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RESEARCH ARTICLE

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Poor durability of the neutralizing response against XBB sublineages after a bivalent mRNA COVID-19 booster dose in persons with HIV

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Abstract

We estimated the dynamics of the neutralizing response against XBB sublineages and T cell response in persons with HIV (PWH) with previous AIDS and/or CD4 < 200/mm^3 receiving the bivalent original strain/BA.4-5 booster dose in fall 2022. Samples were collected before the shot (Day 0), 15 days, 3, and 6 months after. PWH were stratified by immunization status: hybrid immunity (HI; vaccination plus COVID-19) versus nonhybrid immunity (nHI; vaccination only). Fifteen days after the booster, 16% and 30% of PWH were nonresponders in terms of anti-XBB.1.16 or anti-EG.5.1 nAbs, respectively. Three months after, a significant waning of anti-XBB.1.16, EG.5.1 and -XBB.1 nAbs was observed both in HI and nHI but nAbs in HI were higher than in nHI. Six months after both HI and nHI individuals displayed low mean levels of anti-XBB.1.16 and EG.5.1 nAbs. Regarding T cell response, IFN-γ values were stable over time and similar in HI and nHI. Our data showed that in PWH, during the prevalent circulation of the XBB.1.16, EG.5.1, and other XBB sublineages, a mRNA bivalent vaccine might not confer broad protection against them. With a view to the 2023/2024 vaccination campaign, the use of the monovalent XBB.1.5 mRNA vaccine should be urgently warranted in PWH to provide adequate protection.

KEYWORDS

AIDS, COVID-19 vaccine, neutralizing response, SARS-CoV-2 variants, XBB-sublineages

1 | INTRODUCTION

Due to the changing epidemiologic scenario of COVID-19, the scientific rationale to support COVID-19 mRNA vaccines has evolved. Last fall, the original strain/BA.4/5 bivalent COVID-19 vaccine was considered necessary to provide broad protection against severe illness, hospitalization, and death caused by circulating SARS-CoV-2 variants and the monovalent vaccines encoding the original strain alone were no longer recommended.[1]

Since then, epidemiologic, preclinical, and clinical lines of evidence support the use of monovalent vaccines encoding the most recently circulating variant of the Omicron sublineages.[2,3]

For the fall 2023–2024 campaign, vaccines have been updated to a monovalent formulation with an XBB-lineage of the Omicron variant, and, following discussion of the evidence, WHO expressed a preference for XBB.1.5.[2] This recommendation derives from the absence of circulation of the original variant included so far in vaccine preparations and the high immune-evasive ability of the XBB.1 descendant lineage, including XBB.1.5 and XBB.1.16. Because of the antigenic similarity of the XBB family of subvariants, it is believed that a vaccine designed against XBB.1.5 should protect against the others.[4]

In addition, since BA.2, BA.4 and BA.5 strains are no longer circulating, in March 2023, the ECDC de-escalated these viruses from its list of SARS-CoV-2 variants of concern (VOC). While there are currently no SARS-CoV-2 variants meeting the VOC criteria, several circulating viral strains are classified either as variants of interest (VOI) or variants under monitoring (VUM).[5] As of end of November 2023, XBB.1.5 and XBB subvariants accounted for 54% (range 40%–67%) of circulating strains, BA2.75 and BQ.1.1 were disappearing from the landscape of viruses responsible for current infections, BA.2.86 and HV.1 (an EG.5 descendant) showed an increasing trend.[6–8]

To date, the neutralizing response remains the most widely used correlate of protection from COVID-19,[9] and some reports showed that the levels of neutralizing antibodies (nAbs) as well as vaccine efficacy tend to wane over time from infection or vaccination.[10–12]

Nevertheless, the proportion of vaccinated individuals and people who experienced natural infection(s) is constantly increasing with a demonstrated benefit of hybrid immunity (infection plus vaccination-driven immunity) in neutralizing SARS-CoV-2.[12,13]

It is a matter of debate to whom the updated XBB vaccine shot should be administered,[4,14] nevertheless, the target population for vaccination certainly includes elderly people and severely immunocompromised individuals. In Italy, by the guidelines from the Ministry of Health on the vaccination campaign released in August 2023,[15] a further booster dose is also advised for persons with HIV (PWH) on antiretroviral therapy (ART) who, at the time of their first vaccine dose, showed a CD4 < 200/mm^3 or were previously diagnosed with AIDS, or based on clinical judgment.

We previously reported the effectiveness of inducing nAbs of a bivalent "original strain/BA.4/5" vaccine given as a fifth dose to PWH on ART with a CD4 count <200 cells/mm^3 and/or previous AIDS.[16] The bivalent vaccines determined an increase in nAbs against four variants tested, namely: W-D614G, Omicron BA.5, BQ.1.1, and XBB.1. Despite the increase in titers, the levels of nAbs against the XBB.1 were significantly lower compared to the other strains, and a neutralizing response against the XBB.1 strain was not observed in 8% of vaccinated PWH.

