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Humoral immune response in people living with HIV after administration of SARS-CoV-2 vaccine CoronaVac or BNT162b2 or CoronaVac/BNT162b2 booster sequence: A cross-sectional study

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ABSTRACT

Background: The evidence of SARS-CoV-2 vaccine effectiveness in people living with HIV (PLWH) is limited. This study evaluated the humoral immune response to CoronaVac™ (virus inactivated) and BNT162b2 (mRNA-based) vaccines in PLWH and HIV-negative controls, with and without a booster sequence.

Methods: We conducted a cross-sectional study on PLWH and HIV-negative controls who received CoronaVac or BNT162b2, with a subgroup receiving a CoronaVac/BNT162b2 booster. Blood samples were collected 4–6 months after primary vaccination and tested for anti-SARS-CoV-2 protein S (aSAb) and neutralizing antibodies (NtAb) using validated assays. Immune response was evaluated by age, sex, previous COVID-19 history, and CD4 + cell count.

Findings: One hundred and eighty nine participants were enrolled with 161 (85%) being PLWH. Among participants without previous known COVID-19, median aSAb levels were significantly lower in PLWH who received CoronaVac compared to BNT162b2 (32 U/mL vs. 587 U/mL, $p < 0.001$), with similar results in HIV-negative controls. NtAb presence was also significantly lower after CoronaVac compared to BNT162b2 (30% vs. 93%, $p < 0.001$). The booster sequence group showed a significant increase in aSAb titers in both PLWH and HIV-negative controls (from 33 U/ml to 2500 U/ml, $p < 0.001$), and NtAb positivity increased from 20% to 95 % in PLWH, and 27% to 100% in HIV-negative controls. Prior COVID-19 led to significantly higher post-vaccine antibody titers particularly in the BNT162b2 group. PLWH with CD4 + count < 200 cells/mL showed a weaker immune response to both vaccines.

Interpretation: CoronaVac resulted in a weaker immune response in both PLWH and HIV-negative controls compared to BNT162b2, particularly in immunosuppressed PLWH without prior COVID-19. Hybrid immunity and heterologous booster vaccination increased antibody levels.

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1. Introduction

Mass vaccination campaigns with the virus inactivated SARS-CoV-2 vaccine CoronaVac ™ (Sinovac Life Sciences Co, Ltda, Beijing, China) have occurred since early 2021 in large countries like Brazil, Turkey, Indonesia, Mexico and smaller like Chile and Dominican Republic, with approval for emergency use in more than 52 low-income and middle-income countries with over 2 billion doses delivered world-wide by early 2022 [1]. Numerous studies have been conducted to assess the immunogenicity of mRNA-based SARS-CoV-2 vaccines (i.e. BNT162b2; Pfizer with BioNTech and Fosun Pharma, New York, NY, USA) in people living with HIV (PLWH) [2,3]. However, the available information on the immunogenicity of inactivated vaccines, such as CoronaVac, in this population is limited [4].

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COVID-19 is more severe and has a higher lethality rate in individuals with certain high-risk factors, including older age, comorbidities like hypertension, obesity, diabetes, and asthma, [5,6] and immunosuppressive conditions like cancer, transplantation, or immunosuppressant medication and advanced HIV [7,8]. While there is controversy surrounding the risk and severity of COVID-19 in PLWH [9], evidence suggests that those receiving successful antiretroviral therapy with adequate levels of CD4 + lymphocytes and suppressed viral replication have a similar or minimally worse clinical course and risk of death due to SARS-CoV-2 as HIV-negative controls [10,11]. However, in PLWH who are untreated or have progressed to AIDS, the course of COVID-19 can be worse, particularly in the presence of non-HIV-related high-risk comorbidities [12–14].

Vaccination against COVID-19 is recommended for PLWH. PLWH with weaker immune systems may have a diminished response to the COVID-19 vaccine, but the relationship between CD4 + lymphocyte count and vaccine response is not well-defined [2,4]. There is currently no clear understanding of whether there is a gradual decrease in vaccine response as the CD4 + lymphocyte count decreases, and there is also no established threshold for CD4 + lymphocyte count below which a diminished vaccine response is evident in PLWH with weaker immune systems [2,4]. The humoral immune response may be influenced by the type of vaccine, with mRNA-based vaccines having the strongest potential [15,16]. Regardless of the vaccine used, there is a continuous decay in antibody levels over time, a phenomenon associated with decreased protection as also seen in the general population [17,18].

