

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

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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 antispikes antibodies from 8 to 150 days following dose 2. Antibody titers were compared in PWH with CD4⁺ T-cell count less than 200 cells/ μ l, 200 < CD4⁺ T-cell counts < 500 cells/ μ l and CD4⁺ T-cell count greater than 500 cells/ μ l at vaccination.

Results: One hundred and five PWH were included: $n = 54$ in the CD4⁺ T-cell count less than 500 cells/ μ l group ($n = 18$ with CD4⁺ < 200 cells/ μ l, $n = 36$ with 200 < CD4⁺ < 500 cells/ μ l) and 51 in the CD4⁺ T-cell count greater than 500 cells/ μ l 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/ μ l group but 89% in participants with CD4⁺ T-cell counts less than 500 cells/ μ l (22 and 5.5% seronegative in the CD4⁺ T-cell counts < 200 cells/ μ l and 200 < CD4⁺ < 500 cells/ μ l groups, respectively). Median antibody titers were 623.8 BAU/ml [262.2–2288] in the CD4⁺ greater than 500 cells/ μ l group versus 334.3 BAU/ml [69.9–933.9] in the CD4⁺ less than 500 cells/ μ l group ($P = 0.003$). They were lowest in the CD4⁺ less than 200 cells/ μ l 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/ μ l and notably less than 200 cells/ μ l had significantly lower seroconversion rates and antispikes antibody titers compared with PWH with CD4⁺ T-cell counts greater than 500 cells/ μ l, warranting the consideration of targeted vaccine strategies in this fragile population.

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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/ μ l.

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 antispikes 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/ μ l 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 antispikes 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 $\times 0.142$: assay positivity threshold 50 AU/ml = 7.1 BAU/ml; 260 BAU threshold = 1831 AU/ml. Statistical comparisons by Kruskal–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/ μ l ($n = 18$), $200 < CD4^+ < 500$ cells/ μ l ($n = 36$) and CD4⁺ T-cell counts greater than 500 cells/ μ l ($n = 51$) (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/m² 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/ μ l = 51.5 days [14.25–76], $200 < CD4^+ < 500$ cells/ μ l = 77.5 days [32.5–97] and CD4⁺ T-cell counts greater than 500 cells/ μ l = 79 days [30–103] ($P = 0.14$).

In the CD4⁺ T-cell counts greater than 500 cells/ μ l 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/ μ l 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/ μ l reference group in the $200 < CD4^+ < 500$ cells/ μ l group (396.5 BAU/ml [105.8–1174], $P = 0.046$) and further reduced in the CD4⁺ T-cell counts less than 200 cells/ μ l

Table 1. Participant characteristics.

	CD4 ⁺ T-cell count less than 500 cells/ μ l		CD4 ⁺ T-cell count greater than 500 cells/ μ l	<i>P</i>
	<200	200–500		
<i>n</i>	18	36	51	–
Male: <i>n</i> (%)	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/ μ l: <i>n</i> [IQR]	106 [61–165]	365 [295–432]	712 [593–871]	–
Vaccine (<i>n</i>): BNT162b2/mRNA-1273/ChAdOx1-nCoV19	15/1/2	25/6/5	39/2/10	–
Comorbidities (hypertension, diabetes, respiratory disease, BMI >30 kg/m ²): <i>n</i> (%)	4 (22.2)	23 (63.8)	20 (39.2)	0.008
Nadir CD4 ⁺ T cells/ μ l: <i>n</i> [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: <i>n</i> (%)	12 (66.7)	34 (94.4)	50 (98.0)	0.0002
HIV-1 RNA viral load closest to vaccination <50 copies/ml: <i>n</i> (%)	8 (44.4)	30 (83.3)	49 (96)	<0.0001
Days since vaccine dose 2 to serology sampling: <i>n</i> [IQR] (min/max)	51.5 [14–76] (10/137)	77.5 [32–97] (8/135)	79 [30–103] (8/148)	0.14
Antispikes antibodies: median BAU/ml [IQR]	247.9 [5.88–434.9]	396.5 [105.8–1174]	623.8 [262.2–2288]	0.004
Antispikes antibodies <260 BAU/ml: <i>n</i> (%)	10 (55.6)	16 (44.4)	12 (23.5)	0.02

BAU, binding antibody units; IQR, interquartile range.

