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Covid-19 vaccine immunogenicity in people living with HIV-1

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ABSTRACT

Introduction: COVID-19 vaccine efficacy has been evaluated in large clinical trials and in real-world situation. Although they have proven to be very effective in the general population, little is known about their efficacy in immunocompromised patients. HIV-infected individuals' response to vaccine may vary according to the type of vaccine and their level of immunosuppression. We evaluated immunogenicity of an mRNA anti-SARS CoV-2 vaccine in HIV-positive individuals.

Methods: HIV-positive individuals (n = 121) were recruited from HIV clinics in Montreal and stratified according to their CD4 counts. A control group of 20 health care workers naïve to SARS CoV-2 was used. The participants' Anti-RBD IgG responses were measured by ELISA at baseline and 3–4 weeks after receiving the first dose of an mRNA vaccine).

Results: Eleven of 121 participants had anti-COVID-19 antibodies at baseline, and a further 4 had incomplete data for the analysis. Mean anti-RBD IgG responses were similar between the HIV negative control group (n = 20) and the combined HIV+ group (n = 106) (p = 0.72). However, these responses were significantly lower in the group with <250 CD4 cells/mm³. (p < 0.0001). Increasing age was independently associated with decreased immunogenicity.

Conclusion: HIV-positive individuals with CD4 counts over 250 cells/mm³ have an anti-RBD IgG response similar to the general population. However, HIV-positive individuals with the lowest CD4 counts (<250 cells/mm³) have a weaker response. These data would support the hypothesis that a booster dose might be needed in this subgroup of HIV-positive individuals, depending on their response to the second dose.

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Anti-COVID-19 vaccines have been developed at an extraordinary pace and have proven to be extremely effective in clinical trials [1–3] and in a real-world setting [4,5]. However, these studies provided little information on vaccine immunogenicity in immunocompromised individuals. Several studies have evaluated anti-COVID-19 vaccine responses in immunocompromised patients, mostly in transplant patients or patients with autoimmune disease, cancer, or on dialysis [6–14]. They showed a range of antibody responses from 14% in solid organ transplant

recipient to 57–96% in hemodialysis patients [14]. Few studies have addressed vaccine immunogenicity in HIV-infected individuals [15–19]. We seek to evaluate immunogenicity of an mRNA anti-SARS CoV-2 vaccine in HIV-positive individuals, and determine the impact of CD4 T cell counts on vaccine response.

1. Methods

1.1. Study population and design

121 HIV-positive individuals treated with antiretroviral therapy were recruited from HIV clinics in Montreal and stratified according to their CD4 counts (<250 cells/mm³, between 250 and 500 cells/mm³, and >500 cells/mm³). A control group of 20 health

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care workers naïve to COVID-19 was used. The participants' immunogenicity was measured at baseline and between 3 and 4 weeks after receiving the first dose of an mRNA vaccine (Moderna mRNA-1273 lot #3001652 in the HIV+ subgroups, Pfizer BNT162b2 in the HIV- control group, right deltoid intramuscular injection with 2.5 cm needle). The differential allotment of vaccine types between the two groups is a consequence of the limited availability of vaccine doses during the early phases of the vaccination program in the province of Quebec and is not an intentional part of the study design.

1.2. Antibody measurement

Plasmid: The plasmid expressing SARS-CoV-2 S RBD was previously reported [20].

Protein expression and purification: FreeStyle 293F cells (Invitrogen) were grown in FreeStyle 293F medium (Invitrogen) to a density of 1×10^6 cells/mL at 37 °C with 8 % CO₂ with regular agitation (150 rpm). Cells were transfected with a plasmid coding for SARS-CoV-2 S RBD (using ExpiFectamine 293 transfection reagent), as directed by the manufacturer (Invitrogen). One week later, cells were pelleted and discarded. Supernatants were filtered using a 0.22 µm filter (Thermo Fisher Scientific). Recombinant RBD was purified by nickel affinity column, as directed by the manufacturer (Invitrogen). The RBD preparations were dialyzed against phosphate-buffered saline (PBS) and stored in aliquots at –80 °C until further use. To assess purity, recombinant proteins were loaded on SDS-PAGE gels and stained with Coomassie Blue.

Plasma and antibodies: Plasma samples were heat-inactivated for 1 h at 56 °C and stored at –80 °C until ready to use in subsequent experiments. Plasma from uninfected donors collected before the pandemic were used as negative controls and used to calculate the seropositivity threshold in our ELISA assay. The monoclonal antibody CR3022 was used as a positive control in the ELISA assay and was previously described [14,20–24]. Horseradish peroxidase (HRP)-conjugated antibody specific for the Fc region of human IgG (Invitrogen) was used as secondary antibody to detect antibody binding in ELISA experiments.

