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PII: S1201-9712(23)00632-X
DOI: https://doi.org/10.1016/j.ijid.2023.06.010
Reference: IJID 6769

To appear in: *International Journal of Infectious Diseases*

Received date: 23 March 2023
Revised date: 26 April 2023
Accepted date: 12 June 2023

Please cite this article as: Alessandra Vergori , Giulia Matusali , Alessandro Cozzi Lepri , Eleonora Cimini , Marisa Fusto , Francesca Colavita , Roberta Gagliardini , Stefania Notari , Valentina Mazzotta , Davide Mariotti , Stefania Cicalini , Enrico Girardi , Francesco Vaia , Fabrizio Maggi , Andrea Antinori , on behalf of the HIV-VAC Study group, Neutralizing activity and T Cell response after bivalent fifth dose of mRNA vaccine in person living with HIV, *International Journal of Infectious Diseases* (2023), doi: https://doi.org/10.1016/j.ijid.2023.06.010

Highlights

- The bivalent BD increases neutralizing antibodies against BA.5,BQ.1.1,XBB.1 in PLWH
- PLWH with a hybrid immunity developed higher and broader neutralization against BA.5
- A cross neutralization activity was found for BQ.1.1. and XBB.1
- Our data support to offer bivalent mRNA vaccine booster to advanced PLWH

Title page

Neutralizing activity and T Cell response after bivalent fifth dose of mRNA vaccine in person living with HIV

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Abstract

Objectives

To investigate immunogenicity of SARS-CoV-2 vaccine third booster (3BD; fifth dose) with bivalent vaccine original/BA4/5 vaccine in people living with HIV (PLWH).

Study design

This is an observational cohort study to evaluate the outcomes of SARS-CoV-2 vaccination (HIV-VAC study). We analyzed microneutralization assay and IFN-γ production in 48 PLWH on ART with CD4 count <200 cell/mm^3 and/or previous AIDS according to immunization status: vaccinated PLWH who had a previous SARS-CoV-2 infection (hybrid immunization, HI) vs. those only vaccinated (non-hybrid immunization, nHI) and current CD4 count

Results

After 15 days from its administration (T1), the 3BD bivalent mRNA vaccine elicited a statistically significant increase of neutralizing antibodies (nAbs) geometric mean titers (GMTs) from T0 to T1 against W-D614G (fold-increase 4.8; p<0.0001), BA.5 (8.6 p<0.0001), BQ.1.1 (6.4, p<0.0001) and XBB.1 (6.5, p<0.0001). When compared to BA.5, nAbs GMTs against BQ.1.1 and XBB.1 decreased by 3.5 and 4.1-fold, respectively. After controlling for age, years from AIDS diagnosis, CD4 count at administration and CD4 count nadir, the fold change reduction in nAbs response to other VoCs as compared to BA.1, was larger in participants with HI vs. those nHI: 0.59 lower (95%CI 0.36, 0.97, p=0.04) for BQ.1.1 and 0.67 lower (95% CI: 0.47, 0.96, p=0.03) for XBB.1.

In contrast, the analysis carried little evidence for an association between current CD4 count and response to the fifth dose of bivalent vaccine. Furthermore, cell-mediated immunity remained stable.

Conclusions

Our data support the current recommendation of offering bivalent mRNA vaccine booster doses to PLWH with low CD4 count or previous AIDS at first vaccination, especially in those who never previously acquired SARS CoV2 and regardless of current CD4 count.

Keywords: AIDS; mRNA bivalent vaccine; Omicron sub-variants; neutralizing antibodies; T-specific cell immunity

Background

It is well known that the SARS-CoV-2 omicron and its sub-lineages contain additional spike mutations that may allow virus to evade neutralizing antibody response and consequently affect mRNA vaccine effectiveness [1,2]. Immune evasiveness and waning immunity could be considered the main factors behind breakthrough infections [3], particularly for immunocompromised populations, including persons living with HIV (PLWH).

Regulatory and public health agencies currently recommend the use of booster doses with mRNA bivalent vaccines in fragile immunosuppressed populations, specifically those targeting the ancestral strain and BA.4/5 omicron sub-lineage [4].

All previous studies showed an increased levels of neutralizing activity against all Omicron sub-lineages after the administration of a bivalent vaccine [5,6, 7-11]. Some more recent reports, however, also showed significant neutralizing titers reductions against both BQ.1.1 and XBB.1 as compared to those seen with the ancestral strain and BA.5 sub-lineages.

