

People With Human Immunodeficiency Virus Receiving Suppressive Antiretroviral Therapy Show Typical Antibody Durability After Dual Coronavirus Disease 2019 Vaccination and Strong Third Dose Responses

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Background. Longer-term humoral responses to 2-dose coronavirus disease 2019 (COVID-19) vaccines remain incompletely characterized in people living with human immunodeficiency virus (HIV) (PLWH), as do initial responses to a third dose.

Methods. We measured antibodies against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein receptor-binding domain, angiotensin-converting enzyme 2 (ACE2) displacement, and viral neutralization against wild-type and Omicron strains up to 6 months after 2-dose vaccination, and 1 month after the third dose, in 99 PLWH receiving suppressive antiretroviral therapy and 152 controls.

Results. Although humoral responses naturally decline after 2-dose vaccination, we found no evidence of lower antibody concentrations or faster rates of antibody decline in PLWH compared with controls after accounting for sociodemographic, health, and vaccine-related factors. We also found no evidence of poorer viral neutralization in PLWH after 2 doses, nor evidence that a low nadir CD4⁺ T-cell count compromised responses. Post-third-dose humoral responses substantially exceeded post-second-dose levels, though Omicron-specific responses were consistently weaker than responses against wild-type virus. Nevertheless, post-third-dose responses in PLWH were comparable to or higher than controls. An mRNA-1273 third dose was the strongest consistent correlate of higher post-third-dose responses.

Conclusion. PLWH receiving suppressive antiretroviral therapy mount strong antibody responses after 2- and 3-dose COVID-19 vaccination. Results underscore the immune benefits of third doses in light of Omicron.

Keywords. HIV; COVID-19; vaccines; immune response; humoral; antibodies; neutralization; third dose.

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Because people living with human immunodeficiency virus (HIV) (PLWH) may be at increased risk of severe coronavirus disease 2019 (COVID-19) owing to immunosuppression, higher rates of multimorbidity, and/or social determinants of health [1–4], vaccination is expected to benefit this group. Although 2-dose COVID-19 vaccination protects against severe disease [5–7], impaired responses have been observed in certain immunocompromised groups [8–12], prompting research into COVID-19 vaccine responses in PLWH. This is because, while antiretroviral therapy can reverse HIV-induced immune dysfunction to a large extent [13–16], persistent HIV-related immunopathology can nevertheless blunt vaccine responses

[17–19]. Clinical trials [20, 21] and real-world studies, however [22–28], including an initial study of the present cohort [29], have found generally strong immune responses to 2-dose COVID-19 vaccination in PLWH with controlled HIV loads on therapy and preserved CD4⁺ T-cell counts [20–24, 29], though weaker responses have been observed in PLWH who are not receiving therapy or who have CD4⁺ T-cell counts <200/ μ L [22, 25–27].

However, vaccine-induced antibody responses decline over time, which can increase the risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [30–32], particularly with the more transmissible Omicron variant [33–37]. Although immune response durability after 2-dose COVID-19 vaccination has been examined among PLWH participants in the ChAdOx1 clinical trial [38], few real-world studies have investigated this. Furthermore, no studies to our knowledge have investigated immune responses in PLWH to third vaccine doses, despite their widespread recommendation to maintain protection [39–41]. We extend our previous report [29] to characterize humoral responses to both wild-type (WT) and Omicron SARS-CoV-2 variants up to 1 month after the third vaccine dose, in 99 PLWH and 152 controls without HIV.

METHODS

Participants

We recruited 99 adult PLWH and 152 controls without HIV, the latter predominantly healthcare workers, in British Columbia (BC), Canada [29]. Serum and plasma (collected in ethylenediaminetetraacetic acid [EDTA] for all PLWH and 16% of controls, or anticoagulant citrate dextrose for the remainder) were collected before vaccination; 1 month after the first dose; 1, 3, and 6 months after the second dose; and 1 month after the third dose. Here, we extend the previous study [29] to include all post-second-dose, and the 1-month post-third dose, study visits. A cohort flowchart is shown in [Supplementary Figure 1](#).

Ethical Approval

All participants provided written informed consent. This study was approved by the University of British Columbia/Providence Health Care and Simon Fraser University Research Ethics Boards.

Data Sources

Sociodemographic, health and COVID-19 vaccine data were collected through self-report and medical records. We assigned a score of 1 for each of 11 chronic conditions: hypertension, diabetes, asthma, obesity (body mass index ≥ 30 , calculated as weight in kilograms divided by height in meters squared), chronic diseases of lung, liver, kidney, heart or blood, cancer; and immunosuppression due to chronic conditions or

medication. For PLWH, a recent CD4⁺ T-cell count <200/ μ L constituted immunosuppression.

Binding Antibody Assays

Binding antibodies were measured using 2 commercial assays. We measured total binding antibodies against SARS-CoV-2 nucleocapsid and spike (S) receptor-binding domain (RBD) in serum samples using the Elecsys Anti-SARS-CoV-2 and Anti-SARS-CoV-2 S assays, respectively, on a cobas e601 module analyzer (Roche Diagnostics). After infection, results of both assays should be positive, whereas after vaccination only the S assay result should be positive. The anti-S assay reports results in arbitrary units per milliliter. For the S assay, serum samples were tested undiluted, with samples above the upper limit of quantification (ULOQ) retested at 1:100 dilution, allowing a measurement range of 0.4–25 000 U/mL. Anti-RBD binding immunoglobulin G (IgG) concentrations in serum were also quantified using the V-plex SARS-CoV-2 (IgG) Panel 22 enzyme-linked immunosorbent assay kit (Meso Scale Diagnostics) on a Meso QuickPlex SQ120 instrument. This assay quantifies both WT- and Omicron-specific IgG. Serum samples were diluted 1:10 000, allowing a broader dynamic range than the Roche assay. Results are reported in arbitrary units per milliliter.

