People with HIV receiving suppressive antiretroviral therapy show typical antibody durability after dual COVID-19 vaccination, and strong third dose responses

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ABSTRACT

Background: Longer-term humoral responses to two-dose COVID-19 vaccines remain incompletely characterized in people living with HIV (PLWH), as do initial responses to a third dose.

Methods: We measured antibodies against the SARS-CoV-2 spike protein receptor-binding domain, ACE2 displacement and viral neutralization against wild-type and Omicron strains up to six months following two-dose vaccination, and one month following the third dose, in 99 PLWH receiving suppressive antiretroviral therapy, and 152 controls.

Results: Though humoral responses naturally decline following two-dose vaccination, we found no evidence of lower antibody concentrations nor faster rates of antibody decline in PLWH compared to controls after accounting for sociodemographic, health and vaccine-related factors. We also found no evidence of poorer viral neutralization in PLWH after two 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 anti-Omicron responses were consistently weaker than against wild-type. 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 two- and three-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

INTRODUCTION

As people living with HIV (PLWH) may be at increased risk of severe COVID-19 due to immunosuppression, higher rates of multi-morbidity and/or social determinants of health [1-4], COVID-19 vaccination is expected to benefit this group. Two-dose COVID-19 vaccination protects against severe disease [5-7], but impaired responses have been observed in certain immunocompromised groups [8-12]. 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], prompting initial concern that PLWH may respond sub-optimally to COVID-19 immunization. Data from clinical trials [20, 21] and real-world studies however [22-27], including from our group [28], described strong initial immune responses to two-dose COVID-19 vaccination in PLWH with controlled HIV loads on therapy and preserved CD4+ T-cell counts [20-24, 28], though weaker responses have been observed in PLWH who are not receiving therapy or who have CD4+ T-cell counts <200 cells/mm^3 [22, 25-27].

Vaccine-induced antibody responses decline over time, which can increase the risk of post-vaccination SARS-CoV-2 infection [29-31], particularly with the more transmissible Omicron variant [32-36]. Though immune response durability following two-dose COVID-19 vaccination has been examined among PLWH participants of the ChAdOx1 clinical trial [37], 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 [38-40]. Here, we extend our previous report [28] to characterize binding and neutralizing antibody responses up to six months following two-dose COVID-19 vaccination, as well as one month following the third dose, in 99 PLWH and 152 controls without HIV. We assess responses to both wild-type and Omicron SARS-CoV-2 variants.

METHODS

Participants. We previously recruited 99 adult PLWH and 152 controls without HIV, the latter predominantly health care workers, in British Columbia (BC), Canada [28]. Serum and plasma (collected in either ethylenediaminetetraacetic acid [EDTA] or anticoagulant citrate dextrose [ACD]) were collected before vaccination; one month after the first dose; one, three and six months after the second dose; and one month following the third dose. Specimens were processed same-day and frozen at -80°C until analysis. Here we report on the post-second- and third-dose time points.

Ethics 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 by self-report and confirmed through medical records where available. We assigned a score of 1 for each of 11 chronic conditions: hypertension; diabetes; asthma; obesity (body mass index $\geq$30 kg/m^2); 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 cells/mm^3 constituted immunosuppression.

Binding antibody assays. We measured total binding antibodies against SARS-CoV-2 nucleocapsid (N) and spike (S) receptor binding domain (RBD) in serum using the Elecsys Anti-SARS-CoV-2 and Anti-SARS-CoV-2 S assays, respectively, on a Cobas e601 module analyzer (Roche Diagnostics). Post-infection, both assays should be positive, whereas post-vaccination only the S assay should be positive. Both tests are electro-chemiluminescence sandwich immunoassays, and report results in arbitrary

Units/mL. For the S assay, the manufacturer indicates that these arbitrary Unit (U) values can be considered equivalent to WHO-defined international binding antibody units [41]. For the S assay, sera were tested undiluted, with samples above the upper limit of quantification (ULOQ) re-tested at 1:100 dilution, allowing a measurement range of 0.4-25,000 U/mL. Anti-RBD binding IgG concentrations in serum were quantified using the V-plex SARS-CoV-2 (IgG) Panel 22 ELISA kit (Meso Scale Diagnostics), which features wild-type and Omicron antigens, on a Meso QuickPlex SQ120 instrument. Sera were diluted 1:10000, with results reported in arbitrary Units/mL.

ACE2 displacement assay. We assessed the ability of serum antibodies to block the RBD-ACE2 receptor interaction by competition ELISA (Panel 22 V-plex SARS-CoV-2 [ACE2]; Meso Scale Diagnostics) on a Meso QuickPlex SQ120 instrument. Sera were diluted 1:40 and results reported as % 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 # EPI_ISL_9805779) on VeroE6-TMPRSS2 (JCRB-1819) target cells. Viral stock was adjusted to 50 $TCID_{50}$/200 µl in Dulbecco's Modified Eagle Medium in the presence of serial 2-fold plasma dilutions (from 1/20 to 1/2560), incubated at 4°C for 1 hour and added to target cells in 96-well plates in triplicate. Cultures were maintained at 37°C with 5% CO_2 and the appearance of viral cytopathic effect (CPE) was recorded three days post-infection. Neutralizing activity is reported as the reciprocal of the highest plasma dilution able to prevent CPE in all triplicate wells. Samples exhibiting partial or no neutralization at 1/20 dilution were assigned a reciprocal dilution of 10, defined as below the limit of quantification (BLOQ).

