

# Antibody neutralization capacity after coronavirus disease 2019 vaccination in people with HIV in Canada

Cecilia T. Costiniuk<sup>a,b,c</sup>, Joel Singer<sup>d,e,f</sup>, Terry Lee<sup>e,f</sup>,  
 Yannick Galipeau<sup>g</sup>, Pauline S. McCluskie<sup>g</sup>, Corey Arnold<sup>g</sup>,  
 Marc-André Langlois<sup>g</sup>, Judy Needham<sup>e,f</sup>, Mohammad-Ali Jenabian<sup>h</sup>,  
 Ann N. Burchell<sup>i,j</sup>, Hasina Samji<sup>k,l</sup>, Catharine Chambers<sup>j,m</sup>,  
 Sharon Walmsley<sup>n</sup>, Mario Ostrowski<sup>o</sup>, Colin Kovacs<sup>p</sup>,  
 Darrell H.S. Tan<sup>m,n,q</sup>, Marianne Harris<sup>r</sup>, Mark Hull<sup>r</sup>,  
 Zabrina L. Brumme<sup>k,r</sup>, Hope R. Lapointe<sup>r</sup>, Mark A. Brockman<sup>k,r,s</sup>,  
 Shari Margolese<sup>e</sup>, Enrico Mandarino<sup>e</sup>, Suzanne Samarani<sup>a</sup>,  
 Branka Vulesevic<sup>e,t</sup>, Bertrand Lebouché<sup>a,b,u,v</sup>, Jonathan B. Angel<sup>g,t</sup>,  
 Jean-Pierre Routy<sup>a,b,w</sup>, Curtis L. Cooper<sup>t</sup>, Aslam H. Anis<sup>d,e,f</sup>,  
 for the COVAXHIV Study Group

**Objectives:** Many vaccines require higher/additional doses or adjuvants to provide adequate protection for people with HIV (PWH). Here, we compare coronavirus disease 2019 (COVID-19) vaccine-induced antibody neutralization capacity in PWH vs. HIV-negative individuals following two vaccine doses.

<sup>a</sup>Division of Infectious Diseases/Chronic Viral Illness Service, McGill University Health Centre, Royal Victoria Hospital, <sup>b</sup>Infectious Diseases and Immunity in Global Health Research Program, Research Institute of McGill University Health Centre, <sup>c</sup>Department of Experimental Medicine, McGill University, Montreal, Québec, <sup>d</sup>School of Population and Public Health, University of British Columbia, <sup>e</sup>CIHR Canadian HIV Trials Network (CTN), <sup>f</sup>Centre for Health Evaluation and Outcome Sciences, St. Paul's Hospital, Vancouver, British Columbia, <sup>g</sup>Department of Biochemistry, Microbiology and Immunology, University of Ottawa, Ottawa, Ontario, <sup>h</sup>Department of Biological Sciences, Université du Québec à Montréal, Montreal, Québec, <sup>i</sup>Department of Family and Community Medicine, St Michael's Hospital, Unity Health Toronto, <sup>j</sup>Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, <sup>k</sup>Faculty of Health Sciences, Simon Fraser University, Burnaby, <sup>l</sup>British Columbia Centre for Disease Control, Vancouver, British Columbia, <sup>m</sup>MAP Centre for Urban Health Solutions, St Michael's Hospital, <sup>n</sup>Division of Infectious Diseases, Department of Medicine, University of Toronto, <sup>o</sup>Clinical Sciences Division and Department of Immunology, University of Toronto, Li Ka Shing Knowledge Institute, St. Michael's Hospital, <sup>p</sup>Maple Leaf Medical Clinic, <sup>q</sup>Institute of Public Health Policy, Management and Evaluation, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, <sup>r</sup>British Columbia Centre for Excellence in HIV/AIDS, Vancouver, <sup>s</sup>Department of Molecular Biology and Biochemistry, Faculty of Science, Simon Fraser University, Burnaby, British Columbia, <sup>t</sup>Division of Infectious Diseases, Department of Medicine, University of Ottawa and the Ottawa Hospital Research Institute, Ottawa, Ontario, <sup>u</sup>Department of Family Medicine, Faculty of Medicine and Health Sciences, McGill University, <sup>v</sup>Canadian Institutes of Health Research Strategy for Patient-Oriented Research Mentorship Chair in Innovative Clinical Trials, and <sup>w</sup>Division of Hematology, Department of Medicine, McGill University Health Centre, Montreal, Québec, Canada.

Correspondence to Cecilia T. Costiniuk, MD FRCPC, Division of Infectious Diseases and Chronic Viral Illness Service, Research Institute of the McGill University Health Centre, 1001 Boulevard Decarie, Room EM2.3226, Montreal (QC) Canada H3A 3J1. Tel: +1 514 934 1934x76195; fax: +1 514 843 2209; e-mail: cecilia.costiniuk@mcgill.ca  
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**Design:** In Canadian prospective observational cohorts, including a multicentre study of PWH receiving at least two COVID-19 vaccinations (mRNA or ChAdOx1-S), and a parallel study of HIV-negative controls (Stop the Spread Ottawa Cohort), we measured vaccine-induced neutralization capacity 3 months post dose 2 ( $\pm 1$  month).

**Methods:** COVID-19 neutralization efficiency was measured by calculating the half maximal inhibitory dilution (ID50) using a high-throughput protein-based neutralization assay for Ancestral (Wuhan), Delta and Omicron (BA.1) spike variants. Univariable and multivariable quantile regression were used to compare COVID-19-specific antibody neutralization capacity by HIV status.

