline Characteristics of Patients With HIV Receiving 2 Doses of the BNT162b2 mRNA COVID-19 Vaccine

Characteristic	Value
Age, median (IQR), y	44 (37–52)
Male sex, No. (%)	109 (79.6)
Female, No. (%)	28 (20.4)
Smoking, No. (%)	39 (44.8)
Diabetes, No. (%)	2 (2.3)
Hypertension, No. (%)	8 (9.2)
Ischemic heart disease, No. (%)	2 (2.3)
Obesity, No. (%)	6 (7)
MSM, No. (%)	90 (69.8)
FSU, No. (%)	3 (2.3)
IVDU, No. (%)	5 (3.9)
INSTI-based regimen, No. (%)	130 (94.2)
CD4, mean (SD)	756 (314)
Time from HIV diagnosis, median (IQR), y	9 (5–14)
Time from second vaccine dose, mean (SD), mo	4.5 (3.5–5.2)

Abbreviations: COVID-19, coronavirus disease 2019; FSU, Former Soviet Union; INSTI, integrase inhibitor; IQR, interquartile range; IVDU, intravenous drug user; MSM, men who have sex with men.

The first 30 vaccinated patients provided blood samples for cellular immune response assessment, in addition to the serology testing. Their results were compared with 9 COVID-19 convalescent, unvaccinated PWH who had recovered 3–6 months earlier and with 8 HIV-negative vaccinated HCWs who provided blood samples for cellular immunity testing 4 months after the second vaccine dose.

Humoral Immune Response

All the patients in both the PWH and HCW groups had received BNT162b2 Pfizer mRNA vaccine with a 21-day interval between the first and the second doses. The mean time between the second vaccine dose and a serological test was 4.5 months in the PWH group and 6.7 months in HCWs ($P < .0001$). The serological test results did not differ between the groups, with a median of 118 BAU/mL for the HIV patients and 101.4 BAU/mL for the HCWs ($P = .231$) (Table 2). We performed next a multivariable linear regression analysis to control the anti-RBD IgG level for age, gender, and time from the second vaccine dose, and no significant association was observed between the groups ($P = .697$).

Table 3 displays the results of our evaluation of an association between the patients' characteristics and the level of anti-RBD IgG antibodies. Patients with a CD4 count <300 cells/μL had a

Table 2. Demographic Characteristics and Serological Response of PWH vs Non-HIV HCWs

Variable	PWH	HCWs	*P* Value
No.	136	61	
Age, median (IQR), y	44 (37–52)	49 (42–63)	.002
Male, No. (%)	109 (79)	32 (52)	.0001
Anti-RBD IgG, median (IQR), BAU/mL	118 (61.2–238.6)	101.4 (52.5–185)	.231
Time from second vaccine dose, mean (SD), mo	4.5 (0.7)	6.7 (0.3)	<.0001

Abbreviations: HCWs, health care workers; IgG, immunoglobulin G; IQR, interquartile ranges; PWH, people with HIV; RBD, receptor-binding domain.

diminished humoral immune response compared with patients with a CD4 count >300 cells/μL (25.1 BAU/mL vs 119.3 BAU/mL, respectively; $P = .047$). While there were only a few patients with a CD4 count <200 cells/μL to reach a level of statistical significance (3 patients), none of them had detectable anti-RBD IgG antibodies. The mean age of patients with a CD4 count <300 cells/ μL did not differ from the age of patients with a higher CD4 count (44.7 vs 45.2, respectively; $P = .676$). The mean time from the second vaccine dose to the serological test in patients with a CD4 count <300 cells/μL (SD) was 4 (0.96) months, and 4.5 (0.7) months for patients with higher CD4 counts ($P = .0456$).

Time from the second vaccine dose was also found to influence antibody level, with longer time from the second vaccine dose being associated with lower anti-RBD IgG levels (Spearman's rank correlation coefficient, –0.349; $P < .001$).

