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Humoral and Cellular Immune Response Elicited by Two Doses of mRNA BNT162b2 Vaccine Against SARS-CoV-2 in People Living with HIV

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Abstract

At present, whether severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines can elicit robust humoral and cellular immune responses in people living with HIV (PLWH) is still controversial. We assessed humoral and cellular immune response after the administration of the BNT162b2-mRNA-vaccine in seven ART-treated PLWH patients and in nine HIV-negative health care workers (PWOH) over a 3-month span of time from the first vaccine dose. The neutralizing antibody activity against both the European and the Delta variants declined after 3 months equally in both PLWH and PWOH. The gene expression analysis of factors involved in the antiviral immune response did not show any significant difference between H+ and H–; among circulating cytokines/chemokines, a progressive decline was observed in the mean values of IL-1β, IL-5, IL-6, IL-13, and IL-15 in both PLWH and PWOH. Conversely, the ratio between naive and terminally differentiated T-CD4$^+$ effector memory showed a reduction trend over time in PLWH. Our findings showed no significant differences in the ability to mount an immune response after the administration of two SARS-CoV-2 mRNA BNT162b2 doses in PLWH and PWOH. However, as BNT162b2 vaccinated PLWH display an early waning immunity in the T cell compartment, the administration of a booster dose may be necessary to maintain a SARS-CoV-2-specific immune response.

Keywords: vaccines, SARS-CoV-2, immune response, HIV

Immunity to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) induced by vaccination has been shown to give a degree of protection and to reduce the risk of clinically significant outcomes in the general population.[1] However, at present, whether SARS-CoV-2 vaccines can elicit robust immune response in people living with HIV (PLWH) and the role of HIV status on vaccine immunogenicity is still controversial.

Previous studies claim that certain vaccines prompt suboptimal immune responses, seroconversion rates, and antibody titers in PLWH, compared with the healthy population. For instance, PLWH exhibit an inadequate response to hepatitis B vaccination, experience a more rapidly waning of neutralizing antibody titers in response to yellow fever vaccine, and do not mount equivalent immune responses to other vaccines in comparison with the healthy counterpart.[2] CD4$^+$ cell count and viral load at the time of vaccination are the main factors affecting seroconversion.[3]

In this setting, recent studies on the elicitation of anti-SARS-CoV-2 immune response after natural infection in PLWH provide essential clues. Alrubayyi et al.[4] reported that PLWH recovery from mild COVID-19 was accompanied, as for healthy individuals, by a detectable and hence comparable humoral and cellular immune response to SARS-CoV-2, even persisting up to 5–7 months. Notably, the global magnitude of SARS-CoV-2-specific T cell responses was

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correlated with the size of naive $CD4^+$ T cell pool[4,5] and the CD4:CD8 ratio.[4] Conversely, in another study on a larger PLWH cohort, showing mild to severe symptoms, anti-spike IgG concentrations and neutralizing titers were lower compared with the general population, suggesting a diminished response to natural SARS-CoV-2 infection.[6] Moreover, PLWH with lower CD4 cell count or unsuppressed viral load might be at increased risk of developing severe COVID-19[7,8] with important implications not only on the clinical management but also on vaccine effectiveness in PLWH.

Preliminary findings suggest that ChAdOx1 nCoV-19 (AZD1222),[9] mRNA-1273,[10] and BNT162b2[11] vaccines AU5 ▶ stimulate comparable immune responses in ART-responder PLWH and seronegative adult population.

AU6 ▶ Neutralizing activity (NA) is considerate a predictor of protection against SARS-CoV-2.[12] Focusing on mRNA vaccines, both Lombardi et al.[10] and Woldemeskel et al.[11] proved that PLWH have similar neutralizing antibody titers as healthy donors. It is interesting to notice that Lombardi et al. registered a higher NA in sera of PLWH who previously experienced COVID-19 infection, than COVID-19-naive PLWH. However, data on the long-term maintenance of this immunity and protection against SARS-CoV-2 variants of concern (VOC) in this unique population are still missing.