**Results:** Neutralization assays were performed on 256 PWH and 256 controls based on specimen availability at the timepoint of interest, having received two vaccines and known date of vaccination. There was a significant interaction between HIV status and previous COVID-19 infection status in median ID50. There were no differences in median ID50 for HIV+ vs. HIV-negative persons without past COVID-19 infection. For participants with past COVID-19 infection, median ID50 was significantly higher in controls than in PWH for ancestral SARS-CoV-2 and Omicron variants, with a trend for the Delta variant in the same direction.

**Conclusion:** Vaccine-induced SARS-CoV-2 neutralization capacity was similar between PWH vs. HIV-negative persons without past COVID-19 infection, demonstrating favourable humoral-mediated immunogenicity. Both HIV+ and HIV-negative persons demonstrated hybrid immunity.

**Trial registration:** [clinicaltrials.gov NCT04894448](https://clinicaltrials.gov/ct2/show/study/NCT04894448).

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## Introduction

People with HIV (PWH) are vulnerable to acquisition and severe COVID-19 outcomes because of combined risk factors [1,2] and sub-optimal immunogenicity to routine vaccines [3,4]. Studies in PWH early in the pandemic frequently excluded those with risk factors for sub-optimal response to vaccination, including advanced age or lower CD4<sup>+</sup> T-cell counts [5,6]. Knowledge gaps fuelled the establishment of a pan-Canadian prospective cohort of PWH receiving COVID-19 vaccines to: assess humoral immunogenicity in diverse PWH; compare immunogenicity responses in PWH vs. HIV-negative controls, and describe safety and tolerability of COVID-19 vaccines in PWH [7,8].

Antibody neutralization capacity is highly predictive of immune protection and vaccine efficacy [9,10]. We previously demonstrated that COVID-19 vaccine-specific immunity, defined as co-positivity for anti-IgG against SARS-CoV-2 Spike (S) and receptor binding domain (RBD) proteins, was achieved in over 90% of PWH and HIV-negative controls at 3 and 6 months post second and 1 month post third doses [8]. Proportions of participants achieving comparable anti-RBD levels were similar by HIV status at each timepoint. We previously

observed that anti-S IgG levels were lower in PWH than HIV-negative controls at 3 and 6 months post second vaccine dose [8]. As we had more specimens available at the 3 month rather than 6 month post second-vaccine dose timepoint, we chose to focus on the 3 month post second-dose timepoint for neutralization studies. We chose this timepoint as we had hypothesized that differences in neutralization capacity, if present between PWH vs. HIV-negative controls, may become more evident at this time point.

## Methods

The CTN 328 study is a multicentre prospective observational cohort study of PWH recruited from four sites of Canadian cities, as described [8]. Written informed consent was obtained from all participants (Supplementary Information, <http://links.lww.com/QAD/C948>).

## Participants

For PWH in the CTN 328 study, inclusion criteria included: age at least 16 years; having received, or planning

to receive, at least one dose of COVID-19 vaccine; HIV-seropositive. Exclusion criteria included: receipt of any blood product or immunoglobulin preparation within 1 month of vaccination; signs/symptoms of active COVID-19 at enrolment [8]. Subpopulations of PWH included at least 55 years, HIV immune nonresponders (CD4<sup>+</sup> T-cell count remains <350 cells/ $\mu$ l despite suppressed viral load on ART) and PWH with multimorbidity ( $\geq 2$  comorbidities). We aimed to enrol a diversity of PWH including those who were relatively stable or unstable as evidenced by CD4<sup>+</sup> T-cell count less than 350, CD4<sup>+</sup>/CD8<sup>+</sup> less than 0.75 and suppressed viral load [7,8]. For HIV-negative controls, a subset of immunocompetent Stop the Spread Ottawa (SSO) participants were selected and included if they had undergone parallel blood collection in relation to vaccination time [11]. Equal numbers of HIV+ and HIV- participants were randomly selected from individuals who had specimens available at the time point of interest on whose specimens neutralization assays were performed. Matching by participant characteristics was not performed.

### Study visits

Participants were to attend up to six visits over 12 months: prevaccination; 1 month following first dose; at 3, 6 and 12 months following the second dose; and 1 month after the third dose. For the presented analysis, we performed neutralization assays on samples collected at 3 months post second dose.

### Data collection

Methods related to medical and HIV history, COVID-19 questionnaire administration, sample collection and vaccine safety, in addition to levels of immunoglobulins G (IgG) were previously published [7,8]. Neutralization assays were performed using an automated protein-based surrogate neutralization (sn) ELISA measuring inhibition of ACE2-spike interactions by antibodies. As previously published [12,13], this ELISA-based test functions as a surrogate to live virus neutralization assays for evaluating antibodies that prevent spike and ACE2 receptor interaction. It can measure neutralization efficiency for Ancestral, Delta and Omicron (BA.1) variants. Levels of SARS-CoV-2 Spike trimer (S) protein, receptor-binding domain (RBD) of spike, and nucleocapsid (N) protein were measured using an automated high-throughput chemiluminescent ELISA [12,14]. Vaccine-induced immunity was defined as co-positivity for S and RBD protein and infection-induced immunity was defined as co-positivity of S and N protein (signal to cut-off ratio  $\geq 1.0$ ) [12,14]. This ELISA has been calibrated to the WHO reference standard. As data can be transformed to international units cross-laboratory and cross-assay correlations is facilitated. IgG antibody titers (binding antibody units (BAU)/ml) were generated by a conversion model (four-parameter log-logistic curve based on measurements from the WHO International Standard) (NIBSC 20.136). Assay description was previously published [11,12]. History of previous

COVID-19 infection was defined as having endorsed having a positive SARS-CoV-2 PCR test (based on participant or site report) or evidence of co-positivity of S and N protein.