Other baseline characteristics that were evaluated (age, body mass index, HIV risk group, time from HIV diagnosis, HIV viral load, comorbidities, ART regimen, and CD4/CD8 ratio) were not found to have any influence on anti-RBD IgG levels.

Cellular Immunity

Cellular immunity was assessed in 30 vaccinated PWH and compared with 9 unvaccinated PWH who had recovered from symptomatic COVID-19 3–6 months earlier and with 8 vaccinated HCWs who had not been infected with SARS-CoV-2. The groups did not differ in age (Table 4), and the CD4 counts were similar in the groups of vaccinated and recovered PWH (718 cells/μL vs 672 cells/μL, respectively; $P = .230$). For convalescent PWH, the mean time from positive SARS-CoV-2 test to cellular immunity test (SD) was 3.8 (0.6) months, similar to the time from the second vaccine dose to test in vaccinated PWH (3.6 [0.5] months; $P = .321$). Vaccinated HCWs provided blood samples for cellular immunity 4 months after completing the vaccination schedule. The cellular response to a pooled complete S-peptide mix stimulation did not differ between groups for either $TNF\alpha^+$- or $INF\gamma^+$-producing $CD4^+$ T cells (Table 4, Figure 1). However, anti-RBD IgG antibody levels were significantly lower in the patients who had recovered from COVID-19 compared with the vaccinated HIV-positive noninfected patients (20.9 BAU/mL vs 226.2 BAU/mL, respectively; $P = .001$).

Table 3. Association Between Patient Characteristics and Level of Anti-RBD IgG

Characteristic	Correlation Coefficient, rs	*P* Value
CD4, absolute	0.42	.625
HIV viral load	–0.118	.173
CD4, %	0.111	.201
CD8, absolute	–0.046	.595
CD4/CD8 ratio	0.113	.194
Age, y	–0.007	.934
Body mass index	0.026	.857
Years since HIV diagnosis	–0.16	.063
CD4 <300 cells/μL	–1.983	**.047**
Time from second vaccine dose	–0.349	**<.001**

Bold formatting indicates statistical significance.

Abbreviations: IgG, immunoglobulin G; RBD, receptor-binding domain; rs, Spearman's rank correlation coefficient

DISCUSSION

We prospectively assessed a cohort of patients who had received 2 doses of the BNT162b2 mRNA COVID-19 vaccine. Previous studies had suggested good responses to vaccines among PWH on ART with high CD4 counts and good viral control [10–14]. For example, Levy et al. reported that 98% of PWH had developed anti-RBD IgG at a median of 18 days after the second vaccine dose compared with 98.9% of HCWs. Three patients with a CD4 count <200 cells/μL were included in 1 of the studies, and all 3 developed anti-RBD IgG shortly after the second vaccine [10]. However, little is known about the sustainability of the serological response.

Our data show that the level of anti-RBD IgG did not differ among PWH compared with HCWs (median, 118 BAU/mL for HIV patients and 101.4 BAU/mL for HCWs; $P = .231$). However, the time since the second vaccine dose differed significantly between the groups, with a mean of 4.5 months in PWH vs 6.7 months in HCWs ($P < .0001$). As we showed in our study, time from the second vaccine dose was associated with lower anti-RBD IgG levels. However, multivariable linear regression analysis did not show a significant difference between the groups when controlling for time from the second vaccine dose. Our patients were younger than the group of HCWs, with more males. Most had high CD4 cell counts (mean [SD], 756 [314] cells/μL) and good viremic control. Previous studies have provided evidence that advanced age is associated with diminished

