Immunogenicity and reactogenicity to COVID-19 mRNA vaccine additional dose in PLWH

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BACKGROUND

The aims of this study were to evaluate Immunogenicity (humoral, neutralizing and cell-mediated responses) measured 15 days after receiving the additional third dose (AD) (T1) by current CD4 count, to investigate on 7 days reactogenicity (self-reported by telephone interview), and to assess the difference in average level of immunogenicity between T-1 (after 1 month from completion of primary cycle) and T1.

METHODS

On September 10th, 2021, the boosting vaccination program against for SARS-CoV-2 started in PLWH, as an additional dose (AD) of a mRNA vaccine with a full single dose of BNT162b2 or mRNA-1273.

STUDY PARTICIPANTS: PLWH attending our institute who, at the time of their first vaccine dose, showed a CD4<200/mm or were previously diagnosed with AIDS and who had completed a primary vaccination cycle for at least 28 days

LAB PROCEDURES:

-anti-S/RBD tests: ARCHITECT SARS-CoV-2 IgG, and ARCHITECT SARS-CoV-2 IgG II Quantitative, Abbott Laboratories, Wiesbaden, Germany respectively) were performed on ARCHITECT® i2000sr (Abbott Diagnostics, Chicago, IL, USA)

-Micro-neutralization assay (MNA) with WT strain:SARS-CoV-2/Human/ITA/PAVIA10734/2020

-IFN-γ production in response to Spike stimulation as a surrogate of specific T-cell function with a pool of peptides spanning the Spike protein (Miltenyi Biotech, Germany)

DEFINITIONS: IgG anti RBD/S positive if >7.1 BAU/mL; MNA positive if titres of neutralizing antibodies (nAbs) >=1:10, IFN-γ positive if > 12 pg/mL;

Severe immunodeficiency, **SID**: <200/mm3; minor immunodeficiency, **MID**: 200-500/mm3; no immunodeficiency, **NID**: >500/mm3

STATISTICAL ANALYSIS: ANOVA was used to compare titers (log2 scale), association between current CD4 count and the lack of immune response was determined by fitting a multivariable logistic regression adjusted for age, time from HIV diagnosis, CD4 nadir, cancer and HIV-RNA a T0.

The third AD of mRNA anti-SARS-CoV-2 vaccine induced a strong humoral and T specific cell response in PLWH and who previously received a complete mRNA 2-dose vaccination cycle. Although clinical implications of the observed immunological response remains uncertain, our data support the use of a third AD in PLWH with immune dysregulation.

RESULTS

We enrolled 216 PLWH on ART (n=44 SID, n=96 MID, n=76 NID): median age 54 yrs (IQR 47-59), median CD4 nadir 45 cell/mm3 (20-122), 93% HIV-RNA <50 c/mL, 7yrs (3-12) since HIV diagnosis and 5yrs (2-8) since AIDS, if diagnosed (see Table 1). Response rate was 95.5% in SID, 100% in MID, 100% in NID for anti-RBD (p=0.02); 86.3%, 97.9% and 98.7% for nAbs (p=0.002), and 70%, 95.6% and 97.2% for IFN-γ (p<0.0001) , respectively. A significant increase of AD immunogenicity was observed in all CD4 count groups (Fig. 1 A-I). 95% reported mild symptoms, 14% moderate symptoms and 2% severe symptoms not requiring hospitalization.

Figure 1 A-C Log2 increase of anti-RBD IgG from T0 to T1 according to immunodeficiency status: SID (A), MID(B), NID (C). D-F Log2 increase of nAbs from T0 to T1 according to immunodeficiency status: SID (D), MID(E), NID (F). G-I Log2 increase of IFN-γ from T0 to T1 according to immunodeficiency status: SID (G), MID(H), NID (I)