Herein, an observational longitudinal prospective study was designed to evaluate the development of immune response induced by the BNT162b2 (Comirnaty) anti-SARS-CoV-2 vaccine. Participants with a history of laboratory-confirmed SARS-CoV-2 infection were enrolled at the Infectious Diseases Unit, ASST Ospedale Fatebenefratelli ''Luigi Sacco,'' Milan (Italy). We evaluated the humoral and SARS-CoV-2-specific T cell response in a cohort of seven PLWH, controlled on ART, compared with nine HIV-negative individuals (PWOH), on a 3 month-spanning period (T0: before vaccine administration; T1: 10 days after the first dose; T2: 30 days after the first dose and 10 days after the second dose; T3: 90 days after the first dose) after the administration of the first dose of Pfizer-BioNTech BNT162b2 mRNA vaccine. Given the highly relevant role of specific SARS-CoV-2 VOC, we performed our analysis on humoral response also against the most aggressive Delta variant.

The clinical characteristics of the subjects enrolled in the study are summarized in Table 1 (mean age ± standard deviation ◀ T1 [SD]: 48.3 ± 13.2 years; range 28–66 years; 8 females; 8 males). According to their serostatus they were divided in PLWH ($n = 7$) and HIV-uninfected (PWOH, $n = 9$). PLWH subjects were all on antiretroviral therapy with undetectable HIV-RNA (<20 copies/mL) and a mean ± SD CD4 cell count of 692 ± 358 cell/mm^3. Three PLWH and six PWOH reported a previous SARS-CoV-2 infection, all of them diagnosed by a PCR test on nasopharyngeal swab or SARS-CoV-2-specific IgG detection at baseline, and none were hospitalized for COVID-19.

Vaccine was administered according to the Pfizer vaccination schedule. The primary endpoint of the study was to characterize the development of SARS-CoV-2-specific NA against the European (EU) and the Delta SARS-CoV-2 variant at the following consecutive time points: 1 day before vaccination (T0), 10 days after dose I (T1), 30 days after dose I (T2), and 90 days after dose I (T3).

Assessment of SARS-CoV-2-specific T cell response was evaluated at all time points by gene expression analysis (Qgeneplex), multiplex cytokine assay, and $CD4^+$ and $CD8^+$ T cell memory profiling (flow cytometry). The study design is summarized in Figure 1A. ◀ F1

NA against both European and Delta variants increased from T1 to T2 and declined at T3 in both PLWH and PWOH and no significant differences were reported comparing the two groups. In both groups the Delta variant showed a moderate immune escape, since a lower NA was observed especially 3 months after the vaccine regimen (T3) compared with European ($p < .05$) (Fig. 1B).

Gene expression analysis of 54 factors involved in the antiviral and immune response did not show any significant difference between PLWH and PWOH iSARS-CoV-2 (heat-inactivated SARS-CoV-2) stimulated PBMCs, during all the ◀ AU7 study period (Supplementary Fig. S1). ◀ SF1

Likewise, the concentration of 27 plasma cytokines and chemokines was comparable in the two groups at all time

Table 1. Clinical Characteristics of the Study Population

Characteristic	*HIV-uninfected* (n = 9)	*People living with HIV* (n = 7)
Age, years (mean ± SD)	48.3 ± 15.8	48.3 ± 11.8
Sex, *n* (%)		
Male	2 (22.2)	6 (85.7)
Female	7 (77.8)	1 (14.3)
HIV status		
HIV RNA <20 cp/mL	NA	7/7
CD4 cell count/mm^3 (mean ± SD)	NA	692 ± 358
SARS-CoV-2 status at baseline		
PCR test, *n* (%)	6 (66.7)	1 (14.3)
SARS-CoV-2-specific IgG		
Positive, *n* (%)	6 (66.7)	3 (42.8)
Concentration (AU/mL, mean ± SD)	10826.9 ± 8177.9	532.1 ± 114.0
SARS-CoV-2 status at week 12 postvaccination		
SARS-CoV-2-specific IgG		
Positive, *n* (%)	9 (100)	7 (100)
Concentration (AU/mL, mean ± SD)	7822.3 ± 5703	12581.2 ± 8563.4

AU, arbitrary unit; NA, not applicable; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation.