Herein, we report the results on the dynamics of neutralizing and T cell response at 3 and 6 months after the fifth dose inoculation of a bivalent original strain/BA.4/5 vaccine. The main aim was to estimate the magnitude and waning of nAbs directed against currently circulating XBB sublineages in this fragile population which represents a target for the coming vaccination campaign. As a secondary aim, we compared the presence and dynamics of nAbs and T cell responses in PWH who experienced or did not experience a natural SARS-CoV-2 infection.

2 | METHODS

2.1 | Study design

This is an observational cohort study to evaluate the outcomes of the SARS-CoV-2 vaccination (HIV-VAC study) approved by the Scientific Committee of the Italian Drug Agency (AIFA) and by the Ethical Committee of the Lazzaro Spallanzani Institute, as National Review Board for COVID-19 pandemic in Italy (approval number 423/2021; amendment adopted with no. 91/2022). The participants included in the present study provided informed written consent. On October 2022, the National Institute for Infectious Diseases Lazzaro Spallanzani in Rome continued the boosting vaccination against SARS-CoV-2 in PWH, as a fifth dose with a mRNA bivalent vaccine [original strain/BA.4/BA.5; BNT162b2 (Pfizer-BioNTech) or (Moderna) mRNA-1273.214). According to the Italian Ministry of Health recommendations, the mRNA bivalent vaccine was administered to those who, at the time of their first vaccine dose showed a CD4 < 200/mm^3 or were previously diagnosed with AIDS. Serum samples were collected at the time of the mRNA bivalent vaccine (Day 0), 15 days, 3, and 6 months after the vaccination.

2.2 | Laboratory procedures

Neutralizing antibody titers (nAbs) were measured by a microneutralization assay based on live SARS-CoV-2 virus (described elsewhere [17]). SARS-CoV-2 were produced through viral culture on VeroE6/TMPRSS2 cells (cells obtained from Dr. Mutsuyo Takayama-Ito, from the National Institute of Infectious Diseases, Tokyo, Japan) of naso-pharyngeal swab derived from COVID-19 infected people (leftovers of diagnostic activities). Viral stocks used in the neutralization assays were produced by a passage on VeroE6/TMPRSS2 cells and viral titers determined by Reed-Muench method. One-hundred doses (TCID50) of the virus were incubated with serial dilutions of

the serum samples and viral titration control was performed in each neutralization experiment for all the variants tested. Inter-assay controls were performed by running selected serum samples in each assay, including a negative control. The sequences of the viral strains used are available on either GISAID (W-D614G hCoV-19/Italy/LOM-INMI-10734/2020 EPI_ISL_568579; BA.5 hCoV-19/Italy/LAZ-INMI-3329/2022 EPI_ISL_13300234) or NCBI (BQ.1.1 SUB13955076 LAZ-INMI-4044 OR772939; XBB.1 SUB13955076 LAZ-INMI-4359 OR772940; XBB.1.16 SUB13955076 LAZ-INMI-5327 OR772941: EG.5.1 SUB13955076 LAZ-INMI-5565 OR772942). The highest serum dilution inhibiting at least 90% of the cytopathic effect on Vero E6 cells (CRL-1586 ATCC) was defined as neutralizing, titerss were expressed as the reciprocal of serum dilution and nAbs were categorized as undetectable if titers were <10, microscope observation of each experiment was performed by two highly experienced researchers.

T-cell specific response to Spike stimulation was analyzed as previously described.[18] Briefly, peripheral blood was either not stimulated, or stimulated with a pool of peptides spanning the Spike protein (0.1 pg/mL; Miltenyi Biotech), or with SEB (200 ng/mL, Sigma-Merck) for positive control. After 16–20 h at 37°C 5% CO_2 plasma was stored at −80° and subsequently analyzed for IFN-γ release by an automatic ELISA assay (ELLA, Protein Simple). The detection limit of these assays was 0.17 pg/mL for IFN-γ and the cut off used in this analysis to define the T-cells specific response was 12 pg/mL.