In Chile, primary COVID-19 immunization was implemented mostly with a virus-inactivated vaccine even for most PLWH [19], but boosters have been mainly heterologous, including adenovirus-based and mRNA-based vaccines. We aimed to evaluate the humoral immune response of CoronaVac compared to BNT162b2, and sequential boosting in an adult cohort of PLWH with and without previous history of COVID-19, and to compare the results with HIV-negative controls.

2. Methods

2.1. Participants

The study was conducted in an HIV care unit within a public general hospital in Santiago, Chile. PLWH older than 17 years who had received primary SARS-CoV-2 vaccination, with no intercurrent illness, and available CD4 + lymphocyte count data up to 6 months before enrolment were included in the study. HIV-negative controls were adult health care workers who had received primary SARS-CoV-2 vaccination and did not have HIV infection, based on a rapid test. Post vaccination SARS-CoV-2 infection that was known to the participants and confirmed with a PCR test was an exclusion criterion.

A written informed consent form was signed by all invited participants who agreed to take part. In addition, health care workers who volunteered as controls signed an extra written informed consent form for rapid HIV testing to ensure they were not infected. The local ethical committee (Comité Ético Científico, Servicio de Salud Metropolitano Central) approved the study design, and it has been registered under approval registry 50/05, 467/2021.

2.2. Procedures

PLWH were enrolled during their regular clinical visits without limitation of age, sex or clinical conditions. For all participants, age, sex, and history of SARS-CoV-2 infection were recorded through anamnesis and/or review of a national compulsory registry, to which the unit had authorized access. Additionally, the following information was collected for PLWH: CD4 + lymphocyte and HIV viral load counts (both up to 6 months prior to enrolment), and antiretroviral therapy. Primary vaccination was defined as a two-dose injection of either the virus-inactivated vaccine CoronaVac or the mRNA-platform-based vaccine BNT162b2 first and second dose separated at least by 28 days. The type and date of vaccine received were checked for accuracy in a national registry.

Blood samples were obtained from participants, deidentified, serum was separated, and kept frozen at −80 °C. The samples were processed at the UC-Christus Laboratory to quantify SARS-CoV-2 anti-Spike protein antibody (aSAb) with the Elecsys test, with a positive result defined as greater than 0.8 U/mL (Roche Diagnostic). Concomitantly for a large, randomly selected subgroup of participants, anti-SARS-CoV-2 neutralizing antibodies (NtAb) were measured from aliquots of the same blood samples at the Hantavirus and Zoonosis laboratory of the Institute of Science and Innovation in Medicine, Facultad de Medicina Clínica Alemana Universidad del Desarrollo, using a pseudotyped replicative-competent vesicular stomatitis virus expressing SARS-CoV-2 spike protein, and the green fluorescent protein (GFP) as a reporter gene sequence in its genome (VSV-GFP-Spike SARS-CoV-2 original Wuhan strain). The half-maximal inhibitory concentration (IC50) was calculated by nonlinear regression analysis and graphed as the reciprocal value (1/IC50) using Graphpad Prism software v9. Results were expressed as the reciprocal value of 50% of cell infection inhibition (1/IC50) [20].

Once the national vaccine reinforcement program was instituted, participants who had received the booster within the timeframe of the study were invited to provide a second blood sample for the same antibody testing.

2.3. Objectives

The main objective of this study was to assess the humoral immune response to primary SARS-CoV-2 CoronaVac vaccine to BNT162b2 in an adult cohort of PLWH according to their CD4 + lymphocytes values, and the history of previous COVID-19, and to compare the results with adults not infected with HIV. Secondary objectives were to assess the immune response in a subgroup of PLWH after receiving a heterologous booster vaccination.

2.4. Statistical analysis

The analyses were performed with Stata 14 software; $\alpha = 5\%$ was considered significant. Demographic and vaccination characteristics were compared between PLWH and HIV-negative controls by the Wilcoxon-Mann-Whitney and Fisher tests for quantitative and categorical variables, respectively. The aSAb and NtAb levels were compared between all PLWHs and HIV-negative controls according to the type of vaccine administered, history of COVID-19 and, in PLWHs, the levels of CD4 + lymphocyte count in cells/mL (<200 and ≥ 200). Spearman's correlation was calculated between the aSAb and NtAb levels in all participants with both measurements from same samples.

