Impaired antibody response to COVID-19 vaccination in advanced HIV infection

Nolan Hassold[a], Ségolène Brichler[b], Elise Ouedraogo[a], Delphine Leclerc[a], Sophie Carroue[a], Yamina Gater[b], Chakib Alloui[b], Etienne Carbonnelle[b,c], Olivier Bouchaud[a], Frederic Mechai[a,c], Hugues Cordel[a] and Heloise Delagreverie[b,c]

Objectives: Coronavirus disease 2019 (COVID-19) vaccination is reportedly efficient in people with HIV (PWH) but vaccine trials included participants with normal $CD4^+$ T-cell counts. We analyzed seroconversion rates and antibody titers following two-dose vaccination in PWH with impaired $CD4^+$ T-cell counts.

Methods: We collected retrospective postvaccination SARS-COV-2 serology results available in a university hospital for PWH vaccinated between March and September, 2021 who were tested for antispike antibodies from 8 to 150 days following dose 2. Antibody titers were compared in PWH with $CD4^+$ T-cell count less than 200 cells/μl, $200 < CD4^+$ T-cell counts < 500 cells/μl and $CD4^+$ T-cell count greater than 500 cells/μl at vaccination.

Results: One hundred and five PWH were included: $n = 54$ in the $CD4^+$ T-cell count less than 500 cells/μl group ($n = 18$ with $CD4^+ < 200$ cells/μl, $n = 36$ with $200 < CD4^+ < 500$ cells/μl) and 51 in the $CD4^+$ T-cell count greater than 500 cells/μl group. They received two doses of BNT162b2 (75%), mRNA-1273 (8.5%), or ChAdOx1 nCoV-19 (16.5%). The median time from vaccine dose 2 to serology was consistent across all groups (73 days, interquartile range [29–97], $P = 0.14$). Seroconversion rates were 100% in the $CD4^+$ T-cell count greater than 500 cells/μl group but 89% in participants with $CD4^+$ T-cell counts less than 500 cells/μl (22 and 5.5% seronegative in the $CD4^+$ T-cell counts <200 cells/μl and $200 < CD4^+ < 500$ cells/μl groups, respectively). Median antibody titers were 623.8 BAU/ml [262.2–2288] in the $CD4^+$ greater than 500 cells/μl group versus 334.3 BAU/ml [69.9–933.9] in the $CD4^+$ less than 500 cells/μl group ($P = 0.003$). They were lowest in the $CD4^+$ less than 200 cells/μl group: 247.9 BAU/ml [5.88–434.9] ($P = 0.0017$) with only 44% achieving antibody titers above the putative protection threshold of 260 BAU/ml.

Conclusion: PWH with $CD4^+$ T-cell counts less than 500 cells/μl and notably less than 200 cells/μl had significantly lower seroconversion rates and antispike antibody titers compared with PWH with $CD4^+$ T-cell counts greater than 500 cells/μl, warranting the consideration of targeted vaccine strategies in this fragile population.

AIDS 2022, **36**:F1–F5

[a]Department of Infectious and Tropical Diseases, [b]Department of Clinical Microbiology, Hôpital Avicenne AP-HP, Bobigny, and [c]INSERM U1137 IAME, Université Sorbonne Paris Nord & Université de Paris, Paris, France.

Correspondence to Heloise Delagreverie, Microbiologie Clinique, Hôpital Avicenne, 125 rue de Stalingrad, 93000 Bobigny, France.

Tel: +33 148955123; e-mail: heloise.delagreverie@aphp.fr
Received: 7 November 2021; accepted: 4 January 2022.

DOI:10.1097/QAD.0000000000003166

Keywords: antibody, CD4$^+$ T cell, coronavirus disease 2019 vaccine, HIV-1, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2)

Introduction

In the coronavirus disease 2019 (COVID-19) pandemics, vaccination is key to worldwide healthcare strategies. Safety and efficacy trials of anti-Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2) vaccines did include a fraction of immunocompromised participants and secondary analyses focusing on people with HIV (PWH) reported unchanged performances in this population, with both adenoviral and mRNA vaccines [1–3]. Therefore, vaccination guidelines applying to PWH are generally those of the general population. However, these validation studies included a vast majority of PWH on antiretroviral therapy presenting with normal CD4$^+$ T-cell counts. Although HIV-related immunodeficiency and the risk for severe intercurrent infections are higher with the decrease in CD4$^+$ T-cell counts in advanced HIV disease, little data is yet available regarding the efficacy of SARS-COV-2 vaccination in PWH with CD4$^+$ T-cell counts less than 500 cells/μl.