Table 4. Cellular Immunity

Characteristic	PWH Vaccinated With BNT162b2 Pfizer mRNA Vaccine	PWH Recovered From SARS-CoV-2 Infection	HCWs Vaccinated With BNT162b2 Pfizer mRNA Vaccine	*P* Value
No.	30	9	8	
Age, mean (SD), y	46 (13)	42 (8)	48 (6)	.44
CD4 count, median (IQR), cells/mm^3	718 (540–879)	672 (176–747)		.23
Time from second vaccine dose or positive SARS-CoV-2 PCR, mean (SD), mo	3.6 (0.5)	3.8 (0.6)		.321
CD4+ INFγ, median (IQR)	384 (87–747)	427 (256–615)	314 (141–862)	.896
CD4+ TNFα, median (IQR)	782 (324–1118)	470 (292–939)	538 (310–1052)	.782

Abbreviations: HCWs, health care workers; INFγ, interferon gamma; IQR, interquartile range; PCR, polymerase chain reaction; PWH, people with HIV; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNFα, tumor necrosis factor alpha.

immune response to the BNT162b2 mRNA vaccine [15–17], especially above the age of 65. Our HCW cohort was significantly older than the PWH cohort (49 vs 44), but still relatively young; therefore, we assumed that the age difference was not a significant factor in our study, and it was further confirmed by multivariable analysis. There is conflicting evidence regarding whether there is a gender difference in the response to the BNT162b2 mRNA vaccine. Jabal et al. did not show a difference in response between male and female HCWs in Israel [15]; however, Vassilaki et al. showed a better serological response in female HCWs in Greece [16].

It is well established that patients with HIV who have low CD4 counts may have a decreased serological response to other vaccines [6–9]. Therefore, we sought to check whether a low CD4 count is associated with diminished response. Although only 3 patients with a CD4 count <200 cells/μL were included in our study, none of them had detectable anti-RBD IgG antibodies at 3–6 months after 2 vaccine doses. In the group of 9 patients with a CD4 count <300 cells/μL (which included also those with CD4 count <200 cells/μL), the level of antibodies was significantly lower than that in the group of patients with higher CD4 counts. The mean time from the second vaccine dose was a bit shorter in PWH with a CD4 count <300 cells/μL compared with patients with higher CD4 counts, reflecting a true diminished response to vaccine in this group of patients. Another factor that was associated with lower antibody level was the time since the second vaccine dose, with decreasing levels of antibodies over time. No other factor was found to influence antibody levels. Studies published recently have shown a waning humoral immune response over time, especially among men, persons above the age of 65, and immunocompromised patients [18, 19]. Waning immune response is associated with a higher susceptibility to SARS-CoV-2; therefore, PWH with a CD4 count <300 cells/ μL should be prioritized for vaccine boosters.

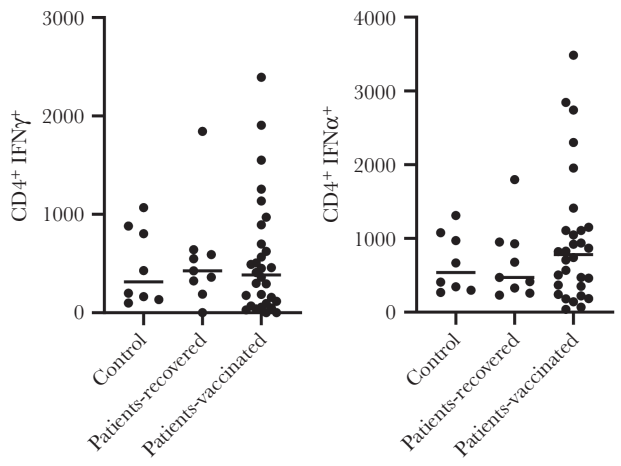

Figure 1. Cellular immune response. Cellular response was evaluated by stimulating PBMCs with an S-peptide mix. Normalized numbers of cytokine-positive CD4$^+$ T cells are shown (left panel – number of INFγ$^+$ cells; right panel – number of TNFα$^+$ cells). Samples were collected from 30 vaccinated PWH, 9 recovered PWH, and 8 vaccinated HCWs. Horizontal lines indicate median number of cytokine-positive cells/10^6 CD4$^+$ cells. Abbreviations: HCWs, health care workers; INFγ, interferon gamma; PWH, people with HIV; TNFα, tumor necrosis factor alpha.