### Outcomes

The main outcome of interest was the difference in median COVID-19 neutralization efficiency, as measured by half maximal inhibitory dilution (ID50) for Ancestral (Wuhan), Delta and Omicron (BA.1) spike variants, in PWH vs. HIV-negative controls stratified by prior COVID-19 infection status. An exploratory objective was to determine COVID-19 vaccine-induced neutralization efficiency in PWH 3 months post second dose, stratified by various sub-populations of PWH and based on history of prior COVID-19 infection.

### Statistical analyses

All analyses were performed using Statistical Analysis System (SAS) software version 9.4 (SAS Institute, Cary, North Carolina, USA). Quantile regression analysis was used to compare neutralization capacity for Ancestral, Delta and Omicron (BA.1) variant ID50 neutralization titers between PWH and control groups as the data did not conform with normality assumption even after log transformation. The analysis adjusted for vaccine-related variables (vaccine type, time between doses) and participant characteristics (age, sex, race and multimorbidity, defined as at least two comorbidities [yes/no]) [9]. An interaction term between participant groups (HIV+ vs. control) and past COVID infection (yes/no) was included in the regression model to allow for potentially different neutralization capacity response by these factors. Within PWH, we further performed univariate quantile regression analysis to determine whether there were factors associated with weaker neutralization capacity. After univariate analysis, age, sex, vaccine-related variables and variables with  $P < 0.1$  in univariate analysis were further included in a multivariable model to further explore associations with participant characteristics. Multivariate analysis was only performed within PWH-naive to natural COVID-19 infection, as there was not enough participants with past COVID-19 infection to perform a separate analysis.

### Results

A total of 375 PWH and 1002 SSO participants were enrolled. Individuals were excluded if they had received less than two vaccine doses, if the date of the second vaccine was unknown, or if samples were unavailable at the time point of interest (Supplemental Figure 1, <http://links.lww.com/QAD/C946>). We then randomly selected 256 samples out of 311 available for PWH, and 256 samples out of 381 available for controls, at the 3-month

post dose 2 (+/- 1 month) time point, to perform neutralization assays.

Baseline characteristics for 256 PWH and 256 HIV-negative controls included in the final analysis are presented in Table 1 and Supplement Table 1, <http://links.lww.com/QAD/C949>. Of 256 in each group, 45 (17.6%) PWH and 56 (21.9%) controls had a history of COVID-19 infection at some point prior to 3 months post dose 2 (+/- 1 month). Median ages were 54.2 (IQR 43.4–62.8) and 45.5 years (IQR 35–57) for PWH and controls, respectively. PWH were 72% men vs. 35% of controls, whereas 48% PWH were aged at least 55 years vs. 31% of controls. Median duration of HIV was 17 (IQR 10–25) years (Table 2). Median CD4<sup>+</sup> T-cell count was 631 (430.5–838.5) cells/ $\mu$ l and 22% had a nadir CD4<sup>+</sup> T-cell count below 100 cells/ $\mu$ l.

Fourteen percent of PWH had a detectable HIV viral load within the last 6 months. Nearly all were on ART (96.9%) and 70% were on integrase strand inhibitors. Frequent comorbidities included obesity (24 vs. 16% in PWH and controls, respectively), dyslipidaemia (17 vs. 11%) and hypertension (16 vs. 13%) (Supplement Table 2a, <http://links.lww.com/QAD/C949>).

In the current analysis, performed on March 2023, 88% of PWH and 86% of controls included in the analysis had

received at least two mRNA vaccines. BNT162b2 and mRNA-1273 were the most commonly administered vaccines. Time interval between vaccine doses is shown in Table 3.

### ID50 after coronavirus disease 2019 vaccination at 3 months post dose 2 (+/- 1 month)

PWH and controls with COVID-19 infection prior to vaccination and during follow-up, up until the time point of interest, were analyzed separately from participants naive to natural COVID-19 infection as the former would be expected to have a more robust response following vaccine administration than the latter [21,22]. In participants naive to natural COVID-19 infection, median ID50 at 3 months post dose 2 (+/- 1 month) did not differ between PWH vs. controls for Ancestral, Delta and Omicron variants using adjusted quantile regression (Table 4). In participants with past COVID-19 infection, median (IQR) ID50 was 89.3 (45.1, 185.7), 137.2 (81.3, 222.1) (adjusted difference (95% CI): -58.2 (-104.2, -12.1) ( $P=0.013$ ) for the Ancestral variant in PWH vs controls. Median (IQR) ID50 for the Delta variant was 61.0 (22.6, 133.0) in PWH vs controls (81.2 (47.7, 159.8) (adjusted difference (95% CI): -24.9 (-61.6, 11.9) ( $P=0.184$ ) and for the Omicron variant 11.5 (4.1, 37.1) vs 20.5 (10.1, 45.8) (adjusted difference (95% CI): -10.4 (-18.2, -2.6)) ( $P=0.009$ ). Comparison of ID50 between cohorts is depicted in Fig. 1.

