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Safety and Antibody Response to Two-Dose SARS-CoV-2 messenger RNA Vaccination in Persons with HIV

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Running title: SARS-CoV-2 vaccine response in PWH

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Summary

This study of SARS-CoV-2 mRNA vaccination in 14 persons with HIV demonstrated uniformly high anti-SARS-CoV-2 receptor binding domain antibody titers after two doses, despite varied titers after a single dose. The majority of vaccine reactions were mild and no adverse events occurred.

Keywords: human immunodeficiency virus**,** COVID-19, SARS-CoV-2, mRNA vaccination, antibody

Early studies indicate that persons with HIV (PWH) may appear to be at increased risk of severe COVID-19 infection, potentially due to increased rates of multimorbidity.[1-3] While the original SARS-CoV-2 mRNA vaccine trials found near-universal robust immune responses in the general population,[4,5] certain immunocompromised populations appear to mount much lower antibody titers.[6-10] Antibody response to SARS-CoV-2 vaccination in PWH has not been reported, and furthermore, given lower antibody response in PWH to common viral vaccine targets such as hepatitis B, [11] it is important to evaluate SARS-CoV-2 vaccine immunogenicity in PWH. After a single dose of a SARS-CoV-2 mRNA vaccine, we demonstrated that PWH showed detectable, yet variable antibody responses, including low titers among persons with CD4 T cell counts <200 cells/mm^3.[12] We thus aimed to study boosted antibody response and safety of the two-dose SARS-CoV-2 mRNA vaccine in PWH.

PWH ≥18 years old were recruited to this prospective observational cohort from 12/7/2020 to 4/25/2021 via social media outreach to national HIV/AIDS organizations. As previously described,[12] self-reported demographics, SARS-CoV-2 infection history, most recent HIV viral load (detectable/undetectable), most recent CD4 count (<200, 200-350, 350-499, or ≥500 cells/mm^3), presence/absence of current antiretroviral therapy (ART), and duration of ART treatment (<6 months or ≥6 months) were collected using the Research Electronic Data Capture (REDCap) tool, a secure, web-based software platform designed to support data capture for research studies.[13]

Prior to dose 2 (titer 1, T1) and one month after D2 (titer 2, T2), participants underwent SARS-CoV-2 antibody testing on the semi-quantitative Roche Elecsys® anti-SARS-CoV-2 S enzyme immunoassay which measures total antibody (IgM, IgG) to the receptor binding domain (RBD), a critical target of neutralizing antibodies within the spike protein encoded by the mRNA vaccines.[14] Results ranged from <0.4 to >250 U/mL (upper reported assay limit) with a positive response defined by the manufacturer as ≥0.8 U/mL. One week after each dose, participants completed a reactogenicity questionnaire indicating local (pain, swelling, or erythema) and systemic symptoms experienced (fatigue, headache, myalgia, chills, fever, diarrhea, or vomiting) on an ordinal scale (similar to reporting in original vaccine trials [15,16]): none, mild (does not interfere with activity), moderate (some interference with activity), or severe (prevents daily activity). Major adverse events were also assessed (i.e.,

incident anaphylaxis, neurologic diagnoses, or infections including SARS-CoV-2). This study was approved by the Johns Hopkins Institutional Review Board (IRB00248540) and participants provided informed consented electronically.

We studied 14 PWH who reported receiving two doses (dose 1 [D1] and dose 2 [D2]) of a SARS-CoV-2 mRNA vaccine (Supplemental Table, http://links.lww.com/QAD/C238). The median (IQR) age was 62 (56, 70), 13 (93%) were male, 12 (86%) were white, and none had a pre-vaccination history of COVID-19. At vaccination, all were on ART for ≥6 months and 13 (93%) had an undetectable HIV viral load. Two (14%) had CD4 counts <200 cells/mm^3, whereas 1 (7%), 3 (21%), and 8 (57%) had CD4 counts of 200-349, 350-499, ≥500 cells/mm^3, respectively.

Five (36%) received the Pfizer/BioNTech BNT162b2 vaccine and 9 (64%) received the Moderna mRNA-1273 vaccine. T1 samples were collected on 10 (71%) participants, whereas all 14 (100%) had T2 samples. Median (IQR) time between D1 and T1 was 21 (16, 27) days, and 29 (28, 32) days between D2 and T2. Median (IQR) T1 was 76 (5, 149) U/mL and all participants had a T2 >250 U/mL apart from 239 U/mL in one participant with a CD4 count <200 cells/mm^3 (Figure).

The majority of local and systemic reactions were mild (Supplemental Figure, http://links.lww.com/QAD/C237). Local mild or moderate symptoms were reported by 12 (86%) after D1 and 13 (93%) after D2, most commonly pain (12, 86% after D1 and 13, 93% after D2). Systemic symptoms were reported by 10 (71%) after D1 and 9 (64%) after D2, most commonly fatigue (6, 43% after D1 and 8, 57% after D2). One (7%) participant reported severe headache after D2. All local and systemic reactions were more common after D2 apart from local injection site erythema (Supplemental Figure, http://links.lww.com/QAD/C237). No participant experienced anaphylaxis or developed a new infection or a neurologic condition.

