DURABILITY OF SARS-COV-2 mRNA VACCINE IMMUNE RESPONSE IN PLWH WITH ADVANCED DISEASE

Stefania Cicalini[1], Alessandra Vergori[1], Alessandro Cozzi-Lepri[2], Silvia Meschi[3], Veronica Bordoni[4], Simone Lanini[1], Daniele Lapa[3], Davide Mariotti[4], Lidya De Pascale[1], Veronica D'Aquila[1], Concetta Castilletti[3], Chiara Agrati[4], Enrico Girardi[5], Francesco Vaia[6], **Andrea Antinori**[1].

00291

[1] HIV/AIDS Unit, National Institute for Infectious Diseases Lazzaro Spallanzani IRCCS, Rome, Italy; [2]Centre for Clinical Research, Epidemiology, Modelling and Evaluation (CREME), Institute for Global Health, UCL, London, UK; [3]Laboratory of Virology, National Institute for Infectious Diseases Lazzaro Spallanzani IRCCS, Rome, Italy; [4]Laboratory of Cellular Immunology and Clinical Pharmacology, National Institute for Infectious Diseases Lazzaro Spallanzani IRCCS, Roma, Italy; [5]Scientific Direction, National Institute for Infectious Diseases Lazzaro Spallanzani IRCCS, Roma, Italy; [6]Health Direction, National Institute for Infectious Diseases Lazzaro Spallanzani IRCCS, Roma, Italy.

BACKGROUND

- Waning of vaccine protection against SARS-CoV-2 infection is currently a concern and durability of specific immunity after vaccination in people living with HIV (PLWH) is still unknown. The aim of this analysis was to evaluate persistence of humoral and cell-mediated immune response to mRNA vaccines in PLWH with advanced disease.

METHODS

- PLWH with a CD4 T-cell count ≤200/mm^3 and/or a previous AIDS diagnosis, enrolled in a SARS-CoV-2 vaccination program at the National Institute for Infectious Diseases Lazzaro Spallanzani in Rome, Italy, were evaluated at >90 days after 2nd dose of BNT162b2 or mRNA-1273 vaccine.
- Anti-Spike RBD-binding by CLIA, neutralizing antibody (nAb) titers by microneutralization assay (MNA_{90}) and IFNγ production in response to Spike stimulation, as a surrogate of a specific T-cell function, were assessed. Response was defined as having anti-RBD >7.1 BAU/mL, nAbs ≥1:10, IFNγ >12 pg/mL.
- Samples were also tested for anti-Nucleocapside (N) antibodies to detect asymptomatic SARS-CoV-2 infection. participants with a positive anti-N response at any time were excluded from this analysis.
- Participants were stratified by CD4 T-cell count (at T1 and T0) into severe immunodeficiency, SID, ≤200/mm^3; minor immunodeficiency, MID, 201-500/mm^3; no immunodeficiency, NID, >500/mm^3.
- Waning of humoral and cell-mediated immune response was evaluated in a subgroup of responders to vaccination for whom values at 1 month (T0) and >90 days (T1) after 2nd dose of vaccine were available.
- Paired t-test was used to test the overall decline. ANOVA and logistic regression analysis controlling for age, viral load, CD4 nadir and cancer were used for comparisons by CD4 groups.

Our data show that a high proportion of **PLWH with CD4<200** /mm^3 **lacks humoral response after a median period of six months** from the 2-dose schedule of their primary cycle with a SARS-CoV-2 mRNA vaccine. All our PLWH showed a **waning of immune response over time**.