133 ***Statistical analysis.*** Continuous variables were compared using the Mann-Whitney U-test (unpaired data)
134 or Wilcoxon test (paired data). Relationships between continuous variables were assessed using
135 Spearman's correlation. Multiple linear regression was used to investigate the relationship between
136 sociodemographic, health and vaccine variables and immune outcomes, except for neutralization at 6
137 months post-second dose, where multiple logistic regression was used due to the high proportion of results
138 BLOQ. Variables included HIV infection (controls as reference group), age (per year), sex at birth (female
139 as reference), ethnicity (non-white as reference), number of chronic conditions (per additional), interval
140 between first and second doses (per day), sampling date after vaccination (per day), dual ChAdOx1 as the
141 initial regimen (mRNA or mixed [ChAdOx1/mRNA] regimen as the combined reference group), and prior
142 COVID-19 (COVID-19-naive as reference). Plasma neutralization models also corrected for the
143 anticoagulant (ACD as reference). Post-third-dose analyses also corrected for the third dose mRNA
144 vaccine brand (BNT162b2 as reference) and the interval between second and third doses (per day). All
145 tests were two-tailed, with $p<0.05$ considered statistically significant. Analyses were conducted using
146 Prism v9.2.0 (GraphPad).
147

RESULTS

Cohort characteristics

All PLWH were receiving antiretroviral therapy and had suppressed plasma HIV loads (**Table 1**). Recent CD4+ T-cell counts, measured a median 44 days before enrolment, were a median 715 cells/mm^3 (Interquartile Range [IQR] 545-943; range 130-1800), where only two participants had values <200 cells/mm^3. Nadir CD4+ T-cell counts were a median 280 cells/mm^3 (IQR 123-490; range <10-1010). The 99 PLWH and 152 controls were broadly similar in age, but the PLWH group included a greater proportion of males and of white ethnicity. PLWH and controls had similar numbers of chronic health conditions (45% and 33%, respectively, had at least one condition). At study entry, 8% of PLWH and 10% of controls had anti-N antibodies, indicating prior SARS-CoV-2 infection. An additional 31 participants (18 PLWH; 13 controls) experienced post-vaccination SARS-CoV-2 infections, 26 of which occurred during the Omicron wave. More PLWH received dual ChAdOx1 vaccines for their first two doses (8%) compared to <1% of controls. On average, the interval between first and second doses was longer for controls (median 89 days versus 58 for PLWH). In British Columbia (BC), third doses began to be offered in October 2021 to priority populations, including PLWH who had one or more of: age ≥ 65 years, prior AIDS-defining illness, prior CD4 count <200 cells/mm^3 or prior CD4 fraction ≤ 15%, any plasma HIV load >50 copies/mL in 2021, or perinatally-acquired HIV. The majority of PLWH in BC met at least one of these criteria. 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 following their second dose. All third doses were mRNA vaccines, and more PLWH (70%) received mRNA-1273 compared to controls (59%). Third mRNA-1273 doses also differed by risk group: 100 mcg was recommended for adults aged ≥70 years and

PLWH who met any priority criterion, whereas the standard booster dose of 50 mcg was recommended for all other adults.

Binding antibody responses after second and third doses

One month following two-dose vaccination, anti-RBD antibody concentrations were a median 3.9 [IQR 3.7-4.1] $\log_{10}$ U/mL in PLWH compared to a median of 4.0 [IQR 3.8-4.2] $\log_{10}$ in controls (p=0.04, **Figure 1A**). By three months following the second dose, antibody concentrations had declined in both groups, to a median of 3.4 [IQR 3.2-3.6] $\log_{10}$ U/mL in PLWH compared to a median of 3.6 [IQR 3.4-3.8] $\log_{10}$ U/mL in controls (p=0.0001). These differences however did not remain significant in multivariable analyses controlling for sociodemographic, health- and vaccine-related variables (p-values for HIV infection p=0.83 and p=0.088, respectively, **Supplemental Table 1**). Rather, a greater number of chronic conditions and dual ChAdOx1 vaccination were independently associated with lower antibody concentrations at both time points, while a longer dose interval was associated with higher antibody concentrations (all p<0.05), regardless of HIV status. Older age was also significantly correlated with lower antibody concentrations one month post-second dose (p=0.0053), and was marginally significant at three months (p=0.055). Participants with prior COVID-19 (where post-vaccination infections are shown as red dots on **Figure 1A**) displayed modestly higher responses at one- and three-months post-second dose, though this did not remain significant after multivariable correction.

