Research Letter

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Determinants of antibody response to severe acute respiratory syndrome coronavirus 2 mRNA vaccines in people with HIV

Frédérique Chammartin[a], Katharina Kusejko[b,c], Chloé Pasin[b,c], Alexandra Trkola[c], Matthias Briel[a], Patrizia Amico[d], Marcel P. Stoekle[e], Anna L. Eichenberger[f], Barbara Hasse[b], Dominique L. Braun[c], Macé M. Schuurmans[g], Thomas F. Müller[h], Michael Tamm[i], Nicolas J. Mueller[b], Andri Rauch[f], Michael T. Koller[j], Huldrych F. Günthard[b,c], Heiner C. Bucher[a], Benjamin Speich[a], Irene A. Abela[b,c] and the Swiss HIV Cohort Study

We identified determinants of SARS-CoV-2 mRNA vaccine antibody response in people with HIV (PWH). Antibody response was higher among PWH less than 60 years, with $CD4^+$ cell count superior to 350 cells/μl and vaccinated with mRNA-1273 by Moderna compared with BNT162b2 by Pfizer-BioNTech. Preinfection with SARS-CoV-2 boosted the antibody response and smokers had an overall lower antibody response. Elderly PWH and those with low $CD4^+$ cell count should be prioritized for booster vaccinations.

Following the approval of Pfizer-BioNTech (BNT162b2; Comirnaty) and Moderna (mRNA-1273; Spikewax) vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by Swiss health authorities, the Swiss HIV Cohort Study (SHCS) [1] and the Swiss Transplant Cohort Study (STCS) rapidly joined forces and built a trial platform embedded in the two cohorts [2,3] that monitors vaccine efficacy and investigates the antibody response in immuno-compromised patients. The continuous emergence of divergent variants requires increased antibody titers to establish vaccine efficacy [4–6]. Hence, nuanced assessment of antibody development to SARS-CoV-2 vaccines is critical for understanding the most important determinants of humoral immune response and for protecting patients at risk of not developing adequate vaccine response. In this post hoc analysis of our trial data [3], we investigated factors that influence the antibody response to both mRNA vaccines in people with HIV (PWH).

PWH participating in the SHCS were enrolled according to the trial protocol of the COrona VaccinE tRiAL pLatform (COVERALL) [2] approved by the local ethical committee (BASEC Nr 2021-000593, https://clinicaltrials.gov/ct2/show/NCT04805125). Written informed consent was obtained from all study participants. Additional patient characteristics were retrieved from the SHCS. We systematically tested the association of antibody titers to SARS-CoV-2 with routinely collected clinical, laboratory and life style factors. In particular, we looked at SARS-CoV-2 vaccine type (BNT162b2 versus mRNA-1273), sociodemographic characteristics, immunological and virological status, infection history and smoking behaviour. In addition, we took into account the presence of co-infection and the influence of antiretroviral therapy.

Antibody reactivity was measured with the immunoassay ABCORA 2 that assesses antibody response to SARS-CoV-2. Seroprofiling with ABCORA 2 also allows for a reliable prediction of neutralization activity against the SARS-CoV-2 Wuhan-Hu-1 strain based on anti-S1 reactivity (sum of S1 signal-over cut-off (SOC) values for IgG, IgA and IgM (sum S1)) [7].

We developed a generalized multivariable linear model on the sum S1 to assess the main factors of the antibody response after two doses of mRNA SARS-CoV-2 vaccines. sum S1 titers were log transformed to address skewness of the data. Model parameters are exponentiated and interpreted as ratio of expected geometric means. Analyses were done in R Project for Statistical Computing (version 4.0.3) software.

Between April 19 and June 9 2021, 352 PWH from the SHCS were enrolled in the COVERALL trial. For the current analysis, we included 333 PWH who received two doses of the vaccines and had an antibody response measured 8 ± 4 weeks after the second vaccination [median time: 56 days; interquartile range (IQR): 55–59). Median time between immunological and viral laboratory measurement and first vaccination was 43 days (IQR: 16–70). Median overall sum S1 was 104 (IQR 59–152).

