Does the co-morbidity burden contribute to suboptimal immunological responses to COVID-19 vaccination in people living with HIV?

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Dear Editor,

We were very interested to read the paper by Lapointe *et al*. [1] regarding the ability of people with HIV (PWH) to mount an efficient antibody response to COVID-19 vaccine. The authors did not find any significant difference in humoral responses to primary vaccination between adult PWH with well-controlled viral loads and preserved CD4+ T cell counts and HIV-negative controls, a finding in line with data from other recent studies [2-4]. However, the multivariate analyses provided by Lapointe *et al*. show that advanced age and the presence of chronic co-morbidities are associated with a poorer humoral response one and three months after a second vaccine dose, an observation that seems to be supported by our analysis of PWH enrolled during the first days of a COVID-19 vaccination campaign that prioritized frail target population groups at our HIV clinical center in Milan, Italy.

We analyzed the humoral responses of 53 PWH and 34 healthy healthcare workers (HCWs) to two doses of the BNT162b2 COVID-19 vaccine administered 21 days apart; none of the subjects had a history of COVID-19. The LIAISON® SARS-CoV-2 TrimericS IgG assay (DiaSorin, Saluggia, Italy) was used to detect the level of IgG antibodies against the viral S1 spike protein (anti-S IgG) elicited by COVID-19 vaccine in plasma samples collected on the day of the first dose, and after 21 days (the day of the second dose), 51 days, and four months ±14 days only for HCWs. A final sample was collected from the PWH and HCWs seven months ±14 days and 10 months ±14 days after the first dose. The samples were also screened for antibodies against the SARS-CoV-2 nucleocapsid protein (anti-N IgG), using Elecsys Anti-SARS-CoV-2 (Roche Diagnostics International AG, Rotkreuz, Switzerland), to detect possible asymptomatic infections. The cut-off values defining serological positivity were ≥1 COI for the anti-N IgG assay and ≥33.8 BAU/mL for the anti-S IgG assay. Multilevel linear regression was used to compare post-vaccination anti-S IgG levels in the two groups, with age, sex at birth, and time as co-variates in the final model.

The PWH were older (median age 55 years, inter-quartile range [IQR] 52-62 *vs* 41 years, IQR 32-53; *p<0.001*) and more frequently males (75.5% *vs* 23.5%; *p<0.001*). All but two of the PWH were Caucasian and 31 (59.6%) had a history of AIDS; the overall median nadir CD4+ cell count was 175 cells/mm^3 (IQR 58-279). All PWH were receiving antiretroviral treatment (ART), and the median time on ART was 20 years (IQR 9-24). At the time of the first vaccine dose, 98.1% of PWH were virologically suppressed (HIV-RNA <50 cp/mL), the median CD4+ cell count was 570 /mm^3 (IQR 445-839), with 17 (32%) having a count of <500/mm^3. Thirty-eight (72%) of the PWH had at least one co-morbidity: dyslipidemia (22, 41.5%), hypertension (19, 35.8%), cardiovascular disease (9, 17%), diabetes (6, 11.3%), cirrhosis (5, 9.4%), chronic obstructive pulmonary disease (4, 7.5%), and obesity (3, 5.7%); moreover, seven (13.2%) had a history of solid neoplasms and four (7.5%) a history of hematological neoplasms; one was undergoing immunosuppressive treatment at the time of the first vaccine dose.

Figure 1 shows the dynamics of post-vaccination anti-S IgG titers in the two groups. The multilevel linear regression model showed that being a PWH was associated with a lower mean anti-S IgG titre (-601 BAU/mL, standard error [SE] 127]; *p<0.0001*) and this was confirmed by the multivariable model (-463 BAU/mL, SE 169; *p=0.0075*).