By six months after the second dose, antibody concentrations had declined to a median of 3.1 [IQR 2.9-3.3] $\log_{10}$ U/mL in PLWH versus a median 3.2 [IQR 3.0-3.4] $\log_{10}$ U/mL in controls (p=0.0021, **Figure 1A**), though this difference did not remain significant after multivariable correction (p=0.64; **Table 2**). Rather, dual ChAdOx1 vaccination was the strongest correlate of weaker responses at this time point, being associated with a nearly a $\log_{10}$ adjusted lower antibody concentration (p<0.0001), regardless

193 of HIV status. Age was no longer a correlate of weaker responses at the six-month time point (p=0.99),
194 while a longer time between vaccination and sampling was associated with marginally higher antibody
195 concentrations (p=0.0067). This is likely driven by 13 control participants aged ≥ 70 years who did not
196 contribute samples to this time point due to receipt of third doses less than six months after the second
197 dose, and 25 participants aged ≥ 65 years who contributed this sample early due to imminently scheduled
198 third doses as per the age-based rollout in BC. Prior COVID-19 was associated with superior antibody
199 concentrations at the six-month time point (**Figure 1A** and **Table 2**), though this is influenced by 11
200 participants with recent infections.

201 We next assessed temporal reductions in antibody concentrations after two vaccine doses (**Figure**
202 **1B)**. Assuming exponential decay, and restricting the analysis to COVID-19-naive participants with a
203 complete post-second-dose longitudinal series with no values above the assay upper limit of quantification
204 (ULOQ), we estimated antibody half-lives to be a median of 53 [IQR 47-70] days in PLWH versus a
205 median of 59 [IQR 51-75] days in controls (p=0.023, **Figure 1C**). This difference however did not remain
206 significant after multivariable correction (p=0.63; **Table 2**).

207 A third vaccine dose boosted antibody concentrations to an average of 0.4-0.5 $\log_{10}$ U/mL higher
208 than peak post-second dose levels (within-group p<0.0001 for both PLWH and controls), to a median of
209 4.3 [IQR 4.2 to >ULOQ] $\log_{10}$ U/mL in PLWH and 4.4 [IQR 4.2 to >ULOQ] $\log_{10}$ U/mL in controls
210 (between-group p=0.83), values that were comparable to those in participants with prior COVID-19
211 (**Figure 1A**). Multivariable analyses were not performed as nearly 50% of values were >ULOQ.

212 Consistent with our previous observations at one and three months post-second vaccine dose [28],
213 we observed no significant relationship between most recent or nadir CD4+ T-cell count and antibody
214 concentrations either six months after the second dose or one month following the third dose in PLWH

(**Supplementary Figure 1**). We also observed no significant relationship between these CD4 parameters and antibody half-life after the second dose (Spearman $\rho \leq 0.16$, $p \geq 0.3$; not shown).

Viral neutralization after second and third doses

One month after the second vaccine dose, SARS-CoV-2 neutralization was achieved at a median reciprocal plasma dilution of 160 (IQR 40-320) in PLWH compared to a median of 80 (IQR 40-160) in controls (Mann-Whitney p=0.06, **Figure 2A**). By three months post-second dose this activity declined to 40 [IQR 20-80] in both PLWH and controls (p=0.23). Multivariable analyses identified older age, a higher number of chronic conditions and dual ChAdOx1 vaccination as significant independent correlates of poorer neutralization one month post-second dose (all $p<0.05$), with negative effects of dual ChAdOx1 vaccination (p=0.0032) and to a lesser extent age (p=0.059) persisting at three months (**Supplemental Table 1**). Prior COVID-19 was associated with higher neutralization at both of these time points following multivariable correction (both $p \leq 0.0002$).

By six months post-second dose, neutralization had declined to below the limit of quantification (BLOQ) in 52% of COVID-19-naive participants, to a median reciprocal dilution of 20 [IQR BLOQ-40] in PLWH and a median BLOQ [IQR BLOQ-20] in controls (p=0.07, **Figure 2A**). Due to the large proportion of BLOQ values, we applied multivariable logistic regression with neutralization as a binary variable, and identified only prior COVID-19 as a biological correlate of neutralization at this time point (p=0.0037; **Supplemental Table 2**). This however is influenced by 11 participants with recent infections.

A third COVID-19 vaccine dose boosted neutralization to an average of fourfold higher than peak post-second-dose levels (within-group $p<0.0001$ for PLWH and controls; **Figure 2A**). In fact, neutralization activities in PLWH (median reciprocal dilution of 640 [IQR 160-1280]) exceeded those of controls (median of 320 [160-320]; Mann-Whitney p=0.0006) at this time point, though this did not

remain significant following multivariable adjustment (p=0.15; **Supplemental Table 3**). Rather, having received mRNA-1273 as a third dose was the strongest independent correlate of better neutralization (p=0.0009). Prior COVID-19 was associated with better neutralization, though it is difficult to disentangle infection- from vaccine-induced responses due to a number of recent infections (red circles in **Figure 2A**).