**Table 1. Characteristics of participants.**

Variable	All participants			Participants without past COVID-19 infection			Participants with past COVID-19 infection		
	HIV+ (n=256)	HIV- (n=256)	P	HIV+ (n=211)	HIV- (n=200)	P	HIV+ (n=45)	HIV- (n=56)	P
COVID infection prior to 3 months post dose 2 ( $\pm$ 1 month) sample [n (%)]	45 (17.6)	56 (21.9)	-	0 (0%)	0 (0%)	-	45 (100.0)	56 (100.0)	-
Time since COVID infection, days prior to sample collection									0.244
Median (IQR)	-	-		-	-		263 (126, 338)	306 (168, 472)	
Range	-	-		-	-		(25-685)	(17-583)	
Missing	-	-		-	-		19	2	
Age			<0.001			<0.001			0.133
Median (IQR)	54.2 (43.4, 62.8)	45.5 (35.0, 57.0)		54.6 (44.0, 63.6)	45.0 (36.0, 56.0)		53.3 (42.8, 60.2)	49.0 (33.0, 58.5)	
Range	(19.7-83.5)	(22.0-79.0)		(19.7-83.5)	(22.0-79.0)		(25.9-73.9)	(23.0-75.0)	
Number missing	1	0	<0.001	1	0	<0.001	0	0	0.342
<35	30 (11.8)	59 (23.0)		24 (11.4)	42 (21.0)		6 (13.3)	17 (30.4)	
35-44	40 (15.7)	62 (24.2)		33 (15.7)	55 (27.5)		7 (15.6)	7 (12.5)	
45-54	64 (25.1)	56 (21.9)		50 (23.8)	44 (22.0)		14 (31.1)	12 (21.4)	
55-64	73 (28.6)	52 (20.3)		60 (28.6)	39 (19.5)		13 (28.9)	13 (23.2)	
65-74	38 (14.9)	24 (9.4)		33 (15.7)	18 (9.0)		5 (11.1)	6 (10.7)	
$\geq$ 75	10 (3.9)	3 (1.2)		10 (4.8)	2 (1.0)		0 (0.0)	1 (1.8)	
Sex			<0.001			<0.001			0.04
Male	183 (71.5)	89 (34.8)		153 (72.5)	64 (32.0)		30 (66.7)	25 (44.6)	
Female	72 (28.1)	167 (65.2)		57 (27.0)	136 (68.0)		15 (33.3)	31 (55.4)	
Prefer to self describe	1 (0.4)	0 (0)		1 (0.5)	0 (0.0)		0 (0.0)	0 (0.0)	
Self-declared race or ethnicity <sup>a</sup>			<0.001			<0.001			<0.001
White	138 (54.5)	228 (89.1)		123 (58.9)	179 (89.5)		15 (34.1)	49 (87.5)	
Black	59 (23.3)	0 (0)		41 (19.6)	0 (0.0)		18 (40.9)	0 (0.0)	
Other	56 (22.1)	28 (10.9)		45 (21.5)	21 (10.5)		11 (25.0)	7 (12.5)	
Unknown	3	0		2	0		1	0	
Subpopulation									
Age >55 years	121/255 (47.5)	79/256 (30.9)	<0.001	103/210 (49.0)	59/200 (29.5)	<0.001	18/45 (40.0)	20/56 (35.7)	0.659
Multimorbidity ( $\geq$ 2 comorbidities)	90/252 (35.7)	56/253 (22.1)	<0.001	74/208 (35.6)	44/199 (22.1)	0.003	16/44 (36.4)	12/54 (22.2)	0.123

<sup>a</sup>Multiple could be selected.

**Table 2. HIV-related characteristics for HIV+ participants.**

Variable	All HIV+ participants	HIV + participants without past COVID-19 infection	HIV+ participants without past COVID-19 infection
	N = 256	N = 211	N = 45
Duration of HIV infection (years)			
Median (IQR)	17.0 (10.0–25.0)	17.0 (10.0–25.5)	18.0 (9.0–24.0)
Range	(0.0–38.0)	(0.0–38.0)	(0.0–34.0)
Missing/unknown	20	15	5
<10	58 (24.6)	47 (24.0)	11 (27.5)
10–19	84 (35.6)	73 (37.2)	11 (27.5)
20+	94 (39.8)	76 (38.8)	18 (45.0)
CD4 <sup>+</sup> nadir (cells/μl)			
Median (IQR)/range			
Unknown	86	73	13
<100	38 (22.4)	26 (18.8)	12 (37.5)
100–199	32 (18.8)	26 (18.8)	6 (18.8)
200–299	36 (21.2)	32 (23.2)	4 (12.5)
300–399	21 (12.4)	19 (13.8)	2 (6.3)
≥400	43 (25.3)	35 (25.4)	8 (25.0)
CD4 <sup>+</sup> cell count (cells/μl)			
Median (IQR)	631.0 (430.5–838.5)	630.0 (431.0–843.0)	660.0 (387.0–805.0)
Range	(9.0–1800.0)	(9.0–1800.0)	(48.0–1050.0)
Missing	16	14	2
CD4 <sup>+</sup> cell count (cells/μl)			
Unknown	16	14	2
<250	22 (9.2)	14 (7.1)	8 (18.6)
250–349	15 (6.3)	14 (7.1)	1 (2.3)
350–499	43 (17.9)	40 (20.3)	3 (7.0)
500–999	136 (56.7)	107 (54.3)	29 (67.4)
≥1000	24 (10.0)	22 (11.2)	2 (4.7)
CD4 <sup>+</sup> /CD8 <sup>+</sup> ratio			
Median (IQR)	0.82 (0.56–1.21)	0.84 (0.55–1.24)	0.80 (0.59–1.20)
Range	(0.00–3.30)	(0.00–2.50)	(0.09–3.30)
Missing	24	22	2
CD4 <sup>+</sup> /CD8 <sup>+</sup> ratio ≥0.75 [n (%)]	129/232 (55.6)	107/189 (56.6)	22/43 (51.2)
Detectable viral load for at least 6 months [n (%)]	35/250 (14.0)	21/207 (10.1)	14/43 (32.6)
If detectable, highest viral load over past 6 months (copies/ml)			
Median (IQR)	116 (40–1940)	189 (62–1940)	42 (25–323)
Range	(20–817096)	(20–680000)	(20–817096)
ART regimen			
None	8 (3.1)	6 (2.8)	2 (4.4)
NRTI-based regimen	5 (2.0)	3 (1.4)	2 (4.4)
NNRTI-based regimen	21 (8.2)	17 (8.1)	4 (8.9)
PI-based regimen	8 (3.1)	7 (3.3)	1 (2.2)
INSTI-based regimen	175 (68.4)	149 (70.6)	26 (57.8)
Other <sup>b</sup>	39 (15.2)	29 (13.7)	10 (22.2)
Subpopulation			
Immune nonresponder <sup>a</sup>	24/243 (9.9)	21/200 (10.5)	3/43 (7.0)
HIV+ stable/reference (CD4 <sup>+</sup> ≥350, suppressed viral load and ≤1 comorbidity)	110/241 (45.6)	94/198 (47.5)	16/43 (37.2)

<sup>a</sup>CD4<sup>+</sup> <350, CD4<sup>+</sup>/CD8<sup>+</sup> <0.75, suppressed viral load.

