COVID-19 vaccine immunogenicity in people with HIV

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Objectives: Many vaccines require higher/additional doses or adjuvants to provide adequate protection for people with HIV (PWH). Our objective was to compare COVID-19 vaccine immunogenicity in PWH to HIV-negative individuals.

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Design: In a Canadian multi-center prospective, observational cohort of PWH receiving at least two COVID-19 vaccinations, we measured vaccine-induced immunity at 3 and 6 months post 2nd and 1-month post 3rd doses.

Methods: The primary outcome was the percentage of PWH mounting vaccine-induced immunity [co-positivity for anti-IgG against SARS-CoV2 Spike(S) and receptor-binding domain proteins] 6 months post 2nd dose. Univariable and multivariable logistic regressions were used to compare COVID-19-specific immune responses between groups and within subgroups.

Results: Data from 294 PWH and 267 controls were analyzed. Immunogenicity was achieved in over 90% at each time point in both groups. The proportions of participants achieving comparable anti-receptor-binding domain levels were similar between the group at each time point. Anti-S IgG levels were similar by group at month 3 post 2nd dose and 1-month post 3rd dose. A lower proportion of PWH vs. controls maintained vaccine-induced anti-S IgG immunity 6 months post 2nd dose [92% vs. 99%; odds ratio: 0.14 (95% confidence interval: 0.03, 0.80; $P = 0.027$)]. In multivariable analyses, neither age, immune non-response, multimorbidity, sex, vaccine type, or timing between doses were associated with reduced IgG response.

Conclusion: Vaccine-induced IgG was elicited in the vast majority of PWH and was overall similar between groups. A slightly lower proportion of PWH vs. controls maintained vaccine-induced anti-S IgG immunity 6 months post 2nd dose demonstrating the importance of timely boosting in this population.

Background and objectives

Vulnerability to acquisition and symptomatic/severe COVID-19 outcomes in people with HIV (PWH) is compounded by aging, multi-morbidity, and socio-demographic factors [1,2]. Although sub-optimal immunogenicity to common vaccines is well documented in PWH [3,4], initial studies on COVID-19 vaccines in PWH excluded those with advanced age or lower $CD4^+$ T-cell counts [5,6]. Subsequent studies yielded divergent findings regarding COVID-19 immune response in HIV immune-responders vs. non-responders [7,8]. Few studies compared responses with COVID-19 vaccine between PWH and HIV-negative participants over longer time periods, and little information is available on response to 3rd or booster vaccination in PWH. To address this knowledge gap, we established a pan-Canadian prospective cohort of PWH receiving COVID-19 vaccines to assess humoral immunogenicity in diverse PWH to compare immunogenicity responses in PWH vs. HIV-negative controls; and to describe the safety and tolerability of COVID-19 vaccines in PWH [9]. An exploratory objective was to determine if subpopulations of PWH respond differently to COVID-19 vaccination [9]. Our study is among few to date reporting on immune responses following 3rd COVID-19 vaccination dose in PWH [10–12].

Study design and methods

The current multi-center prospective observational cohort study (CTN 328) of PWH recruited from sites in Montreal, Toronto, Ottawa, and Vancouver, with the plan to compare the COVID-19 immune response produced by vaccination, with that of HIV-negative controls, who had data collected at the same time points, in a parallel cohort study (Stop the Spread Ottawa-SSO) [13]. The CTN328 protocol was previously published [9], and later amended to accommodate 3rd and 4th doses/boosters. Enrollment occurred from April to June 2021 in Vancouver and June 2021–January 2022 for remaining sites. The SSO study enrolled 1002 individuals from March to August 2021. Written informed consent was obtained from all participants and ethical approval was obtained from all Research Ethics Boards (Supplementary Information, http://links.lww.com/QAD/C715).

Participants

Inclusion criteria included age of 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 or symptoms of active COVID-19 at enrollment. Sites were encouraged to enroll PWH previously excluded from

initial COVID-19 vaccine studies (Supplementary Information, http://links.lww.com/QAD/C715) [9]. Participants who had received two COVID-19 vaccine doses prior to enrolment were eligible to participate if their 2nd vaccine dose had been administered at most 4 months post 1st dose.

A subset of immunocompetent SSO participants was used as HIV-negative controls and was included if they had undergone parallel blood collection in relation to vaccination time. A detailed description of this cohort was recently published [13].

Study visits

In the initial protocol, participants were to attend five visits over 12 months: pre-vaccination; 1 month following 1st dose; and at 3, 6, and 12 months following the 2nd dose. When the 3rd doses/boosters became available in Canada in the summer 2021 [14], we modified our protocol to include an additional visit at 1 month after this dose. Moderately−severely immuno-compromised individuals in some provinces were given a 3rd dose [15] as part of the primary series. In accordance with Public Health Agency of Canada guidelines, 3rd doses of the mRNA-1273 vaccine were 50 μg (vs. 100 μg 1st and 2nd doses) for those under 65 years [16] whereas 3rd doses of the BNT162b2 vaccine were the same as for 1st and 2nd doses (30 μg). For the presented analysis, we evaluated samples collected at 3 and 6 months after 2nd dose and 1 month after the 3rd dose.

Data collection

Methods for medical and HIV history, COVID-19 Questionnaire administration, sample collection, and vaccine safety, as previously published [9] can be found in Supplementary Information, http://links.lww.com/QAD/C715.