To date, neutralizing activity is still the most widely used correlate of protection from SARS-CoV-2 infection [ref]. Nevertheless, its usefulness may be affected by the progressive circulation of new immune-evasive variants, and it is generally waning over time [12]. Although T-cell response is considered a good marker for protection from severe COVID-19 disease, regardless of specific viral variants, data on T-cell immunity elicited by the bivalent vaccine are still limited, especially in PLWH, [13].

Objectives

The main aim of this analysis was to measure the neutralizing activity against W-D614G, BA.5, BQ.1.1, XBB.1 and T cell response after receiving a 3rd booster dose (3BD; fifth vaccine shot) of bivalent mRNA vaccine (original/BA.4/5), in PLWH with a previous history of AIDS or current CD4 count <200 cells/mm^3, on antiretroviral therapy (ART) at the time of their first mRNA vaccine cycle.

As a secondary objective, we also aimed at comparing vaccine responses according to immunization status and to most recent CD4 count at time of 3BD (<500/mm^3 or >=500/mm^3).

Study design

On October 17th, 2022, the National Institute for Infectious Diseases Lazzaro Spallanzani in Rome continued the boosting vaccination against SARS-CoV-2 in PLWH, as a third booster (fifth dose) with a mRNA bivalent vaccine (original strain/BA.4/BA.5; BNT162b2 or mRNA-1273.214), according to the Italian Ministry of Health recommendations, for those who, at the time of their first vaccine dose showed a CD4 < 200/mm^3 or were previously diagnosed with AIDS. Participants in this analysis are a subset of those who, following written informed consent, had been enrolled in an observational cohort study to evaluate the outcomes of SARS-CoV-2 vaccination (the HIV-VAC study); 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). Details of this study have been described elsewhere [14].

Included participants were classified according to whether they acquired natural infection with SARS-CoV2 prior to receiving the 3BD vaccination (the hybrid immunity group, HI) or to whether they only received the vaccination (the nHI group). Previous natural infection was established by means of an anti-N IgG positive test result recorded at any time prior to the administration of the bivalent vaccination and participants self-report about the possible date of infection.

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Participants were also grouped according to the value of the most recent CD4 count measured at the time of receiving the 3BD dose using the threshold of 500 cells/mm^3. In a sensitivity analysis we have also used the threshold of 350 cells/mm^3.

Participants' demographic, epidemiologic, clinical and laboratory characteristics at time of the third booster dose were collected and compared by exposure groups.

Neutralizing antibodies responses were retrospectively measured in blood samples which were stored at time of the 3BD (T0) and approximately 15 days after the 3BD (T1). T-cell response was measured on fresh blood collected at the same timepoints.

Results

A total of 48 PLWH were included in the analysis, 19 (39.5%) who naturally acquired SARS-CoV-2 and were vaccinated (classified in the HI group) and 29 (60.5%) who were only vaccinated (classified in the nHI group, Supplementary Table 1), according to participants' self-reports, most

of the natural infections (15/19) occurred over June-November 2022 when BA4/5 strains were the predominant circulating VoCs. The main characteristics according to immunization status are reported in Supplementary Table 1.

We did not detect significant differences in participants' demographic and clinical characteristics according to CD4 count at the time of 3BD (<500/mm^3 in 29 vs. ≥500/mm^3 in 19 participants Supplementary Table 2).

After 15 days from the administration (T1), the 3BD with original/BA.4/5 bivalent mRNA vaccine elicited a statistically significant increase of neutralizing antibodies (nAbs) geometric mean titers (GMTs) from T0 to T1 against W-D614G (fold-increase 4.8; p<0.0001), BA.5 (8.6 p<0.0001), BQ.1.1 (6.4, p<0.0001) and XBB.1 (6.5, p<0.0001). Despite the 6 fold increase of titers for BQ.1.1 and XBB.1 the neutralization titers against BQ.1.1 and XBB.1 were substantially lower compared to those measured against BA.5.

At T1, the fold change reduction (FCR) of GMTs compared to those against W-D614G were 2.5 for BA.5, 7.8 for BQ.1.1 and 8.0 for XBB.1 in nHI; in HI the FCR were 1.6, 6.4 and 8.0, respectively. FCR of GMTs versus each variants in HI and nHI group are shown in Figure 1A and Table 1.