<sup>b</sup>regimens containing combinations of above and/or other drug classes (i.e. cell-entry inhibitor).

Three months post second vaccine dose (+/−1 month), there was no difference in ID50 within subgroups of PWH in univariate analyses using quantile regression (Table 5). For example, there was no difference in PWH who were immune nonresponders with multimorbidity in univariate analyses (Table 5) or when stratified by sex (Table 6).

Association between ID50 and participant characteristics by multivariate quantile regression is shown in Table 7.

Within PWH naive to natural COVID-19 infection, when adjusted for age, sex, CD4<sup>+</sup> cell count, vaccine type and time between vaccine doses, black African/black Caribbean participants had significantly higher neutralization capacity than white participants for Ancestral but not for Delta or Omicron variants. Correlation between ID50 and antibody level within PWH at month 3 postdose 2 (±1 month) (Supplemental Figure 2, <http://links.lww.com/QAD/C947>), illustrated high concordance between the two levels.

**Table 3. Types of coronavirus disease 2019 vaccination of participants.**

Variable	All participants			HIV + participants without past COVID-19 infection			HIV+ participants without past COVID-19 infection		
	HIV+	HIV-	P	HIV+	HIV-	P	HIV+	HIV-	P
Types of COVID-19 vaccines received, dose 1 and 2 (%)			0.004			0.002			0.341
mRNA-mRNA	225 (87.9)	220 (85.9)		181 (85.8)	169 (84.5)		44 (97.8)	51 (91.1)	
ChAdOx1-mRNA	17 (6.6)	22 (12.9)		17 (8.1)	30 (15.0)		0 (0.0)	3 (5.4)	
ChAdOx1-ChAdOx1	13 (5.1)	2 (0.8)		12 (5.7)	1 (0.5)		1 (2.2)	1 (1.8)	
Ad26.COVS.2 or Other	1 (0.4)	1 (0.4)		1 (0.5)	0 (0.0)		0 (0.0)	1 (1.8)	
Time between first and second doses in days			<0.001			<0.001			0.566
Median (IQR)	61.0 (51.0-77.0)	57.0 (34.0-77.0)		62.0 (51.0-79.0)	56.0 (31.0-78.0)		57.0 (36.0-67.0)	62.0 (35.0-77.0)	
Range	(20.0-238)	(19.0-125.0)		(20.0-135.0)	(19.0-125.0)		(21.0-238.0)	(21.0-112.00)	
Number missing or N/A (Ad26.COVS.2)	1	1		1	1		0	0	
Time between first and second doses in days			<0.001			<0.001			0.754
≤30	1	1		1	1		0	0	
31-60	24 (9.4)	56 (22.0)		18 (8.6)	49 (24.6)		6 (13.3)	7 (12.5)	
>60	94 (36.9)	84 (32.9)		75 (35.7)	64 (32.2)		19 (42.2)	20 (35.7)	
Number missing or N/A (Ad26.COVS.2)	137 (53.7)	115 (45.1)		117 (55.7)	86 (43.2)		20 (44.4)	29 (51.8)	

## Discussion

We previously reported that the vast majority of PWH obtained a detectable antibody titre at 3 and 6 months following second dose, and 1 month following a third or booster dose [8]. We also reported that vaccine-induced antibody titres were overall similar between PWH vs. HIV-negative controls [8]. PWH aged older than 55 years, immune nonresponders and those with multimorbidity achieved similar antibody levels to COVID-19 vaccines compared with HIV-negative controls. In the current study examining neutralization capacity, we focused on the 3 months post second dose timepoint. Reassuringly, we did not find any difference in PWH vs. controls in persons without prior COVID-19 infection. Within PWH without past COVID-19 infection, younger age (<35), higher CD4<sup>+</sup> cell count or CD4<sup>+</sup>/CD8<sup>+</sup> ratio, and vaccine type (mRNA) was associated with higher neutralization capacity. Shorter duration between doses was associated with higher neutralization capacity but only in univariate analyses. We

had intended to evaluate PWH with past COVID-19 infection, however, our sample size was insufficient to assess all key variables.

In general, hybrid immunity acquired through combined vaccination and natural infection is associated with more robust immune response than either vaccination or natural infection alone [15-17]. Hybrid immunity is thought to specifically enhance Omicron variant neutralization. Verburgh *et al.* compared severe SARS-CoV-2 vaccine-induced and hybrid B-cell and T-cell responses in middle-aged PWH vs. HIV-negative controls who were highly comparable in terms of demographics and lifestyle [18]. PWH mounted equally robust immunity following vaccination and even more robust stronger immunity was observed in both groups following naturally acquired SARS-CoV-2 infection [18]. Meanwhile, Lu *et al.* examined humoral longitudinal observational study in PWH following primary inactivated SARS-CoV-2 vaccination. Neutralizing antibodies were detected 1 month following booster vaccine in all PWH