3. Results

Between Sept 1, 2021, and January 31, 2022 a total of 189 participants were enrolled, 161(85%) were people living with HIV (PLWH) and 28 (15%) were HIV-negative controls.

The PLWH were older, more frequently men and had a shorter interval between vaccination and evaluation than HIV-negative controls (Table 1). 156/161 (97%) PLWH were receiving antiretroviral treatment, and 147/156 (94%) were virologically suppressed. A higher number of HIV-negative controls compared to PLWH had received BNT162b2 for primary vaccination as per Ministry of Health prioritization. The proportion of PLWH and HIV-negative controls that had a history of COVID-19 before the vaccine administration was similar.

In total, 157/161 (98%) PLWH had aSAb titers considered positive (Table 2). In 116 CoronaVac-vaccinated PLWH without prior COVID-19, the median aSAb level was 32 U/mL compared with 586 U/mL in 17 PLWH who had received BNT162b2 ($p = 0.001$). In addition, NtAb were present in 30% and 93% of these participants, respectively ($p = 0.001$). Among 28 PLWH with previous history of COVID-19, aSAb levels and

Table 1
Demographic and general information of the participants.

Variable[a]	PLWH (n = 161)	HIV-negative (n = 28)	p[b]
Age, years	43 (34–50)	34 (30–43)	0.007
Male sex	147 (91%)	9 (32%)	<0.001
Pre vaccination COVID-19	28 (17%)	5 (18%)	0.57
CoronaVac primary vaccination	140 (87%)	21 (75%)	0.09
BNT162b2 primary vaccination	21 (13%)	7 (25%)	
CD4 + lymphocyte count (cells/mm^3)*	476 (280–750)	NA	NA
≥200 cells/mm^3	140	NA	NA
<200 cells/mm^3	21	NA	NA
Antiretroviral therapy	156 (97%)	NA	NA
Viral suppression	147/156 (94%)	NA	NA
Primary vaccination to sampling in days*	154 (138–160)	188 (187–191)	<0.001
Booster vaccination to sampling in days*	83 (72–100)	107 (84–119)	0.006

*Values expressed in median and IQR 25–75.
Abbreviations: PLWH people living with HIV.

NtAb positivity were higher than in PLWH who had not had COVID-19. HIV-negative controls showed similar results to PLWH, with higher aSAb levels and NtAb positivity in those who had received BNT162b2. All participants who had a history of COVID-19, had NtAb presence regardless of type of vaccine received. There were significantly lower aSAb levels and NtAb positivity in PLWH with CD4 + lymphocyte < 200 cells/mL, regardless of the vaccine, but more so in CoronaVac receptors (Table 3) and four of them had ASAb levels below the threshold of positivity.

In the subgroup of 34 PLWH and 16 HIV-negative controls who received a sequential booster with BNT162b2 there was a significant increase in aSAb levels (up to the upper limit of detection) and NtAb presence (except 1 case) with much higher 1/IC50 values (Table 4), regardless of whether they had prior known COVID-19. Seven cases and five controls without prior COVID-19 and who had received primary and booster BNT162b2 had a similar response pattern but with much higher antibody levels than those who received heterologous vaccination (data not shown).

There were 155 serum samples run in parallel by both techniques, aSAb and NtAb. The Spearman correlation coefficient between the paired values was 0.89 ($p < 0.0001$). Overall, 93% of NtAb-positive samples had aSAb levels > 150 U/mL and 96% of those without NtAb

Table 2
SARS-CoV-2 anti-S antibody levels and neutralising antibody presence after CoronaVac or BNT162b2 primary vaccination.

Variable		PLWH		HIV -negative		p[a]
Without prior COVID-19		(n = 133)		(n = 23)		
Vaccine: n (%)	CoronaVac	116	(87%)	16	(70%)	0.04
	BNT162b2	17	(13%)	7	(30%)	
aSAb by vaccine: median (IQR), U/mL	CoronaVac	32	(15–127)	32	(23–81)	0.9
	BNT162b2	587	(370–918)	826	(142–2500)	0.9
	p[b]	<0.001		0.005		
NtAb presence by vaccine: n (%)	CoronaVac	16	(30%)	3	(25%)	0.5
	BNT162b2	14	(93%)	5	(100%)	0.8
	p[c]	<0.001		0.009		
With prior COVID-19		(n = 28)		(n = 5)		
Vaccine: n (%)	CoronaVac	24	(86%)	5	(100%)	0.5
	BNT162b2	4	(14%)	0	(0.0%)	
aSAb by vaccine: median (IQR), U/mL*	CoronaVac	685	(173–1310)	500.6	(483–852)	0.6
	BNT162b2	2500	(2486–2500)	-	-	-
	p[b]	0.002		–		
NtAb by vaccine:n (%)	CoronaVac	19	(100%)	5	(100%)	–
	BNT162b2	2	(100%)	-	-	-