Humoral immunity (SARS-CoV-2 binding antibodies): For each time point, we evaluated levels of IgG targeting the SARS-CoV-2 Spike trimer (S) protein, receptor-binding domain (RBD) of spike, and nucleocapsid (N) protein using an automated high-throughput chemilu-minescent ELISA [17,18]. We distinguished vaccine-induced immunity by co-positivity for S and RBD protein and infection-induced immunity by co-positivity of S and N protein (signal to cutoff ratio ≥1.0) [17]. IgG antibody titers [binding antibody units (BAU)/ml] were generated by a conversion model (4-parameter log-logistic curve based on measurements from the WHO International Standard) (NIBSC 20.136). Assay descrip-tion was previously published [13,18] and it has been used in other Canadian studies [13,19,20], enabling future results comparison across cohorts.

Outcomes

The primary outcome was the percentage of PWH with COVID-19 vaccine-induced immunity, as assessed by COVID-19-specific IgG ELISA 6 months post 2nd dose. Given changes in vaccine policies advocating for a 3rd/ booster dose, a secondary outcome was added to assess the percentage of individuals with COVID-19-specific IgG antibodies and 6 months post 2nd vs. 1-month post 3rd dose. Anti-S and Anti-RBD levels were also examined between groups. An exploratory objective was to determine the percentage of PWH with COVID-19-specific IgG at 6 months post 2nd dose, stratified by various sub-populations of PWH.

Statistical analyses

All analyses were performed using Statistical Analysis System (SAS) software version 9.4 (SAS Institute, Cary, NC, USA). Logistic regression analysis was used to compare the humoral immune response between the PWH and control groups. Confounder adjustment was not considered due to insufficient participants with unsatisfac-tory immune responses. Quantile regression adjusted for vaccine-related variables (vaccine type, time between doses) and participant characteristics (age, sex, race, 'stable'/'reference' population − CD4$^+$cell count >350 cells/μl, suppressed viral load and ≤ 1 comorbidity) and multi-morbidity, defined as at least two comorbidities (yes/no) [9] was used for IgG S, RBD and N levels as the data did not conform with normality assumption even after log transformation. We performed univariate analysis to determine whether there were factors associated with IgG S and RBD proteins level in PWH. Following univariate analysis, age, sex, vaccine-related variables, and variables with *P* less than 0.1 in univariate analysis were further included in a multivariable model to further explore associations with participant characteristics.

Results

A total of 375 PWH were enrolled. Two hundred and sixty-seven of 1002 SSO participants were included as controls. PWH and controls with COVID-19 infection prior to vaccination and during follow-up, up until the time point of interest, were excluded from further analysis (Fig. 1) as they would be expected to have a more robust response following vaccine administration than those who were naïve to natural COVID infection [21,22]. Individuals were also excluded if they had received less than two vaccine doses or if samples were unavailable at the time points of interest.

Baseline characteristics for 294 PWH and 267 HIV-negative controls included in the final analysis are presented in Table 1a and Supplement Table 1, http:// links.lww.com/QAD/C717. Median ages were 54.4 [interquartile range (IQR) 42.3, 62.8] and 42.0 years (IQR 34.0, 54.0) for PWH and controls, respectively. PWH were 77% male vs. 26% of controls, while 47% PWH were aged at least 55 years vs. 23% of controls.
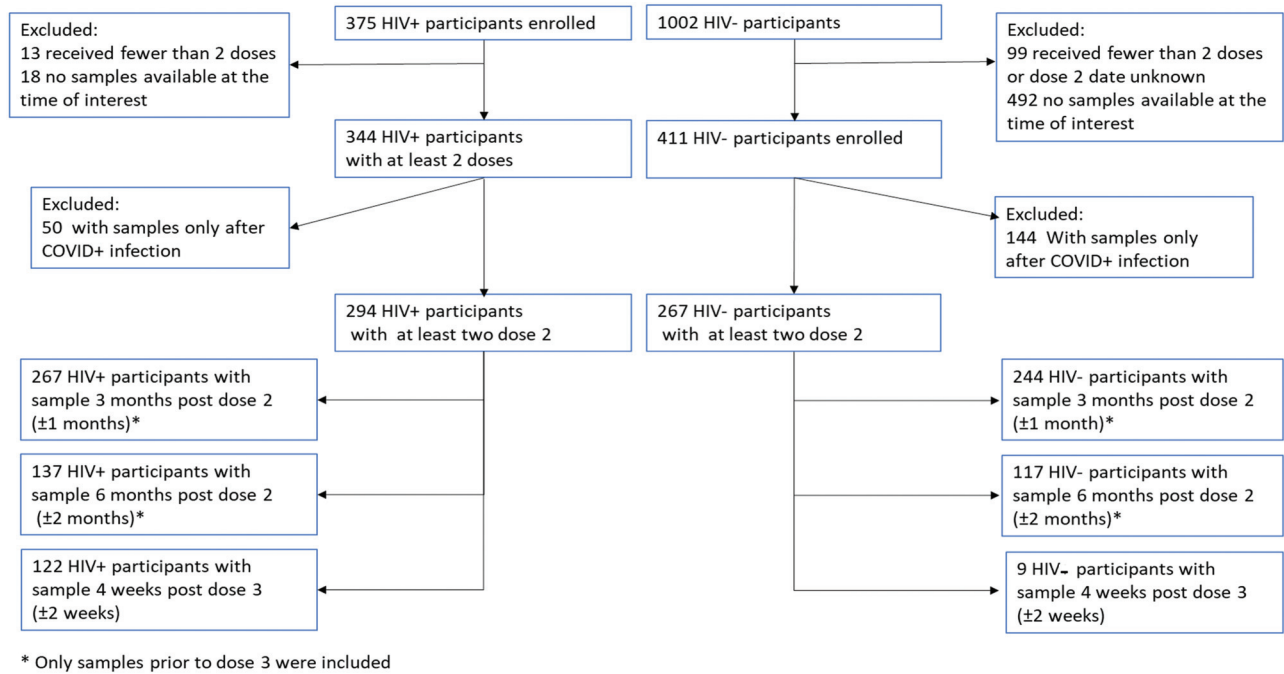
Fig. 1. *Study profile:* **Total of 1377 participants (375 HIV+ and 1002 HIV−) from two observational cohorts were assessed for the study.** Eighty-one people with HIV and 735 HIV− were excluded because of: receiving fewer than two doses, not having samples at the time of interest, or having a positive SARS-CoV-2 PCR test prior to vaccination. Time points of interested were: 3 and 6 months after dose two and 4 weeks after dose 3.