3 | RESULTS

3.1 | Study population

Thirty-seven PWH provided samples at Day 0, 15 days, and 3 months after the vaccination (31 males/6 females; at baseline: median age: 56, IQR: 48–63, CD4 count: 416 cell/mm^3 IQR: 286-588, HIV-RNA < 50 copies/mL), 31 out of 37 also provided samples 6 months after the vaccination (26 males/5 females; at baseline: median age: 56, IQR: 49–60, median CD4 count: 416 cells/mm^3 IQR: 301–552, HIV-RNA < 50 copies/mL). At Day 0, 15 days, 3 months, and 6 months after the vaccination we analyzed the neutralizing response against XBB.1.16, EG.5.1, and XBB.1. At Day 0, 15 days, and 3 months after the vaccination we also evaluated nAbs against the previously circulating variants, namely W-D614G, BA.5, and BQ.1.1. Twenty-five PWH provided peripheral blood samples for T cell response analysis at the same timepoints; 21 also provided samples 6 months afterthe vaccination. A previous natural infection was established by means of an anti-SARS-CoV-2 nucleoprotein IgG positive result recorded at any time during the HIV-VAC study and participants self-report about the possible date of infection. PWH who naturally acquired SARS-CoV-2 and were vaccinated were classified in the HI group, those who were only vaccinated classified in the nHI group, the main characteristics according to immunization status are reported in Table 1.

TABLE 1 Characteristics of the study population.

Characteristics	HI *N* = 19	nHI *N* = 18	*p* value*	Total *N* = 37
Age, years median (IQR)	57 (48–64)	56 (48–62)	0.5422	56 (48–63)
Female, *n* (%)	2 (11)	4 (22)	0.3347	6 (16)
Caucasian, *n* (%)	14 (73)	17 (94)	0.1482	31 (84)
Nadir CD4 count, cells/mm^3 median (IQR)	31 (14–92)	64 (41–135)	0.1723	45 (16–110)
Time from AIDS diagnosis, years median (IQR)	5 (3–9)	6 (3–10)	0.7903	6 (3–9)
AIDS, *n* (%)	16 (84)	17 (94)	0.3163	33 (89)
Year of starting ART median (IQR)	2015 (2005–2019)	2016 (2012–2020)	0.5497	2016 (2011–2019)
CD4 count cells/mm^3 at Day 0 Median (IQR)	416 (191–552)	427 (294–615)	0.5783	416 (286–588)
CD4 count cells/mm^3 <200 *n* (%)	5 (26)	1 (6)	0.0868	6 (16)
Anti-XBB.1.16 nabs at Day 0 GMT (95% CI)	11.6 (6.9–19.4)	5.8 (4.8–7.0)	0.0242	8.3 (6.2–11.1)
Anti-XBB.1.16 nabs 15 days after the booster dose GMT (95% CI)	55.6 (33.2–92.9)	22.5 (11.1–45.3)	0.0261	35.8 (23.1–55.4)
Anti-EG.5.1 nabs at Day 0 GMT (95% CI)	6.9 (4.9–9.8)	5 (n.a.)	0.0463	5.9 (5.0–7.1)
Anti- EG.5.1 nabs 15 days after the booster dose GMT (95% CI)	28.8 (17.9–46.4)	12.6 (6.7–23.8)	0.0160	19.3 (12.9–28.7)
IFN-γ pg/mL at Day 0 Median (IQR)	422.8 (168.8–779.2)	221.0 (107.8–427.7)	0.5830	318.0 (129.1–547.7)
IFN- γ pg/mL 15 days after the booster dose	368,1 (76.2–835.5)	294.4 (82.3–552.4)	0.3652	300.0 (80.3–651.9)

Abbreviations: ART, antiretroviral therapy; IQR, interquartile range.

*Chi-square or Mann-Whiney test as appropriate.

3.2 | Induction and 3 months waning of neutralizing response against XBB sublineages

The mRNA bivalent vaccine determined a 4. Threefold increase ($p < 0.0001$) from Day 0 to 15 after the booster of anti-XBB.1.16 nAbs, and a 3. 3 ($p < 0.0001$) increase for anti-EG5.1 nAbs (Table 1). In six individuals the mRNA bivalent vaccine did not induce the generation of nAbs against XBB.1.16 (16%), and 11 participants did not show seroconversion for anti-EG5.1 nAbs (30%).

Regarding the kinetics of the neutralizing response and the role of hybrid immunity in its maintenance over time, at 3 months postvaccine booster, we observed a significant waning of nAbs against XBB.1.16 which was observed in both PWH with (hybrid immunity, HI, $n = 19$) and without (nHI, $n = 18$) a history of SARS-CoV-2 infection (Figure 1A). Indeed, compared to the levels observed 15 days and 3 months after we measured a fold change reduction (FRed) of 2.0 in HI (T1 GMT 55.5, 95% CI 33.2–92.9 vs. T3 27.7, 17.2–44.8; $p = 0.008$) and 1.85 in nHI (T1 22.5, 11.1–45.3 vs. T3 12.1, 6.4–23.1; $p = 0.018$) (Figure 1A, Supporting Information S1: Table 1). A similar trend was observed for anti-EG5.1 -XBB.1 nabs levels, (Figure 1B, Supporting Information S1: Table 1). On the contrary, nAbs levels against the W-D614G, Omicron BA.5, and BQ.1.1 showed stable levels 3 months after compared to those found 15 days after the booster (Figure 1D–F and Supporting Information S1: Table 1).