a: Comparison between PLWH and controls: quantitative variables: Wilcoxon-Mann-Whitney's test, categorical variables: Fisher's exact test.
b: Comparison of aSAb between vaccines: Wilcoxon-Mann-Whitney's test.
c: Comparison of NtAb positivity between vaccines: Fisher's exact test.
Abbreviations: PLWH, people living with HIV; CD4, CD4$^+$ lymphocyte; aSAb: anti-S protein antibodies (* 2500 is the upper limit of dilution); NtAb: neutralising antibody.
Decimals rounded to the tenth or nearest whole number, except in statistically significative p values.

Table 3
SARS-CoV-2 anti S antibody levels and neutralizing antibody presence after CoronaVac or BNT162b2 primary vaccination in people living with HIV by CD4 + lymphocyte category and SARS-CoV-2 prior infection.

Antibodies	CD4 (cells/mm^3)	n	CoronaVac		BNT162b2			p[a]
Without prior COVID								
aSAb: median (IQR) U/mL	<200	15	18	(5–36)	3	232	(215–370)	0.02
	≥200	101	37	(16–168)	14	655	(453–1035)	<0.001
NtAb: n (%)	<200	7	1	(14%)	3	3	(100%)	0.03
	≥200	46	15	(34%)	12	1	(92%)	<0.001
With prior COVID								
aSAb median (IQR)	<200	3	26	(25–392)	0	–	–	–
U/mL	≥200	21	699	(237–1449)	4	2500*	(2486–2500)	0.002
NtAb: n (%)	<200	3	3	(100%)	0	–	–	–
	≥200	16	16	(100%)	2	2	(100%)	–

a: Comparison between vaccines: quantitative variables: Wilcoxon-Mann-Whitney's test, categorical variables: Fisher's exact test.
Abbreviations: CD4: CD4 + lymphocyte; aSAb: anti S antibody titers (*aSAb 2500 is the upper limit of dilution); NtAb: neutralizing antibody..
Decimals rounded to the tenth or nearest whole number, except in statistically significant p values.

Table 4
Evolution of SARS-CoV-2 anti-S antibody levels and neutralising antibody presence for individuals who received CoronaVac for primary vaccination and BNT162b2 for booster vaccination.

Variable		n	PLWH		n	HIV-negative		p[a]
Without prior COVID								
aSAb (U/mL): median (IQR)	Pre	30	33	(15–447)	13	33	(20–82)	0.7
	Post	30	2500	(2500–2500*)	13	2500	(2500–2500)	0.6
	p[b]		<0.001			<0.001		
NtAb n+/n tested	Pre	3/15		(20%)	3/11		(27%)	0.5
	Post	18/19		(95%)	8/8		(100%)	0.8
	p[c]		<0.001			0.002		
NtAb titer in +: (1/IC50) median (IQR)	Pre	3	400	(**)	3	105	(-)	0.2
	Post	18	2871	(1524–6868)	8	5461	(1776–6670)	0.7
	p[d]		<0.001			0.008		
With prior COVID								
aSAb (U/mL): median (IQR)	Pre	4	1151	(466–1975)	3	483	(**)	–
	Post	4	2500	(2500–2500)	3	2500	(**)	-
	p[b]			0.250			0.250	
NtAb in +/n tested	Pre			(100%)	3/3		(100%)	–
	Post	3/3 4/4		(100%)	1/1		(100%)	-
	p[c]	–					–	–
NtAb titer in +: 1/IC50 median (IQR)	Pre	3	850	(**)	3	565	(**)	–
	Post	4	14,627	(6171–42894)	1	4405	(**)	-
	p[d]			0.250			1.000	

Pre and Post refer to booster dose.
a: Comparison between PLWH and controls: quantitative variables: Wilcoxon-Mann-Whitney's test, categorical variables: Fisher's exact test.
b: Comparison of aSAb between pre booster and post booster: Wilcoxon signed-rank test.
c: Comparison of NtAb positivity between pre booster and post booster: Fisher's exact test.
d: Comparison of aSAb between pre booster and post booster: Wilcoxon signed-rank test.
**IQR included only if more than 3 individual values available.
Abbreviations: PLWH: People living with HIV; CD4: CD4 + lymphocyte; aSAb: anti S antibody titers (*2500 is the upper limit of dilution); NtAb: neutralizing antibody..
Decimals rounded to the nearest whole number, except in statistically significant p values.

had aSAb levels < 150 U/mL.

