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.
**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.

**Keywords:** COVID-19, COVID-19 vaccines, HIV, observational study, vaccine immunogenicity
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The primary outcome was the percentage of PWH with specific IgG ELISA 6 months post 2nd dose. 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 unsatisfactory immune responses. Quantile regression adjusted for vaccination time 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 protein levels 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 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.
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 after 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 log₁₀ 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                                       | 63 (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/Philippine                              | 19 (6.5)      | 6 (3.4)       |
| 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 (17.3)  |
| 300–399                                  | 20 (12.0)  |
| ≥400                                     | 48 (28.9)  |
| CD4+ cell count (cells/μl) (n = 273)      |            |
| Median (IQR)/Range                       | 650 (434, 855)/(0, 1800) |
| CD4+/CD8+ ratio (n = 261)                 |            |
| Median (IQR)/Range                       | 0.85 (0.58, 1.24)/(0.00, 2.50) |
| Detectable viral load for at least 6 months, n (%) | 151/261 (57.9) |
| If detectable, highest viral load over past 6 months (n = 240) (copies/ml)/Median (IQR)/Range | 269 (62, 2479)/(20, 1.0E + 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) |
| Othera                                    | 38 (12.9)  |
| Subpopulation                              |            |
| Immune non-responderb                     | 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.

*aRegimens containing combinations of above and/or other drug classes (i.e., cell-entry inhibitor).

bCD4+ cell count <350, CD4+/CD8+ cell count <0.75, suppressed VL.
were not statistically different between PWH and controls at 3 months post 2nd dose [adjusted difference in median: \(0.13 \log_{10} \text{BAU/ml} (95\% \text{ CI}: 0.26, 0.01) (P = 0.062)\)] and 6 months post 2nd dose (adjusted difference in median: \(0.30 \log_{10} \text{BAU/ml} (95\% \text{ CI}: 0.31, 0.30) (P = 0.960)\)]. At 4 weeks post 3rd dose, median anti-S, and anti-RBD IgG were not statistically significantly different between groups [adjusted difference in median: \(0.13 \log_{10} \text{BAU/ml}\)].

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) | 214 (72.8) |
| 3 | 27 (9.2) | 26 (8.8) |
| 4 | | |
| Types of COVID-19 vaccines received, doses 1 and 2 | | |
| Unknown | | 0 |
| 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 (34.0) | 139 (51.9) |
| mRNA-1273 | | |
| Received same type of vaccine for all 3 doses | | |
| Unknown | 2 | |
| Yes, BNT162b2 | 59 (24.8) | |
| Yes, mRNA-1273 | 47 (17.7) | |
| No | 132 (52.5) | |
| 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: \(-0.13 \log_{10} \text{BAU/ml} (95\% \text{ CI}: -0.26, 0.01) (P = 0.062)\)] and 6 months post 2nd dose (adjusted difference in median: \(0.01 \log_{10} \text{BAU/ml}\)).

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 ratioa 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-referenceb 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.
aUnadjusted odds ratio was presented.
bCD4+ cell count \(\geq 350\), suppressed VL and \(\leq 1\) comorbidity.
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(95% CI: −0.61, 0.35) \( (P = 0.599) \) and −0.06 log_{10}\text{BAU/mL} \ (95\% \ 	ext{CI:} \ −0.80, 0.68) \ (P = 0.875), \text{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]. Cosu 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, 0.00) | 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, 0.11) | 0.119 |
| Female | 0.02 (0.00, 0.04) | 0.043 | 0.03 (-0.01, 0.06) | 0.122 | -0.02 (-0.06, 0.02) | 0.350 |
| CD4+ cell count (per 100 cells/μl increase) | 0.02 (0.00, 0.04) | 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 | 0.06 (0.07, 1.00) | <0.001 | 1.32 (1.06, 1.58) | <0.001 | 0.07 (-0.46, 0.59) | 0.804 |
| mRNA–mRNA | 0.05 (0.06, 1.03) | <0.001 | 1.32 (0.96, 1.67) | <0.001 | -0.14 (-0.88, 0.60) | 0.713 |
| ChAdOx1–mRNA | Referent | Referent | Referent | Referent | Referent | Referent |
| ChAdOx1–ChAdOx1 | 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 |
| Yes, BNT162b2 (n = 59) | | | | | | |
| No (n = 132) | Referent | Referent | Referent | Referent | Referent | 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, 0.01) | 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 | Referent | Referent | Referent |
| Self-declared race or ethnicity | | | | | | |
| Black | 0.16 (-0.01, 0.34) | 0.071 | 0.01 (-0.28, 0.30) | 0.931 | -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 | 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 | 0.65 (0.27, 1.02) | <0.001 | 0.87 (0.40, 1.33) | <0.001 | -0.19 (-0.76, 0.37) | 0.497 |
| mRNA–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–mRNA | Referent | Referent | Referent | 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 |
| Yes, BNT162b2 | | | | | | |
| Yes, mRNA–1273 | | | | | | |
| No | Referent | Referent | Referent | Referent | Referent | Referent |
| Time between 2nd and 3rd doses (per 10 days increase) | -0.31 (-0.60, -0.01) | 0.043 | 0.06 (-0.24, 0.36) | 0.703 | 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.

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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.

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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, Tieu Y, Beer L, Neblett Fanfair R, House 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. Cum-Cani fluone 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. Cum-Cani fluone 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. ElBioMedicine 2021; 74:103705.
6. Levy J, 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 DDR, Du J, Garcia-Gralt N, Gonzalez-Cao M, et al. Anti-SARS-CoV-2 specific immunity in HIV immunonological nonresponders after mRNA-based COVID-19 vaccination. Front Immunol 2022; 13:994173.
9. Costiniuk CT, Singer J, Langlois MA, Kulic J, 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:e0054208.
10. Antonini A, Ciccalini S, Meschi S, Bordoni V, Lorenzin 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:e532–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, et al. Characteristics associated with serological responses to 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.
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/public-health/services/publications/healthy-living/canadian-immunization-guide-part-4-active-vaccines/page-26-covid-19-vaccine-as-a-booster-shot.html. [Accessed 12 November 2021]
17. Cholette F, Fabia R, Harris A, Ellis H, Cacherio K, Schroeder L, et al. Comparative performance data for multiplex SARS-CoV-2 serological assays from a large panel of dried blood spot specimens. Hembym 2022; 8:e10270.
18. Colwill K, Galipeau Y, Stuble 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. Fahkrai 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, Tailllon E, Gamon L, Pisoni A, Most 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; 325:1896–1899.
22. Saadat S, Rikhtegaran Tehran Z, Logue J, Newman M, Fischl MA, et al. Binding and neutralization antibody titres after a single vaccine dose in healthcare workers previously infected with SARS-CoV-2. JAMA 2021; 325:1467–1469.
23. Gustafson CE, Kim C, Weyard CM, Goronzy JJ. Influence of immune aging on vaccine responses. J Allergy Clin Immunol 2020; 145:1309–1321.
24. Pallikkuth S, De Armis 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, Fraguia 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, Mwimanz F, Lapointe HR, Sang Y, Agaffie 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. Coosu MV, Miletto D, Giacomelli A, Aleni L, Bracchitta F, Pellicciotta M, et al. The evolution of greater humoral immunity to SARS-CoV-2 infection and vaccination. BMJ Open 2022; 22:e062187.
28. Ministry of Health. COVID-19 vaccine booster recommendation. Version 8.3. 22 July 2022.
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, Ochna 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, Songkanaparg S, Powderly WG, Seyfried W, Groger RK, Abern 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, Poulwels KB, Stoesser N, Matthews PC, Diamond L, 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.