ELISA: Anti-RBD IgG responses were measured by ELISA 4 weeks after the first dose. The SARS-CoV-2 RBD assay used was previously described [20,23]. Briefly, recombinant SARS-CoV-2 S RBD (2.5 µg/ml), or bovine serum albumin (BSA) (2.5 µg/ml) as a negative control, were prepared in PBS and were adsorbed to plates (MaxiSorp Nunc) overnight at 4 °C. Coated wells were subsequently blocked with blocking buffer (Tris-buffered saline [TBS] containing 0.1% Tween20 and 2% BSA) for 1 h at room temperature. Wells were then washed four times with washing buffer (Tris-buffered saline [TBS] containing 0.1% Tween20). CR3022 mAb (50 ng/ml) or human plasma (1/500) were prepared in a diluted solution of blocking buffer (0.1 % BSA) and incubated with the RBD-coated wells for 90 min at room temperature. Plates were washed four times with washing buffer followed by incubation with secondary Abs (diluted in a diluted solution of blocking buffer (0.4% BSA)) for 1 h at room temperature, followed by four washes. HRP enzyme activity was determined after the addition of a 1:1 mix of Western Lightning oxidizing and luminol reagents (Perkin Elmer Life

Sciences). Light emission was measured with a LB941 TriStar luminometer (Berthold Technologies). Signal obtained with BSA was subtracted for each plasma and was then normalized to the signal obtained with CR3022 mAb present in each plate. The seropositivity threshold was established using the following formula: mean of all pre-pandemic plasma + (3 standard deviation of the mean of all pre-pandemic plasma).

1.3. Statistical analysis

Anti-RBD IgG values were log transformed for the analysis. The HIV-negative control group [24] and HIV-infected combined group were compared with a two-tailed *t* test for anti-RBD titer, and a chi-square test for proportions of individuals reaching measurable anti-RBD antibodies. The association between age, sex and levels of CD4 was assessed using uni and multivariable linear regression models, with factors showing an association in the univariable models included into the multivariable model. Tukey-Kramer tests were used for between group comparisons. Immune compromise was described categorically (CD4 count <250, between 250 and 500, above 500, and HIV- control). Age was integrated as a continuous variable. Type 3 sums of squares were used to account for design imbalance (small number of participants in the CD4 < 250 group). No significant interaction was detected between the independent variables. Statistical analysis was conducted using R version 4.1.

2. Results

We present the immunogenicity results at week 3–4 after the participants' first vaccine dose. Participants' characteristics are described in Table 1. Eleven of 121 participants had anti-COVID-19 antibodies at baseline, suggesting prior exposure to COVID-19, and were excluded from the analysis. Four additional participants had incomplete CD4+ count information and were not included in the analysis. Almost all participants had no detectable viral load. In the low CD4 stratification group, of the two individuals with detectable viral loads, one had >18000 copies/ml and showed no immunogenic response, the other had 219 copies/ml and showed a moderate response. There were no statistically significant differences in immunogenicity between the HIV- control group (n = 20) and the combined HIV+ group (n = 106) either in magnitude (difference of means, two tailed *t* test, *p* = 0.72) or in the proportion of individuals mounting a measurable immune response (HIV-: 19/20 (95%) vs HIV+: 100/106 (94.3%), *p* = 0.91). Results from the multivariable linear regression, showing the associations between CD4 levels, age and anti-RBD antibody titers, are presented in Table 2. Both CD4 stratification and age were significantly associated with immunogenicity. Between group comparisons show that mean anti-RBD IgG responses were significantly lower in the CD4 < 250 group compared to all other groups, independent of age (*p* < 0.001) (Fig. 1). The mean anti-RBD antibody levels in log relative luminescence units normalized to CR3022 (log(RLU)) was 1.35 in participants with CD4 < 250, compared to 3.52 in the remainder of the study population. There were no significant dif-

Table 1

Participant characteristics. *: Detectable Viral Load is either > 20 or > 40 copies per mL depending on the assay. †: n = 21 missing data. ‡: n = 1 missing data. §: n = 3 missing data. ¶: n = 17 missing data.