Low rates of antibody seroconversion following vaccination are well documented in other immunosuppressed groups, such as organ recipients and chemotherapy and immunotherapy patients [4,5]. These data prompted population-specific guidelines to enhance protection, including early access to three-dose strategies and customized injection timelines. Furthermore, the value of antispike antibodies as a surrogate marker of vaccine-induced immunity and clinical protection against COVID-19 was emphasized by recent reports of clinically relevant antibody thresholds associated with disease protection [6,7].

We analyzed postvaccination antibody levels and seroconversion rates in PWH vaccinated with a standard two-dose strategy with CD4$^+$ T-cell counts less than 500 cells/μl and compared them to PWH with conserved CD4$^+$ T-cell counts.

Patients and methods

We collected retrospective postvaccination SARS-COV-2 serology results available for PWH followed in the Department of Infectious Diseases of Hôpital Avicenne (Assistance Publique-Hôpitaux de Paris, Bobigny, France) who completed a two-dose vaccination between 5 March 2021 and 17 September 2021 and were tested for antispike antibodies from 8 to 150 days following dose 2. PWH below 18 years of age, transplant recipients, receiving chemotherapy or immunosuppressive agents, without available CD4$^+$ T-cell count in the 6-month period around vaccination, with a history of SARS-COV-2 infection at any time or of a positive SARS-COV-2 serology prior to vaccination were excluded. All participants consented to participating to our institution's digitalized HIV medical records database and the study was registered by the local ethics committee (n°CLEA-2021-215). Anti-Spike antibodies were quantified in serum and plasma samples using the Architect SARS-COV-2 IgG Quant II kit (Abbott, North Chicago, Illinois, USA) with an i1000SR automated platform. BAU normalization factor × 0.142: assay positivity threshold 50 AU/ml = 7.1 BAU/ml; 260 BAU threshold = 1831 AU/ml. Statistical comparisons by Kruskall–Wallis, Mann–Whitney and chi-square tests were run using GraphPad6 software.

Results

Anti-SARS-COV-2 antibody titers from 105 fully vaccinated PWH meeting our inclusion criteria were included into three groups: CD4$^+$ T-cell count less than 200 cells/μl ($n = 18$), $200 < \text{CD4}^+ < 500$ cells/μl ($n = 36$) and CD4$^+$ T-cell counts greater than 500 cells/μl ($n = 51$) (Table 1). The median age of participants was 54 years (interquartile range IQR [46–60]) and 35.2% were women. They were inoculated with two doses of BNT162b2 (75%), mRNA-1273 (8.5%) or ChAdOx1 nCoV-19 (16.5%). COVID-19 risk factors among hypertension, diabetes, BMI greater than 30 kg/m^2 and/or chronic respiratory disease were present in 45.7% of participants. Ninety-one percent were on a prescription for antiretroviral therapy whenever vaccinated. The time from vaccine dose 2 to serology testing (overall 73 days [29–97]) was consistent across all groups: CD4$^+$ T-cell counts less than 200 cells/μl = 51.5 days [14.25–76], $200 < \text{CD4}^+ < 500$ cells/μl = 77.5 days [32.5–97] and CD4$^+$ T-cell counts greater than 500 cells/μl = 79 days [30–103] ($P = 0.14$).

In the CD4$^+$ T-cell counts greater than 500 cells/μl group, the median postvaccination antibody titer was 623.8 BAU/ml [262.2–2288]. In contrast, PWH with CD4$^+$ T-cell counts less than 500 cells/μl had a lower antibody response to vaccination with a global median antibody titer of 334.3 BAU/ml [69.9–933.9] ($P = 0.003$) (Fig. 1a). In a three-group comparison, antibody levels were lower than in the CD4$^+$ T-cell counts greater than 500 cells/μl reference group in the $200 < \text{CD4}^+ < 500$ cells/μl group (396.5 BAU/ml [105.8–1174], $P = 0.046$) and further reduced in the CD4$^+$ T-cell counts less than 200 cells/μl

Table 1. Participant characteristics.