We observed no significant relationship between most recent CD4+ T-cell count and neutralization at either six months post-second dose nor at one month post-third dose in COVID-19 naive PLWH; nor any relationship between nadir CD4+ T-cell count and neutralization at six months post-second dose (**Supplemental Figure 1**). An inverse relationship between nadir CD4+ T-cell count and neutralization one month after the third dose however was found (Spearman ρ= -0.28; p=0.04).

Humoral responses against Omicron following two and three vaccine doses

To estimate the extent to which a third dose boosts protection against the now-dominant Omicron variant, we compared peak responses against wild-type and Omicron variants one month following the second and third doses. To avoid confounding by infection-induced immunity, we restricted this analysis to COVID-19-naive individuals. For both PLWH and controls, serum IgG concentrations capable of binding Omicron RBD were on average ~0.6 $\log_{10}$ U/mL lower than those capable of binding wild-type RBD at both time points (all within-group comparisons p<0.0001; **Figure 3A**). Nevertheless, the third dose significantly boosted anti-Omicron IgG concentrations to an average of 0.3-0.5 $\log_{10}$ U/mL higher than those observed after two doses in both groups (within-group comparisons p<0.0001). One month post-second dose, anti-Omicron IgG concentrations were a median 4.12 [IQR 3.93-4.35] $\log_{10}$ U/mL in PLWH and a median of 4.28 [IQR 3.97-4.56] $\log_{10}$ U/mL in controls (p=0.04), but after three doses, these responses reached equivalence, with medians of 4.51 [IQR 4.26-4.93] $\log_{10}$ U/mL in PLWH versus 4.56 [IQR 4.24-4.74] $\log_{10}$ U/mL in controls (p=0.63). In fact, a multivariable analysis of Omicron-specific

IgG concentrations after three doses identified HIV infection as being associated with an adjusted 0.36 $\log_{10}$ U/mL *higher* anti-Omicron IgG concentrations (p=0.0017; **Table 3**). Having received mRNA-1273 for the third dose, as well as longer interval between second and third doses, were also associated with higher anti-Omicron IgG responses (both p<0.05); male sex was associated with lower responses (p=0.032).

We also assessed the ability of plasma to block the RBD-ACE2 interaction, which estimates potential viral neutralization [42]. This activity was significantly weaker against Omicron compared to wild-type for both groups at both time points (all within-group comparisons p<0.0001; **Figure 3B**), where the discrepancy was most pronounced after two doses (*e.g.* median activities against wild-type and Omicron in PLWH were 97% versus 42%, respectively, at this time). The third dose nevertheless universally boosted anti-Omicron responses to above second-dose levels (all within-group comparisons p≤0.0009), with median anti-Omicron activity in PLWH rising from 42% after two doses to 57% after three (p=0.0009). Anti-Omicron ACE2 % displacement activities were comparable between groups at both time points: one month after the second dose these were a median 42% [IQR 27-61] in PLWH compared to 39% [IQR 20-62] in controls (p=0.55), rising to a median 57% [IQR 33-77] in PLWH compared to 62% [IQR 44-77] in controls one month after the third dose (p=0.37). In multivariable analyses, male sex was the only independent (negative) correlate of anti-Omicron ACE2 displacement activity after three doses (p=0.031, **Table 3**). After three doses, we observed a weak inverse relationship between nadir CD4+ T-cell count and anti-Omicron ACE2 % displacement (Spearman ρ= -0.3; p=0.02), but no relationship between other CD4+ T-cell count measures and anti-Omicron responses (**Supplemental Figure 1**).

Finally, we assessed plasma neutralization against live wild-type and Omicron viruses at one month following the second and third doses in a subset of COVID-19-naive participants (**Figure 4**). While

284 neutralization against Omicron was significantly weaker compared to wild-type at both time points in both
285 PLWH and controls (all within-group comparisons $p<0.0001$), the third dose nevertheless significantly
286 boosted anti-Omicron neutralization above second dose levels (both within-group comparisons $p<0.0001$).
287 One month after the second dose, both PLWH and controls neutralized Omicron at a median reciprocal
288 dilution of 20 [IQR BLOQ - 40] ($p=0.71$). One month after the third dose, anti-Omicron neutralization
289 activity increased to a median reciprocal dilution of 80 [IQR 40-160] in PLWH compared to a median 40
290 [IQR 40-80] in controls ($p=0.03$). This was consistent with the superior neutralization of wild-type virus
291 observed in PLWH at this timepoint (**Figure 2**). Neutralization of wild-type and Omicron viruses
292 correlated significantly with their respective ACE2 displacement activities (all $p<0.0001$, **Supplemental**
293 **Figure 2**).