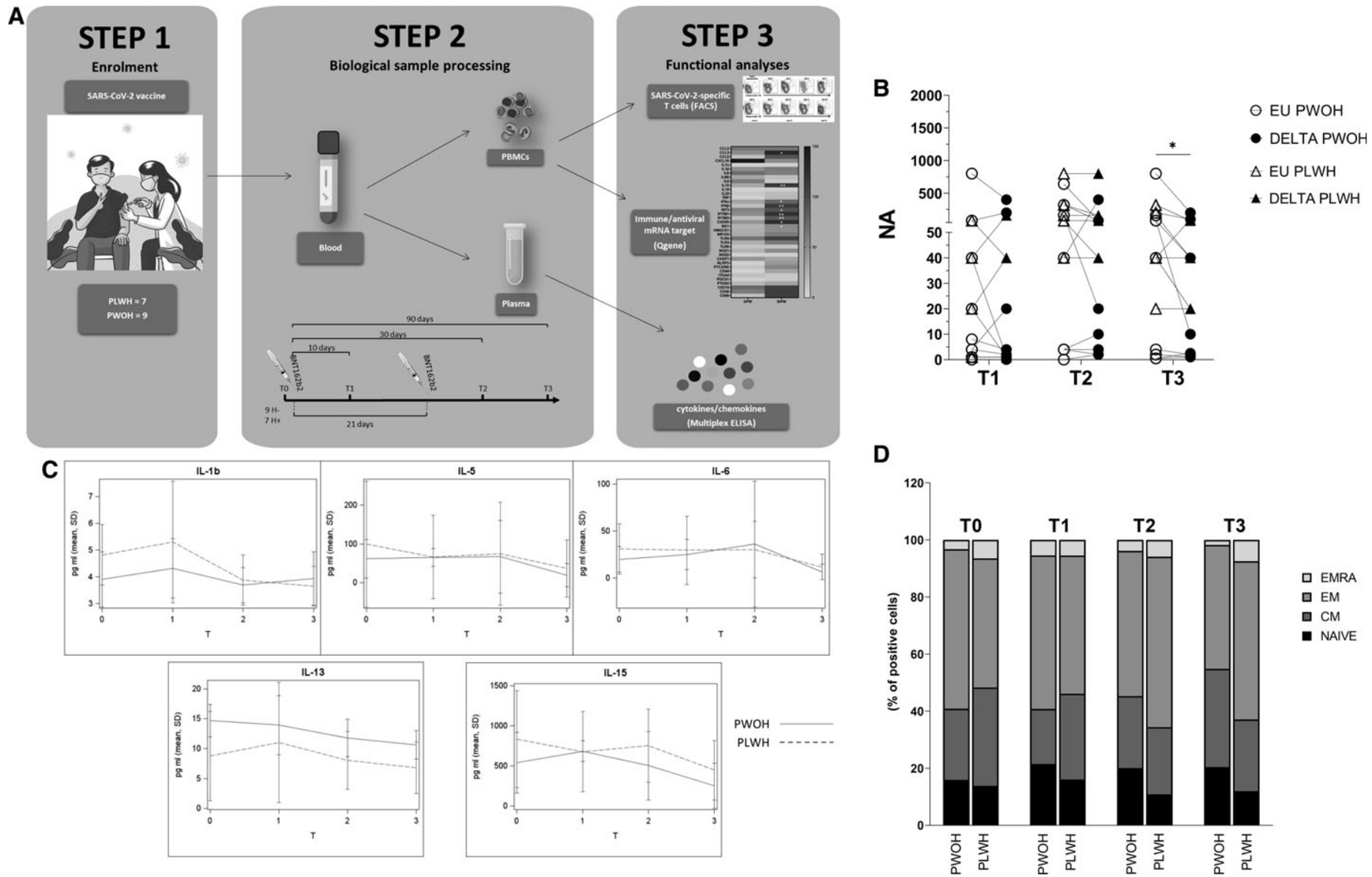

FIG. 1. **(A)** Study design. **(B)** Single values from each subject of NA increment at T1, T2, and T3 over T0 against EU (*white*) and DELTA (*black*) variants in PWOH (*circles*) and PLWH (*triangles*). *White* and *black circles/triangles* are coupled for each subject. Statistically significant differences ($p < .05$) are indicated; $^*p < .05$. **(C)** Plasma IL-1β, IL-5, IL-6, IL-13, and IL-15 concentration (pg/mL) over time from T0 to T3; HIV-uninfected (PWOH) subjects are represented as blue lines, PLWH subjects as red lines. Results are reported as mean values ± SD. **(D)** $CD4^+$ T cell subpopulations (naive = black, CM = dark gray, EM = gray, EMRA = light gray) in PLWH and HIV-uninfected (PWOH) subjects over time; results are reported as mean percentages. CM, central memory; EM, effector memory; EMRA, terminally differentiated effector memory; EU, European; PLWH, people living with HIV; PWOH, HIV-negative health care workers.

SF2 ▶ points (Supplementary Fig. S2). Notably, a progressive decline in the mean values of IL-1β ($p = .02$), IL-5 ($p = .008$), IL-6 ($p = .002$), IL-13 ($p = .009$), and IL-15 ($p = .001$) was observed from T0 to T3 in both PLWH and PWOH ($p = .02$) (Fig. 1C).

As wane immunity in response to several vaccination has been repeatedly documented in PLWH, we assessed SARS-CoV-2-specific T cell memory over time (Fig. 1D). Although no differences were observed in $CD8^+$ T cell compartment (data not shown), the ratio between naive and terminally differentiated T $CD4^+$ effector memory showed a reduction trend over time in PLWH compared with PWOH (Supple-
SF3 ▶ mentary Fig. S3), reaching a statistically significant difference 3 months after the vaccine administration (T3).

It has been reported that the antibody-mediated NA mounted both after natural infection[13] and vaccination[12] is a predictor of protection against SARS-CoV-2. However, T cell immunity has been underestimated, even though it supports vaccine efficacy as it plays a central role in SARS-CoV-2 infection.[14] For these reasons, to evaluate immunogenicity of two doses of the mRNA BNT162b2 vaccine, we assessed both humoral and adaptive immune responses in PLWH and in a control group of PWOH. Overall, our findings confirmed results previously reported[10,11] showing no significant differences in the ability to mount an immune response after SARS-CoV-2 vaccination in PLWH and PWOH.