Despite the similar trend of nAbs waning in HI and nHI vaccinated PWH, the levels of nAbs in individuals with an history of SARS-CoV-2 infection are constantly higher than those observed in SARS-CoV-2 infection naive participants, at day 0, 15 days, and 3 months after and against all the viral strains challenged in the neutralization assays (Table 1, Supporting Information S1: Table 1, Figure 1).

We previously demonstrated that the mRNA bivalent vaccine did not boost the SARS-CoV-2 ancestral strain specific T cell response which remained stable in both HI and nHI PWH.[16] IFN-γ release median values measured at day 0 and 15 days after the booster for the PWH included in the study ($n = 25$) are shown in Table 1. No significant changes in the magnitude of T cell response were observed at 3 months postvaccine booster (median pg/ml: T0 318.0 IQR 129.1-547.7; T1 300.0 IQR 80.3-651.9; T3 225.3 IQR 72.6-622.0). No statistically significant differences were observed in the release of IFN-γ when comparing HI to nHI PWH (Table 1 and Figure 2).

3.3 | Neutralizing response against prevalent XBB sublineages at 6 months from the mRNA bivalent vaccine

At 6 months from mRNA bivalent vaccine, we obtained serum samples from a subset of PWH ($n = 31$), these samples were collected from the beginning of April to the end of May 2023. In this longitudinal cohort, by measuring anti-SARS-CoV-2-N and anti-SARS-CoV-2-RBD IgG we detected 4 breakthrough infections 3 months after the vaccine booster, one of which was in a previously infected individual, and two further breakthrough infections 6 months after, for a total of 16 (52%) individual with hybrid immunity 3 months after and 18 (58%) 6 months after.

Six months after the vaccine booster, we observed low levels of anti-XBB.1.16 (GMT: 11.44; 95% CI: 8.1–16.2) and EG5.1 (GMT: 10.00; 95% CI: 7.0–14.2) nAbs, values next to the detection limit of the assay and significantly lower than those measured at 15 days for both XBB.1.16 (34.2, CI: 20.9–56.1; FRed: 2.99, $p < 0.0001$) and EG5.1 (17.49, CI: 11.2–27.4; FRed: 1.8, $p = 0.0054$). Compared to valuesfound 3 months after the booster, lower levels were observed for anti-XBB.1.16 nAbs (17.10, CI: 11.0–26.5; FRed 1.49; $p = 0.004$) while those against EG5.1 were already at the detection limit after 3 months (11.69, CI: 8.2–16.7; FRed: 1.2, $p = 0.3672$) (Figure 3). Compared to the titerss measured before the mRNA bivalent vaccine (Day 0) nAbs were still slightly higher 6 months after (Figure 3) than Day 0.

When looking at the percentage of reactive samples, 58.0% of serum samples tested 6 months after showed anti-XBB.1.16 nAbs, compared to 67.7% tested at 3 months, 83.9% at 15 days, and 29% at Day 0 (Figure 3 and Table 2). The fraction of reactive samples 6 months after is significantly lower than those found at 15 days ($p = 0.049$), but still higher than at day 0 ($p = 0.040$) (Table 2). An even lower number of reactive serum samples was observed when measuring anti-EG.5.1 nAbs with only 45% of positive samples 6 months after, 54% 3 months after, 65% 15 days after, and 13% at day 0 (Figure 3 and Table 2).

Among the 18 individuals with detectable anti-XBB.1.16 nAbs 6 months after the booster, 13 (72%) had a proven history of infection either before or after the mRNA bivalent vaccine. Of the 14 individuals showing anti-EG.5.1 nAbs 6 months from mRNA bivalent vaccine, 11 (79%) had hybrid immunity.

Both HI and nHI individuals displayed similar low mean levels of anti-XBB.1.16 (HI: 13.09, CI: 8.40–20.42; nHI: 9.48, CI: 5.06–17.76) and -EG.5.1 (HI 11,67, CI: 7.43–18.31; nHI: 801, CI: 4.32–15.10) nAbs (Figure 3). Despite the observation of a higher percentage of serum with detectable nAbs in HI (XBB.1.16: 13/18, 72%; EG.5.1: 11/18, 61%) compared to nHI (XBB.1.16: 5/13, 38%; EG.5.1: 3/13, 23%), no statistically significant differences in mean titerss were measured (Figure 4).

Six months after no statistically significant changes in specific anti-Spike T cell response were observed when comparing IFN-γ values with measurement at previous time points or according to immunization status (HI vs. nHI) (Supporting Information S1: Table 2).