DISCUSSION

Our study confirms that antibody concentrations and neutralizing activities naturally decline following two-dose COVID-19 vaccination [31, 43]. Nevertheless, we found no evidence that PLWH receiving suppressive antiretroviral therapy exhibited lower antibody concentrations at any time point up to six months following two-dose vaccination, nor did they exhibit faster rates of antibody decline during this period compared to controls, after accounting for sociodemographic, health- and vaccine-related factors. Similarly we found no evidence that PLWH exhibited poorer neutralization at any time point after two doses compared to controls. These observations are consistent with data from PLWH participants of the original ChAdOx1 trial, which reported no significant difference in immune response decline in PLWH compared to controls following two vaccine doses [37].

Our results also showed that a third vaccine dose boosted binding antibody concentrations and function to significantly higher levels than those observed after two doses. After three doses, antibody concentrations in PLWH were equivalent to controls, while neutralization activities were slightly higher. The higher neutralization is attributable to PLWH more frequently receiving mRNA-1273 (vs. BNT162b2) third doses, which was the strongest correlate of higher neutralization after three-dose vaccination (**Supplemental Table 3**). In fact, the majority of PLWH were eligible for full (100 mcg) mRNA-1273 third doses, which likely boosted responses still further, though we were not able to confirm this due to incomplete dose information. Consistent with accumulating evidence [44-47], antibody responses against Omicron were universally weaker than against wild-type after two and three vaccine doses, though the third dose significantly boosted anti-Omicron responses. Indeed, post-third-dose anti-Omicron responses in PLWH were equivalent to or higher than controls, again possibly attributable to a higher proportion of PLWH receiving (full) mRNA-1273 third doses.

316 Our study has several limitations. Our results may not be generalizable to PLWH who are not
317 receiving antiretroviral therapy, who have multiple co-morbidities or who have CD4+ T-cell counts <200
318 cells/mm^3. We found no evidence that a low nadir CD4+ T-cell count negatively influenced COVID-19
319 vaccine response however, indicating that prior low CD4 T+ cell counts will not necessarily compromise
320 immune responses to COVID-19 vaccines presently. We did not investigate T-cell responses, which may
321 play critical protective roles, particularly against variants [48, 49]. Individuals ≥70 years old and PLWH
322 meeting priority criteria were eligible for full mRNA-1273 third doses, but we could not directly assess
323 mRNA-1273 dose-related effects on immune responses due to incomplete dosing information. Finally,
324 while immune correlates of vaccine-mediated protection are being elucidated for SARS-CoV-2 [50], the
325 implications of our results on individual-level protection from infection and disease remain uncertain,
326 particularly in the context of Omicron.

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

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FIGURE LEGENDS

Figure 1. Concentrations of total binding antibodies in serum to spike RBD following two and three COVID-19 vaccine doses. *Panel A:* Binding antibody responses to the SARS-CoV-2 spike RBD in serum at one, three and six months following the second dose, and one month following the third vaccine dose, in PLWH (orange) and controls (blue) who were COVID-19 naive at the studied time point, as well as individuals who had recovered from COVID-19 at the studied time point (COVID group, black). Participants who experienced a post-vaccination infection were relocated from their original group into the COVID group at their first post-infection study visit, where they are denoted by a red symbol. Participant Ns are shown at the bottom of the plot. The thick horizontal red bar represents the median; thinner horizontal red bars represent the 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. ULOQ: upper limit of quantification; LLOD: lower limit of detection. *Panel B:* Temporal declines in serum binding antibody responses to spike-RBD following two vaccine doses in PLWH (orange) and controls (blue) who remained COVID-19 naive during this period. Only participants with a complete longitudinal data series with no values above the ULOQ are shown. *Panel C*: Binding antibody half-lives following two COVID-19 vaccine doses, calculated by fitting an exponential curve to the data shown in panel B. Ns are indicated at the bottom of the plot. Red bars and whiskers represent the median and IQR. P-value computed using the Mann-Whitney U-test.

Figure 2. Live virus neutralization activities following two and three COVID-19 vaccine doses. Viral neutralization activity in plasma at one, three and six months following the second dose, and one month following the third vaccine dose, in PLWH (orange) and controls (blue) who were COVID-19 naive at the

377 studied time point, as well as individuals who had recovered from COVID-19 at the studied time point
378 (COVID group, black). Plasma neutralization was defined as the reciprocal of the highest plasma dilution
379 at which vial cytopathic effect was prevented in all triplicate assay wells. Plasma samples showing
380 neutralization in fewer than three wells at the lowest plasma dilution of 1/20 were coded as having a
381 reciprocal dilution of 10, corresponding to the lower limit of quantification (LLOQ) in this assay. The
382 highest dilution tested was 1/2560, which corresponds to the upper limit of quantification (ULOQ).
383 Participants who experienced a post-vaccination infection were relocated from their original group into the
384 COVID19 group at their first post-infection study visit, where they are denoted by a red symbol.
385 Participant Ns are shown at the bottom of the plot. The thick horizontal red bar represents the median;
386 thinner horizontal red bars represent the IQR. P-values were computed using the Mann-Whitney U-test
387 (for comparisons between groups) or the Wilcoxon matched pairs test (for comparisons across time points
388 within a group) and are uncorrected for multiple comparisons.
389
390 **Figure 3: Anti-Omicron IgG binding and ACE2 displacement activities one month after the second**
391 **and third COVID-19 vaccine doses.** *Panel A:* Binding IgG responses in plasma to the wild-type (WT)
392 and Omicron (OM) spike-RBD (S-RBD), measured using the Meso Scale Diagnostics V-Plex assay, in
393 PLWH (orange) and controls (blue) who remained COVID-19 naive throughout the study. Participant Ns
394 are shown at the bottom of the plot. Thick horizontal red bar represents the median; thinner horizontal red
395 bars represent the IQR. P-values were computed using the Wilcoxon matched pairs test (for all within-
396 group comparisons) or the Mann-Whitney U-test (for between-group comparisons) and are uncorrected
397 for multiple comparisons. *Panel B:* same as A, but for ACE2 displacement activity, measured using the V-
398 plex SARS-CoV-2 (ACE2) assay, where results are reported in terms of % ACE2 displacement.
399