In this study of antibody response to two-dose SARS-CoV-2 mRNA vaccination in PWH with excellent virologic control on ART, all participants developed high titers of anti-RBD antibodies. Reactions were generally mild, increased after D2, and comparable to those seen in both the original trials[15,16] and in other immunocompromised populations.[17,18] While titers after a single dose varied across a range of CD4 counts, all participants had titers near or above the upper reported assay limit after two doses. Although no specific titer has been precisely correlated with protection from COVID-19 after vaccination, plasma antibody titers from 15-133 U/mL using the Roche Elecsys anti-RBD assay have been correlated with neutralizing serum activity in vitro.[19, 20] Additionally, the post-D2 titers observed in this study are comparable to those seen in immunocompetent, HIV-uninfected populations (i.e. median titers >250 U/mL after D2).[21,22] These results contrast with antibody response after SARS-CoV-2 mRNA vaccination in other immunocompromised patients on lymphocyte-modulating agents (e.g., antimetabolites and rituximab), which have been shown to severely impair antibody production.[6-9]

PWH with CD4 counts <200 cells/mm^3 have shown diminished SARS-CoV-2 antibody production after acute infection,[23,24] as well as blunted immune responses to multiple vaccine types.[11,25-27] However, although two participants with CD4 counts <200 cells/mm^3 demonstrated low T1s (2 and 3 U/mL), both exhibited substantial boosting with a second dose (239 and >250 U/mL).

Limitations of this study include a small, non-randomized sample, relatively homogeneous in sex and race, and representing PWH with excellent virologic control on ART. These initial results show encouraging immunogenicity and safety of the two-dose mRNA vaccine series, suggesting that all PWH with viral suppression, regardless of CD4 count, may benefit from vaccination. Future study should include serial antibody sampling as well as integration of cellular immune responses to further characterize the durability and breadth of immune response to COVID-19 vaccination in PWH.

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References

1. Mirzaei H, McFarland W, Karamouzian M, Sharifi H. COVID-19 Among People Living with HIV: A Systematic Review. AIDS Behav. 2021;25(1):85-92. doi:10.1007/s10461-020-02983-2
2. Tesoriero JM, Swain CE, Pierce JL, et al. COVID-19 Outcomes Among Persons Living With or Without Diagnosed HIV Infection in New York State. JAMA Netw Open. 2021;4(2):e2037069. Published 2021 Feb 1. doi:10.1001/jamanetworkopen.2020.37069
3. Fung M, Babik JM. COVID-19 in Immunocompromised Hosts: What We Know So Far. Clin Infect Dis. 2021;72(2):340-350. doi:10.1093/cid/ciaa863
4. Widge AT, Rouphael NG, Jackson LA, et al. Durability of Responses after SARS-CoV-2 mRNA-1273 Vaccination. N Engl J Med. 2021;384(1):80-82. doi:10.1056/NEJMc2032195

5. Walsh EE, Frenck RW Jr, Falsey AR, et al. Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates. N Engl J Med. 2020;383(25):2439-2450. doi:10.1056/NEJMoa2027906
6. Ruddy JA, Connolly CM, Boyarsky BJ, et al. High Antibody Response to Two-Dose SARS-CoV-2 Messenger RNA Vaccination in Patients with Rheumatic and Musculoskeletal Diseases [in press]. Ann Rheum Dis. 2021; annrheumdis-2021-220656.
7. Boyarsky BJ, Werbel WA, Avery RK, et al. Antibody Response to 2-Dose SARS-CoV-2 mRNA Vaccine Series in Solid Organ Transplant Recipients [published online ahead of print, 2021 May 5]. JAMA. 2021;10.1001/jama.2021.7489. doi:10.1001/jama.2021.7489
8. Palich R, Veyri M, Marot S, et al. Weak immunogenicity after a single dose of SARS-CoV-2 mRNA vaccine in treated cancer patients [published online ahead of print, 2021 Apr 28]. Ann Oncol. 2021;S0923-7534(21)01184-4. doi:10.1016/j.annonc.2021.04.020
9. Deepak P, Kim W, Paley MA, et al. Glucocorticoids and B Cell Depleting Agents Substantially Impair Immunogenicity of mRNA Vaccines to SARS-CoV-2. Preprint. medRxiv. 2021;2021.04.05.21254656. Published 2021 Apr 9. doi:10.1101/2021.04.05.21254656
10. Kennedy NA, Goodhand JR, Bewshea C, et al. Anti-SARS-CoV-2 antibody responses are attenuated in patients with IBD treated with infliximab. Gut. 2021;70(5):865-875. doi:10.1136/gutjnl-2021-324388
11. Crum-Cianflone NF, Wallace MR. Vaccination in HIV-infected adults. AIDS Patient Care STDS. 2014;28(8):397-410. doi:10.1089/apc.2014.0121
12. Ruddy JA, Boyarsky BJ, Werbel WA, et al. Safety and Antibody Response to the First Dose of SARS-CoV-2 messenger RNA Vaccine in Persons with HIV [in press]. AIDS. 2021; AIDS-D-21-00298R1.
13. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019;95:103208. doi:10.1016/j.jbi.2019.103208
14. Higgins V, Fabros A, Kulasingam V. Quantitative Measurement of Anti-SARS-CoV-2 Antibodies: Analytical and Clinical Evaluation. J Clin Microbiol. 2021;59(4):e03149-20. Published 2021 Mar 19. doi:10.1128/JCM.03149-20
15. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020;383(27):2603-2615. doi:10.1056/NEJMoa2034577
16. Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2021;384(5):403-416. doi:10.1056/NEJMoa2035389
17. Connolly CM, Ruddy JA, Boyarsky BJ, et al. Safety of the first dose of mRNA SARS-CoV-2 vaccines in patients with rheumatic and musculoskeletal diseases