	$CD4^+$ T-cell count less than 500 cells/μl		$CD4^+$ T-cell count greater than 500 cells/μl	
	<200	200–500		*P*
n	18	36	51	–
Male: *n* (%)	9 (50)	24 (66)	35 (68)	0.28
Age: year [IQR]	52.5 [39.3–57.5]	54.9 [46.9–59.6]	54.2 [47.1–61.4]	0.27
$CD4^+$ T-cells/μl: *n* [IQR]	106 [61–165]	365 [295–432]	712 [593–871]	–
Vaccine (*n*): BNT162b2/mRNA-1273/ChAdOx1-nCoV19	15/1/2	25/6/5	39/2/10	–
Comorbidities (hypertension, diabetes, respiratory disease, BMI >30 kg/m^2): *n* (%)	4 (22.2)	23 (63.8)	20 (39.2)	0.008
Nadir $CD4^+$ T cells/μl: *n* [IQR]	36.5 [21.8–67.3]	107 [41.3–202.5]	313 [222.3–440.3]	<0.0001
On a prescription of antiretroviral therapy when vaccinated: *n* (%)	12 (66.7)	34 (94.4)	50 (98.0)	0.0002
HIV-1 RNA viral load closest to vaccination <50 copies/ml: *n* (%)	8 (44.4)	30 (83.3)	49 (96)	<0.0001
Days since vaccine dose 2 to serology sampling: *n* [IQR] (min/max)	51.5 [14–76] (10/137)	77.5 [32–97] (8/135)	79 [30–103] (8/148)	0.14
Antispike antibodies: median BAU/ml [IQR]	247.9 [5.88–434.9]	396.5 [105.8–1174]	623.8 [262.2–2288]	0.004
Antispike antibodies <260 BAU/ml: *n* (%)	10 (55.6)	16 (44.4)	12 (23.5)	0.02

BAU, binding antibody units; IQR, interquartile range.

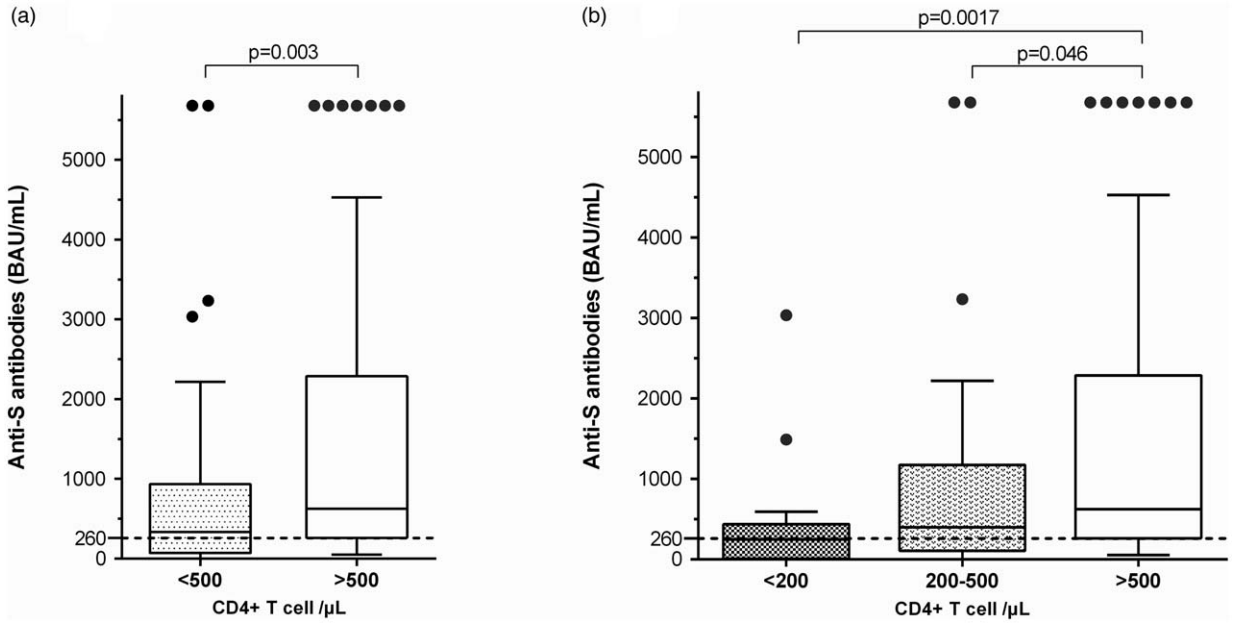

Fig. 1. Anti-SARS-COV-2 spike antibody titers following two-dose vaccination in people with HIV. Data is presented according to $CD4^+$ T-cell counts at the time of vaccination, in two groups with a threshold of 500 cells/μl (a) or three groups isolating participants with AIDS/$CD4^+$ T-cell count of less than 200 cells/μl (b). Antispike antibodies are quantified in normalized binding antibody units (BAU).Tukey bars with dots for outliers. Dotted line: putative protection threshold of 260 BAU/ml.