Figure 4: Anti-Omicron neutralization activities one month after the second and third 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 (OM) virus isolates a subset of PLWH (orange) and controls (blue) who remained COVID-19 naive throughout the study. Participant Ns are shown at the bottom of the plot. Thick horizontal red bar represents the median; thinner horizontal red bars represent the IQR. 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.

SUPPLEMENTAL FIGURES

Supplemental Figure 1: Relationships between most recent and nadir CD4+ T-cell counts and humoral responses following two and three vaccine doses. Relationships were assessed using Spearman's correlation. Measurements against wild-type SARS-CoV-2 at six months post-second-dose are indicated by red symbols; measurements against wild-type SARS-CoV-2 at one month post-third-dose are indicated by blue symbols; measurements against Omicron at one month post-third-dose are indicated by open symbols. Analyses are restricted to COVID-19-naive PLWH. LLOQ: Lower limit of quantification; ULOQ: Upper limit of quantification.

Supplemental Figure 2: Relationships between ACE2 % displacement and viral neutralization activity against wild-type and Omicron after two and three COVID-19 vaccine doses. Relationships were assessed using Spearman's correlation. Measurements against wild-type SARS-CoV-2 are indicated by blue symbols; measurements against Omicron are indicated by open symbols. Reported Ns reflect all

measurements completed on all study participants (PLWH and controls) regardless of prior COVID-19 (while Figures 3 and 4 report only results from COVID-19-naive participants). LLOQ: Lower limit of quantification.

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542

Table 1: Participant characteristics

Characteristic	PLWH (n=99)	Controls (n=152)
HIV-related variables		
Receiving antiretroviral therapy, n (%)	99 (100%)	-
Most recent plasma viral load, copies HIV RNA/mL, median [IQR]	<50 [<50 - <50]	-
Most recent CD4+ T-cell count in cells/mm3, median [IQR]	715 [545-943]	-
Nadir CD4+ T-cell count in cells/mm3, median [IQR]	280 [123-490]	-
Sociodemographic and health variables		
Age in years, median [IQR]	54 [40-61]	47 [35-70]
Male sex at birth, n (%)	87 (88%)	50 (33%)
Ethnicity, n (%)		
white/Caucasian	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%)
Number of chronic health conditions, median [IQR]	0 [0-1]	0 [0-1]
Hypertension, n (%)	15 (15%)	22 (14.5%)
Diabetes, n (%)	6 (6%)	6 (3.9%)
Asthma, n (%)	7 (7%)	15 (9.9%)
Obesity, n (%)	15 (15%)	14 (9.2%)
Chronic lung disease, n (%)	4 (4%)	3 (2%)
Chronic liver disease, n (%)	4 (4%)	1 (0.7%)
Chronic kidney disease, n (%)	1 (1%)	1 (0.7%)
Chronic heart disease, n (%)	1 (1%)	4 (2.6%)
Chronic blood disease, n (%)	1 (1%)	2 (1.3%)
Cancer, n (%)	4 (4%)	4 (2.6%)
Immunosuppression, n (%)	3 (3%)	0 (0%)
At least one of the above, n (%)	45 (45%)	50 (33%)
COVID-19 status		
COVID-19 convalescent (anti-N Ab+) at study entry, n (%)	8 (8%)	15 (10%)
COVID-19 post-vaccination	18 (18%)	13 (9%)
Vaccine details		
Initial two-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 first and second doses in days, median [IQR]	58 [53-67]	89 [65-98]
Third dose		
BNT162b2	23 of 80 (29%)	55 of 134 (41%)
mRNA-1273	56 of 80 (70%)	79 of 134 (59%)
Unknown	1 of 80 (1%)	-
Time between second and third doses in days, median [IQR]	183 [143-191]	198 [173-216]
Specimen collection		
Specimen one month after second dose, n (%)	97 (97%)	151 (99%)
Day of collection one month after second dose, median [IQR]	30 [29-30]	30 [29-32]
Specimen three months after second dose, n (%)	96 (96%)	148 (97%)
Day of collection three months after second dose, median [IQR]	90 [90-91]	90 [89-91]
Specimen six months after second dose, n (%)	62 (62%)	136 (89%)
Day of collection six months after second dose, median [IQR]	180 [177-182]	180 [178-182]
Specimen one month after third dose, n (%)	80 (80%)	134 (88%)
Day of collection one month after third dose, median [IQR]	30 [30-32]	30 [29-32]