Our results show that the predicted neutralization capacity (sum S1) is higher among PWH who are vaccinated with mRNA-123 compared with BNT162b2 [ratio of mean 1.39; 95% confidence interval (CI) 1.18–1.63], who are younger than 60 years old (ratio of means 1.33; 95% CI 1.11–1.60), and have $CD4^+$ cell counts above 350 cells/μl prior to the first vaccine dose (ratio of means 1.53; 95% CI 1.12–2.09) (Fig. 1). COVERALL excluded patients with PCR-confirmed previous SARS-CoV-2 infection in the last 3 months prior to randomization; however, 33 (9.9%) showed antibody reactivity for nucleoprotein at baseline mostly indicating asymptomatic seroconversion. As previously described [8], preinfection with SARS-CoV-2 significantly improved the antibody response (ratio of means 2.35; 95% CI 1.78–3.09).

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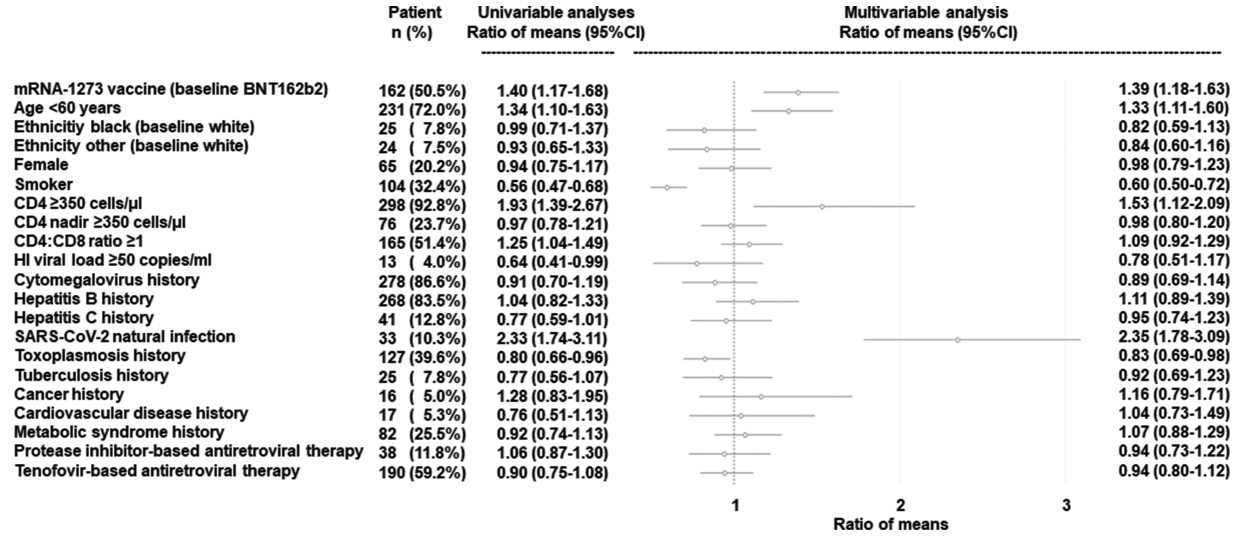