Angiotensin-Converting Enzyme 2 (ACE2) Receptor Displacement Assay

We assessed the ability of serum antibodies to block the RBD/angiotensin-converting enzyme 2 (ACE2) receptor interaction by competition enzyme-linked immunosorbent assay (Panel 22 V-plex SARS-CoV-2 [ACE2]; Meso Scale Diagnostics) on a Meso QuickPlex SQ120 instrument. This represents a higher-throughput approach to estimate potential virus neutralizing activity and is commonly used as a surrogate for this function [42]. Serum samples were diluted 1:40 and results reported as the percentage of ACE2 displacement.

Live Virus Neutralization

Neutralizing activity in plasma was examined in live SARS-CoV-2 assays using isolate USA-WA1/2020 (BEI Resources) and a local Omicron BA.1 isolate (GISAID accession no. EPI_ISL_9805779) on Vero E6–TMPRSS2 (JCRB-1819) target cells. As described elsewhere [29], viral stock was adjusted to 50 times the median tissue culture infectious dose per 200 μ L in the presence of serial 2-fold plasma dilutions (from 1:20 to 1:2560) and added to target cells in 96-well plates in triplicate. The appearance of viral cytopathic effects was recorded 3 days after infection. Neutralizing activity is reported as the reciprocal of the highest plasma dilution able to prevent cytopathic effects in all triplicate wells. Samples exhibiting partial or no neutralization at 1:20 dilution were defined as below the limit of quantification (BLOQ).

Table 1. Participant Characteristics

Characteristic	Participants, No. (%) ^a	
	PLWH (n = 99)	Controls (n = 152)
HIV-related variables		
Receiving antiretroviral therapy	99 (100)	...
Most recent plasma viral load, median (IQR), HIV RNA copies/mL	<50 (<50 to <50)	...
Most recent CD4 ⁺ T-cell count, median (IQR), cells/ μ L	715 (545–943)	...
Nadir CD4 ⁺ T-cell count, median (IQR), cells/ μ L	280 (123–490)	...
Sociodemographic and health variables		
Age, median (IQR), y	54 (40–61)	47 (35–70)
Male sex at birth	87 (88)	50 (33)
Ethnicity		
White	69 (69)	78 (51)
Black	5 (5)	1 (0.7)
Asian	10 (10)	59 (38)
Latin American	8 (8)	4 (2.6)
Middle Eastern/Arab	3 (3)	0 (0)
Mixed ethnicity	3 (3)	8 (5.3)
Not disclosed	1 (1)	2 (1.3)
No. of chronic conditions, median (IQR)	0 (0–1)	0 (0–1)
Chronic condition		
Hypertension	15 (15)	22 (14.5)
Diabetes	6 (6)	6 (3.9)
Asthma	7 (7)	15 (9.9)
Obesity	15 (15)	14 (9.2)
Chronic lung disease	4 (4)	3 (2)
Chronic liver disease	4 (4)	1 (0.7)
Chronic kidney disease	1 (1)	1 (0.7)
Chronic heart disease	1 (1)	4 (2.6)
Chronic blood disease	1 (1)	2 (1.3)
Cancer	4 (4)	4 (2.6)
Immunosuppression	4 (4)	0 (0)
≥ 1 Condition	45 (45)	50 (33)
COVID-19 status		
COVID-19 convalescent (anti-nucleocapsid antibody positive) at study entry	8 (8)	15 (10)
COVID-19 after vaccination	18 (18)	13 (9)
Vaccine details		
Initial 2-dose regimen		
mRNA-mRNA	82 (82)	148 (97)
ChAdOx1-mRNA (heterologous)	8 (8)	3 (2)
ChAdOx1-ChAdOx1	8 (8)	1 (0.7)
ChAdOx1-not disclosed	1 (1)	...
Time between 1st and 2nd doses, median (IQR), d	58 (53–67)	89 (65–98)
3rd dose		
BNT162b2	23/80 (29)	56/137 (41)
mRNA-1273	56/80 (70)	81/137 (59)
Unknown	1/80 (1)	...
Time between 2nd and 3rd doses, median (IQR), d	183 (143–191)	198 (173–216)
Specimen collection		
Specimen 1 mo after 2nd dose	97 (97)	151 (99)

Table 1. Continued

Characteristic	Participants, No. (%) ^a	
	PLWH (n = 99)	Controls (n = 152)
Day of collection 1 mo after 2nd dose, median (IQR)	30 (29–30)	30 (29–32)
Specimen 3 mo after 2nd dose	96 (96)	148 (97)
Day of collection 3 mo after 2nd dose, median (IQR)	90 (90–91)	90 (89–91)
Specimen 6 mo after 2nd dose	62 (62)	136 (89)
Day of collection 6 mo after 2nd dose, median (IQR)	180 (177–182)	180 (178–182)
Specimen 1 mo after 3rd dose	80 (80)	137 (90)
Day of collection 1 mo after 3rd dose, median (IQR)	30 (30–32)	30 (29–32)

Abbreviations: COVID-19, coronavirus disease 2019; HIV, human immunodeficiency virus; IQR, interquartile range; mRNA, messenger RNA; PLWH, people living with human immunodeficiency virus.

^aData represent no. (%) of participants unless identified as median (IQR).