Table 2: Multivariable analyses of the relationship between sociodemographic, health and vaccine-related variables on antibody concentrations 6 months after the second dose, and antibody half-lives following the second dose

Variable[a]	Log_{10} antibody concentration 6 mo after 2nd dose[b]			Antibody half-lives after the 2nd dose[c]		
	Estimate	95% CI	p-value	Estimate	95% CI	p-value
HIV infection	-0.036	-0.19 to 0.11	0.64	6.33	-19.92 to 32.59	0.63
Age (per year)	0.000019	-0.0043 to 0.0043	0.99	0.53	-0.12 to 1.17	0.11
Male sex	-0.059	-0.19 to 0.072	0.37	9.36	-12.83 to 31.54	0.41
White ethnicity	-0.0078	-0.13 to 0.11	0.90	-7.03	-26.97 to 12.90	0.49
# Chronic conditions (per additional)	-0.028	-0.11 to 0.056	0.51	-7.58	-21.67 to 6.51	0.29
Dual ChAdOx1 as initial regimen	-0.94	-1.39 to -0.49	**<0.0001**	2.84	-76.02 to 81.70	0.94
Interval between first and second doses (per day)	0.0024	-0.00036 to 0.0052	0.087	-0.17	-0.63 to 0.29	0.47
Days since second dose	0.012	0.0033 to 0.020	**0.0067**	-	-	-
Prior COVID-19	0.50	0.35 to 0.65	**<0.0001**	-	-	-

[a] Dashes indicate variables not included in the model

[b] quantified using the Roche Elecsys anti-S assay

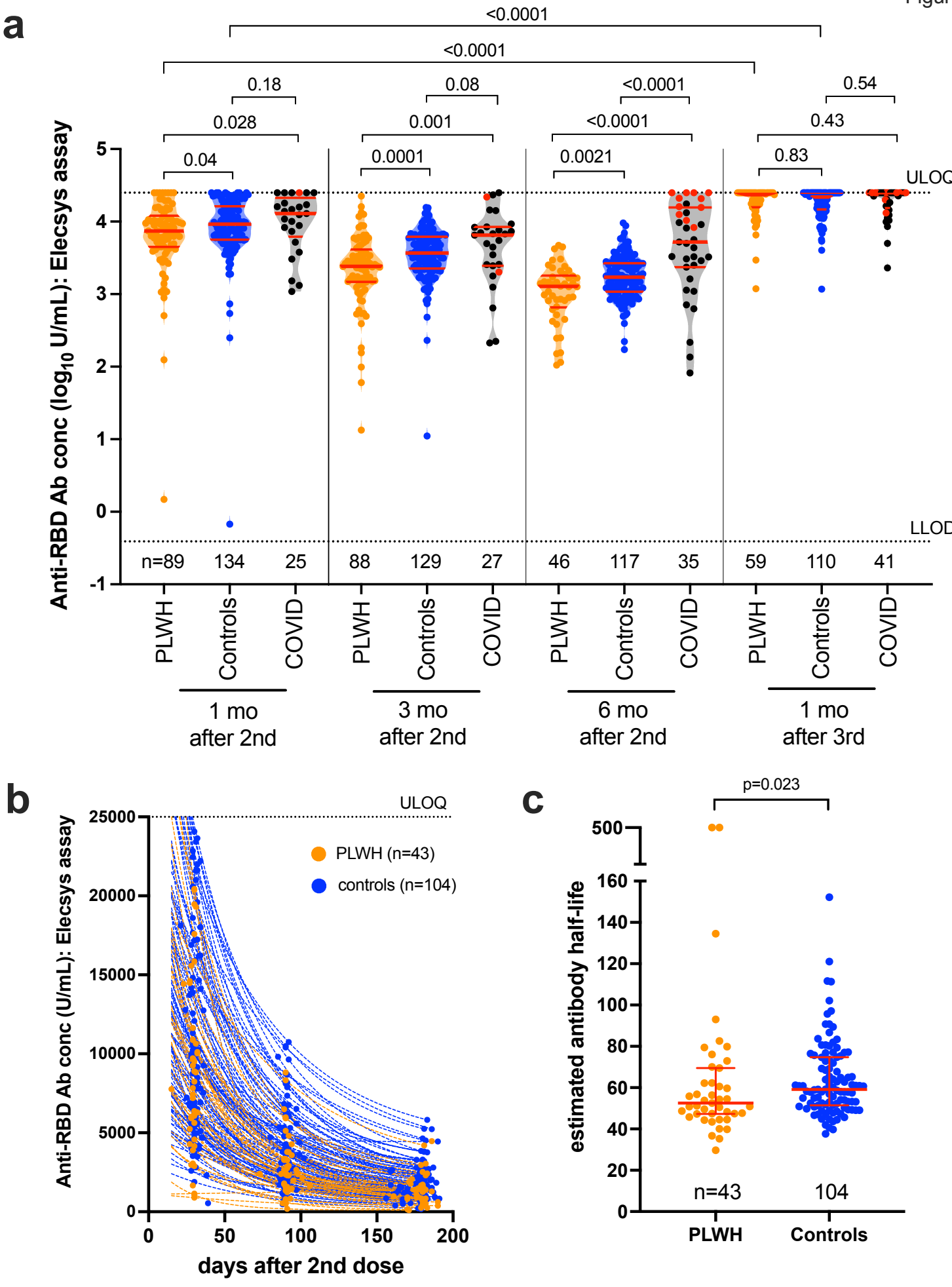
[c] Calculated from all participants with a complete longitudinal data series following the second dose with no values above the ULOQ, and no evidence of prior COVID-19