Both groups share similar NA, characterized by a waning immunity against the Delta variant, indicating the urgency of further doses to protect against VOCs. Likewise, PLWH and PWOH display overlapping SARS-CoV-2 specific cell-mediated immune responses, as shown by the gene expression analysis of the anti-viral factors and by the proteomic investigation. However, the analysis of $CD4^+$ T cell memory revealed a faster decline in naive subset in favor of terminally differentiated cells in PLWH. An increase in terminally differentiated T cells has been reported to be functional in other special population after SARS-CoV-2 infection,[15] and somehow dysfunctional, for example, in people affected by multiple sclerosis upon SARS-CoV-2 vaccination.[16]

A concomitant decreasing in the naive pool could be a feature of the HIV population, and it has already been reported that an inadequate full reconstitution on ART can drive to poor responsiveness to SARS-CoV-2 infection.[4] Although the limited number of enrolled subjects does not allow to draw conclusive assumptions, such trend possibly indicates that in PLWH SARS-CoV-2-vaccine-induced memory is less persistent, and these patients should be carefully monitored over time to optimize their vaccine schedule.

Authors' Contributions

Conceptualization, methodology, and writing—original draft preparation by L.M., D.T., and M.B. Subject enrolment by L.M. Experiments by C.V., F.A., and G.C. Data curation and formal analysis by C.V., L.M., F.A., L.O, D.T., and M.B. Writing—review and editing by C.V., L.M., L.O, D.T., and M.B. All authors have read and agreed to the published version of the article.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patients to publish this article.

Data Availability

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

Ethics Approval Statement

The study was approved by the ethical committee of the University of Milan (Comitato Etico Università degli Studi di Milano, no. 23/21) and conducted in compliance with Good Clinical Practice guidelines and the Declaration of Helsinki.

Author Disclosure Statement

No competing financial interests exist.

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Supplementary Material ◀ AU8

Supplementary Data
Supplementary Figure S1
Supplementary Figure S2
Supplementary Figure S3

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