Statistical Analysis

Continuous variables were compared using the Mann-Whitney *U* test (unpaired data) or Wilcoxon test (paired data). Relationships between continuous variables were assessed using Spearman's correlation. Multiple linear regression was used to investigate the relationship between HIV infection and COVID-19 vaccine-related immune outcomes using a confounder model that adjusted for variables that could influence vaccine responses and/or that differed in prevalence between PLWH and controls. For neutralization at 6 months after the second dose, we used multiple logistic regression owing to the high proportion of results that were BLOQ. Variables included HIV infection (controls as reference group), age (per year), sex at birth (female as reference), ethnicity (nonwhite as reference), number of chronic conditions (per additional), interval between first and second doses (per day), sampling date after vaccination (per day), dual ChAdOx1 as the initial regimen (messenger RNA [mRNA] or mixed [ChAdOx1/mRNA] regimen as the combined reference group), and prior COVID-19 (COVID-19 naive as reference). Plasma neutralization models also corrected for anticoagulant (anticoagulant citrate dextrose as reference), and post-third-dose analyses also corrected for third dose mRNA vaccine brand (BNT162b2 as reference) and the interval between second and third doses (per day). All tests were 2 tailed, with differences considered statistically significant at $P < .05$. Analyses were conducted using Prism v9.2.0 software (GraphPad).

RESULTS

Cohort Characteristics

As described elsewhere [29], all PLWH had suppressed plasma HIV loads while on therapy (Table 1). Recent and nadir CD4⁺ T-cell counts were a median of 715/ μ L (interquartile range

[IQR], 545–943/ μ L; range, 130–1800/ μ L) and 280/ μ L (123–490/ μ L; range, <10/ μ L to 1010/ μ L), respectively. PLWH and controls were broadly similar in age and number of chronic conditions, but the PLWH group included more participants who were male and more who were white. Because the majority of controls were healthcare workers who were vaccinated before the general population (including PLWH), some vaccine-related variables differed between groups. The interval between first and second doses was longer for controls (median, 89 vs 58 days for PLWH), because those vaccinated earlier in Canada's campaign waited up to 112 days between doses owing to initially limited vaccine supply [43]. Fewer controls received dual ChAdOx1 vaccines as their initial regimen (<1% vs 8% of PLWH), because initially only mRNA vaccines were available in Canada. Vaccine timing also indirectly influenced postvaccination SARS-CoV-2 infection incidence. While a comparable number of PLWH (8%) and controls (10%) were anti-nucleocapsid seropositive at study entry, a larger proportion of PLWH (18%) experienced postvaccination infections (18% vs 9% of controls). This is unlikely to be due to increased infection susceptibility but rather because the first Omicron "wave" occurred just before the post-third-dose study visit for many PLWH, whereas most controls had already completed this visit.

Third dose eligibility and timing also differed between groups. In October 2021, third doses began to be offered in BC to priority populations, including PLWH who had ≥ 1 of the following: age ≥ 65 years, prior AIDS-defining illness, prior CD4⁺ T-cell count <200/ μ L or prior CD4 fraction $\leq 15\%$, any plasma HIV load >50 copies/mL in 2021, or perinatally acquired HIV. The majority of PLWH in BC met ≥ 1 criterion, though not all eligible individuals were vaccinated immediately. By January 2022, all remaining adults in BC aged ≥ 18 years were eligible for a third dose 6 months after their second dose. At the time of writing, 80% of PLWH participants and 88% of controls had received a third dose, on average 6.3 months after their second dose. All third doses were mRNA vaccines, and more PLWH than controls received mRNA-1273 (70% vs 59%, respectively). Third mRNA-1273 dose recommendations also differed by risk group: 100 μ g was recommended for adults aged ≥ 70 years and PLWH meeting any priority criterion, whereas the standard 50- μ g booster was recommended for all other adults.

Binding Antibody Responses

Initial responses to 2-dose vaccination in this cohort have been described elsewhere [29]. Briefly, 1 month after 2-dose vaccination, anti-RBD antibody concentrations were a median (IQR) of 3.9 (3.7–4.1) \log_{10} U/mL in PLWH, compared with 4.0 (3.8–4.2) \log_{10} in controls ($P = .04$; Figure 1A). Only 2 participants were nonresponders: 1 in the PLWH group with non-HIV-related immunodeficiency and 1 >80-year-old control participant with 3 chronic conditions. By 3 months after the second dose, antibody concentrations had declined to a median (IQR) of 3.4 (3.2–3.6) \log_{10} U/mL in PLWH, compared with 3.6

(3.4–3.8) \log_{10} U/mL in controls ($P < .001$). HIV infection, however, did not remain significantly associated with antibody concentrations at these 2 time points after controlling for socio-demographic, health-related, and vaccine-related variables (HIV-related estimates and P values shown in Table 2; full models shown in Supplementary Table 1). Rather, older age, more chronic conditions, and dual ChAdOx1 vaccination were associated with lower antibody concentrations at both time points, while a longer dose interval was associated with higher antibody concentrations, regardless of HIV status.

By 6 months after the second dose, anti-RBD antibody concentrations had declined to a median (IQR) of 3.1 (2.9–3.3) \log_{10} U/mL in PLWH versus 3.2 (3.0–3.4) \log_{10} U/mL in controls ($P = .002$; Figure 1A), though no effect of HIV infection on antibody concentrations remained after multivariable correction ($P = .64$; Table 2; full model in Supplementary Table 2). Rather, dual ChAdOx1 vaccination was the strongest correlate of poorer responses at this time point, while a longer time between vaccination and sampling was associated with marginally higher antibody concentrations. The latter observation is likely due to confounding by age; 13 controls aged ≥ 70 years did not contribute samples at this time point because they had already received third doses per BC's age-based rollout, and another 25 participants aged ≥ 65 years contributed this sample early owing to imminently scheduled third doses. Prior COVID-19 was also associated with superior antibody concentrations at this time point, though 11 recent infections (red symbols in Figure 1A) influenced this result.