After controlling for age, years from AIDS diagnosis, CD4 count at T1 and CD4 count nadir, the fold change reduction in nAbs response to other VoCs as compared to BA.1, was larger in participants with HI vs. those nHI: 0.59 lower (95%CI 0.36, 0.97, p=0.04) for BQ.1.1 and 0.67 lower (95% CI: 0.47, 0.96, p=0.03) for XBB.1.

At T1, the FCR of GMTs compared to those against W-D614G were 2.05 for BA.5, 6.93 for BQ.1.1 and 8.0 for XBB.1 in PLWH with CD4 count<500 and in those with CD4 count >500 were 2.1, 7.7 and 9.3, respectively. FCR of GMTs compared to those against BA.5 were 3.4 for BQ.1.1 and 3.9 for XBB.1 in PLWH with CD4 count<500/mm^3 and 3.6 and 4.3 in those with CD4 count >500/mm^3 (Supplementary Figure 1A and Supplementary Table 3).

Even after controlling for the same set of potential confounders, no significant differences in GMTs were observed in relation to the CD4 strata both when using the threshold of 500 cells/mm^3 and of 350 cells/mm^3 (Supplementary Tables 3 and 4).

Concerning T-specific cellular immunity, no significant increase in levels of IFN-γ release from T0 to T1 was observed [from a median Log_2 8.0 pg/ml log_2 (2.0-12.1) to 8.3 pg/ml log2 (4.2-12.8), p=0.06]. Also, no evidence for a difference in IFN-γ response was observed between T0 and T1 overall in the unadjusted analysis (p=0.12 and p=0.45, respectively (Figure 1B), and according to

immunization status after controlling for confounding factors [Average Treatment effect, ATE 0.04 (-1.61, 1.68); p=0.964] (Supplementary Table 5).

When we evaluated the association with CD4 count at the time of 3BD and T-cell response, we found only a slight increase of IFN-γ values from T0 to T1 in those participants with CD4<500/mm^3 (p= 0.01) vs. those with CD4>500/mm^3 (p=0.85) (Supplementary figure 1B). However, there was no evidence for a difference after controlling for confounding in the ATE analysis [-0.50 (-4.78, 3.78); p=0.758] (Supplementary Table 5).

Discussion

To our knowledge, this is the first study reporting levels of live-virus neutralization after a bivalent mRNA (original/BA.4/5) 3BD (fifth shot) in PLWH who had advanced diseases when they first started their COVID-19 vaccination cycle (previous AIDS and/or low current CD4 count). According to our data, even in this considered vulnerable population and despite the greater immunological escape of new circulating VOCs, bivalent mRNA vaccine elicited a robust neutralizing response against all omicron sub-lineages, with an almost 9-fold increase in the nAbs GMTs for BA.5, and over 6-fold increase for BQ.1.1 and XBB.1.

Cross-neutralization against BQ.1.1 and XBB.1, when compared to W-D614G, was lower than that previously observed, although in different settings [7,11], but a direct comparison is not possible because the response to a 5th vaccine dose was not evaluated in the other studies.

Participants with a history of natural infection with SARS-CoV-2 (i.e. those who developed a hybrid immunity), showed a higher and broader neutralization against BA.5 after receiving the 3BD with a mean of the absolute numbers of titers which appeared to be high also for BQ.1.1. and XBB.1, suggesting cross-neutralization activity. The result is somewhat expected given that, according to self-reported data, most participants might have been infected with BA4/5 strains. Therefore, our data confirm a key role of previous SARS-CoV-2 infection in enhancing the magnitude of neutralization titers after booster vaccination [15, 16] also in PLWH with a previous history of severe immunosuppression. This is despite the fact that omicron sub-lineages have a greater immunological escape [17].

In contrast, our data carried little evidence that a current CD4 count<500 cells/mm^3 (or <350 cells/mm^3) is associated with a worse response to the fifth dose of the BA.5 bivalent vaccine. Unfortunately, we did not have the data to evaluate the possible association with lower thresholds.

It is well known that HIV infection is characterized by a profound disruption of the adaptive immune system, in both its cellular and humoral components [18]. Indeed, PLWH with low CD4+T-cell counts and/or previous AIDS were found to have weaker humoral and T-cell responses

to mRNA vaccines [19], suggesting that they may benefit from additional vaccine doses. In addition, the 3BD dose appeared to have no effect in increasing T-cell-mediated response. In this respect, we previously showed that a third additional dose of a mRNA vaccine following the primary cycle is able to strongly boost humoral but not T-cell responses in PLWH with advanced disease at the time of HIV diagnosis [20].