group (247.9 BAU/ml [5.88–434.9], $P = 0.0017$) (Fig. 1b). The putative protection threshold of 260 BAU/ml was achieved in 44.4% of samples in the $CD4^+$ T-cell counts less than 200 cells/μl group and 55.6% in the $200 < CD4^+ < 500$ cells/μl group, versus 76.5% in the $CD4^+$ T-cell counts greater than 500 cells/μl group ($P = 0.01$ and $P = 0.04$, respectively). All PWH vaccinated with $CD4^+$ T-cell counts above 500 cells/μl tested positive for anti-SARS-COV-2 antibodies after two vaccine doses. In contrast, six of 54 (11%, $P < 0.001$) participants were seronegative in the $CD4^+$ T-cell counts less than 500 cells/μl group: four of 18 (22%) in the $CD4^+$ T-cell counts less than 200 cells/μl subgroup with 20, 27, 50, and 169 $CD4^+$ T cells/μl and two of 36 (5.5%) in the $200 < CD4^+ < 500$ cells/μl subgroup with 290 and 366 $CD4^+$ T cells/μl; five of six received BNT162b2.

Discussion

The low $CD4^+$ T-cell counts and well known immunodeficiency associated with advanced HIV disease may raise concerns regarding the efficacy of COVID-19

vaccines. We report reduced seroconversion rates and low antispike antibody levels in vaccinated PWH with unrestored $CD4^+$ T-cell counts followed in Hôpital Avicenne, France.

The available data in this population is scarce, including one case report in a patient with 20 $CD4^+$ T-cells/μl who did not respond to two doses of mRNA vaccination [8] and a report of a positive association between antibody titers and $CD4^+$ T-cell counts, with lower antibody titers in 14 PWH with $CD4^+$ T-cell count less than 200 cells/μl than with $CD4^+$ T-cell count more than 200 cells/μl [9]. Our results are in line with these reports, and the growing concern regarding SARS-COV-2 vaccines seems legitimate in view of the impaired antibody response of PWH to a number of vaccines [10]. Of note, our real-world retrospective data in PWH with $CD4^+$ T-cell count greater than 500 cells/μl matches the 75% seroconversion greater than 260 BAU rate reported in the substudy of ChAdOx1 nCoV-19 (NCT04444674) in 32 PWH receiving antiretroviral therapy with a median $CD4^+$ cell count of 695 cells/μl [2].

Our data in over 50 PWH with impaired $CD4^+$ T-cell counts show a striking difference in vaccine-elicited antibody levels in this population compared with PWH with conserved $CD4^+$ T-cell counts from the same healthcare center. The group of PWH with AIDS/$CD4^+$ T-cell count less than 200 cells/μl had no detectable antibodies in 22% of cases and impaired levels when detectable, with median antibody titers below the threshold of 260 BAU/ml. This threshold is currently put forward as a clinical protection threshold and is of great significance in some healthcare policies, such as the authorization for use of casirivimab with imdevimab antibodies in France [11]. These results are significant for the care of PWH as patients with low $CD4^+$ T-cell counts are not rare, if not as many as to allow for large prospective studies in an acceptable time frame. For instance, in a recent US study, 28% of new HIV diagnoses revealed $CD4^+$ T-cell counts less than 200 cells/μl [12]. Our results in this population can translate to PWH not (yet) on antiretroviral therapy, immune nonresponders, or infections with multidrug resistant viruses.

Despite a retrospective design, we were able to analyze similar numbers of PWH as in available sub-studies of COVID-19 vaccine trials. We compared homogeneous groups of participants in terms of delay from vaccination to serology, reducing the bias of time-related antibody fading. Of note, prevaccination serology was not generally available because of the retrospective design and some samples with a history of asymptomatic COVID-19 may have been included, which would likely increase antibody levels. The design also forbade the exploration of the T-cell side of COVID-19 immunity in the absence of cryopreserved cell samples.

In conclusion, we observed low antibody responses to two doses of COVID-19 vaccines in PWH with $CD4^+$ T-cell counts less than 500 cells/μl. Antibody levels were the lowest in the $CD4^+$ T-cell counts less than 200 cells/μl group. These results should prompt immediate attention to this population, which is not openly enlisted as 'at-risk' in current healthcare policies and may benefit from targeted intensive strategies involving postvaccination serology and/or expedited access to additional vaccine doses. Further studies of immune responses to third doses and boosters will be critical to design the most efficient strategies for fragile PWH.