4. Discussion

Our study found that the inactivated vaccine (CoronaVac) generated a weaker humoral immune response against SARS-CoV-2 compared to the mRNA-based vaccine (BNT162b2) among both PLWH and HIV-negative controls after primary immunization. These results were obtained after a longer period from vaccination than most previous studies have included [4,17,21].

In the CoronaVac group we observed low antibody concentrations in both PLWH and healthy controls, as measured by the Elisa commercial test and NtAb test. We observed a trend of decreasing immune response potency with decreasing CD4 + lymphocyte count, which was significant at < 200 cells/mL, similar to other studies [3,22]. Further studies with larger participant numbers, especially those with more severe immunosuppression, are needed for a better understanding of the situation. We didńt find significant difference in antibody response according to sex and age, but there were no participants from the much older age group where impaired antibody response has been found [23] and there were too few female PLWH participant for meaningful comparison, and we could not evaluate the impact of antiretroviral therapy as almost all PLWH were receiving it, with only a few not being virologically suppressed.

The humoral immune response to BNT162b2 was significantly higher in PLWH and healthy controls than CoronaVac, as evident from aSAb levels and NtAb positivity and titers, just as it had been demonstrated in other group of healthy health care workers by the authors [24]. This difference is consistent with the field effectiveness of COVID-19 prevention and attenuation observed in Chile when comparing both vaccines during national vaccination programs [25] and, later, the homologous CoronaVac and heterologous CoronaVac/ BNT162b2 booster sequence [26], similar to this evaluation in PLWH. Besides the lower humoral immune response, CoronaVac vaccination has demonstrated faster loss of antibody titers and lower preventive effects, more so with the newer Omicron variants [26–28]. Studies examining the immunogenicity of mRNA-based SARS-CoV-2 vaccines in PLWH have demonstrated that these vaccines are effective in inducing both humoral and cellular immune responses, even with low CD4 T-lymphocyte count [2,29].

Prior COVID-19 infection was found to strongly enhance the response to vaccination, as reported in other studies [30,31], resulting in higher levels of aSAb and NtAb with little difference between PLWH and healthy controls. However, individuals who received BNT162b2 exhibited a much superior response compared to those who received CoronaVac. In addition, we were able to follow-up some of the same participants who later received a BNT162b2 booster as part of the national vaccine reinforcement program. This heterologous immunization resulted in a strong response in both cases and controls, with high levels of aSAb and nearly 100% presence of NtAb measured 3–4 months after boosting. However, the response was quantitatively superior in individuals with prior COVID-19 and those who received BNT162b2 for primary vaccination. Strong BNT162b2 booster response in CoronaVac-primed individuals, with poor initial antibody levels, aligns with better clinical protection in heterologous versus homologous reinforcement also seen in a national program in Malaysia [32].

A commercially available aSAb test has a good correlation with NtA titers and eventually, if these results are confirmed, it could serve as a surrogate marker for a neutralizing antibody presence as it has shown to correlate with clinical response [33].

There are several limitations to this study, including differences in demographic characteristics and evaluation intervals between PLWH and healthy controls. Additionally, COVID-19 cases were identified through both national registry reports and self-reported symptoms, potentially missing asymptomatic cases.

In conclusion, BNT162b2 induced a stronger immune response than

CoronaVac in both PLWH and healthy controls, and severely immunocompromised PLWH who had received CoronaVac responded even more poorly. Hybrid immunization elicited a stronger response in all circumstances and heterologous booster vaccination with BNT162b2 in people who had received CoronaVac for primary vaccination overcame its weaker response.

Our study has implications in the context of the new Omicron variants which have higher immune evasion capacity for all vaccines, especially CoronaVac, even after heterologous booster [34]. CoronaVac has been widely used in resource-limited settings, but its lower immunogenicity, a feature that may lead to lower vaccine effectivity and increased susceptibility to new variants, pose challenges for vaccination reinforcement as it was shown in a large comparative study in Chile among the general population [26].

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.

Data availability

Data will be made available on request.

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