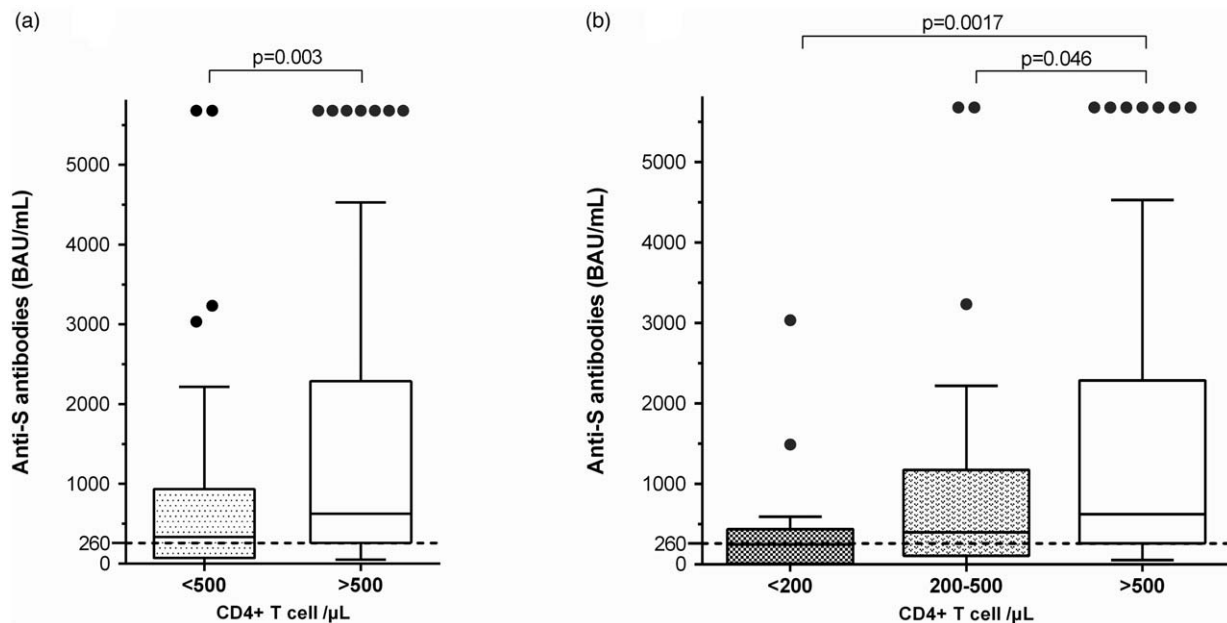


Fig. 1. Anti-SARS-CoV-2 spike antibody titers following two-dose vaccination in people with HIV. Data is presented according to CD4⁺ T-cell counts at the time of vaccination, in two groups with a threshold of 500 cells/ μ l (a) or three groups isolating participants with AIDS/CD4⁺ T-cell count of less than 200 cells/ μ l (b). Antispikes 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/ μ l group and 55.6% in the 200 < CD4⁺ < 500 cells/ μ l group, versus 76.5% in the CD4⁺ T-cell counts greater than 500 cells/ μ l group (*P* = 0.01 and *P* = 0.04, respectively). All PWH vaccinated with CD4⁺ T-cell counts above 500 cells/ μ l 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/ μ l group: four of 18 (22%) in the CD4⁺ T-cell counts less

than 200 cells/ μ l subgroup with 20, 27, 50, and 169 CD4⁺ T cells/ μ l and two of 36 (5.5%) in the 200 < CD4⁺ < 500 cells/ μ l subgroup with 290 and 366 CD4⁺ T cells/ μ l; 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/ μ l 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/ μ l than with CD4⁺ T-cell count more than 200 cells/ μ l [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/ μ l 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/ μ l [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/ μ l 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/ μ l [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/ μ l. Antibody levels were the lowest in the CD4⁺ T-cell counts less than 200 cells/ μ l 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.

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Conflicts of interest

There are no conflicts of interest.

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