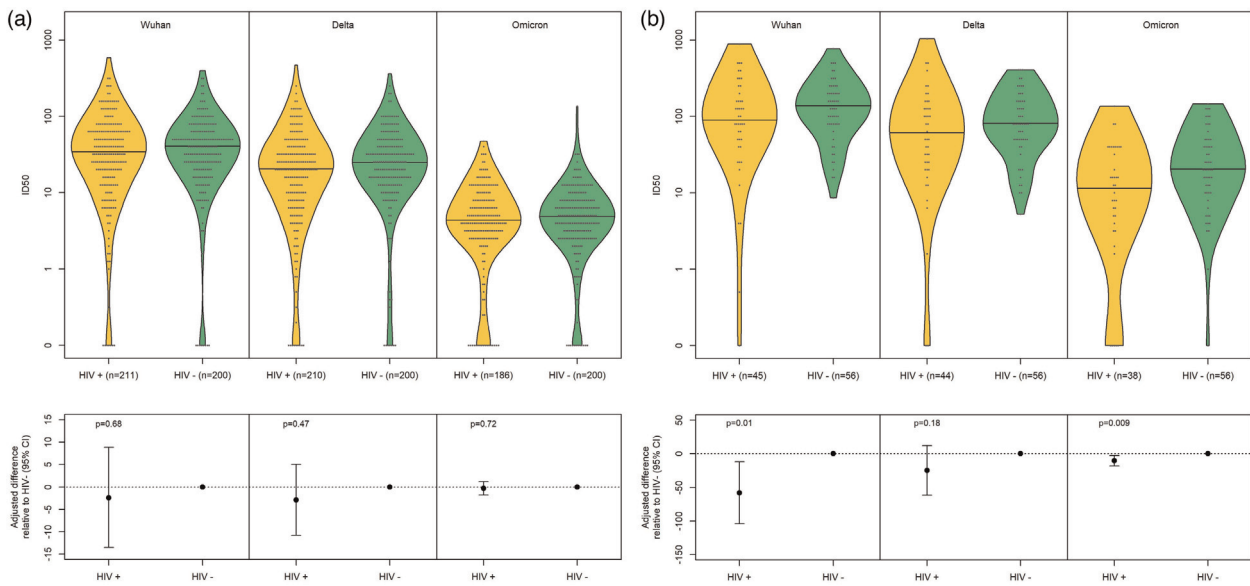
**Table 4. Median (interquartile range) ID50 after COVID-19 vaccination at 3 months post dose 2 (±1 month).**

Antigen	HIV + participants without past COVID-19 infection <sup>a</sup>				HIV+ participants with past COVID-19 infection <sup>a</sup>				<i>p</i> <sup>phomo</sup>
	HIV+	HIV-	Difference in median for HIV+ vs. HIV- (95% CI) <sup>b</sup>	<i>P</i>	HIV+	HIV-	Difference in median for HIV+ vs. HIV- (95% CI) <sup>~</sup>	<i>P</i>	
Wuhan	34.1 (14.4-67.3)	40.2 (19.9-66.1)	-2.4 (-13.5 to 8.8)	0.676	89.3 (45.1)	137.2 (81.3-222.1)	-58.2 (-104.2 to -12.1)	0.013	0.026
Delta	20.4 (7.6-37.8)	24.7 (13.2-44.3)	-2.9 (-10.8 to 5.0)	0.465	61.0 (22.6-133.0)	81.2 (47.7-159.8)	-24.9 (-61.6 to 11.9)	0.184	0.269
Omicron	4.4 (2.7-8.6)	4.9 (2.7-8.3)	-0.3 (-1.8 to 1.2)	0.716	11.5 (4.1-37.1)	20.5 (10.1-45.8)	-10.4 (-18.2 to -2.6)	0.009	0.017

*p*<sup>phomo</sup> is the *P* value from the test of homogeneity by COVID infection status.

<sup>a</sup>Based on site report, participant questionnaires and IgG assay.

<sup>b</sup>Based on quantile regression with an interaction term between HIV status and COVID infection status and adjusted for age, sex, race (white/black/other), multimorbidity (≥2 comorbidities), vaccine type and time between vaccine doses.



**Fig. 1. Difference in ID50 between cohorts to Ancestral, Delta and Omicron variants in participants without past COVID-19 infection and (a) and with past COVID-19 infection (b) in HIV+ and HIV- participants at 3 months after dose 2 (+/-1 month).**

and the titre increased six-fold compared with that associated with the primary vaccination, similar to what was observed in HIV-negative controls [19]. Neutralizing antibody titre declined over time after booster vaccine but remained higher at 6 months than following primary vaccine [19]. Neutralizing antibody response was elevated after booster vaccine in PWH with CD4<sup>+</sup> cell count less than 200 cells/ $\mu$ l, although this boosting effect was lower compared with higher CD4<sup>+</sup> cell count subgroups [19]. It is unclear why PWH with previous COVID-19 infection in our study exhibited higher neutralization capacity than PWH without past infection but weaker neutralization capacity for Ancestral and Omicron variants when compared with HIV-negative controls who also had past infection. As many SSO participants were healthcare workers and individuals working in

public-facing environments, these individuals received vaccination, on average, earlier and with shorter intervals between doses than the general population. We speculate that timing of natural infection in relation to vaccination may have contributed to our observation. Therefore, it is possible that uncontrolled confounding may have accounted for this difference between groups. As time of infection was unknown for fewer than half of the HIV+ participants, it was not possible to control for time of infection as a variable.