Median duration of HIV infection was 17 (IQR 8, 25) years (Table 1b). Median $CD4^+$ T-cell count was 650 (434, 855) cells/µl and $CD4^+$ T-cell nadir was 256 (IQR 120, 444) cells/µl. Approximately 20% had a history of an AIDS-defining illness. Eleven percent had a detectable HIV viral load within the last 6 months. Nearly all were on antiretroviral therapy (ART) (97.6%). Over 70% of participants were on integrase strand inhibitor-based regimens. Common comorbidities included obesity (21% vs. 14% in PWH and controls, respectively), dyslipidemia (15% vs. 8%), and hypertension (14% vs. 9%) (Supplement Tables 2a and b, http://links.lww.com/QAD/C717). At enrollment, 71 PWH had not yet received any COVID-19 vaccine doses, 106 had received a single dose, and 117 had received a second dose (Table 2). By the time of data analysis in June 2022, 54 individuals had received a 2nd, 214 had received a 3rd, and 26 had received a 4th dose (samples collected after the 4th dose were not included in the current analysis). BNT162b2 and mRNA-1273 were the most commonly administered vaccines (94% in PWH and 99% in controls).

Humoral immune response: anti-receptor-binding domain binding antibody response after 2nd and 3rd vaccine doses

Ninety-six percentage of PWH mounted detectable positive RBD and S levels 3 months after the 2nd dose and 92% of PWH maintained detectable RBD and S levels at 6 months post 2nd dose (Table 3). One month post 3rd/booster dose, 100% of PWH had detectable RBD and S levels. There was no difference in antibody levels between PWH and controls at 3 months after 2nd dose [odds ratio (OR): 0.67 (95% confidence interval (CI): 0.25, 1.81)]. There were less PWH than controls with detectable antibody responses at 6 months post 2nd dose [OR: 0.14 (95% CI: 0.03, 0.80); $P = 0.027$]. There was no difference between PWH and controls when stratified by sex. The same trend as the overall cohort was observed at the 6-month time point with fewer PWH having a positive response in both sexes. Of PWH in the 'stable'/'reference' population, 96.2% achieved a response 3 months post 2nd dose, 95.2% maintained this response at 6 months post 2nd dose and 100% obtained a response 1-month post 3rd dose (Table 3). No difference in immunogenicity was detected between this group and the 'nonstable' PWH populations.

Antibody responses to SARS-CoV-2 full-length receptor-binding domain proteins − IgG RBD and spike protein in PWH and controls are presented in Supplemental Fig. 1, http://links.lww.com/QAD/C716 and Supplement Table 3, http://links.lww.com/QAD/C717. In both groups, IgG titers declined at 6 months after the 2nd dose relative to 3 months post 2nd dose, and were higher at 4 weeks post 3rd dose/booster (Supplemental Figs. 2 and 3, http://links.lww.com/QAD/C716). Median anti-S IgG was lower in PWH than the controls at 3 and 6 months post 2nd dose [adjusted difference in median: $-0.15 \log_{10}$ BAU/ml (95% CI: $-0.24, -0.07$) ($P < 0.001$) and -0.21 (95% CI: $-0.35, -0.06$) ($P = 0.005$), respectively]. Median anti-RBD levels

Table 1. Characteristics of participants with samples prior to COVID infection, HIV+ participants, and controls.

(a) Characteristics of participants with samples prior to COVID infection, *n* (%)

Variable	HIV$^+$, $n = 294$	HIV$^-$, $n = 267$
Median (IQR)/Range	54.4 (42.3, 62.8)/(19.7, 83.5)	42.0 (34.0, 54.0)/(20.0, 79.0)
Age		
<35	36 (12.4)	68 (25.5)
35–44	46 (15.8)	78 (29.2)
45–54	70 (24.1)	60 (22.5)
55–64	85 (29.2)	40 (15.0)
65–74	43 (14.8)	19 (7.1)
≥75	11 (3.8)	2 (0.7)
Sex		
Male	227 (77.2)	70 (26.2)
Female	65 (22.1)	197 (73.8)
Prefer to self describe	2 (0.7)	0 (0.0)
Self-declared race or ethnicity		
White	186 (63.3)	241 (90.3)
Indigenous	5 (1.7)	3 (1.1)
Asian/Filipino	19 (6.5)	6 (3.24)
Black	54 (18.4)	0 (0.0)
Latin American	23 (7.8)	3 (1.1)
Arab/West Asian	5 (1.7)	5 (1.9)
Prefer to self-describe/Other	16 (5.4)	8 (3.0)
Subpopulation		
Age >55 years	139/291 (47.8)	61/267 (22.8)
Multi-morbidity (≥2 comorbidities)	84/288 (29.2)	46/265 (17.4)