4 | CONCLUSIONS

In fall 2022, updated bivalent mRNA COVID-19 vaccines directed against both the ancestral strain and the Omicron subvariant BA.4/BA.5 were recommended for individuals at high risk of severe COVID-19 and subsequently for the general population. At the same

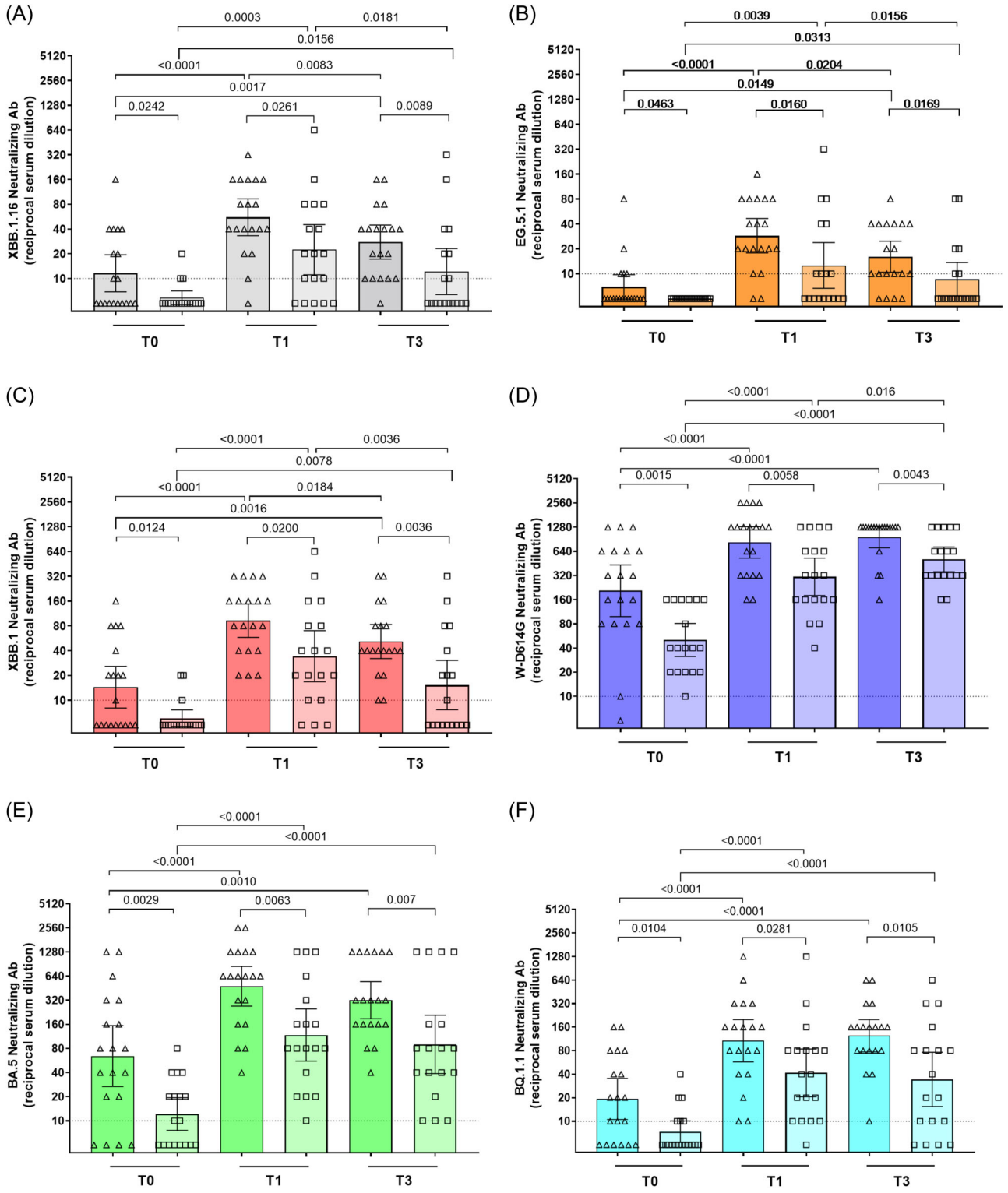

FIGURE 1 Induction and waning of neutralizing response against SARS-CoV-2 variants in PWH who received a mRNA bivalent vaccine. Levels of nAbs against XBB.1.16 (A), EG5.1 (B), XBB.1 (C), W-D614G (D), BA.5 (E), and BQ.1.1 (F) were measured at Day 0, Day 15, and 3 months in both PWH with hybrid immunity (HI, triangles, $n = 19$) or with no history of natural SARS-CoV-2 infection (nHI, squares, $n = 18$). Wilcoxon test was used to compare nabs levels in paired samples, Mann-Whitney test to compare nabs levels in HI versus nHI participants.

time, as in the normal course of events related to SARS-CoV-2 evolution, the landscape of circulating variants varied giving rise to the spread of several newly emerged strains including BQ.1.1, XBB.1, XBB.1.5, XBB.1.16, and EG.5.1 and more recently BA.2.86, JN.1 and HV.1.