Fig. 1. Univariable and multivariable analyses of the sum S1. Black vertical dot line on the forest plot at 1 indicates equality of expected geometric mean titers for two given covariates categories, keeping all the other covariates fixed. Cytomegalovirus history: at least one positive cytomegalovirus IgG test; hepatitis B history: at least one positive HBsAG, anti-HBs or anti-HBc test/all patients with positive HBsAG were on active tenofovir and emtricitabine-based treatment; hepatitis C history: at least one positive anti-HCV test or hepatitis C RNA test/the only patient with active hepatitis C was on active treatment; SARS-CoV-2 preinfection: reactivity to SARS-CoV-2 nucleocapsid protein according to ABCORA test; toxoplasmosis history: at least one positive toxoplasmosis IgG test; tuberculosis history: at least one positive purified protein derivative skin test or interferon-based test or past diagnosis of active tuberculosis and treatment; cardiovascular disease: any record of coronary heart disease (angina, angioplasty, bypass graft or myocardial infarction) or stroke; metabolic syndrome: having any three of the conditions abdominal obesity (waist circumference >102 cm in male individuals, >88 cm in female individuals) / triglyderides at least 1.69mmol/l / low HDL cholesterol (<1.03 mmol/l in men, <1.29 mmol/l in women) / blood pressure superior to 130/at least 85 mmHg / diabetes; tenofovir-based antiretroviral therapy include tenofovir disoproxil fumarate and tenofovir alafenamide.

We did not find an effect of co-infections, such as cytomegalovirus seropositivity, active hepatitis B and C or latent or past active tuberculosis on vaccine response. Patients with IgG positivity for toxoplasmosis had an overall lower predicted neutralization capacity (ratio of means 0.83; 95% CI 0.69–0.98). Current smokers among PWH showed reduced antibody reactivity to the vaccine (ratio of means 0.60; 95% CI 0.50–0.72). Some antiretroviral therapy drug classes or agents, such as tenofovir-disoproxil fumarate have previously been described to be protective for SARS-CoV-2 infections [9,10]. However, we did not detect an influence on vaccine-specific antibody response.

Our analysis reveals that PWH with a well controlled HIV infection above 60 years of age and with $CD4^+$ cell counts below 350 cells/µl show blunted antibody response after vaccination. Our findings are in line with those of studies that have reported seroconversion after SARS-CoV-2 vaccines with well controlled HIV infection [11–17]. However, compared with the small numbers that limited these studies, the nested design of the randomized controlled COVERALL trial within the SHCS enabled the distinction of the different mRNA vaccines in a large cohort of PWH and allowed identifying risk factors of reduced antibody response within this well characterized population.

We report significantly higher response among recipients of the mRNA-1273 vaccine than among recipients of the BNT162b2 vaccine in PWH. These findings are consistent with reports from un-randomized studies in healthcare workers [18] and solid organ transplant recipients [19]. A recent publication showed an improved humoral response after mRNA vaccine compared with ChAdOx1 (Vaxzevria® from Astra Zeneca) [17] but did not report on differences between the mRNA vaccines.

Co-infections have been reported to influence the effect on vaccine-specific responses [20]. Our study suggests that patients with positive serology for toxoplasmosis show attenuated humoral immune response to mRNA vaccines. Further investigation is needed to understand this association with vaccine-specific responses and identifying potential immunological mechanisms induced through latent toxoplasma infection [21]. Of note, we did not find statistically significant effects of other co-infections on SARS-CoV-2 vaccine response, which is largely explained by the fact that those co-infections were successfully treated (hepatitis B, C and tuberculosis) or

well controlled (cytomegalovirus) in this population on highly successful antiretroviral therapy. Our study also adds to a growing body of evidence that show the negative impact of smoking on COVID-19 vaccine response [22].

A limitation of our study is that it focuses on humoral immune response only, which reflects only a fraction of the immune response elicited by SARS-CoV-2 vaccines.

With current emerging variants, we strongly encourage PWH, most importantly older patients and those with lower $CD4^+$ cell counts, to receive mRNA vaccine boosters to improve SARS-CoV-2 neutralizing antibody titers [23].