(b) HIV-related characteristics of HIV$^+$ participants with samples prior to COVID infection, *n* (%)

Duration of HIV infection, years ($n = 273$)	
Median (IQR)/Range	17.0 (8.0, 25.0)/(0.0, 39.0)
Duration of HIV infection, years ($n = 273$)	
<10	76 (27.8)
10–19	92 (33.7)
20+	105 (38.5)
CD4$^+$ nadir (cells/μl) ($n = 166$)	
Median (IQR)/Range	256 (120, 444)
<100	36 (21.7)
100–199	33 (19.9)
200–299	29 (17.5)
300–399	20 (12.0)
≥400	48 (28.9)
CD4$^+$ cell count (cells/μl) ($n = 273$)	
Median (IQR)/Range	650 (434, 855)/(9, 1800)
CD4$^+$ cell count (cells/μl) ($n = 273$)	
<250	18 (6.6)
250–349	17 (6.2)
350–499	57 (20.9)
500–999	149 (54.6)
≥1000	32 (11.7)
CD4$^+$/CD8$^+$ ratio ($n = 261$)	
Median (IQR)/Range	0.85 (0.58, 1.24)/(0.00, 2.50)
CD4$^+$/CD8$^+$ ratio ≥0.75, *n* (%)	151/261 (57.9)
Detectable viral load for at least 6 months, *n* (%)	31/289 (10.7)
If detectable, highest viral load over past 6 months ($n = 240$) (copies/ml)/Median (IQR)/Range	269 (62, 2479)/(20, 1.00E + 07)
ART regimen	
None	7 (2.4)
NRTI-based regimen	3 (1.0)
NNRTI-based regimen	25 (8.5)
PI-based regimen	8 (2.7)
INSTI-based regimen	213 (72.4)
Other[a]	38 (12.9)
Subpopulation	
Immune non-responder[b]	23/276 (8.3)
HIV+ stable/reference (CD4$^+$ cell count ≥350, suppressed VL and ≤1 comorbidity)	145/271 (53.5)

ART, antiretroviral therapy; IQR, interquartile range; INSTI, integrase strand transfer inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; VL, viral load.
[a]Regimens containing combinations of above and/or other drug classes (i.e., cell-entry inhibitor).
[b](CD4$^+$ cell count <350, CD4$^+$/CD8$^+$ cell count <0.75, suppressed VL).

Table 2. COVID-19 vaccination of participants with samples prior to COVID infection.

Variable	HIV+, $n = 294$	HIV−, $n = 267$
Number of COVID-19 vaccine dose received at *study enrollment*		
None	71 (24.1)	
Received 1 dose of a 2-dose schedule	106 (36.1)	
Received 2 doses of a 2-dose schedule, or 1 dose of a 1-dose schedule	117 (39.8)	
Number of COVID-19 vaccine dose received at *time of data analysis*		
2	54 (18.4)	
3	214 (72.8)	
4	26 (8.8)	
Types of COVID-19 vaccines received, doses 1 and 2		
Unknown	0	1
mRNA−mRNA	252 (85.7)	230 (86.5)
ChAdOx1−mRNA	23 (7.8)	35 (13.2)
ChAdOx1−ChAdOx1	18 (6.1)	1 (0.4)
Ad26.COV2.S	1 (0.3)	0 (0.0)
Types of COVID-19 vaccines received, dose 3		
Unknown	6	
BNT162b2	95 (40.6)	
mRNA-1273	139 (59.4)	
Received same type of vaccine for all 3 doses		
Unknown	2	
Yes, BNT162b2	59 (24.8)	
Yes, mRNA-1273	47 (19.7)	
No	132 (55.5)	
Time between first and second doses in days		
Median (IQR)/Range	61 (52, 76)/(20, 135)	46 (31, 75) (19, 125)
No. of missing or N/A (Janssen)	1	1
Time between second and third doses in days		
Median (IQR)/Range	181 (162, 191)/(55, 285)	

IQR, interquartile range.

were not statistically different between PWH and controls at 3 months post 2nd dose [adjusted difference in median: $-0.13 \log_{10} BAU/ml$ (95% CI: $-0.26, 0.01$) ($P = 0.062$) and 6 months post 2nd dose (adjusted difference in median: $0.01 \log_{10} BAU/ml$ (95% CI: $-0.30, 0.31$) ($P = 0.960$)]. At 4 weeks post 3rd dose, median anti-S, and anti–RBD IgG were not statistically significantly different between groups [adjusted difference in median: $-0.13 \log_{10} BAU/ml$

Table 3. (a) Number of participants positive for vaccine Immunity (anti-S and receptor-binding domain) after COVID-19 vaccination, *n* (%).