We next assessed temporal reductions in antibody concentrations after 2 vaccine doses (Figure 1B). Assuming exponential decay, and restricting the analysis to COVID-19-naïve participants with a complete post-second-dose longitudinal series with no values above the assay ULOQ, we estimated antibody half-lives to be a median of (IQR) of 53 (47–70) days in PLWH versus 59 (51–75) days in controls ($P = .02$; Figure 1C). This difference, however, did not remain significant after multivariable correction ($P = .63$; Table 2; full model in Supplementary Table 2).

A third vaccine dose boosted antibody concentrations to an average of 0.4–0.5 \log_{10} U/mL higher than peak post-second dose levels (within-group $P < .001$ for both PLWH and controls), to a median (IQR) of 4.3 (4.2 to >ULOQ) \log_{10} U/mL in PLWH and 4.4 (4.2 to >ULOQ) \log_{10} U/mL in controls (between-group $P = .83$), values comparable to those in participants with prior COVID-19 (Figure 1A). Multivariable analyses were not performed, because nearly 50% of values were above the ULOQ.

Consistent with previous observations at 1 and 3 months after the second vaccine dose [29], we observed no significant relationship between the most recent or nadir CD4⁺ T-cell count and antibody concentrations either 6 months after the second dose or 1 month after the third dose in PLWH (Supplementary Figure 2). We also observed no significant

