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Short Communication

SARS-CoV-2 mRNA vaccination and short-term changes in viral load and CD4/CD8 T-cell counts in people living with HIV

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ABSTRACT

Objectives: To investigate whether SARS-CoV-2 messenger RNA (mRNA) vaccination has an impact on HIV-related viro-immunological parameters.
Methods: People with HIV (PWH) in the VAXICONA-ORCHESTRA cohort who received one or more doses of SARS-CoV-2 mRNA vaccine and for whom paired measures of immuno-virological markers (viral load, clusters of differentiation [CD]4, and CD8 count 1 month before and after a vaccine dose [VD]) were available were included. Paired *t*-test and generalized estimating equation linear regression analyses were used to study changes over ± 1 month around the VD. Subgroup analyses were performed.
Results: A total of 510 PWH were enrolled: the median age was 55 years (interquartile range 46-60 years), the CD4 and CD8 count were 489 (287-719) and 790 (59-1104) cells/mm^3, respectively, and 81% received three VDs. After a median of 28 (3-53) days from VD, CD4 count increased by +15 cells/mm^3 (SD ± 129.7, $P = 0.001$) and CD8 by +12 (±250.5, $P = 0.199$) and the viral load decreased by −0.11 $\log_{10}$ (±0.88, $P = 0.001$). Similar results were observed after restricting the analysis to viro-suppressed PWH, with CD4 ≤200/mm^3, more than 6 months of antiretroviral therapy before VD and after excluding previous COVID-19.
Conclusions: A small significant increase in CD4 count and a negligible drop in HIV RNA were observed. Our findings are consistent with the hypothesis that SARS-CoV-2 mRNA vaccine can prime CD4 T spike-specific cells, even in the more immuno-compromised PWH.

Introduction

A great body of evidence reassures the safety of SARS-CoV-2 vaccination in people with HIV (PWH), who can mount a satisfactory immune response [1] comparable to those of the general

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population, except for cases with a low clusters of differentiation (CD)4$^+$ T-cell count recovery [1]. Notwithstanding, some concerns emerged because of the possible detrimental effects of SARS-CoV-2 vaccination on HIV viral load (VL) and CD4 and CD8 T cells, although most of the evidence is anecdotal or comes from limited case series with conflicting results [2–5]. In addition, some previous studies have found transient increases in VL after flu, *Streptococcus pneumoniae,* and hepatitis B virus vaccination, whereas other papers have shown no effect [6–8].

Whether there is immuno-virological impairment associated with SARS-CoV-2 messenger RNA (mRNA) vaccination remains to be established.

Methods

Study population

The criteria to be included in the present analyses were the following: (i) enrolled in the Vax ICONA ORCHESTRA cohort, (ii) have received at least one vaccine dose (VD) of SARS-CoV-2 mRNA vaccine, and (iii) have been tested for immuno-virological markers (VL, CD4 count, and CD8 count approximately ±1 month before and after any VD).

Details of the design of the Vax ICONA ORCHESTRA cohort are described in the supplementary appendix. The study has been approved centrally by the ethics committee of INMI Lazzaro Spallanzani for Italian centers and by the ethics committees of all participating centers outside Italy. The study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all subjects involved.

Endpoints

We evaluated the changes in CD4 count, CD8 count (natural scale), and HIV VL ($\log_{10}$ scale) over 1 month around each VD. We also reported the percentage of marker pairs in whom VL went from ≤50 copies/ml before the VD to VL >50 copies/ml after the VD and *vice versa*.

Statistical analysis

The main characteristics of the study population were described overall and according to the time elapsed from antiretroviral therapy (ART) initiation to the VD.

Dot plots were used to show the distribution of markers before VD (T0) and after VD (T1) and their change. A paired *t*-test was used to test the mean difference against the null hypothesis of no change 1 month after each VD. The McNemar test was used to evaluate the change in the proportion of VL suppression before and after VD. To account for the extra correlation of marker pairs coming from the same participant, we also conducted a generalized estimating equation linear regression model.

Several sensitivity descriptive analyses were done after restricting to the following subsets of markers pairs: (i) those with pre-VD value >6 months after starting ART, (ii) with pre-VD VL ≤50 copies/ml, (iii) with pre-VD CD4 count ≤200 cells/mm^3, (iv) no evidence of COVID-19, and (v) after restricting to pairs measured around the first VD.