Subgroup and time point	HIV+	HIV−	Odds ratio[a] HIV+ vs. HIV− (95% CI)	P
All participants				
3 months post dose 2 (±1 month)	257/267 (96.3)	238/244 (97.5)	0.67 (0.25, 1.81)	0.428
6 months post dose 2 (±2 months)	126/137 (92.0)	116/117 (99.1)	0.14 (0.03, 0.80)	0.027
4 weeks post dose 3 (±2 weeks)	122/122 (100.0)	9/9 (100.0)	−	
Among males				
3 months post dose 2 (±1 month)	200/208 (96.2)	62/64 (96.9)	0.94 (0.22, 4.01)	0.937
6 months post dose 2 (±2 months)	99/109 (90.8)	29/29 (100.0)	0.16 (0.01, 2.96)	0.219
4 weeks post dose 3 (±2 weeks)	107/107 (100.0)	3/3 (100.0)	−	
Among females				
3 months post dose 2 (±1 month)	55/57 (96.5)	176/180 (97.8)	0.57 (0.12, 2.76)	0.482
6 months post dose 2 (±2 months)	26/27 (96.3)	87/88 (98.9)	0.30 (0.03, 3.12)	0.316
4 weeks post dose 3 (±2 weeks)	14/14 (100.0)	6/6 (100.0)	−	

(b) Number of HIV+ stable/reference[b] and non-stable participants positive for vaccine Immunity (anti-S and receptor-binding domain) after COVID-19 vaccination, *n* (%)

	HIV+ stable/reference participants			
Time point	No	Yes	Odds ratio (95% CI)	P
3 months post dose 2 (±1 month)	107/112 (95.5)	127/132 (96.2)	1.19 (0.35, 4.00)	0.783
6 months post dose 2 (±2 months)	56/63 (88.9)	60/63 (95.2)	2.29 (0.61, 8.68)	0.221
4 weeks post dose 3 (±2 weeks)	47/47 (100.0)	61/61 (100.0)	−	

CI, confidence interval; VL, viral load.
[a]Unadjusted odds ratio was presented.
[b]CD4+ cell count ≥350, suppressed VL and ≤1 comorbidity.

(95% CI: -0.61, 0.35) ($P = 0.599$) and $-0.06 \log_{10}$ BAU/mL (95% CI: -0.80, 0.68) ($P = 0.875$), respectively] (Supplemental Fig. 2, http://links.lww.com/QAD/C716 and Supplement Table 3, http://links.lww.com/QAD/C717).

In univariate analysis, the presence of single or multiple comorbidities did not influence IgG response in PWH (Supplement Table 4, http://links.lww.com/QAD/C717). Examining differences in median IgG RBD and IgG S protein in relation to HIV-related characteristics by univariate quantile regression suggested that $CD4^+$ nadir and $CD4^+$ cell count predicted first time point immunogenicity. No other HIV-related variables (HIV infection status or being immune non-responder) showed this effect. Similarly, neither having a detectable vs. undetectable viral load in the past 6 months nor type of ART regimen was predictive of IgG response (Supplement Table 5, http://links.lww.com/QAD/C717). In multivariable comparisons within the PWH group, neither age nor sex was predictive of IgG levels. Higher $CD4^+$ cell count and having received an mRNA type of vaccine were positively associated with IgG RBD and S levels at both 3 and 6 months post 2nd dose but not at 4 weeks post 3rd dose/booster (Table 4).

Tolerability and safety
Overall, vaccines were very well tolerated in PWH. Most participants experienced pain at the injection site within the first 7 days after 2nd dose (65%) and 3rd dose/booster (66%) and fatigue after the booster. The severity of local and systemic reactions is outlined in Supplement Fig. 3, http://links.lww.com/QAD/C716.

Discussion

We present findings from a large and comprehensive study cohort of PWH receiving COVID-19 vaccination. Reassuringly, we found that the vast majority of PWH obtained a detectable antibody response at 3 and 6 months following 2nd dose and 1 month following a 3rd or booster dose. Importantly, PWH aged more than 55 years, immune non-responders (HIV-positive individuals in whom the administration of ART, although successful in suppressing viral replication, cannot properly rebuild circulating $CD4^+$ cell numbers), and those with multi-morbidity achieved similar antibody levels to COVID-19 vaccines compared with HIV-negative controls. In line with other studies, we also found that COVID-19 vaccines were safe and well tolerated in PWH [10–12].

The importance of advanced age on diminished vaccine immunogenicity is well documented [23]. Poor antibody production following influenza vaccination has been observed in older PWH [24,25]. In HIV-negative individuals, antibody levels to COVID-19 mRNA vaccines were lower in older adults after 1st and 2nd doses, in adjusted multivariable analyses, including sociodemographic and chronic health and vaccine-related variables [26]. Cossu *et al.* found reduced anti-S response to vaccination in PWH vs. HIV-negative controls, despite most PWH in their study having $CD4^+$ cell count of more than 500 cells/μl [27]. They attributed this discrepancy to multi-morbidity burden in older adults [27]. In our study, age did not influence COVID-19 vaccine response. Similar to findings of other reports [10,11,12], our data suggest that PWH may retain antibodies for a shorter duration of time following initial vaccination when compared with controls, with a 3rd vaccine dose resulting in improved levels of immune response. We believe that our data support timely, serial booster administration to PWH.

$CD4^+$ cell count and HIV viral load are used by clinicians to predict vaccine immunogenicity [3,4]. Although we only had 18 (6.6%) PWH with $CD4^+$ cell counts less than 250 cells/μl, neither low-level $CD4^+$ cell count nor detectable viral load, was a predictor of diminished antibody levels. In line with our findings, Vergori *et al.* [12] stratified PWH by $CD4^+$ cell count and found robust response 15 days after 3rd dose. Antinori *et al.* [10] also stratified participants by current $CD4^+$ cell count. Similarly to our study, a fewer proportion of individuals with lower $CD4^+$ cell counts mounted detectable antibody responses, but this proportion increased with increasing vaccine doses [10]. Furthermore, we did not find that ability to mount antibody responses was affected by sex, age, baseline $CD4^+$ cell count, a finding which is in keeping with other studies [11].