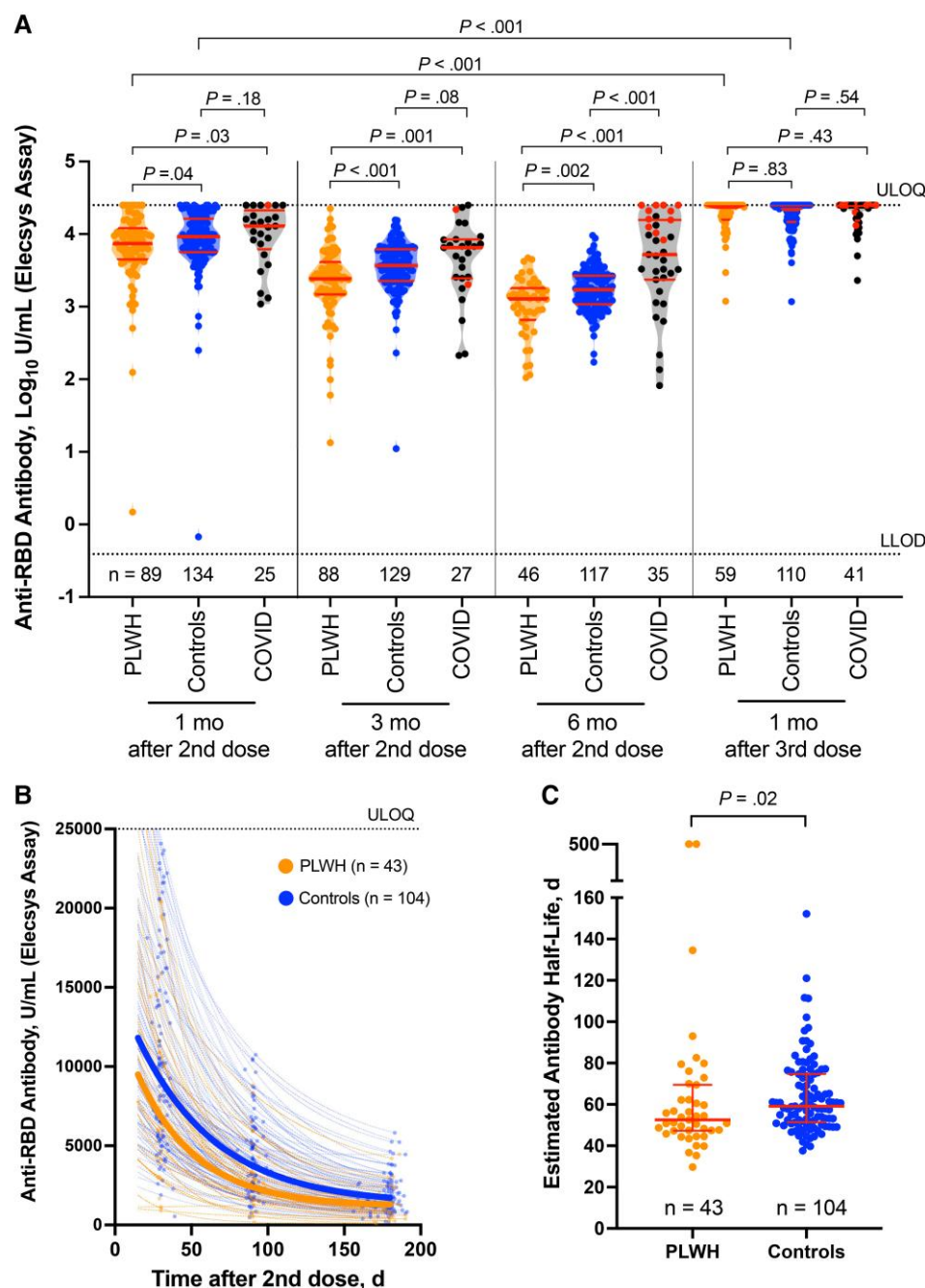


Figure 1. Concentrations of total binding antibodies in serum to spike receptor-binding domain (RBD) after 2 and 3 coronavirus disease 2019 (COVID-19) vaccine doses. **A**, Binding antibody responses to the severe acute respiratory syndrome coronavirus 2 spike RBD in serum samples 1, 3, and 6 months after the second vaccine dose and 1 month after the third dose, in people living with human immunodeficiency virus (PLWH) (orange) and controls (blue) who were COVID-19 naive at the studied time point, as well as in individuals who had recovered from COVID-19 at the studied time point (COVID group [black]). Participants who experienced a postvaccination infection were relocated from their original group into the COVID group at their first postinfection study visit, where they are denoted by red symbols. Numbers of participants are shown at the bottom of the plot. The thick horizontal red bar represents the median; thinner horizontal red bars, the interquartile range (IQR). P-values were computed using the Mann-Whitney *U* test (for comparisons between groups) or the Wilcoxon matched-pairs test (for comparisons across time points within a group) and are uncorrected for multiple comparisons. Abbreviations: LLOD, lower limit of detection; ULOQ, upper limit of quantification. **B**, Temporal declines in serum binding antibody responses to spike RBD after 2 vaccine doses in individual PLWH (light orange) and controls (light blue) who remained COVID-19 naive during this period. Thick lines in corresponding colors denote averages for each group. Only participants with a complete longitudinal data series with no values above the ULOQ are shown. **C**, Binding antibody half-lives after 2 COVID-19 vaccine doses, in PLWH (orange) and controls (blue) who remained COVID-19 naive during this period. Values were calculated by fitting an exponential curve to the data shown in **B**. The 2 outliers are individuals whose antibody levels did not decay or decayed exceedingly slowly, producing half-lives >500 days. For visualization purposes, their half-lives are shown as 500 days. Numbers are indicated at the bottom of the plot. Red bars and whiskers represent medians and interquartile ranges, and P-values were computed using the Mann-Whitney *U* test.

Table 2. Impact of Human Immunodeficiency Virus Infection on Humoral Responses to Coronavirus Disease 2019 Vaccination: Summary of Estimates from Multivariable Analyses^a

Humoral Measure	SARS-CoV-2 Strain	Study Time Point	HIV Infection Estimates From Multivariable Model			
			Estimate	95% CI	P Value	Full Model
Log ₁₀ anti-RBD antibodies ^b	WT	1 mo after 2nd dose	−0.017	−.18 to .14	.83	Supplementary Table 1
	WT	3 mo after 2nd dose	−0.13	−.27 to .019	.09	Supplementary Table 1
	WT	6 mo after 2nd dose	−0.036	−.19 to .11	.64	Supplementary Table 2
Antibody half-life after 2nd dose (in days) ^c	WT	Calculated from all post-2nd-dose time points	6.33	−19.92 to 32.59	.63	Supplementary Table 2
	WT	1 mo after 2nd dose	0.20	−.47 to .86	.56	Supplementary Table 1
Log ₂ viral neutralization ^d	WT	3 mo after 2nd dose	−0.063	−.74 to .62	.86	Supplementary Table 1
	WT	6 mo after 2nd dose ^e	OR = 0.51 ^e	.12 to 1.77	.32	Supplementary Table 3
	WT	1 mo after 3rd dose	0.58	−.22 to 1.37	.15	Supplementary Table 4
Omicron-specific log ₁₀ binding IgG ^f	Omicron	1 mo after 3rd dose	0.36	.14 to .58	.002 ^g	Supplementary Table 5
Omicron-specific ACE2 displacement (as %) ^f	Omicron	1 mo after 3rd dose	3.49	−8.48 to 15.47	.57	Supplementary Table 5

Abbreviations: ACE2, angiotensin-converting enzyme 2; CI, confidence interval; HIV, human immunodeficiency virus; Ig, immunoglobulin; RBD, receptor-binding domain; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WT, wild type.

^aThis table summarizes the estimates (coefficients or OR, as appropriate), 95% CI, and *P* values of the relationship between HIV infection and specific humoral responses to coronavirus disease 2019 (COVID-19) vaccination at the time points shown. All estimates were calculated using multivariable linear regression, except for viral neutralization at 6 months after the 2nd dose (see footnote *d*). Full models, adjusted for clinical, demographic and SARS-CoV-2 vaccination variables, are shown in supplementary tables as indicated.

^bQuantified in serum samples using the Roche Elecsys anti-spike protein assay.

^cAntibody half-lives were calculated from anti-RBD antibody concentrations from all participants with a complete longitudinal data series after the second vaccine dose, with no values above the upper limit of quantification and no evidence of prior COVID-19.

^dFor viral neutralization, reciprocal plasma dilutions were log₂ transformed before multivariable analysis.

^eResults for the time point 6 months after the second dose are presented as the adjusted OR and associated 95% CI of detectable viral neutralization activity at this time point, calculated using multivariable logistic regression.

^fQuantified in serum using the Meso Scale Diagnostics V-Plex assay (panel 22).

^gSignificant at *P* < .05.

relationship between these CD4 parameters and antibody half-life after the second dose (Spearman $\rho \leq .16$; $P \geq .3$; not shown).

Viral Neutralization

One month after the second vaccine dose, SARS-CoV-2 neutralization was achieved at a median (IQR) reciprocal plasma dilution of 160 (40–320) in PLWH, compared with 80 (40–160) in controls (Mann-Whitney *P* = .06; [Figure 2A](#)). By 3 months after the second dose this activity declined to a median (IQR) of 40 (20–80) in both PLWH and controls (*P* = .23). Multivariable analyses confirmed no association between HIV infection and neutralization at these time points (HIV-related estimates in [Table 2](#); full model in [Supplementary Table 1](#)). Rather, older age, more chronic conditions, and dual ChAdOx1 vaccination were associated with weaker neutralization at one or both of these time points, while prior COVID-19 was associated with stronger neutralization. By 6 months after the second dose, neutralization had declined to BLOQ in 52% of COVID-19-naïve participants, to a median (IQR) reciprocal dilution of 20 (BLOQ to 40) in PLWH, compared with BLOQ (BLOQ to 20) in controls (*P* = .07; [Figure 2A](#)). Owing to the large proportion of BLOQ values, we applied multivariable logistic regression with neutralization as a binary variable, and we confirmed no association between HIV infection and neutralization at this time point (HIV-related estimates in [Table 2](#); full model in [Supplementary Table 3](#)). We identified only prior COVID-19