RESULTS

- 314 PLWH were included. All participants were on antiretroviral therapy. Main characteristics of PLWH stratified by T1 CD4 T-cell count groups were reported in **Table 1**.
- After a median of 175 (IQR 166-186) days after 2nd dose, a detectable anti-RBD response was still present in 72% of SID, 96% of MID and 99% of NID (P<0.0001); nAbs in 38% of SID, 79% of MID and 85% of NID (P<0.0001); and IFNγ in 65% of SID, 91% of MID and 93% of NID (P<0.0001).
- Mean level of humoral immune response at T1 was significantly lower in SID (**Figure 1A**).
- By logistic regression, risk of undetectability at T1 was higher in SID vs. NID for anti-RBD (aOR 19.76; 95% CI 1.42-275.6), and in SID (aOR 7.36; 95% CI 1.73-31.34) and MID (aOR 4.68; 1.48-14.76) vs. NID for nAbs; no evidence for a difference was found for IFNγ.
- Overall, a significant decline of immune response was observed over T0-T1 for all immune parameters [mean log_2 (SD)]: -2.89 (0.93), p<0.0001, for anti-RBD; -1.53 (1.44), p<0.0001, for nAbs; and -0.57 (2.06), p=0.004, for IFNγ, with no evidence for a difference between T0 CD4 groups (**Figure 1B/C**).

Table 1. Main characteristics of participants stratified by CD4 T- cell count

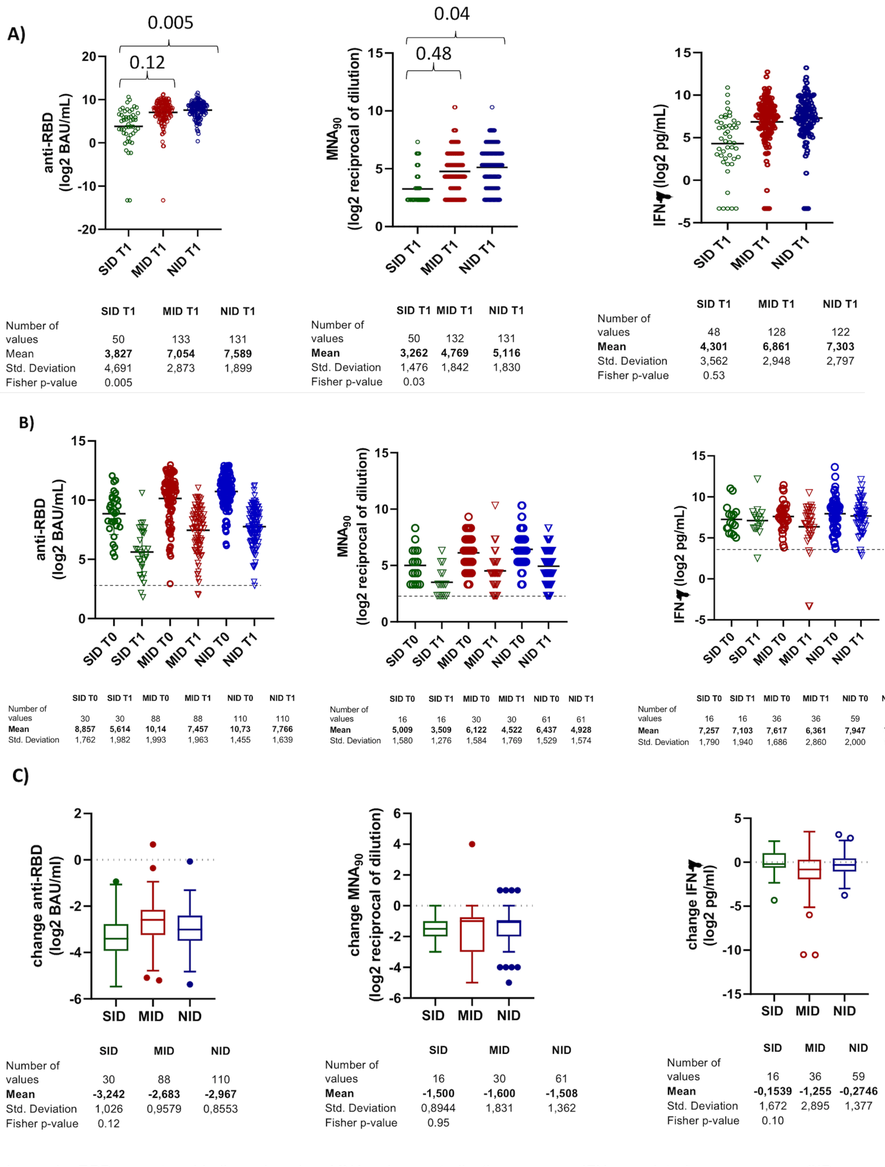
	SID CD4<200/mm^3 N=50	MID CD4 201-500/mm^3 N=133	NID CD4>500/mm^3 N=131	p-value*	Overall N=314
Age, median (IQR)	58 (53-63)	56 (50-61)	56 (49-61)	ns	56 (50-61)
Gender, n (%) • Female	11 (22.0)	25 (18.8)	20 (15.3)	ns	56 (17.8)
Ethnicity, n (%) • Caucasian	38 (76.0)	86 (64.7)	105 (80.2)	0.016	229 (72.9)
Time from HIV diagnosis, years, median (IQR)	16 (2-24)	6 (3-14)	9 (6-19)	ns	9 (4-21)
AIDS diagnosis, n(%)	10 (20.4)	38 (31.7)	25 (21.2)	ns	73 (25.4)
Time from AIDS diagnosis, years, median (IQR)	2 (2-2)	5 (2-6)	6 (5-10)	0.025	5 (4-8)
Nadir CD4, median (IQR)	39 (10-72)	43 (16-93)	143 (44-256)	<0.001	58 (23-162)
HIV-RNA ≤50 copies/mL, n (%)	27 (61.4)	118 (92.2)	113 (93.4)	<0.001	258 (88.1)
Cancer, n(%)	2 (4.0)	6 (4.5)	12 (9.2)	ns	20 (6.4)
Comorbidities, n (%)				ns	
• CKD	8 (16.3)	8 (6.7)	9 (7.6)		25 (8.7)
• Hypertension	8 (16.3)	17 (14.2)	11 (9.3)		36 (12.5)
• Myocardial infarction	1 (2.0)	1 (0.8)	1 (0.8)		3 (1.0)
• Liver diseases	17 (34.0)	28 (21.0)	28 (21.4)		73 (23.2)
• COPD	3 (6.1)	6 (5.0)	4 (3.4)		13 (4.5)