[published online ahead of print, 2021 Mar 19]. Ann Rheum Dis. 2021;annrheumdis-2021-220231. doi:10.1136/annrheumdis-2021-220231
18. Ou MT, Boyarsky BJ, Motter JD, et al. Safety and Reactogenicity of 2 Doses of SARS-CoV-2 Vaccination in Solid Organ Transplant Recipients [published online ahead of print, 2021 Apr 9]. Transplantation. 2021;10.1097/TP.0000000000003780. doi:10.1097/TP.0000000000003780
19. Resman Rus K, Korva M, Knap N, Avšič Županc T, Poljak M. Performance of the rapid high-throughput automated electrochemiluminescence immunoassay targeting total antibodies to the SARS-CoV-2 spike protein receptor binding domain in comparison to the neutralization assay. J Clin Virol. 2021;139:104820. doi:10.1016/j.jcv.2021.104820
20. Rubio-Acero R, Castelletti N, Fingerle V, et al. In Search of the SARS-CoV-2 Protection Correlate: Head-to-Head Comparison of Two Quantitative S1 Assays in Pre-characterized Oligo-/Asymptomatic Patients [published online ahead of print, 2021 Jun 16]. Infect Dis Ther. 2021;10.1007/s40121-021-00475-x. doi:10.1007/s40121-021-00475-x
21. Mueller T. Antibodies against severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) in individuals with and without COVID-19 vaccination: A method comparison of two different commercially available serological assays from the same manufacturer [published online ahead of print, 2021 Mar 17]. Clin Chim Acta. 2021;518:9-16. doi:10.1016/j.cca.2021.03.007
22. Cavalcanti E, Isgrò MA, Rea D, et al. Vaccination strategy and anti - SARS-CoV-2 S titers in healthcare workers of the INT - IRCCS "Fondazione Pascale" Cancer Center (Naples, Italy). Infect Agent Cancer. 2021;16(1):32. Published 2021 May 12. doi:10.1186/s13027-021-00375-2
23. Mondi A, Cimini E, Colavita F, et al. COVID-19 in people living with HIV: Clinical implications of dynamics of the immune response to SARS-CoV-2. J Med Virol. 2021;93(3):1796-1804. doi:10.1002/jmv.26556
24. Wang M, Luo L, Bu H, Xia H. One case of coronavirus disease 2019 (COVID-19) in a patient co-infected by HIV with a low CD4+ T-cell count. Int J Infect Dis. 2020;96:148-150. doi:10.1016/j.ijid.2020.04.060
25. Vardinon N, Handsher R, Burke M, Zacut V, Yust I. Poliovirus vaccination responses in HIV-infected patients: correlation with T4 cell counts. J Infect Dis. 1990;162(1):238-241. doi:10.1093/infdis/162.1.238
26. Kojic EM, Kang M, Cespedes MS, et al. Immunogenicity and safety of the quadrivalent human papillomavirus vaccine in HIV-1-infected women. Clin Infect Dis. 2014;59(1):127-135. doi:10.1093/cid/ciu238
27. Vaccination of Adults with HIV. Centers for Disease Control and Prevention. https://www.cdc.gov/vaccines/adults/rec-vac/health-conditions/hiv.html. Published May 2, 2016. Accessed May 3, 2021.

Figure. Anti-SARS-CoV-2 RBD antibody titers of PWH on antiretroviral therapy who underwent two-dose SARS-CoV-2 mRNA vaccination. T1 (titer 1, n=10) and T2 (titer 2, n=14) denote anti- SARS-CoV-2 RBD titers measured before and one month after the second dose of SARS-CoV-2 mRNA vaccination; lines indicate the change in an individual participant's titer. Assay results could range from <0.4 to >250 U/mL.