Results

A total of 510 PWH included the following: 19% females, median age 55 years (interquartile range 46-60), and 81% Caucasian. Overall, 97% of participants were on ART, the CD4 count nadir was 83 (30-185) cells/mm^3, the CD4 count before the first VD was 489 cells/mm^3 (287-719 cells/mm^3, higher in those who started ART ≥6 months before vaccination [510 (323-741) cells/mm^3] vs <6 months (L6m) (397 [198, 678]; P <0.001), the median CD8 count was 790 (594-1104) cells/mm^3, with no evidence for a difference between the two groups (P = 0.139); as expected, HIV RNA ≤50 copies/ml was more frequently found in those who started ART ≥ 6 months than in those who started ART <6 months (93% vs 80%, P <0.001, Table S1).

A comparison between the characteristics of the study population and those of PWH in the whole cohort who were excluded from the analyses is reported in Table S2.

The included individuals contributed 723 marker pairs measured ±1 month of a VD. The median time between the pre- and post-VD values was 28 (3-53) days. Overall, 461 (63%) pairs were around the first dose, 230 (32%) around the second dose, and only 33 (4.5%) around the third dose (Table S3).

Changes of CD4 and CD8 and HIV RNA

Figure 1 shows the median, interquartile range, and the whole CD4 and CD8 count distribution before and after vaccination and their changes. The CD4 count significantly increased by a mean of +15.5 cells/mm^3 (SD ± 129.7, paired *t*-test P = 0.001) and CD8 by +12.0 (±250.5, P = 0.199) (Table 1). In contrast, the VL decreased by −0.11 $\log_{10}$ (±0.88, P = 0.001). The results were similar after restricting the analysis to pairs measured around the first VD (Table S4). The significance of these results was confirmed in the generalized estimating equation analysis (Table S5).

Similar results were observed after controlling for potential sources of confounding by stratification, as described in the Methods (Table 1).

Finally, among PWH with VL ≤50 copies/ml before VD, only 2.2% (14 of 639) had VL >50 copies/ml after VD and in 36% of those with VL >50 copies/ml VD achieved a VL ≤50 copies/ml (McNemar test P = 0.10). Among those with an elevation of VL to a value >50 copies/ml after VD, in 10 of 14 (71%), the subsequent VL was back to <50 copies/ml, without a change in ART.

Table 1
Overall mean (SD) changes from pre- to post-VD and paired *t*-test results and in specific subsets.

Analysis of marker changes - crude analysis				
HIV-marker	N	Mean	SD	*P*-value[a]
Overall results				
HIV-RNA	710	−0.11	0.88	0.001
CD4 count	723	15.47	126.1	0.001
CD8 count	720	12.00	250.5	0.199
Pre-VD VL less than 50				
HIV-RNA	639	−0.01	0.76	
CD4 count	641	14.39	127.8	
CD8 count	638	8.28	238.7	
Pre-VD CD4 count less than 200				
HIV-RNA	99	−0.37	1.05	
CD4 count	102	26.36	65.35	
CD8 count	102	42.74	224.2	
ART initiation >6 months				
HIV-RNA	529	−0.06	0.81	
CD4 count	539	13.48	127.5	
CD8 count	536	2.55	218.8	
No previous SARS-CoV-2 infection				
HIV-RNA	672	−0.11	0.90	
CD4 count	684	12.67	125.4	
CD8 count	681	9.81	253.4	

ART, antiretroviral therapy; CD, cluster of differentiation; VD, vaccine dose; VL, viral load.
[a] Paired *t*-test.