These findings support the current recommendation of offering bivalent mRNA vaccine booster doses to PLWH with low CD4 count or previous AIDS at first vaccination and importantly, especially to those who never acquired natural infection. Indeed, our data confirm a key role of previous SARS-CoV-2 infection in enhancing the magnitude of neutralization titers against BA.5 (versus W-D614G) in this vulnerable population, despite the greater immunological escape of the omicron sub-lineages.

Acknowledgements

HIV-VAC Study Group:

Alessandra Amendola, Francesco Baldini, Rita Bellagamba, Aurora Bettini, Licia Bordi, Marta Camici, Rita Casetti, Sabrina Coen, Flavia Cristofanelli, Federico De Zottis, Massimo Francalancia, Marisa Fusto, Roberta Gagliardini, Paola Gallì, Simona Gili, Germana Grassi, Elisabetta Grilli, Susanna Grisetti, Denise Iafrate, Daniele Lapa, Alessandra Marani, Erminia Masone, Stefano Marongiu, Silvia Meschi, Klizia Mizzoni, Annalisa Mondi, Sandrine Ottou, Carmela Pinnetti, Maria Maddalena Plazzi, Adriano Possi, Eleonora Tartaglia

Competing interests The authors declare no competing interests.

Funding: the study was supported by Ricerca Corrente Line 1 and 2 from Italian Ministry of Health and by SHARP JA Grant Number 848096.

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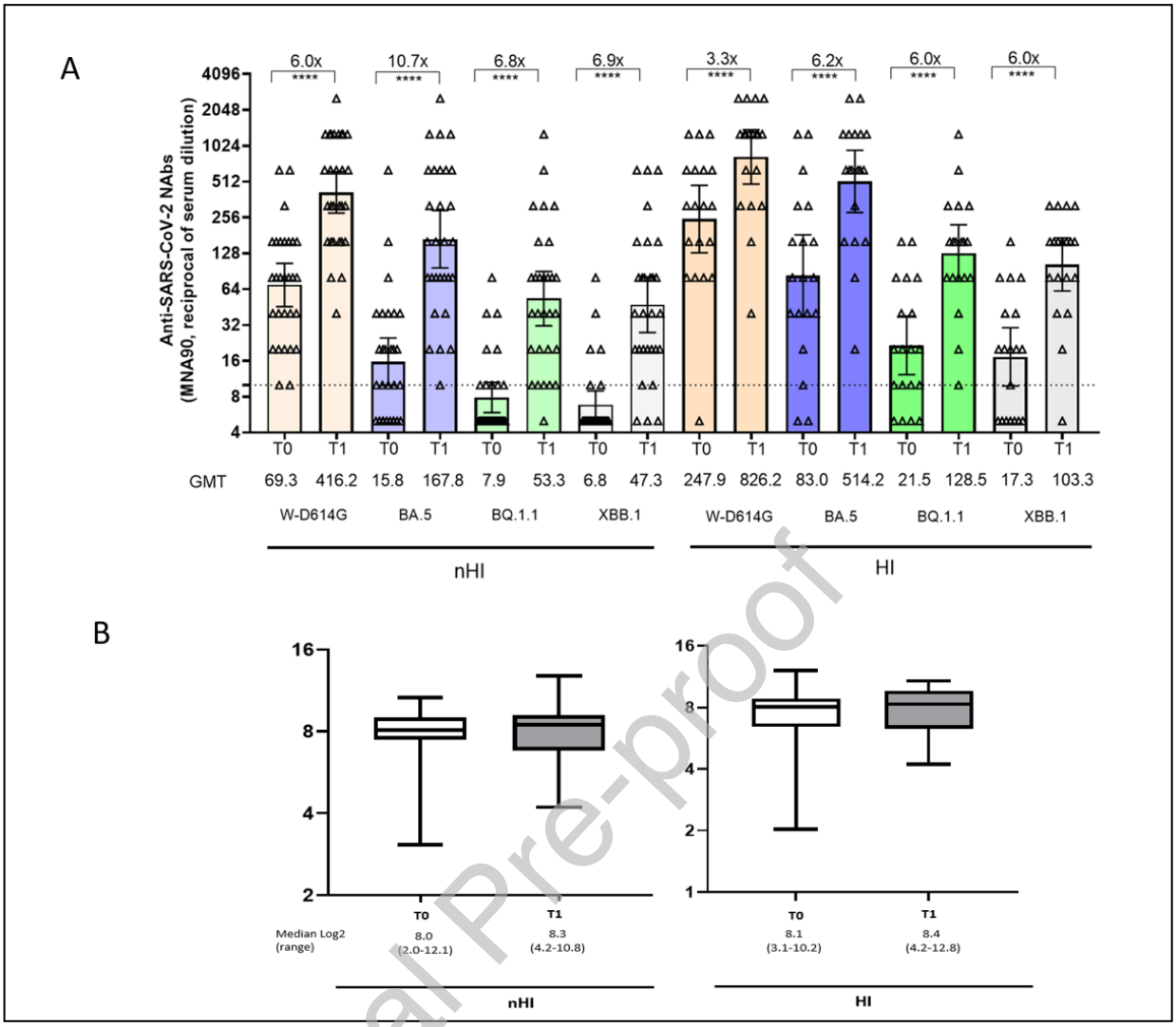