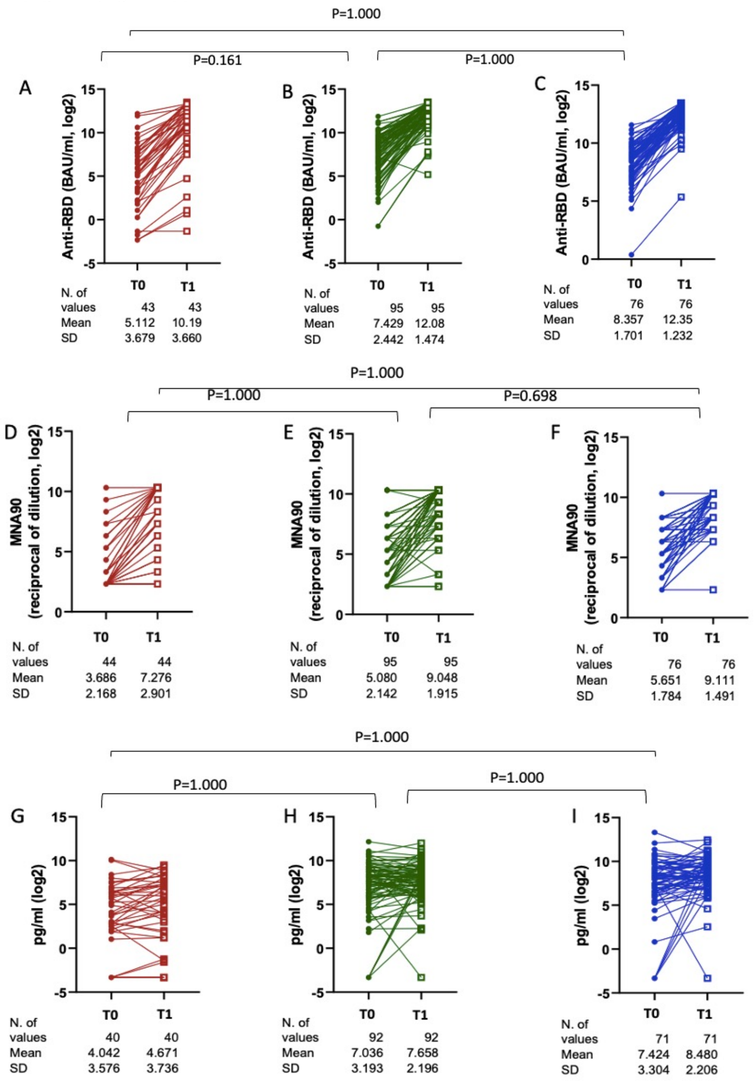

Table 1. Characteristics	SID (N=44)	MID (N=96)	NID (N=76)	p-value*
Age, years, median (IQR)	57 (48, 63)	55 (47, 60)	52 (47, 58)	0.074
Female, n(%)	10 (22.7)	17 (17.7)	12 (15.8)	0.632
Caucasian, n(%)	30 (68.2)	63 (65.6)	63 (82.9)	0.035
Nadir CD4 count, cells/mm3, median (IQR)	40 (15, 76)	41 (16, 92)	83 (26, 168)	0.007
Time from HIV diagnosis, years, median (IQR)	15 (2, 25)	6 (3, 11)	6 (4, 11)	0.135
AIDS, n(%)	15 (34.1)	79 (82.3)	73 (96.1)	<.001
HIV-RNA<=50 at third dose, n(%)	35 (79.5)	90 (93.8)	74 (98.7)	<.001
Time from second dose to AD, days, median (IQR)	154 (134, 159)	145 (132, 157)	138 (130, 151)	0.006
*Chi-square or Kruskal-Wallis test as appropriate				

Of note, the comparison between the mean log2 of anti-RBD IgG at T-1 and T1 were 9.79 BAU/mL (SD 2.90) and 11.8 (SD 2.14) (p=0.003); mean log2 increase of 2.0 (SD 1.56) (p<0.0001); the mean log2 of nAbs were 4.90 (SD 2.20) and 8.28 (SD 2.41) (p=0.018); mean increase of 3.37 (SD 2.15) (p<0.0001). The level of T cell mediated response appeared to be stable comparing values achieved post 2nd dose with those observed post the AD (6.80 pg/mL (SD 3.17) and 7.25 (SD 2.92) (p=0.39); mean increase [0.44 pg/mL (SD 2.45; p=0.12]

In the multivariable logistic regression model, using NID as the comparator, SID showed a largely increased risk of failing to achieve nAbs>1:10 and IFN-γ >12 pg/mL , after adjusting for the main identified confounders although not statistically significant (Table 2).

Table 2	Logistic regression of the risk of no response to additional dose				
	Unadjusted		Adjusted*		
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value	&Type III p-value
CD4 count (cells/mm³)					
	nAbs				
501+	1		1		0.410
201-500	1.61 (0.14, 18.13)	0.699	2.28 (0.15, 33.93)	0.550	
0-200	11.84 (1.38, 101.9)	0.024	7.45 (0.33, 168.1)	0.206	
	IFN-gamma				
501+	1		1		0.221
201-500	1.59 (0.28, 8.94)	0.598	0.55 (0.07, 4.66)	0.584	
0-200	15.00 (3.15, 71.37)	<.001	2.93 (0.35, 24.47)	0.320	

*adjusted for age, time from HIV diagnosis, CD4 count nadir,VL<=50 copies/mL at T0 and concomitant cancer; &from the adjusted model

CONCLUSIONS

- ✓ Humoral and T cell-mediated response showed a significant increase after the AD;
- ✓ No significant association was be found with the current level of CD4 count, but we cannot rule out a difference in both the magnitude of response and risk of no-response when comparing SID with NID.
- ✓ The observed increase in humoral response is consistent with the hypothesis that AD induces a robust B cell memory response, previously elicited by the primary vaccination series and highlights the fact that the SARS-CoV-2 mRNA vaccines are able to stimulate a satisfactory humoral response even in immunocompromised patients.

The study is funded by RF COVID-2020-12371675 and Ricerca Corrente Line 1; *contact: alessandra.vergori@inmi.it*