Comparing neutralization data obtained against the vaccine components and other variants, different reports, including our previous study on PWH, demonstrated decreased response against BQ.1.1 and more importantly against XBB sublineages.[16,19–21]

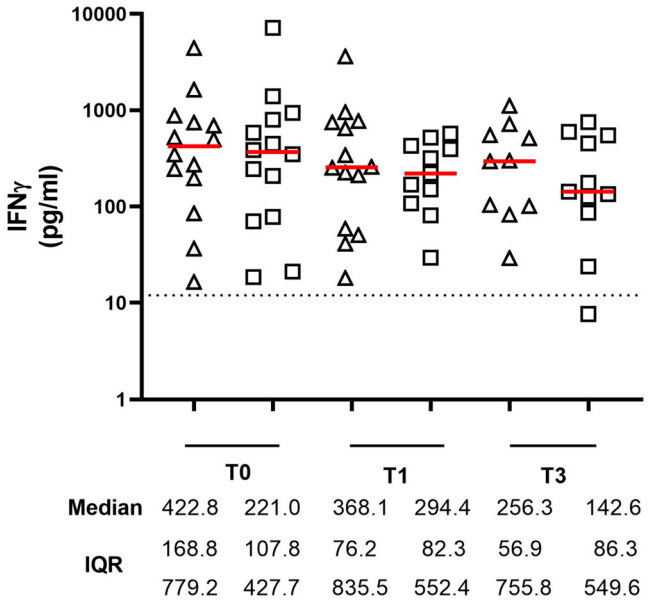

FIGURE 2 IFN-γ release at Day 0, Day 15, and 3 months according to immunization status. IFN-γ release was measured in HI (triangle) and nHI (square) PWH. Horizontal red bars represent median values, error bars show interquartile range (IQR), horizontal dot line represents the test cut-off for a positive response. Wilcoxon test was used to compare IFN-γ in each group, Mann-Whitney test for comparison between HI and nHI.

In PWH, we reported the ability of the mRNA bivalent vaccine to induce an increase in the neutralizing response against the strains included in the bivalent vaccine and, at a lower level, against the strains mainly circulating at the time of the previous study: BQ.1.1 and XBB.1.[16] In the meantime, further changes occurred in the proportion and types of SARS-CoV-2 variants and we now assessed the ability of mRNA bivalent vaccine to neutralize newly emerged strains, which became the prevalent ones, at 3 and 6 months from dose receipt.

Firstly, we observed 15 days after the booster an induction of anti-XBB.1.16 (84%) and anti-EG.5.1(70%) nAbs in a lower percentage of tested PWH compared to anti-XBB.1 (92%) or anti-W-D614G (100%), Omicron BA.5 (100%), and BQ.1.1(100%) nAbs. At 3 months postvaccine booster, we observed a significant decrease in the levels of nAbs against XBB.1.16 and EG.5.1 in both PWH with and without a history of SARS-CoV-2 infection, the same trend was observed for XBB.1 nAbs levels but not for those against the W-D614G, Omicron BA.5, and BQ.1.1 whose titers remained stable. Similarly, in a recent report, Lasrado and colleagues described in a study population including 30 individuals naïve to SARS-CoV-2 infection a 2.1 and 1.8 fold decrease in nAbs levels against XBB.1.5 and XBB.1 at 3-months from mRNA bivalent vaccine.[22] We confirmed the role of hybrid immunity, defined as the history of SARS-CoV-2 natural infection in vaccinated people, in achieving higher levels of nAbs against all the tested variants. Indeed, in line with previous reports, nAbs titers were constantly higher in HI than in nHI at each time point and against all the variants tested.[23–26]

When assessing the ability to neutralize the currently prevalent variants, namely XBB.1.16 and EG.5.1, at 6 months from the mRNA bivalent vaccine, we observed low mean levels of nAbs, next (in HI) or below (in nHI) the detection limit of the assay. The mean titers of nAbs against these variants were similar, a result in line with previous findings,[27] nAbs against XBB.1.16 and EG.5.1 were even undetectable in 42% and 55% of PWH, respectively.