Participant characteristics	HIV- Controls (n = 20)	HIV+ Combined (n = 106)	CD4 < 250 (n = 6)	250 < CD4 < 500 (n = 18)	CD4 > 500 (n = 82)
Age, mean [range]	47 [21, 59]	43 [21, 65]	48 [24, 61]	49 [34, 60]	41 [21, 65]
Sex – Male, n (%)	7 (35.0%)	90 (84.9%)	5 (86.3%)	15 (88.9%)	69 (84.1%)
Sex – Female, n (%)	13 (65.0%)	16 (15.1%)	1 (16.7%)	3 (11.1%)	13 (15.9%)
Detectable Viral Load*, n	n/a	4 [†]	2 [‡]	0 [§]	2 [¶]

Table 2

Uni- and multi-variable regression models. Immunogenicity (the dependent variable) was log transformed for the analysis. Sex was not found to be significantly associated in the univariate model and was not included in the multivariate model. No significant interaction was detected between the age and stratification variables (not shown).

Variable	Univariable models Beta coefficient [95% CI]	p-value	Multivariable models Beta coefficient [95% CI]	p-value
Age (per 10 year increase in age)	−0.317 [−0.489, −0.144]	<0.001	−0.289 [−0.456, −0.121]	<0.001
Sex (male vs female)	0.289 [−0.732, 0.154]	0.199		
CD4 stratification (each group compared to the entire study population)				
<250	−1.593 [−2.199, −0.987]	<0.0001	−1.547 [−2.129, −0.965]	<0.0001
250–500	0.439 [0.032, 0.846]	0.035	0.536 [0.141, 0.930]	0.008
>500	0.608 [0.313, 0.902]	<0.001	0.453 [0.156, 0.749]	0.003
HIV-	0.546 [0.152, 0.941]	0.007	0.558 [0.180, 0.937]	0.004

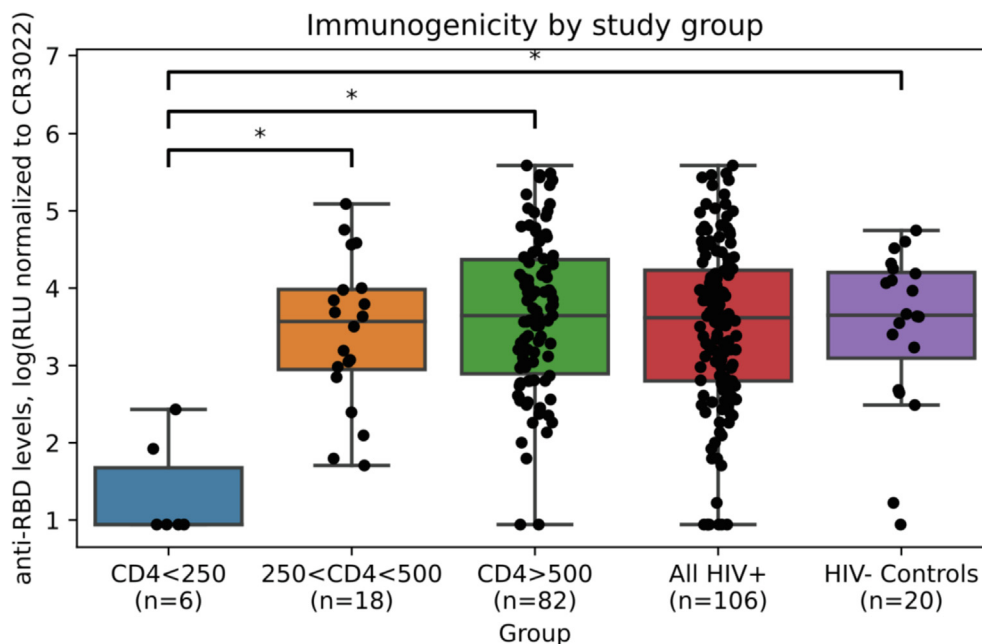


Fig. 1. Immunogenicity in each study group. Immunogenicity (anti-RBD IgG response) was measured by ELISA and reported in RLU (relative luminescence units) normalized to CR3022. RLU values log transformed for analysis. Statistically significant mean differences are denoted by * (Tukey-Kramer test, $p < 0.001$).