A recent study by Weldemeskel et al. [12] evaluated cellular response in 12 patients with HIV 7 and 17 days after the second dose of the BNT162b2 vaccine, and the results were compared with healthy donors. There was no difference in the INFγ spot-forming units or in the stimulation index between the study and control groups. In accordance with their findings, our current results demonstrated that the cellular response after stimulation with pooled complete S-peptide mix did not differ between vaccinated PWH and vaccinated HCWs, with both groups showing comparable numbers of TNFα- and INFγ-producing CD4$^+$ T cells. Time from the second vaccine dose to cellular immunity test was similar between the groups. However, the anti-RBD IgG levels for the PWH who recovered from SARS-CoV-2 were significantly lower than those for vaccinated PWH, regardless of CD4 counts, which were similar for both groups. A previous study of non-HIV SARS-CoV-2 convalescent individuals showed that even though there was a decline in humoral response over time, T-cell response remained robust [19]. Our study shows similar results, with comparable cellular response of convalescent and vaccinated PWH over time, even with waning anti-RBD IgG levels. It could be of great interest to perform an analysis of cellular immune response to vaccine in a population of PWH with a low CD4 count (<300 or even <200 cells/μL) to better understand vaccine efficacy in preventing SARS-CoV-2 infection and severe illness in this particular group.

The strengths of our study include the evaluation of both humoral and cellular immune responses among PWH 3–6 months after vaccination, and not after a short time frame of 1–2 weeks. We also assessed the cellular response in a larger cohort of vaccinated PWH than reported previously and compared it with both PWH who had been infected with SARS-CoV-2 and with vaccinated HCWs.

Our study has several limitations that bear mentioning. First, we performed an assessment of cellular and humoral responses during a wide time frame of 3–6 months. In addition, the group of HCWs was smaller and was not properly matched to the group of PWH in age, gender, or time from second vaccine dose. All those could influence the study results. However, multivariable analysis that controlled for age, gender, and time from second vaccine dose did not show significant differences between the groups. Second, patients with very low CD4 counts were underrepresented in our study, and evaluating the sustainability of immune response in this group of patients would have been of considerable interest. Third, our cohort was relatively healthy; only 9% of patients had hypertension, and 7% were obese. The majority of the patients were MSM. These characteristics reflect the population of PWH in Tel-Aviv, who are younger and healthier, but do not necessarily reflect the general population of PWH in Israel.

Finally, our study aimed to assess humoral and cellular immune response, and not the clinical efficacy of preventing SARS-CoV-2 infection or severe illness.

In conclusion, after vaccination, PWH showed anti-RBD IgG levels similar to those of HIV-negative HCWs. However, PWH who had a CD4 count <300 cells/μL had a decreased level of anti-RBD IgG compared with PWH with higher CD4 counts. Cellular immune response did not differ between vaccinated PWH, PWH who had recovered from SARS-CoV-2, and vaccinated HCWs. However, anti-RBD IgG was higher in vaccinated PWH compared with PWH who had recovered from COVID-19 infection.

Supplementary Data

Supplementary materials are available at *Open Forum 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.

Acknowledgments

The authors thank Esther Eshkol for manuscript revision.

Financial support. None. The study was supported by the Israeli Ministry of Health, which supplied the serological testing kits.

Potential conflicts of interest. All 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.

Author contributions. Study concept and study design, patient recruitment, manuscript writing: L.T., D.T., T.H. Serological testing: R.M., S.A., I.L., N.M., T.H. Cellular immunity testing and supervision: T.F., D.H., T.H. Manuscript preparation: S.L., G.G. Laboratory supervision: A.A., Statistical analysis: T.Z.-B. Provision of control group: A.G.

Patient consent. The patient's written consent was obtained. The design of the work has been approved by the Tel-Aviv Sourasky Medical Center's Ethical Review Board (TLV-046-20).

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