In our study PWH showed a reduced antibody response to BNT162b2 COVID-19 vaccination in comparison with the healthy HCWs although most of the PWH had a CD4+ cell count of >500 cells/mm^3. This apparently conflicts with the findings of recent studies showing comparable vaccine efficacy in subjects with well-controlled HIV infection and CD4+ cell counts of >350-500/mm^3 and controls [1-4]. However, PWH are a very heterogeneous population whose immunological competence may not be restricted to current or previous CD4+ cell counts. One possible reason for their poorer humoral response may have been their burden of co-morbidities and cancer, the prevalence of which

1 was much higher than that reported by Lapointe *et al*. (respectively 70% *vs* 45% and 19.7% *vs* 4%)
2 even though the median age of the PWH in the two studies was comparable (55 *vs* 54 years). It has
3 recently been suggested that the comorbidity burden may contribute to hypo-responsiveness to
4 COVID-19 vaccination in older general populations [5] and, given the complexity and heterogeneity of
5 aging PWH, more specific population studies are warranted.

6

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Notes

Authors' contributions. MVC, DM and ALR designed the study; LO made the statistical analyses and DM, FB, FS and MP the laboratory analyses; MVC, AG, ALR, and PM enrolled the subjects; SA, GR and ALR supervised the project; AG drafted the letter. All of the authors critically reviewed and approved the final version.

Potential conflicts of interest. None of the authors have any conflict of interest related to the manuscript, and all of them have submitted an ICMJE Form for Disclosure of Potential Conflicts of Interest.

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Figure legend

Figure 1. Anti-S IgG antibody titres in PWH and healthy HCWs over time. There was no between-group difference in mean anti-S IgG titres 21 days after the first vaccine dose (444 BAU/mL, standard deviation [SD] 665 *vs* 478 BAU/mL, SD 353; p=0.785), but the PWH had a lower mean anti-S IgG titre (1551 BAU/mL, SD 1093 *vs* 2275 BAU/mL, SD 994; *p=0.002*) 51 days after the first dose. After seven months, the PWH had a mean anti-S IgG titre of 309 BAU/mL (SD 216), whereas the mean anti-S IgG titers of the HCW after four and 10 months were respectively 1218 BAU/mL (SD 649) and 361 BAU/mL (SD 368). Three PWH (5.5%) had an anti-S IgG titer of <33.8 BAU/mL after seven months. List of abbreviations: SD: standard deviation; HCW: healthcare workers; PWH: people living with HIV; anti-S: antibodies against the viral S1 spike protein.

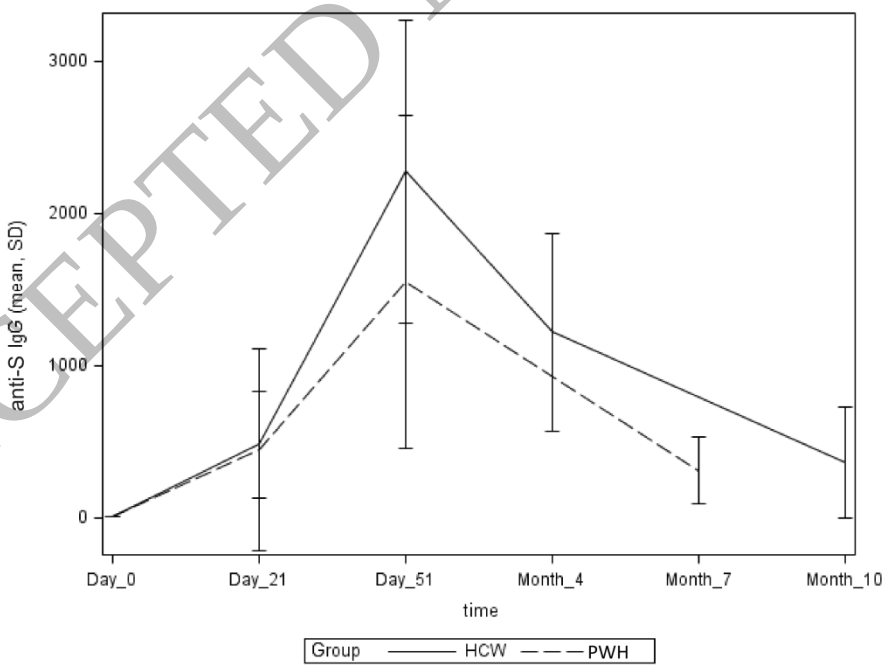

Figure 1
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