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Members of the Swiss HIV Cohort Study: Abela IA, Aebi-Popp K, Anagnostopoulos A, Battegay M, Bernasconi E, Braun DL, Bucher HC, Calmy A, Cavassini M, Ciuffi A, Dollenmaier G, Egger M, Elzi L, Fehr J, Fellay J, Furrer H, Fux CA, Günthard HF (President of the SHCS), Hachfeld A, Haerry D (deputy of 'Positive Council'), Hasse B, Hirsch HH, Hoffmann M, Hösli I, Huber M, Kahlert CR (Chairman of the Mother & Child Substudy), Kaiser L, Keiser O, Klimkait T, Kouyos RD, Kovari H, Kusejko K (Head of Data Centre), Martinetti G, Martinez de Tejada B, Marzolini C, Metzner KJ, Müller N, Nemeth J, Nicca D, Paioni P, Pantaleo G, Perreau M, Rauch A (Chairman of the Scientific Board), Schmid P, Speck R, Stöckle M (Chairman of the Clinical and Laboratory Committee), Tarr P, Trkola A, Wandeler G, Yerly S.

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Conflicts of interest

H.C.B. has received in the 36 months prior to the submission of this manuscript grants, support for travelling, consultancy fees and honorarium from Gilead, BMS, Viiv Healthcare, Roche and Pfizer that were not related to this project. He serves as the president of the Association contre le HIV et autres infections transmissibles. In this function, he has received support for the Swiss HIV Cohort Study from ViiV Healthcare, Gilead, BMS, and MSD. A.T. received a consultant fee from Roche and has received unrestricted research funding from Gilead and Roche not related to this study. D.L.B. received honoraria for advisory boards from the companies Gilead, MSD and ViiV outside of the study. H.F.G. outside of this study, reports grants from the Swiss National Science Foundation, National Institutes of Health (NIH), and the Swiss HIV Cohort Study, unrestricted research grants from Gilead Sciences, Roche, and Yvonne Jacob Foundation, personal fees from consulting or advisory boards or data safety monitoring boards for Merck, Gilead Sciences, ViiV Healthcare, Mepha, and Sandoz. H.F.G.'s institution received money for participation in the following clinical COVID-19 studies: 540-7773/5774 (Gilead), TICO (ACTIV-3, INSIGHT/NIH), and the Morningsky study (Roche). D.L.B. reports honoraria for advisory boards from the companies Gilead, Merck, ViiV. N.J.M. reports honoraria for advisory boards from MSD, Pfizer. D.L.B. reports honoraria for advisory boards from the companies Gilead, Merck, ViiV. N.J.M. reports honoraria for advisory boards from MSD, Pfizer. A.R. reports support to his institution for advisory boards and/or travel grants from MSD, Gilead Sciences, Pfizer and Abbvie, and an investigator initiated trial (IIT) grant from Gilead Sciences. All remuneration went to his home institution and not to A.R. personally, and all remuneration was provided outside the submitted work. M.S. reports honoraria for advisory boards from the companies Gilead, MSD, ViiV, Pfizer, Moderna and travel grants from

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[a]*Basel Institute for Clinical Epidemiology and Biostatistics, Department of Clinical Research, University Hospital Basel, University of Basel, Basel;* [b]*Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zürich;* [c]*Institute of Medical Virology, University of Zürich, Zürich;* [d]*Clinic for Transplantation Immunology and Nephrology;* [e]*Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, University of Basel;* [f]*Department of Infectious Diseases, Inselspital, Bern University Hospital, University of Bern, Bern;* [g]*Division of Pulmonology, University Hospital Zürich, Zürich;* [h]*Nephrology Clinic, University Hospital Zürich, Zürich;* [i]*Clinic of Respiratory Medicine and Pulmonary Cell Research; and* [j]*Swiss Transplant Cohort Study, University Hospital Basel, University of Basel, Basel, Switzerland.*

Correspondence to Frédérique Chammartin, PhD, Basel Institute for Clinical Epidemiology and Biostatistics, Department of Clinical Research, University Hospital Basel, University of Basel, Spitalstrasse 12, 4056 Basel, Switzerland.
E-mail: frederique.chammartin@usb.ch

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