Figure 1 A, B. Mean values of MNA90 and fold increase (A), IFN-γ release (B) from T0 to T1 according to immunization status [Hybrid immunity (HI) vs non-Hybrid Immunity (nHI)]. Pink plots represent nAbs against W-D614G, blue plots represent nAbs against BA.5, green plots represent nAbs against BQ.1.1 and XBB.1 are grey plots. Wilcoxon test was used to compare nAbs, IFN-γ in each group, Mann-Whitney test for comparisons between different groups. Abbreviations: nHI, no hybrid immunity; HI, hybrid immunity. **** p<0.0001; *** p<0.001; ** p<0.01; * p<0.05

Table 1. Geometric mean titers of fold change reduction (FCR) at day 15 post third booster dose (3BD; fifth shot) with bivalent vaccine and difference from fitting a generalized linear model (raw dilution scale) in hybrid (HI) and non-hybrid immunity (nHI) (only vaccine immunization).

Author contributions

Conceptualization, AV, GM and AA. Methodology, AV, GM, ACL, AA, FM; Investigation, AV, GM, EC, FC, DM, SN; Data Curation, AV, MF, SC, RG; Writing-Original Draft, AV and GM; Writing, Review & Editing, AV, GM, ACL, FM, EC, AA, VM, EG; Supervision, EG, FV, FM, AA.

Data availability

Data used in this analysis is available upon reasonable request.

Table 1. Geometric mean titers of fold change reduction (FCR) at day 15 post third booster dose (3BD; fifth shot) with bivalent vaccine and difference from fitting a generalized linear model (raw dilution scale) in hybrid (HI) and non-hybrid immunity (nHI) (only vaccine immunization).

	Mean GMT FCR at day 15 post vaccine and difference from fitting a generalised linear model (raw dilution scale)					
	GMT in HI (95% CI)	GMT in nHI (95% CI)	Unadjusted difference (95% CI)	p-value	Adjusted difference* (95% CI)	p-value
BA.5 vs. Wuhan	1.61 (1.15, 2.24)	2.48 (1.90, 3.24)	1.54 (1.01, 2.36)	0.046	1.29 (0.87, 1.91)	0.203
BQ.1.1 vs. Wuhan	6.43 (4.35, 9.49)	7.81 (5.70, 10.71)	1.22 (0.74, 2.01)	0.446	0.77 (0.50, 1.17)	0.217
XBB.1 vs. Wuhan	8.00 (5.76, 11.12)	8.80 (6.75, 11.49)	1.10 (0.72, 1.68)	0.658	0.86 (0.60, 1.24)	0.420
BQ.1.1 vs. BA.5	4.00 (2.76, 5.81)	3.15 (2.33, 4.26)	0.79 (0.49, 1.27)	0.328	0.59 (0.36, 0.97)	0.036
XBB.1 vs. BA.5	4.98 (3.77, 6.58)	3.55 (2.83, 4.45)	0.71 (0.50, 1.02)	0.064	0.67 (0.47, 0.96)	0.027

*adjusted for age, years from AIDS diagnosis, CD4 count at T5 and CD4 count nadir

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: