NEUTRALIZING ACTIVITY AND T CELL RESPONSE AFTER BIVALENT THIRD BOOSTER DOSE IN PLWH

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BACKGROUND

- Omicron subvariants contain additional spike mutations that may affect vaccine effectiveness with consequent breakthrough infections, of particular importance for immune-depressed populations, including persons living with HIV infection (PLWH).
- Since new bivalent vaccines approval, other sublineages appeared in the omicron scenario, such as BQ.1.1 and XBB.1, for which the neutralizing activity elicited by a booster dose with a bivalent vaccine (original strain/BA.4/BA.5) has been widely investigated by in vitro studies in the general population

Aim of the study was to analyze the neutralizing activity against W-D614G, BA.5, BQ.1.1, XBB.1 and T cell response after 3rd booster dose (fifth vaccine shot) with original/BA.4/5 bivalent vaccine according to immunization status [hybrid immunity (HI) or not (nHI) and CD4 count (<500/mm³ or >=500/mm³) in advanced PLWH

METHODS

STUDY PARTICIPANTS

PLWH who, at the time of their first vaccine dose, showed CD4<200/mm³ or were previously diagnosed with AIDS and receiving a bivalent mRNA vaccine (original strain/BA.4/5) as third booster dose (3BD), after a second booster dose with a monovalent vaccine.

LAB PROCEDURES

Micro-neutralization assay (MNA): incubation of live SARS-CoV-2 (100 TCID50) on duplicate serial dilution of serum samples (starting dilution 1:10) for 30'. Virus-serum mix were incubated on VeroE6 cells for 72 hours. Cytopathic effect (CPE) was estimated by microscopic observation and neutralizing antibodies (nAbs) titre (MNA_{90}) assigned as the highest dilution preventing at least 90% of CPE. MNA_{90} positive if >=1:10. For T cell response, IFNγ in supernatants was quantified by an automated ELISA; positive if ≥ 12 pg/mL

ENDPOINTS

Immunogenicity was assessed at time of 3BD (T0) and at day 15 (T1) by MNA_{90} against W-D614G, Omicron BA.5, BQ.1.1, XBB.1 and by IFN-γ.

STATISTICAL ANALYSIS

Neutralizing antibodies (nAbs) expressed in natural scale and fold changes, IFNγ and all values for regression analyses in log_2 scale, paired t-test used to test changes over T0-T1. Two 2-arms parallel trials were emulated: HI and CD4 count as exposure, log_2 nAbs and IFNγ as outcome. Average treatment effect (ATE) of the two exposures were estimated by marginal models weighted for potential confounders (age, CD4 nadir, years from AIDS; when HI was the exposure also CD4 count).

RESULTS

N=48 PLWH on antiretroviral therapy (ART) were included: n=19 with a HI and 29 nHI, n=29 with CD4 count <500/mm³ and n=19 with CD4 count >=500/mm³; main characteristics of study participants according to immunization status are shown in Table 1. Regarding the stratification of the study population according to CD4 count (< or >= 500/mm³) at the time of 3BD, the two groups were quite similar in terms of demographic and clinical characteristics, as well as nAbs titres at T0 against the VOCs investigated in this analysis (table not shown).

Table 1

Characteristics	Immunization status HI N=19	nHI N=29	p-value*
Female, n (%)	1 (5.3)	6 (20.7)	0.143
Age, years, median (IQR)	55 (44, 60)	57 (47, 61)	0.520
>=1 comorbidity, n (%)	17 (89.5)	29 (100.0)	0.077
Nadir CD4 count, cells/mm³ ,median (IQR)	44 (14, 92)	44 (18, 112)	0.616
CD4 count at T0, cells/mm³,median (IQR)	416 (257, 552)	404 (271, 611)	0.866
IFNγ at T0, Median (IQR)	272.4 (177.6, 522.4)	269.5 (94.5, 448.0)	0.617
W-D614G nAbs at T0, GMTs (95%CI)	247.9 (129-476)	69.3 (45-105)	0.0005
BA.5 nAbs T0, GMTs (95%CI)	83.0 (38-183)	15.8 (10-25)	0.0003
BQ.1.1 nAbs T0, GMTs (95%CI)	21.5 (12-38)	7.9 (6-11)	0.0008
XBB.1 nAbs T0, GMTs (95%CI)	17.3 (10-30)	6.8 (5-9)	0.0014

&In those with at least one comorbidity; *Chi-square or Mann-Whitney test as appropriate. Abbreviations: HI, Hybrid Immunity; nHI, non-Hybrid Immunity; nAbs, neutralizing antibodies; GMTs, geometric mean titres

The 3BD showed a satisfactory neutralizing activity with a significant increase from T0 to T1 of nAbs titres 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, the nAbs titres of BQ.1.1 and XBB.1 decreased by 3.5 and 4.1, respectively. Neutralization activity of 3BD against W-D614G and Omicron BA.5, BQ.1.1 and XBB.1 according to immunization status is shown in Fig. 1.