In the general older population, comorbidity burden contributes to poor COVID-19 vaccine response [28]. Multi-morbidity did not affect humoral immune response in our study. One possible explanation is that our study participants are closely followed in clinic and their comorbidities are generally well-managed. To date, no other studies examining PWH have identified an association between obesity and vaccine immunogenicity. There is evidence for sex-based differences in humoral immune response with certain types of vaccinations in HIV-negative populations [29]. However, we and others have not observed any sex difference in the context of COVID-19 vaccination [10–12,19].

Several limitations are acknowledged. As recruitment began in May 2021, we missed obtaining baseline samples from many elderly and Indigenous participants who were considered priority vaccination groups in Canada and therefore received vaccination in early 2021 [14]. Provinces differed based on type of vaccine administered and vaccine dosing intervals [14]. Our results may not be generalizable to PWH who are not on ART [30,31]. The number of PWH participants with low $CD4^+$ cell counts and without full HIV RNA suppression, and those with data at the 1-month post 3rd dose time were low which limited the robustness of our analysis. As most participants

Table 4. Association between IgG spike (a) and receptor-binding domain response (b) and PWH characteristics by multivariable quantile regression.

(a) Association *between IgG spike* response and participant characteristics by multivariable quantile regression

Time point	3 months post dose 2 (±1 month)		6 months post dose 2 (±2 months)		4 weeks post dose 3 (±2 weeks)	
Comparison	Difference (95% CI)	P	Difference (95% CI)	P	Difference (95% CI)	P
Age (per 10 years increase)	−0.01 (−0.03, 0.02)	0.719	0.02 (−0.05, 0.10)	0.539	−0.02 (−0.11, 0.06)	0.618
Sex now						
Male	−0.02 (−0.15, 0.11)	0.752	−0.09 (−0.29, 0.11)	0.388	−0.27 (−0.60, 0.07)	0.119
Female	Referent		Referent		Referent	
CD4$^+$ cell count (per 100 cells/µl increase)	0.02 (0.00, 0.03)	0.043	0.03 (−0.01, 0.06)	0.122	−0.02 (−0.06, 0.02)	0.350
Types of COVID-19 vaccines received, doses 1 and 2						
mRNA−mRNA	0.69 (0.37, 1.00)	<0.001	1.32 (1.06, 1.58)	<0.001	0.07 (−0.46, 0.59)	0.804
ChAdOx1−mRNA	0.65 (0.28, 1.03)	<0.001	1.32 (0.96, 1.67)	<0.001	−0.14 (−0.88, 0.60)	0.713
ChAdOx1−ChAdOx1	Referent		Referent		Referent	
Time between 1st and 2nd doses (per 10 days increase)	−0.01 (−0.04, 0.02)	0.488	−0.05 (−0.13, 0.02)	0.174	−0.02 (−0.09, 0.06)	0.679
Received same type of vaccine for all 3 doses						
Yes, BNT162b2 ($n = 59$)					−0.44 (−0.75, −0.12)	0.007
Yes, mRNA-1273 ($n = 47$)					−0.10 (−0.37, 0.17)	0.465
No ($n = 132$)					Referent	
Time between 2nd and 3rd doses (per 10 days increase)					0.02 (−0.02, 0.06)	0.246

(b) Association *between IgG* receptor-binding domain response and participant characteristics by multivariable quantile regression

Time point	3 months post dose 2 (±1 month)		6 months post dose 2 (±2 months)		4 weeks post dose 3 (±2 weeks)	
Comparison	Difference (95% CI)	P	Difference (95% CI)	P	Difference (95% CI)	P
Age (per 10 years increase)	−0.03 (−0.07, 0.02)	0.223	0.00 (−0.10, 0.09)	0.939	0.02 (−0.09, 0.12)	0.750
Sex						
Male	0.09 (−0.10, 0.29)	0.348	−0.09 (−0.37, 0.19)	0.535	−0.19 (−0.62, 0.25)	0.403
Female	Referent		Referent		Referent	
Self-declared race or ethnicity						
Black	0.16 (−0.01, 0.34)	0.071	0.01 (−0.28, 0.30)	0.933	−0.06 (−0.56, 0.45)	0.820
Other	0.00 (−0.19, 0.19)	0.964	0.08 (−0.18, 0.34)	0.543	0.18 (−0.18, 0.54)	0.316
White	Referent		Referent		Referent	
CD4$^+$ cell count (per 100 cells/µl increase)	0.04 (0.02, 0.07)	0.001	0.03 (−0.02, 0.07)	0.279	−0.01 (−0.05, 0.03)	0.505
Types of COVID-19 vaccines received, doses 1 and 2						
mRNA−mRNA	0.65 (0.27, 1.02)	<0.001	0.87 (0.40, 1.33)	<0.001	−0.19 (−0.76, 0.37)	0.497
ChAdOx1−mRNA	0.46 (−0.01, 0.94)	0.055	0.67 (−0.04, 1.39)	0.066	−0.42 (−1.24, 0.41)	0.320
ChAdOx1−ChAdOx1	Referent		Referent		Referent	
Time between 1st and 2nd doses (per 10 days increase)	0.00 (−0.04, 0.04)	0.965	−0.05 (−0.15, 0.05)	0.310	−0.02 (−0.09, 0.05)	0.594
Received same type of vaccine for all 3 doses						
Yes, BNT162b2					−0.31 (−0.60, −0.01)	0.043
Yes, mRNA-1273					0.06 (−0.24, 0.36)	0.703
No					Referent	
Time between 2nd and 3rd doses (per 10 days increase)					0.03 (−0.01, 0.07)	0.173