*Chi-square or Kruskal-Wallis test as appropriate; ns, not significant

CONCLUSIONS

- A high proportion of PLWH with CD4 count <200/mm^3 showed a lack of humoral response after a median of 6 months from vaccination compared to participants with CD4 count >500/mm^3. All our PLWH showed a significant rate of waning of immune response.
- These findings support the need for a three dose schedule as primary vaccination in PLWH with advanced disease.
- Further studies are needed to establish the most appropriate dose intervals.

Figure 1. A) Mean (SD) concentrations of anti-RBD, neutralizing antibody titers (expressed as MNA_{90}) and IFNγ at >90 days [median 175 (IQR 166-186) days] after 2nd dose of vaccine (T1) according to T1 CD4 T-cell groups. B) Mean (SD) levels of anti-RBD, MNA_{90} and IFNγ at one month after 2nd dose of vaccine (T0) and at T1, according to T0 CD4 T-cell groups. C) Median (IQR) waning of anti-RBD, MNA_{90} and IFNγ from T0 to T1, according to T0 CD4 T-cell groups.



Legend: RBD=receptor binding domain; MNA=microneutralization assay; IFNg = interferon gamma; SID, severe immunodeficiency (CD4 T-cells ≤200/mm^3); MID, minor immunodeficiency (CD4 T-cells 201-500/mm^3); NID, no immunodeficiency (CD4 T-cells >500/mm^3); T0= one month after 2nd dose of vaccine; T1= at least 90 days after 2nd dose of vaccine; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

Author Contacts: stefania.cicalini@inmi.it andrea.antinori@inmi.it