We previously demonstrated that the mRNA bivalent vaccine did not boost T cell responses against the ancestral strain, and no

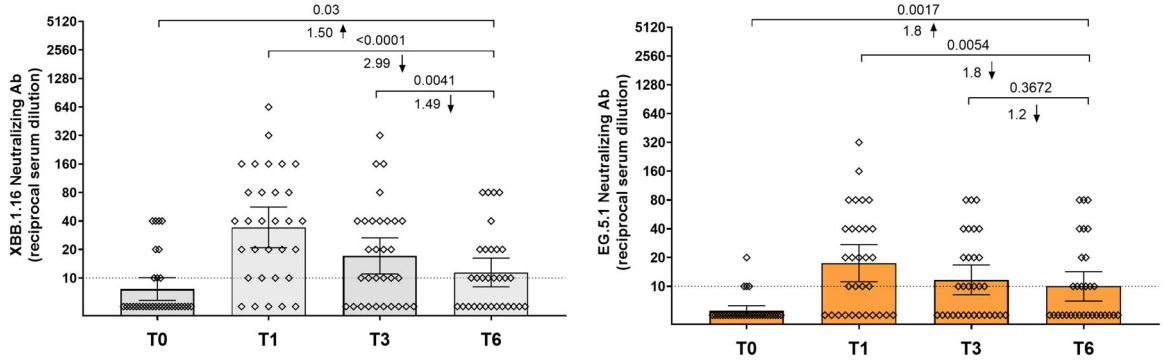

FIGURE 3 Waning of anti-XBB.1.16 and anti-EG.5.1 nAbs at 3 and 6 months from the mRNA bivalent vaccine. Anti-XBB.1.16 and anti-EG.5.1 nAbs in 31 PWH measured at the time of the mRNA bivalent vaccine (Day 0) and after 15 days, 3 months, and 6 months. Wilcoxon test was used to compare nAbs levels measured at Day 0, Day 15, and 3 months with those observed at 6 months, *p* values are indicated above the comparison bar. Fold change increase (arrow up) or decrease (arrow down) is indicated below the bar. The percentages of reactive samples are visualized in the donut graphs.

TABLE 2 Number of serum samples showing anti XBB.1.16 and anti-EG.5.1 nAbs.

nAbs	Reactive	Nonreactive	Versus Day 0	Versus 15 days after the booster dose	Versus 3 months after the booster dose
XBB.1.16 at day 0	9	22	–	<0.0001	0.005
XBB.1.16 15 days after the booster dose	26	5	<0.0001	–	0.235
XBB.1.16 3 months after the booster dose	21	10	0.005	0.235	–
XBB.1.16 6 months after the booster dose	18	13	0.040	0.049	0.60
EG.5.1 at day 0	4	27	–	<0.0001	0.001
EG.5.1 15 days after the booster dose	20	11	<0.0001	–	0.605
EG.5.1 3 months after the booster dose	17	14	0.001	0.605	–
EG.5.1 6 months after the booster dose	14	17	0.011	0.202	0.612

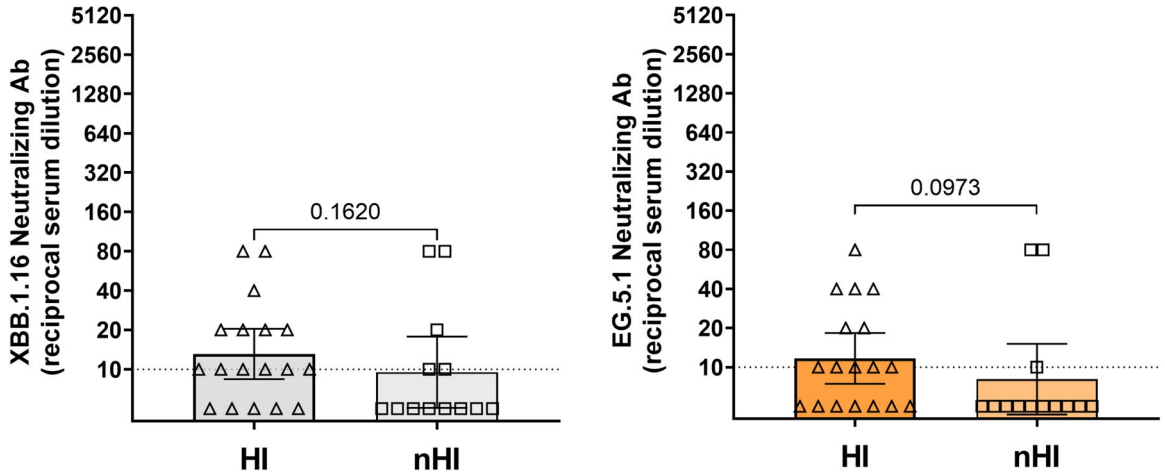

FIGURE 4 Anti-XBB.1.16 and anti-EG.5.1 nAbs levels in PWH with hybrid and nonhybrid immunity at 6 months from the mRNA bivalent vaccine. Anti-XBB.1.16 (gray) and anti-EG.5.1 nAbs were measured at 6 months in 31 PWH with hybrid immunity (triangles, $n = 18$) or with no history of natural SARS-CoV-2 infection (squares, $n = 13$). Wilcoxon test was used to compare nAbs levels in paired samples, Mann-Whitney test to compare nabs levels in HI vs nHI participants. Mann-Whitney test was used to compare nAbs levels. The percentages of reactive samples are visualized in the donut graphs.

changes were observed neither 3 months or 6 months after the vaccine booster nor did we demonstrate a difference due to hybrid immunity. We did not investigate the role and dynamics of T cell response directed against XBB sublineages, nevertheless, the impact of variants associated mutations on T cell responses seems to be limited,[28,29] by meaning that the preservation of T cells response directed toward more conserved targets in vaccine composition may be considered as a possible tool to increase vaccine effectiveness against future variants.