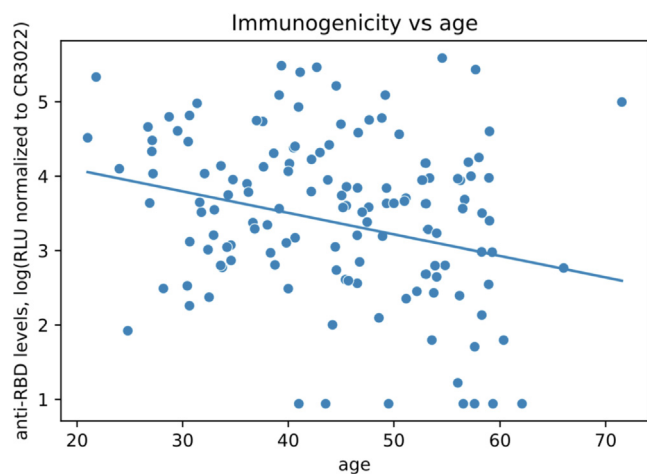


Fig. 2. As part of the regression model, immunogenicity was found to be statistically significantly correlated with age ($p < 0.001$). The magnitude of the association is weak, with an increase in 10 years corresponding to a decrease in 0.29 log(RLU). The range of RLU normalized to CR3022 in this population was 2.56 (detection limit) to 236.03 (0.94 to 5.46 in log(RLU)).

ferences in immunogenicity among other groups (CD4 > 250 or HIV negative.) Independently, age was also significantly, but weakly, associated with decreased immunogenicity. For every increase of 10 years in age, the model predicted a decrease of 0.29 log(RLU). The range of anti-RBD levels (RLU normalized to CR3022) in this population was 2.56 (detection limit) to 236.03 (0.94 to 5.46 in log(RLU)). Sex was not associated with immunogenicity. Although the regression model fit was significant ($p < 0.00001$), the adjusted R squared was only 0.24, meaning that CD4 counts and age combined only account for a relatively small proportion of the variance in immunogenicity in the study population (Fig. 2).

3. Discussion

COVID-19 mRNA vaccines have been shown to be extremely efficacious in protecting against symptomatic disease, hospitalizations and death [1,2]. They were designed during the first wave of the pandemic when the main circulating strains were the original strain from Wuhan (D614) and the first variant of importance D614G [25]. Although these vaccines remain efficacious against most variants such as the Delta variant, a higher level of antibodies is required to confer optimal protection [26,27]. Immunocompromised populations are known to have weaker immune responses

after vaccination. In the context of the emergence of variants which have a higher level of resistance to neutralization, it is important to ensure that this patient population mount an adequate response to vaccination. The level of vaccine immunogenicity may vary according to the type of immune deficiency. In recent studies evaluating immune responses to a COVID-19 vaccine in immunocompromised subjects, results varied according to the populations studied such as cancer patients [11], transplant recipients [6,8], hemodialysis patients [13,14], or people treated with immunosuppressors [10]. This is expected as the immunosuppressive therapies used to treat these conditions target different pathways of the immune system, resulting in various degrees of impairment. In HIV-infected individuals, cellular immunity is mostly affected, CD4+ T lymphocytes being the target of this virus. CD4+ T cells are pivotal in orchestrating both the humoral and cellular immune responses to vaccination, and have an important impact on antibody production. In the past, it has been shown that people living with HIV-1 have lower responses to some types of vaccine and that these responses are dependent on the level of CD4+ T cells. With the development of more potent and well tolerated antiretrovirals to treat HIV-infection, a majority of people on treatment achieve an immune recovery with normalization of CD4 counts. However, even in this population, subtle defect in immune function persists [28,29] and may impair vaccine response. Furthermore, a proportion of people living with HIV (PLWH) have very advanced disease with low CD4 counts and are at higher risk of not responding to vaccine. In our present study we show that if we look at the population of HIV-infected individuals as a whole, there is no significant difference in the level of anti-RBD IgG response as compared with a control group of HIV-negative individuals. However, when we stratify by CD4 counts, we see a statistically significant response between the groups, specifically between the group with CD4 below 250 cells/mm³ and the other groups. In pivotal clinical trials of COVID-19 vaccines, there was no statistically significant responses between different age groups. In our patient population, we do see an impact of age on immunogenicity after a single vaccine dose. Overall, our data show that some individuals in the lower CD4 cell stratum developed some responses to the vaccine, which supports the hypothesis that this response could be increased by adding booster shots or modifying the dosing. However, since there is no established correlation between a specific antibody titre and protection, our study is limited in the clinical conclusions it can draw. While other published reports found no association between age and immune response to the vaccine in this population [15], our data shows a statistically significant association after a single dose. These are preliminary data as these individuals will be followed over a one-year period where we will be able to assess the durability and quality of these responses.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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