CI, confidence interval.

received mRNA vaccine, we could not assess temporal differences of immunogenicity based on vaccine type. Furthermore, the assays used only assess binding antibody levels to wildtype or 'original' SARS-CoV-2. BAUs at 3 months post 2nd dose could suggest somewhat diminished COVID-19 vaccine immunogenicity in PWH compared with controls. Further studies, looking into the ratio between IgG–S BAU and protection against infection in PWH and aged individuals are warranted. Wei *et al*. [32] inferred that antibody to S protein of about 100 BAU/ml gave about 67% protection against the delta variant, although after a 2nd dose many individuals did not achieve this antibody level.

In summary, adult PWH with well-controlled HIV on ART mount antibody responses following 2nd and 3rd COVID-19 vaccine doses similar to HIV-negative individuals. Diminishing proportions of PWH with detectable antibody levels argue for timely serial booster dosing to maintain seroprotection. Additional information related to durability of humoral immune response, neutralization capacity, and the contribution of cell-mediated immunity will complement these current findings and inform COVID-19 vaccination clinical guidelines for PWH.

Acknowledgements

Authors' contributions

Co-principal investigators of the study are C.T.C., C.L.C., and A.H.A. C.T.C. and C.L.C. conceived the study and led the proposal and protocol development. C.T.C. wrote the first draft of the article. J.S. is the biostatistician who provided methodological expertise and performed sample size calculations. All other authors contributed to protocol development, study design, and development of the proposal. C.T.C., M.A.L., C.A., Y.G., M.A.J., M.O., M.A.B., and Z.L.B. designed the laboratory evaluations. S.S. oversaw lab specimen processing and lab database development. M.A.L., C.A., and Y.G. were responsible for studies on humoral immunity. J.S. oversaw data analysis between groups and subgroup analyses. T.L. performed data analyses. All authors critically reviewed and approved the final article.

Conflicts of interest

The authors declare that they have no competing interests.

Summary: In a multi-center longitudinal observational cohort of people with HIV in Canada, COVID-19 vaccination humoral immunogenicity was assessed in 294 individuals with and 267 without HIV infection post 2nd and 3rd doses. Robust humoral immune responses were observed.

References

1. Tesoriero JM, Swain CE, Pierce JL, Zamboni L, Wu M, Holtgrave DR, *et al.* **COVID-19 outcomes among persons living with or without diagnosed HIV infection in New York state.** *JAMA Netw Open* 2021; **4**:e2037069.
2. Weiser JK, Tie Y, Beer L, Neblett Fanfair R, Shouse RL. **Racial/ethnic and income disparities in the prevalence of comorbidities that are associated with risk for severe COVID-19 among adults receiving HIV care, United States, 2014–2019.** *J Acquir Immune Defic Syndr* 2021; **86**:297–304.
3. Crum-Cianflone NF, Sullivan E. **Vaccinations for the HIV-infected adult: a review of the current recommendations, Part I.** *Infect Dis Ther* 2017; **6**:303–331.
4. Crum-Cianflone NF, Sullivan E. **Vaccinations for the HIV-infected adult: a review of the current recommendations, Part II.** *Infect Dis Ther* 2017; **6**:333–361.
5. Bergman P, Blennow O, Hansson L, Mielke S, Nowak P, Chen P, *et al.* **Safety and efficacy of the mRNA BNT162b2 vaccine against SARS-CoV-2 in five groups of immunocompromised patients and healthy controls in a prospective open-label clinical trial.** *EBioMedicine* 2021; **74**:103705.
6. 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.
7. Frater J, Ewer KJ, Ogbe A, Pace M, Adele S, Adland E, *et al.* **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.
8. Sistere-Oro M, Andrade N, Wortmann DDJ, Du J, Garcia-Giralt N, Gonzalez-Cao M, *et al.* **Anti-SARS-COV-2 specific immunity in HIV immunological nonresponders after mRNA-based COVID-19 vaccination.** *Front Immunol* 2022; **13**:994173.
9. Costiniuk CT, Singer J, Langlois MA, Kulic I, Needham J, Burchell A, *et al.* **CTN 328: immunogenicity outcomes in people living with HIV in Canada following vaccination for COVID-19 (HIV-COV): protocol for an observational cohort study.** *BMJ Open* 2021; **11**:e054208.
10. Antinori A, Cicalini S, Meschi S, Bordoni V, Lorenzini P, Vergori A, *et al.* **Humoral and cellular immune response elicited by mRNA vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in people living with human**

immunodeficiency virus receiving antiretroviral therapy based on current CD4 T-lymphocyte count. *Clin Infect Dis* 2022; **75**: e552–e563.

11. Gianserra L, Dona MG, Giuliani E, Stingone C, Pontone M, Buonomini AR, et al. **Immunogenicity and safety of BNT162b2 homologous booster vaccination in people living with HIV under effective cART.** *Vaccines (Basel)* 2022; **10**:1243.