Fold change reduction compared to W-D614G or BA.5 at T1 are shown in Table 2. After controlling for confounders, HI was associated with a higher level of neutralizing response against BA.5 but not against BQ.1.1 and XBB.1 as reported by double robust estimates and confirmed also by IPWs and regression adjustment (Table 3) . There was no impact of CD4 count on neutralization after controlling for potential confounding factors (data not shown). No evidence for a difference between T0 and T1 was detected for IFNγ (Fig. 2).

Table 2

	Fold Change Reduction at T1 vs W-D614G			
	HI N=19	p-value*	nHI N=29	p-value*
BA.5	1.6	0.069	2.5	0.0001
BQ.1.1	6.4	<0.0001	7.8	<0.0001
XBB.1	8.0	<0.0001	8.8	<0.0001

	vs BA.5			
BQ.1.1	4.0	0.006	3.1	0.013
XBB.1	5.0	0.0008	3.6	0.0034

*Oneway ANOVA/Dunnet's multiple comparison test

Table 3

	Potential average change at day 15 post vaccine and ATE& from fitting a linear regression model (log_2 scale) Mean (log_2) in exposed (95% CI)	Mean (log_2) in unexposed (95% CI)	ATE* (95% CI)	p-value
Hybrid vs. non Hybrid immunity				
	BA.5 nAbs			
Double Robust	3.55 (2.88, 4.21)	2.38 (1.51, 3.25)	1.17 (0.34, 2.00)	0.006
	BQ.1.1 nAbs			
Double Robust	2.94 (2.26, 3.63)	2.29 (1.57, 3.02)	0.65 (-0.18, 1.48)	0.124
	XBB.1 nAbs			
Double Robust	2.96 (2.22, 3.70)	2.50 (1.78, 3.22)	0.46 (-0.41, 1.33)	0.300
	IFN-γ			
Double Robust	0.42 (-1.91, 2.74)	0.38 (-0.65, 1.41)	0.04 (-1.61, 1.68)	0.964

&Average Treatment Effect; *weighted for age, years from AIDS diagnosis, CD4 count at T5 and CD4 count nadir

CONCLUSIONS

To our knowledge, this is the first study evaluating live-virus neutralization on a fifth shot of bivalent vaccine in PLWH with advanced diseases, which elicited strong neutralization against BA.5, and retained cross-neutralization against BQ.1.1 and XBB.1, even if 3-4 times lower. HI but not CD4 count≥500 appeared to enhance neutralization against BA.5. Importantly, bivalent vaccine as fifth dose appeared to have no effect on T-cell mediated response.

In PLWH, the bivalent vaccine used as a fifth shot (third booster dose) elicited strong neutralization against BA.5, and retained cross-neutralization against BQ.1.1 and XBB.1, even if over 3 times lower than BA.5

Figure 1. Mean values of MNA90 from T0 to T1 according to immunization status: Pink plots represent nAbs against W-D614G, blue plots represent nAbs against BA.5, green plots represent nAbs against BQ.1.1 and grey plots for XBB.1. Wilcoxon test was used to compare nAbs in each group, Mann-Whitney test for comparisons between different groups. Abbreviations: nHI, no hybrid immunity; HI, hybrid immunity. **** p<0.0001

Figure 1

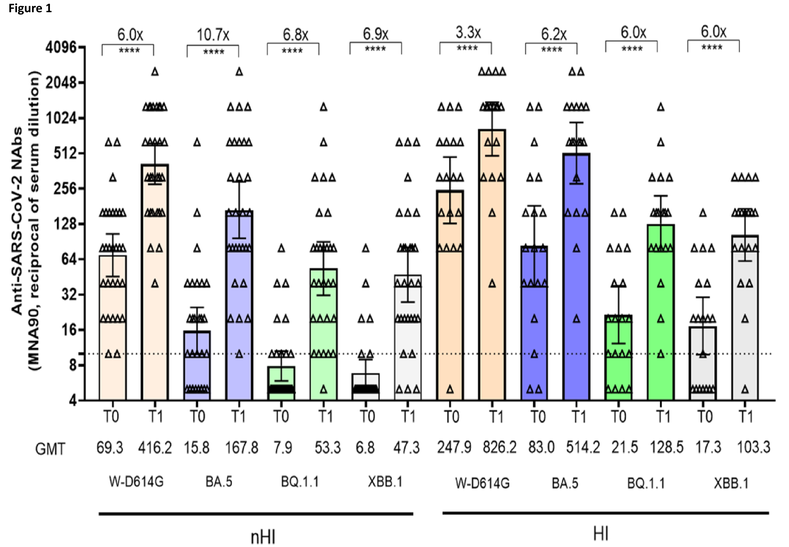
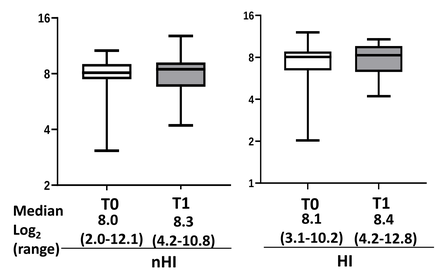


Figure 2. Mean values of IFNγ from T0 to T1 according to immunization status; Wilcoxon test was used to compare IFN-γ levels



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