Within PWH, black African/Caribbeans had higher neutralization capacity than for whites for all variants. In a cross-sectional analysis involving healthcare workers in the United Kingdom, SARS-CoV-2 spike-specific total antibody titre, neutralizing antibody titre and ELISpot

**Table 5. Difference in median interquartile range ID50 by participant characteristics within HIV+ participants using quantile regression.**

Comparison	HIV + participants without past COVID-19 infection (n = 211)						HIV+ participants with past COVID-19 infection (n = 45)					
	Wuhan	P	Delta	P	Omicron	P	Wuhan	P	Delta	P	Omicron	P
Age >55 years	-10.5 (-23.3, 2.3)	0.108	-4.2 (-12.2, 3.8)	0.301	-1.1 (-2.2, 0.1)	0.074	-37.5 (-121.7, 46.7)	0.374	-52.4 (-130.0, 25.1)	0.180	3.3 (-15.8, 22.5)	0.728
Immune nonresponder (CD4 <sup>+</sup> <350 cells/ $\mu$ l, CD4 <sup>+</sup> /CD8 <sup>+</sup> <0.75, suppressed VL)	4.2 (-34.8, 43.1)	0.832	2.1 (-13.7, 17.9)	0.795	1.0 (-3.6, 5.7)	0.669	-	-	-	-	-	-
Multimorbidity ( $\geq$ 2 comorbidities)	-10.2 (-22.7, 2.3)	0.109	-1.3 (-9.1, 6.6)	0.754	-1.3 (-2.5, 0.0)	0.047	59.2 (-61.1, 179.5)	0.326	29.4 (-59.9, 118.6)	0.510	7.2 (-11.2, 25.6)	0.431
HIV+ stable/reference (CD4 <sup>+</sup> $\geq$ 350 cells, suppressed VL and $\leq$ 1 comorbidity)	3.0 (-11.4, 17.4)	0.683	0.0 (-5.9, 6.0)	0.997	0.9 (-0.4, 2.1)	0.167	-66.0 (-146.7, 14.6)	0.106	-33.9 (-114.5, 46.8)	0.401	-7.5 (-24.5, 9.4)	0.372

VL, viral load.

**Table 6. Difference in median interquartile range ID50 by participant characteristics within HIV+ participants using quantile regression.**

Comparison	HIV + participants without past COVID-19 infection (n = 211)				HIV+ participants with past COVID-19 infection (n = 45)							
	Wuhan difference (95% CI)	P	Delta difference (95% CI)	P	Omicron difference (95% CI)	P	Wuhan difference (95% CI)	P	Delta difference (95% CI)	P	Omicron difference (95% CI)	
Age (per 10 years increase)	-3.6 (-8.2, 1.0)	0.122	-1.7 (-4.7, 1.2)	0.252	-0.6 (-1.1, -0.2)	0.003	12.0 (-26.6, 50.6)	0.533	3.3 (-31.3, 37.9)	0.847	2.3 (-2.9, 7.6)	0.375
<35	20.2 (1.7, 38.7)	0.033	16.5 (2.2, 30.7)	0.024	4.5 (2.0, 7.0)	<0.001	-	-	-	-	-	-
35-44	-0.4 (-18.3, 17.5)	0.966	8.6 (-3.3, 20.6)	0.157	1.5 (-0.7, 3.8)	0.179	-	-	-	-	-	-
45-54	1.6 (-22.9, 26.0)	0.900	10.8 (-0.4, 21.9)	0.059	0.7 (-0.8, 2.3)	0.358	-	-	-	-	-	-
55-64	-2.7 (-20.6, 15.2)	0.768	9.3 (-3.0, 21.5)	0.139	0.8 (-0.7, 2.4)	0.273	-	-	-	-	-	-
≥65	Referent	-	Referent	-	-	-	-	-	-	-	-	-
Sex												
Male	-9.7 (-30.5, 11.1)	0.357	-5.8 (-12.1, 0.5)	0.073	-0.6 (-2.5, 1.4)	0.558	-46.4 (-130.7, 37.9)	0.273	-66.6 (-136.3, 3.0)	0.060	-2.5 (-18.8, 13.9)	0.760
Female	Referent	-	Referent	-	-	-	Referent	-	Referent	-	-	-
Self-declared race or ethnicity												
Black	31.7 (15.6, 47.8)	<0.001	16.9 (0.5, 33.3)	0.043	3.6 (1.0, 6.2)	0.006	98.3 (3.9, 192.7)	0.042	76.5 (24.9, 128.1)	0.005	12.6 (-11.1, 36.3)	0.288
Other	4.1 (-7.1, 15.3)	0.469	6.4 (-0.6, 13.3)	0.074	0.3 (-1.0, 1.6)	0.666	21.1 (-57.5, 99.7)	0.591	43.7 (-30.2, 117.7)	0.239	9.9 (-9.7, 29.5)	0.310
White	Referent	-	Referent	-	-	-	Referent	-	Referent	-	-	-
Medical conditions												
Hypertension	4.7 (-27.2, 36.5)	0.773	2.4 (-12.9, 17.7)	0.759	0.0 (-1.8, 1.8)	0.992	-	-	-	-	-	-
Diabetes	6.0 (-27.9, 15.8)	0.588	1.6 (-11.3, 14.4)	0.809	-0.4 (-2.7, 2.0)	0.767	-	-	-	-	-	-
Dyslipidaemia	4.5 (-17.6, 26.5)	0.689	6.0 (-6.8, 18.8)	0.355	-0.2 (-2.1, 1.6)	0.803	-	-	-	-	-	-
Chronic lung disease	-6.0 (-38.0, 25.9)	0.711	-4.1 (18.4, 10.2)	0.576	0.0 (-2.3, 2.2)	0.998	-	-	-	-	-	-
Obesity	1.4 (-22.8, 25.6)	0.910	0.0 (-10.0, 9.9)	0.994	-0.7 (-2.2, 0.9)	0.379	74.8 (-100.9, 250.5)	0.395	41.1 (-79.8, 161.9)	0.496	27.3 (2.4, 52.3)	0.033
BMI per 10-unit increase	-2.7 (-17.9, 12.5)	0.725	-0.7 (-6.7, 5.4)	0.829	-0.1 (-1.0, 0.7)	0.786	95.2 (-47.1, 237.5)	0.184	88.0 (-46.3, 222.3)	0.193	20.0 (-6.7, 46.7)	0.138

CI, confidence interval.