12. Vergori A, Cozzi Lepri A, Cicalini S, Matusali G, Bordoni V, Lanini S, et al. **Immunogenicity to COVID-19 mRNA vaccine third dose in people living with HIV.** *Nat Commun* 2022; **13**:4922.

13. Collins E, Galipeau Y, Arnold C, Bosveld C, Heiskanen A, Keeshan A, et al. **Cohort profile: Stop the Spread Ottawa (SSO)—a community-based prospective cohort study on antibody responses, antibody neutralisation efficiency and cellular immunity to SARS-CoV-2 infection and vaccination.** *BMJ Open* 2022; **22**:e062187.

14. Ministry of Health. COVID-19 vaccine booster recommendation.Version 8.3 22 July 2022.

15. Canada Public Health Agency Canada 2022. Available at: https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/page-26-covid-19-vaccine.html [Accessed 31 May 2022]

16. Public Health Agency of Canada 2022. Available at: https://www.canada.ca/en/health-canada/news/2021/11/health-canada-authorizes-the-use-of-the-moderna-spikevax-covid-19-vaccine-as-a-booster-shot.html. [Accessed 12 November 2021]

17. Cholette F, Fabia R, Harris A, Ellis H, Cachero K, Schroeder L, et al. **Comparative performance data for multiplex SARS-CoV-2 serological assays from a large panel of dried blood spot specimens.** *Heliyon* 2022; **8**:e10270.

18. Colwill K, Galipeau Y, Stuible M, Gervais C, Arnold C, Rathod B, et al. **A scalable serology solution for profiling humoral immune responses to SARS-CoV-2 infection and vaccination.** *Clin Transl Immunol* 2022; **11**:e1380.

19. Vinh DC, Gouin JP, Cruz-Santiago D, Canac-Marquis M, Bernier S, Bobeuf F, et al. **Real-world serological responses to extended-interval and heterologous COVID-19 mRNA vaccination in frail, older people (UNCoVER): an interim report from a prospective observational cohort study.** *Lancet Healthy Longev* 2022; **3**:e166–e175.

20. Fakhraei R, Erwin E, Alibhai KM, Murphy MSQ, Dingwall-Harvey ALJ, White RR, et al. **Prevalence of SARS-CoV-2 infection among obstetric patients in Ottawa, Canada: a descriptive study.** *CMAJ Open* 2022; **10**:E643–E651.

21. Blain H, Tuaillon E, Gamon L, Pisoni A, Miot S, Picot MC, et al. **Spike antibody levels of nursing home residents with or without prior COVID-19 3 weeks after a single BNT162b2 vaccine dose.** *JAMA* 2021; **325**:1898–1899.

22. Saadat S, Rikhtegaran Tehrani Z, Logue J, Newman M, Frieman MB, Harris AD, et al. **Binding and neutralization antibody titers after a single vaccine dose in healthcare workers previously infected with SARS-CoV-2.** *JAMA* 2021; **325**:1467–1469.

23. Gustafson CE, Kim C, Weyand CM, Goronzy JJ. **Influence of immune aging on vaccine responses.** *J Allergy Clin Immunol* 2020; **145**:1309–1321.

24. Pallikkuth S, De Armas LR, Pahwa R, Rinaldi S, George VK, Sanchez CM, et al. **Impact of aging and HIV infection on serologic response to seasonal influenza vaccination.** *AIDS* 2018; **32**:1085–1094.

25. Parmigiani A, Alcaide ML, Freguja R, Pallikkuth S, Frasca D, Fischl MA, et al. **Impaired antibody response to influenza vaccine in HIV-infected and uninfected aging women is associated with immune activation and inflammation.** *PLoS One* 2013; **8**:e79816.

26. Brockman MA, Mwimanzi F, Lapointe HR, Sang Y, Agafitei O, Cheung PK, et al. **Reduced magnitude and durability of humoral immune responses to COVID-19 mRNA vaccines among older adults.** *J Infect Dis* 2022; **225**:1129–1140.

27. Cossu MV, Mileto D, Giacomelli A, Oreni L, Bracchitta F, Pellicciotta M, et al. **Does the co-morbidity burden contribute to suboptimal immunological responses to COVID-19 vaccination in people living with HIV?** *J Infect Dis* 2022:jiac286. doi: 10.1093/infdis/jiac286.

28. Sogaard OS, Reekie J, Johansen IS, Nielsen H, Benfield T, Wiese L, et al. **Characteristics associated with serological COVID-19 vaccine response and durability in an older population with significant comorbidity: the Danish Nationwide ENFORCE Study.** *Clin Microbiol Infect* 2022; **28**:1126–1133.

29. Fink AL, Klein SL. **The evolution of greater humoral immunity in females than males: implications for vaccine efficacy.** *Curr Opin Physiol* 2018; **6**:16–20.

30. 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* 2022; **50**:617–623.

31. Overton ET, Sungkanuparph S, Powderly WG, Seyfried W, Groger RK, Aberg JA. **Undetectable plasma HIV RNA load predicts success after hepatitis B vaccination in HIV-infected persons.** *Clin Infect Dis* 2005; **41**:1045–1048.

32. Wei J, Pouwels KB, Stoesser N, Matthews PC, Diamond I, Studley R, et al. **Antibody responses and correlates of protection in the general population after two doses of the ChAdOx1 or BNT162b2 vaccines.** *Nat Med* 2022; **28**:1072–1082.