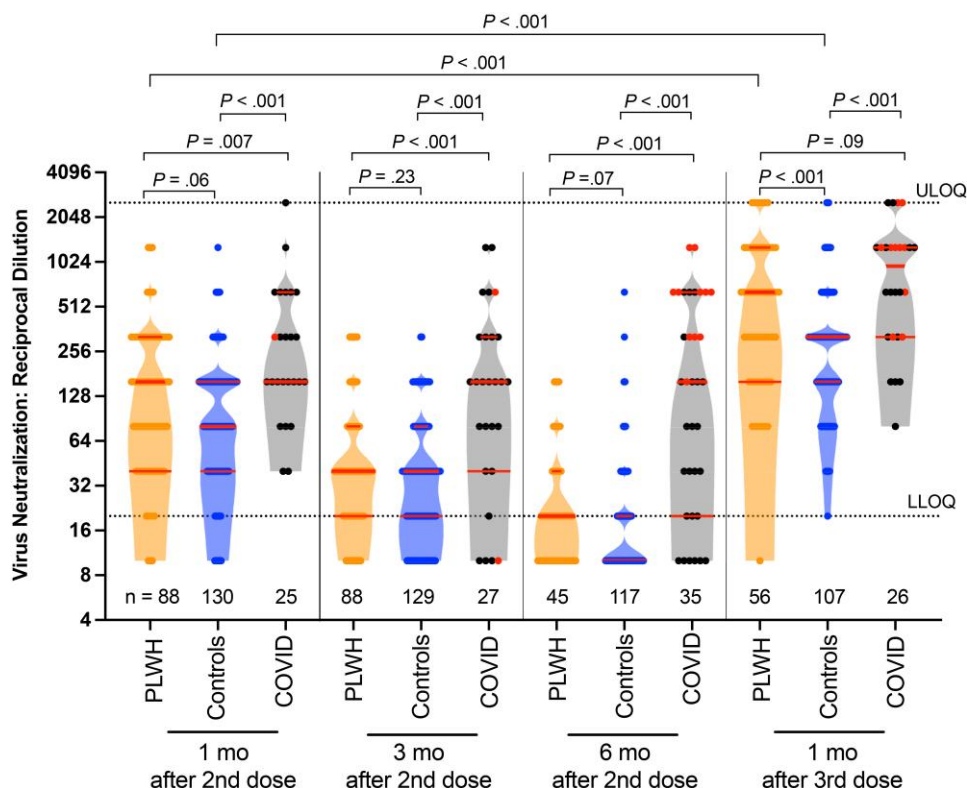
as a biological correlate of neutralization at this time point, though this is influenced by 11 recent infections.

A third COVID-19 vaccine dose boosted neutralization to an average of 4-fold higher than peak post-second-dose levels (within-group *P* < .001 for PLWH and controls; [Figure 2A](#)). In fact, neutralization activities in PLWH (median reciprocal dilution [IQR], 640 [160–1280]) exceeded those in controls (median 320 [160–320]; Mann-Whitney *P* < .001) at this time point, though this difference did not remain significant after multivariable adjustment (*P* = .15; [Table 2](#); full model in [Supplementary Table 4](#)). Rather, having received mRNA-1273 as a third dose and having prior COVID-19 were correlated with better neutralization at this time point, though this is again influenced by numerous recent infections.

We observed no significant relationship between the most recent CD4⁺ T-cell count and neutralization, neither 6 months after the second dose nor 1 month after the third dose in COVID-19-naïve PLWH, nor any relationship between nadir CD4⁺ T-cell count and neutralization 6 months after the second dose ([Supplementary Figure 2](#)). An inverse relationship between nadir CD4⁺ T-cell count and neutralization 1 month after the third dose was found, however (Spearman $\rho = -.28$; *P* = .04).

Omicron-Specific Responses

To estimate the extent to which a third vaccine dose boosts protection against the now-dominant Omicron variant, we compared peak WT- and Omicron-specific responses 1 month