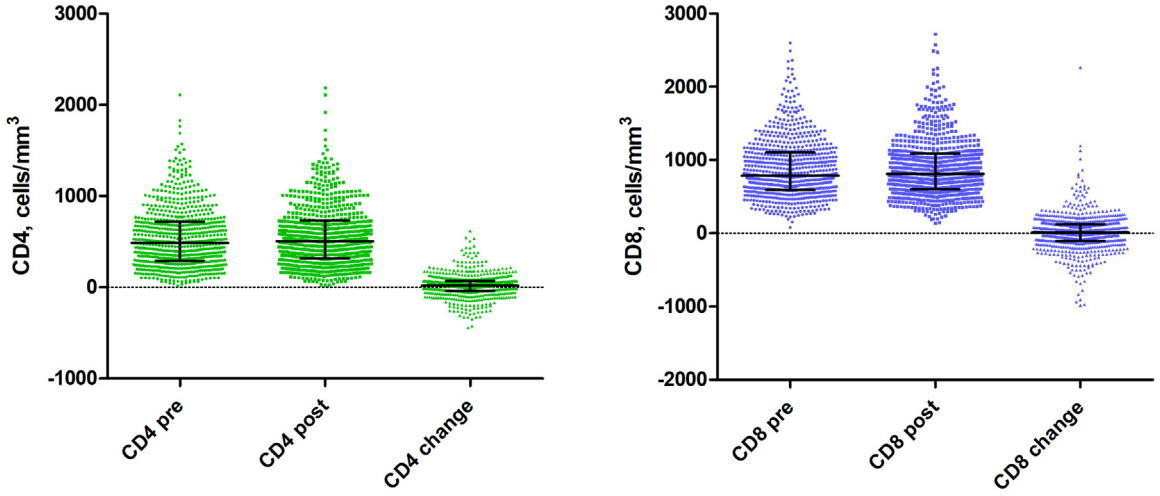

Figure 1. Median changes before and after viral load of CD4 count (a) and CD8 (b) count.
CD, cluster of differentiation.

Discussion

To the best of our knowledge, ours is the first analysis evaluating the immune-virological changes after any mRNA SARS-CoV-2 VD in a large cohort of PWH during a broad vaccination campaign. We found no evidence for a clinically significant impact of SARS-CoV-2 mRNA vaccination on CD4 and CD8 counts or HIV RNA over a mean window of 28 days around VDs. Indeed, although a statistically significant increase in CD4 count and drop in HIV RNA were observed, the magnitude of the changes was of negligible clinical significance. The results were similar to several sensitivity analyses controlling for close initiation of ART, evidence of natural infection, and immuno-virological status before vaccination.

Importantly, our findings do not confirm previous studies showing a potential detrimental effect of SARS-CoV-2 vaccination on CD4 count. Regarding VL, conflicting results were previously reported. One study found a marginal increase in the rate of detectable viremia after 4 weeks after the second VD [9], and two others reported no changes in VL after two VDs [4,5]. Moreover, 1 month after each VD, the proportion of participants with detectable VL remained stable, with no participant experiencing virologic failure. In addition, in our analysis, only 2% of participants appeared to have a VL elevation after vaccination. In 71% of these, the VL returned to a value <50 copies/ml without a change in ART.

Our analysis has some limitations. First, we did not have a control group of unvaccinated PWH with marker changes measured within a month after the same time from ART initiation to compare with. Second, we did not investigate the potential effect of vaccination on the size of the viral reservoir, although a recent study carried little evidence for such an association [10]. Furthermore, the changes were evaluated over an average of 28 days, which may be too long to detect dose-elicited variations. Finally, the characteristics of the included sample differ from those of the whole cohort; therefore, we cannot rule out selection bias.

The strength of our study is the high number of paired pre- and post-vaccination markers and the confirmation of the same results in different settings, including the recent start of ART and different strata of CD4.

In conclusion, our analysis could not confirm the data of previous reports showing a detrimental effect of SARS-CoV-2 vaccination on HIV markers. In contrast, our results are consistent with the hypothesis that mRNA vaccines might be able to rapidly prime CD4 spike-specific cells independently of ART, also in immunosuppressed PWH, and CD8 because it has been previously demonstrated by a clinical case of HIV/SARS-CoV-2 co-infection, in which a reversal of CD8 T-cell exhaustion [11], commonly observed in PLWH [12], or enhanced CD8 T-cell effector function is observed. Moreover, the interplay between CD8 enhancement and transient decreases of HIV RNA found in this study might be similar to what is observed in elite controllers, namely, that HIV-specific CD8 T cells from elite controllers have an increased capacity to produce multiple antiviral cytokines after peptide stimulation (polyfunctionality) and could have increased expansion capacity and increased expression of the effector functions and thus an enhanced antiviral function [13].

Further studies are needed to confirm that there was no immuno-virological impairment associated with SARS-CoV-2 mRNA vaccination.

Declarations of Competing Interest

The authors have no competing interests to declare.

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Author contributions

Vergori A, Antinori A, D'Arminio A, Cozzi Lepri A, Tavelli A: conception and design of the study. Tavelli A, Mazzotta V, Mastrorosa I, Gagliardini R, Azzini AM, Latini A, Pellicanò G: acquisition of data. Cozzi Lepri A: data analysis. Cozzi Lepri A, Vergori A, Antinori A, Tavelli A, D'Arminio A interpretation of data. Vergori A: drafting the article. Vergori A, Antinori A, D'arminio A, Tacconelli E, Marchetti G, Gianella M, Taramasso L, Ceccherini-Silberstein F: revising it critically for important intellectual content. All authors: final approval of the version to be submitted.

Access to data

Data will be available upon reasonable request to the corresponding author.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2024.107065.

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