**Table 7. Association between ID50 and patient characteristics by multivariable quantile regression.<sup>a</sup>**

Comparison	HIV + participants without past COVID-19 infection (n = 195)					
	Wuhan difference (95% CI)	P	Delta difference (95% CI)	P	Omicron difference (95% CI)	P
Age						
<35	11.9 (-3.9, 27.8)	0.140	6.1 (-10.1, 22.4)	0.458	1.8 (-1.4, 5.0)	0.258
35-44	0.5 (-15.4, 16.5)	0.937	-1.1 (-13.7, 11.5)	0.866	0.9 (-1.3, 3.1)	0.435
45-54	6.5 (-9.4, 22.3)	0.476	2.6 (-9.4, 14.6)	0.669	0.7 (-1.4, 2.9)	0.497
55-64	-4.1 (-17.5, 9.4)	0.551	3.7 (-7.9, 15.3)	0.532	0.9 (-0.8, 2.6)	0.286
≥65	Referent		Referent		Referent	
Sex						
Male	2.4 (-8.8, 13.5)	0.676	2.8 (-5.7, 11.3)	0.517	-0.3 (-1.9, 1.4)	0.747
Female	Referent		Referent			
Self-declared race or ethnicity						
Black	20.5 (5.5, 35.6)	0.008	15.6 (-0.7, 31.8)	0.060	1.7 (-1.1, 4.5)	0.232
Other	-5.1 (-18.6, 8.4)	0.458	7.2 (-2.6, 17.0)	0.148	-0.5 (-2.2, 1.1)	0.530
White	Referent		Referent		Referent	
CD4 <sup>+</sup> cell count (cells/μl)						
CD4 <sup>+</sup> cell count (per 100 cells/μl increase)	1.8 (0.1, 3.4)	0.038	0.8 (-0.6, 2.1)	0.271	0.2 (-0.0, 0.4)	0.127
Types of COVID-19 vaccines received, doses 1 and 2						
mRNA-mRNA	27.8 (16.1, 39.4)	<0.001	13.7 (4.2, 23.2)	0.005	2.6 (0.8, 4.5)	0.006
ChAdOx1-mRNA	12.8 (0.1, 25.4)	0.048	10.8 (-0.5, 22.0)	0.060	0.8 (-1.3, 2.9)	0.463
ChAdOx1-ChAdOx1	Referent		Referent		Referent	
Time between first and second doses						
Time between first and second doses (per 10 days increase)	-0.2 (-2.8, 2.4)	0.869	-1.1 (-3.0, 0.8)	0.252	0.2 (-0.2, 0.5)	0.395

CI, confidence interval.

<sup>a</sup>Age, sex, vaccine-related variables and variables with *P* < 0.1 in the univariate analysis were included in the multivariable model.

count were compared by ethnic group [20]. This study found that humoral and cellular immune responses to SARS-CoV-2 vaccination were stronger in South Asian HCWs than white HCWs, and differences were most pronounced early following vaccination [20]. The reasons for our findings are unclear, although we suspect it relates to uncontrolled confounding.

In the current study, we observed that older age was associated with weaker neutralization capacity for Ancestral, Delta and Omicron variants. Advanced age is associated with diminished vaccine immunogenicity [21], due in part to intrinsic defects in B cells leading to sub-optimal antibody function [22-24]. Furthermore, ‘inflammaging’, which refers to increased low-grade systemic inflammation as persons age, is known to impact PWH [25,26].

We previously did not observe differences in antibody titres in PWH with CD4<sup>+</sup> T-cell counts less than 350 cells/μl vs. higher counts. However, other groups have reported diminished anti-S vaccine response and neutralization capacity in PWH vs. HIV-uninfected controls [27,28]. Differences amongst findings in PWH may be because of discrepancies in multimorbidity burden in older adults, type and number of vaccines received and time interval between vaccinations [27-30]. Third dose vaccines elicited better neutralizing antibody responses in PWH with longer time intervals between

vaccines [30]. Furthermore, although there is evidence for sex-based differences in humoral immune response with certain types of vaccinations in HIV-negative populations [30], we and others have not observed any sex difference in antibody level or neutralization capacity in the context of COVID-19 vaccination [10-12,19]. Moreover, in both PWH vs. HIV-negative controls, some participants had a high antibody titre but low ID50. However, given the small number of these individuals who had discordance between antibody titre and neutralization capacity, the importance of this finding, if any, is unclear.

We acknowledge several limitations. COVID-19 vaccinations became available in Canada in December 2020 but recruitment commenced in May 2021, resulting in missed opportunity to obtain baseline prevaccination blood in populations prioritized for vaccination (e.g. elderly, indigenous people) [31]. There were differences in vaccine type and dosing interval by province [31]. Numbers of PWH participants not receiving ART therapy and/or low CD4<sup>+</sup> cell counts were relatively small. Thus, results may not be generalizable to all PWH [32]. The number of PWH with past COVID-19 infection was also relatively low, precluding robust multivariable assessment.

In summary, adult PWH without past COVID-19 infection with well controlled HIV on ART achieved

vaccine-induced SARS-CoV-2 neutralization capacity that is similar to HIV-negative persons. Increasing age is associated with diminished neutralization capacity, and which might be impacted by HIV in those with past COVID-19. This phenomenon requires further exploration. Study of humoral immune response durability, the contribution of cell-mediated immunity and low-grade chronic inflammation will complement our current findings.

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## Conflicts of interest

There are no conflicts of interests.

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