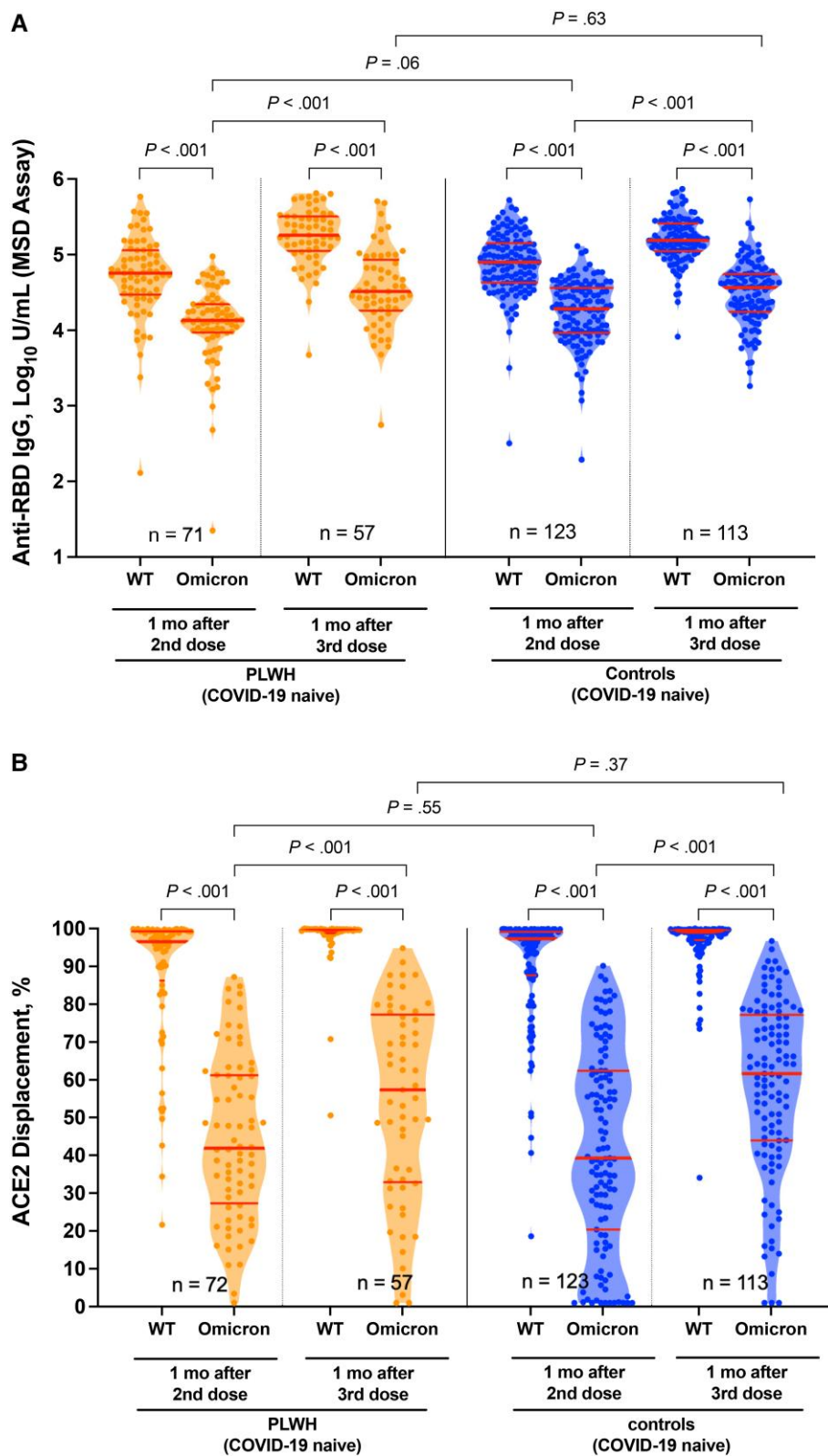


Figure 3. Omicron-specific immunoglobulin G (IgG) binding and angiotensin-converting enzyme 2 (ACE2) displacement activities 1 month after the second and third coronavirus disease 2019 (COVID-19) vaccine doses. *A*, Binding IgG responses in plasma to the wild-type (WT) and Omicron spike receptor binding domain (RBD), measured using the Meso Scale Diagnostics (MSD) V-Plex assay, in people living with human immunodeficiency virus (PLWH) (*orange*) and controls (*blue*) who remained COVID-19 naive throughout the study. Numbers of participants are shown at the bottom of the plot. Thick horizontal red bars represent medians; thinner horizontal red bars, interquartile ranges. *P* values were computed using the Wilcoxon matched-pairs test (for all within-group comparisons) or the Mann-Whitney *U* test (for between-group comparisons) and are uncorrected for multiple comparisons. *B*, Same as *A* but for ACE2 displacement activity, measured using the V-plex severe acute respiratory syndrome coronavirus 2 ACE2 assay, with results reported as the percentage of ACE2 displacement.

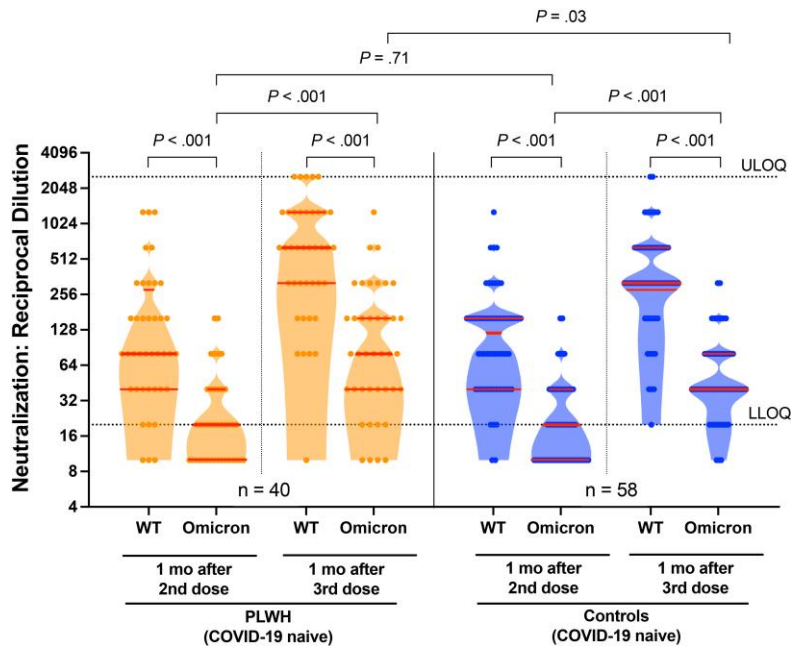


Figure 4. Omicron-specific neutralization activities 1 month after the second and third coronavirus disease 2019 (COVID-19) vaccine doses. Neutralization activities, reported as the reciprocal of the highest plasma dilution at which neutralization was observed in all triplicate assay wells, against the wild-type (WT) and Omicron virus isolates in a subset of people living with human immunodeficiency virus (PLWH) (orange) and controls (blue) who remained COVID-19 naive throughout the study. Numbers of participants are shown at the bottom of the plot. Thick horizontal red bars represent medians; thinner horizontal red bars, interquartile ranges. *P* values were computed using the Wilcoxon matched-pairs test (for within-group comparisons) or the Mann-Whitney *U* test (for between-group comparisons) and are uncorrected for multiple comparisons. Abbreviations: LLOQ, lower limit of quantification; ULOQ, upper limit of quantification.