Of note, SARS-CoV-2 breakthrough infection did not result in severe disease in any of the PWH included in the study, suggesting the vaccine was still effective in preventing severe COVID-19. Nevertheless, the small sample size represents a limitation of our study.

Vaccine effectiveness (VE) of the mRNA bivalent vaccine in preventing COVID-19 has been reported by different networks.[30-33] The waning of VE of the mRNA bivalent vaccine against COVID-19-associated hospitalization was described both in adults without and with immunocompromising conditions[32]: VE declined from 62% (7-59 days from mRNA bivalent vaccine) to 24% (120–179 days) in adults without immunocompromising conditions and from 28% (7–59 days) to 13% (120–179 days) in immunocompromised individuals (IC; 1.8% of IC were PWH), a trend which can be attributed to both time from vaccination and changes in circulating variants. Both laboratory

and epidemiological data supported the switch to a monovalent XBB.1.5 updated formulation of the COVID-19 vaccine and our data are in line with these indications. In mice, monovalent BNT162b2 XBB.1.5 booster vaccine has been demonstrated to induce 5, 7, and threefold higher levels of anti-XBB.1.5, anti EG.5.1 and anti-BA.2.86 neutralizing antibodies compared to the bivalent original-BA.4/5 formulation.[34] Moreover, a monovalent XBB.1.5 mRNA vaccine has been demonstrated to achieve higher nAbs titers against XBB sublineages than a bivalent XBB.1.5 + BA.4/5 formulation.[3]

This study has some limitations: First, the small sample size and the short follow up period, does not allow us to draw firm conclusions about the persistence of neutralizing activity beyond the last timepoint of the study, second, the male/female proportions are unbalanced, so it is not possible to perform a gender response-based analysis in relation to the neutralizing response, third, the lack of a matched HIV-negative control group which is although missing because of the differences in vaccination schedule (number of doses received and time between doses) in PWH and people without HIV during the COVID-19 vaccination campaign.

To our knowledge, this is the first report on neutralizing activity and T cell immunity in PWH over time elicited by the mRNA bivalent original strain/BA.4-5 vaccine and during prevalent circulation of new variants such as the XBB.1.16, EG.5.1, and other XBB sublineages. This mRNA bivalent vaccine might not confer broad protection against them over time. With a view to the 2023/2024 vaccination campaigns, the use of the monovalent XBB.1.5 mRNA vaccine should be urgently warranted in PWH to provide more protection.

The integration of clinical, laboratory, and epidemiological data derived from different studies will help scissoring future vaccination campaigns in the most vulnerable populations.

AUTHOR CONTRIBUTIONS

Giulia Matusali: Conceptualization; methodology; investigation; writing—original draft; writing—review and editing. **Alessandra Vergori**: Conceptualization; methodology; writing—review and editing. **Eleonora Cimini**, **Davide Mariotti**, **Stefania Notari**, **Silvia Meschi**, **Eleonora Tartaglia**, **Francesca Colavita**: Investigation. **Alessandro Cozzi Lepri**: Methodology; writing—review and editing. **Valentina Mazzotta**: Methodology; writing—review and editing. **Marisa Fusto**, **Roberta Gagliardini**: Data curation. **Enrico Girardi**: Writing—review and editing; supervision. **Fabrizio Maggi**: Methodology; writing—review and editing; supervision. **Andrea Antinori**: Conceptualization; methodology; writing—review and editing; supervision.

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CONFLICT OF INTEREST STATEMENT

All authors declare no conflict of interest for the present study.

DATA AVAILABILITY STATEMENT

The data supporting the findings are available, only for sections noninfringing personal information, from the corresponding author upon reasonable request. Viral strain sequences are available in NCBI or GISAID database as reported in methods section.

ETHICS STATEMENT

All the individuals participating in the study provided informed consent. HIV-VAC was approved by the Scientific Committee of the Italian Drug Agency (AIFA) and by the Ethical Committee of the Lazzaro Spallanzani Institute, as National Review Board for COVID-19 pandemic in Italy (approval number 423/2021; amendment adopted with no. 91/2022).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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