Acknowledgements

N.H., H.M.D., S.B., and H.C. contributed to the study's conception, N.H., E.O., F.M., and O.B. provided care and identified eligible participants, S.C., D.L., C.A., and Y.G. collected data, H.M.D., E.C., and H.C. analyzed the data, N.H., H.M.D., H.C., and S.B. wrote the manuscript and all authors read and approved the final version.

Funding: the authors are staff of Paris Hospitals (Assistance Publique-Hôpitaux de Paris) and received no additional funding for this work

Conflicts of interest

There are no conflicts of interest.

References

1. Frater J, Ewer KJ, Ogbe A, Pace M, Adele S, Adland E, *et al.*, Oxford COVID Vaccine Trial Group. **Safety and immunogenicity of the ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 in HIV infection: a single-arm substudy of a phase 2/3 clinical trial.** *Lancet HIV* 2021; **8**:e474–e485.
2. Madhi SA, Koen AL, Izu A, Fairlie L, Cutland CL, Baillie V, *et al.*, Wits VIDA COVID team. **Safety and immunogenicity of the ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 in people living with and without HIV in South Africa: an interim analysis of a randomised, double-blind, placebo-controlled, phase 1B/2A trial.** *Lancet HIV* 2021; **8**:e568–e580.
3. Levy I, Wieder-Finesod A, Litchevsky V, Biber A, Indenbaum V, Olmer L, *et al.* **Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in people living with HIV-1.** *Clin Microbiol Infect* 2021; **27**:1851–1855.
4. Benotmane I, Gautier-Vargas G, Cognard N, Olagne J, Heibel F, Braun-Parvez L, *et al.* **Low immunization rates among kidney transplant recipients who received 2 doses of the mRNA-1273 SARS-CoV-2 vaccine.** *Kidney Int* 2021; **99**:1498–1500.
5. Moor MB, Suter-Riniker F, Horn MP, Aeberli D, Amsler J, Möller B, *et al.* **Humoral and cellular responses to mRNA vaccines against SARS-CoV-2 in patients with a history of CD20 B-cell-depleting therapy (RituxiVac): an investigator-initiated, single-centre, open-label study.** *Lancet Rheumatol* 2021; **3**:e789–e797.
6. Feng S, Phillips DJ, White T, Sayal H, Aley PK, Bibi S, *et al.* **Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection.** *Nat Med* 2021; **27**:2032–2040.
7. Dimeglio C, Herin F, Martin-Blondel G, Miedougé M, Izopet J. **Antibody titers and protection against a SARS-CoV-2 infection.** *J Infect* 2021; Sep 21 doi:10.1016/j.jinf.2021.09.013.

8. Touizer E, Alrubayyi A, Rees-Spear C, Fisher-Pearson N, Griffith SA, Muir L, *et al*. **Failure to seroconvert after two doses of BNT162b2 SARS-CoV-2 vaccine in a patient with uncontrolled HIV.** *Lancet HIV* 2021; **8**:e317–e318.
9. Noe S, Ochana N, Wiese C, Schabaz F, Von Krosigk A, Heldwein S, *et al*. **Humoral response to SARS-CoV-2 vaccines in people living with HIV.** *Infection* 2021; Oct 25;1–7. doi: 10.1007/s15010-021-01721-7.
10. Kernéis S, Launay O, Turbelin C, Batteux F, Hanslik T, Boëlle P-Y. **Long-term immune responses to vaccination in HIV-infected patients: a systematic review and meta-analysis.** *Clin Infect Dis* 2014; **58**:1130–1139.
11. Haute Autorité de Santé, Ministère de la Santé Français. RONAPREVE (casirivimab-imdevimab) (prophylaxie postexposition de l'infection à SARS-CoV-2). Haute Autorité de Santé. 2021. Available at: https://www.has-sante.fr/jcms/p_3281625/fr/ronapreve-casirivimab-imdevimab-prophylaxie-postexposition-de-l-infection-a-sars-cov-2. [Accessed 13 October 2021]
12. Rolle C-P, Berhe M, Singh T, Ortiz R, Wurapa A, Ramgopal M, *et al*. **Dolutegravir/lamivudine as a first-line regimen in a test-and-treat setting for newly diagnosed people living with HIV.** *AIDS* 2021; **35**:1957–1965.