points (all within-group comparisons, $P < .001$; Figure 3B), and the discrepancy was most pronounced after 2 doses (eg, median WT- and Omicron-specific activities in PLWH were 97% and 42%, respectively, at this time). The third dose nevertheless universally boosted Omicron-specific responses to above second-dose levels (all within-group comparisons, $P < .001$), with median Omicron-specific activity in PLWH rising from 42% after 2 doses to 57% after 3 ($P < .001$). Omicron-specific ACE2 displacement activities were comparable between groups at both time points: 1 month after the second dose these were a median (IQR) of 42% (27%–61%) in PLWH versus 39% (20%–62%) in controls ($P = .55$), rising to a median of 57% (33%–77%) in PLWH versus 62% (44%–77%) in controls 1 month after the third dose ($P = .37$). Multivariable analyses confirmed no association between HIV infection and Omicron-specific ACE2 displacement activity after 3 doses ($P = .57$, Table 2; full model in Supplementary Table 5). After 3 doses, we observed a weak inverse relationship between nadir CD4⁺ T-cell count and Omicron-specific ACE2 displacement (Spearman $\rho = -.3$; $P = .02$) but no relationship between other CD4⁺ T-cell count measures and Omicron-specific responses (Supplementary Figure 2).

Finally, we assessed plasma neutralization against live WT and Omicron viruses at 1 month after the second and third doses in a subset of COVID-19-naïve participants (Figure 4). While

Omicron-specific neutralization was significantly weaker than wild type at both time points in both PLWH and controls (all within-group comparisons, $P < .001$), the third dose significantly boosted Omicron-specific neutralization above second-dose levels (both within-group comparisons, $P < .001$). One month after the second dose, both PLWH and controls neutralized Omicron at a median reciprocal dilution of 20 (IQR, BLOQ to 40) ($P = .71$). One month after the third dose, anti-Omicron neutralization increased to a median (IQR) reciprocal dilution of 80 (40–160) in PLWH, compared with 40 (40–80) in controls ($P = .03$). This was consistent with the superior neutralization of WT virus observed in PLWH at this time point (Figure 2). Neutralization of WT and Omicron viruses were significantly correlated with ACE2 displacement activities, as expected (all $P < .001$; Supplementary Figure 4).

DISCUSSION

Our study confirms that anti-SARS-CoV-2 antibody concentrations and neutralizing activities naturally decline after 2-dose COVID-19 vaccination [32, 44]. Nevertheless, we found no evidence that PLWH receiving suppressive antiretroviral therapy exhibited lower antibody concentrations at any time point up to 6 months after 2-dose vaccination, nor did they exhibit faster rates of antibody decline during this period

compared with controls, after accounting for sociodemographic, health-related, and vaccine-related factors. Similarly, we found no evidence that PLWH exhibited poorer neutralization at any time point after 2 doses compared to controls. The lack of significant difference in immune response decline between PLWH and controls after 2-dose vaccination is consistent with data from PLWH participants in the original ChAdOx1 trial [38].

Our results also showed that a third vaccine dose boosted binding antibody concentrations and function to significantly higher than post-second-dose levels [45], including against Omicron [46]. Consistent with accumulating evidence [34, 36, 37, 47], Omicron-specific antibody responses remained universally weaker than WT-specific ones at all times tested. Nevertheless, after 3 doses, antibody concentrations in PLWH were equivalent to controls, while neutralization activities (including against Omicron) were slightly higher. The latter is likely attributable to PLWH more frequently receiving mRNA-1273 (vs BNT162b2) third doses, which was the strongest correlate of higher neutralization after 3-dose vaccination (Supplementary Table 3). In fact, most PLWH were eligible for 100- μ g mRNA-1273 third doses, which likely boosted responses still further, though we could not confirm this directly.

Our study has several limitations. Our results may not be generalizable to PLWH who are not receiving antiretroviral therapy, who have multiple chronic conditions or who have CD4⁺ T-cell counts <200/ μ L, though we found no evidence that a low nadir CD4⁺ T-cell count negatively influenced COVID-19 vaccine response (in fact, initial post-third-dose viral neutralization and Omicron-specific ACE2 displacement functions were slightly higher in PLWH with lower nadir CD4⁺ T-cell counts, possibly owing to their eligibility for 100- μ g mRNA-1273 third doses). We did not investigate T-cell responses, which may play critical roles, particularly against variants [48, 49]. Canada's decision to increase the interval between first and second vaccine doses to 112 days [43] and to mix mRNA and viral-vector vaccines may affect generalizability. Of the participants who received mRNA-1273 third doses, 36% received 100 μ g, 23% received 50 μ g, and data for the remainder were unavailable, so we could not assess dose effects on vaccine responses. Because immune correlates of vaccine-mediated protection are still being elucidated [50], the implications of our results on individual-level protection remain uncertain, particularly in light of Omicron.

In conclusion, adult PLWH with well-controlled viral loads and preserved CD4⁺ T-cell counts mount strong and functional antibody responses to 2- and 3-dose COVID-19 vaccination, including to Omicron, though it will be important to monitor these responses over time. Studies of PLWH who are not receiving antiretroviral treatment or who have low CD4⁺ T-cell counts are also needed.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (<http://jid.oxfordjournals.org/>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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