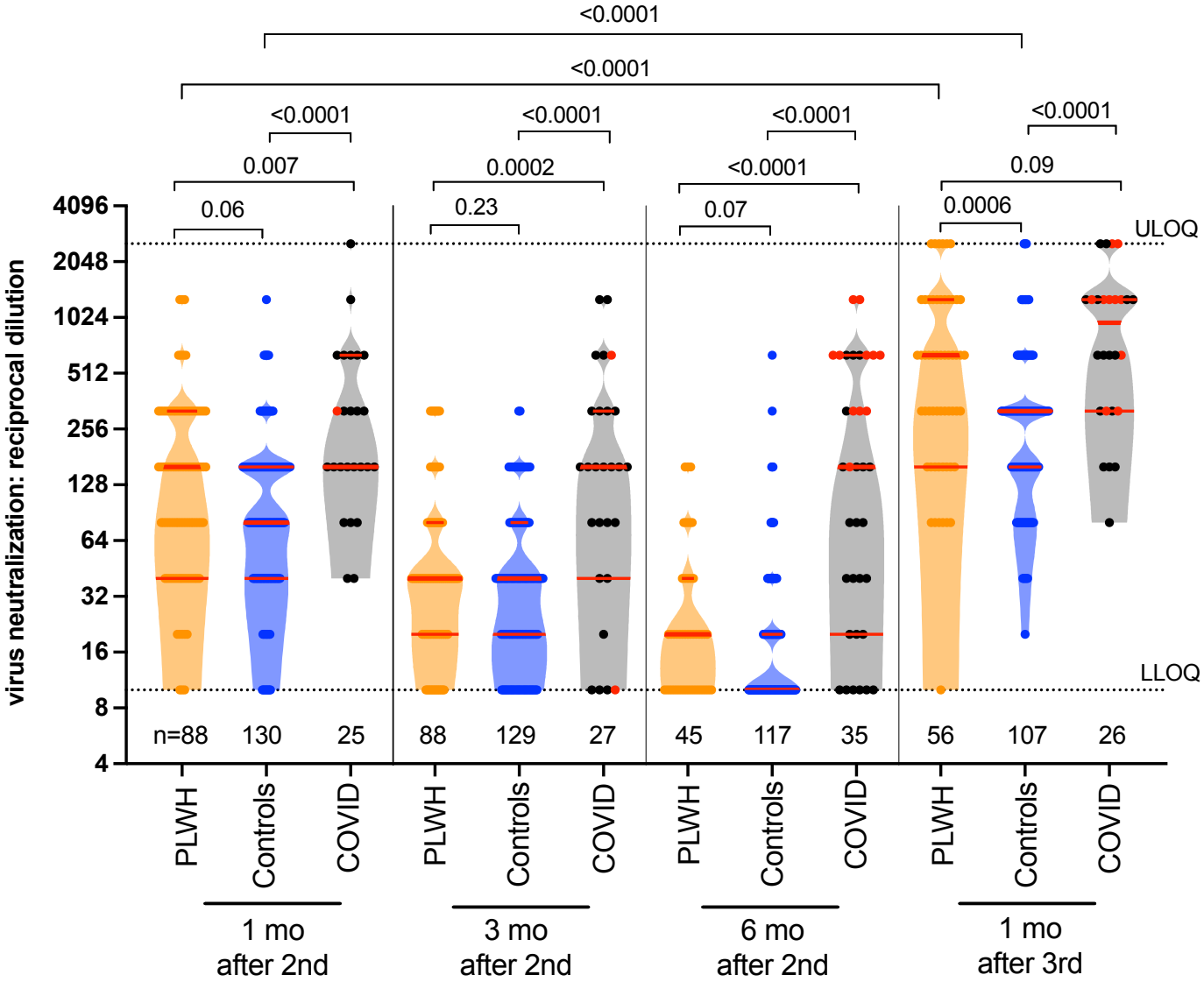
Table 3: Multivariable analyses of the relationship between sociodemographic, health and vaccine-related variables on antibody responses to Omicron after three COVID-19 vaccine doses

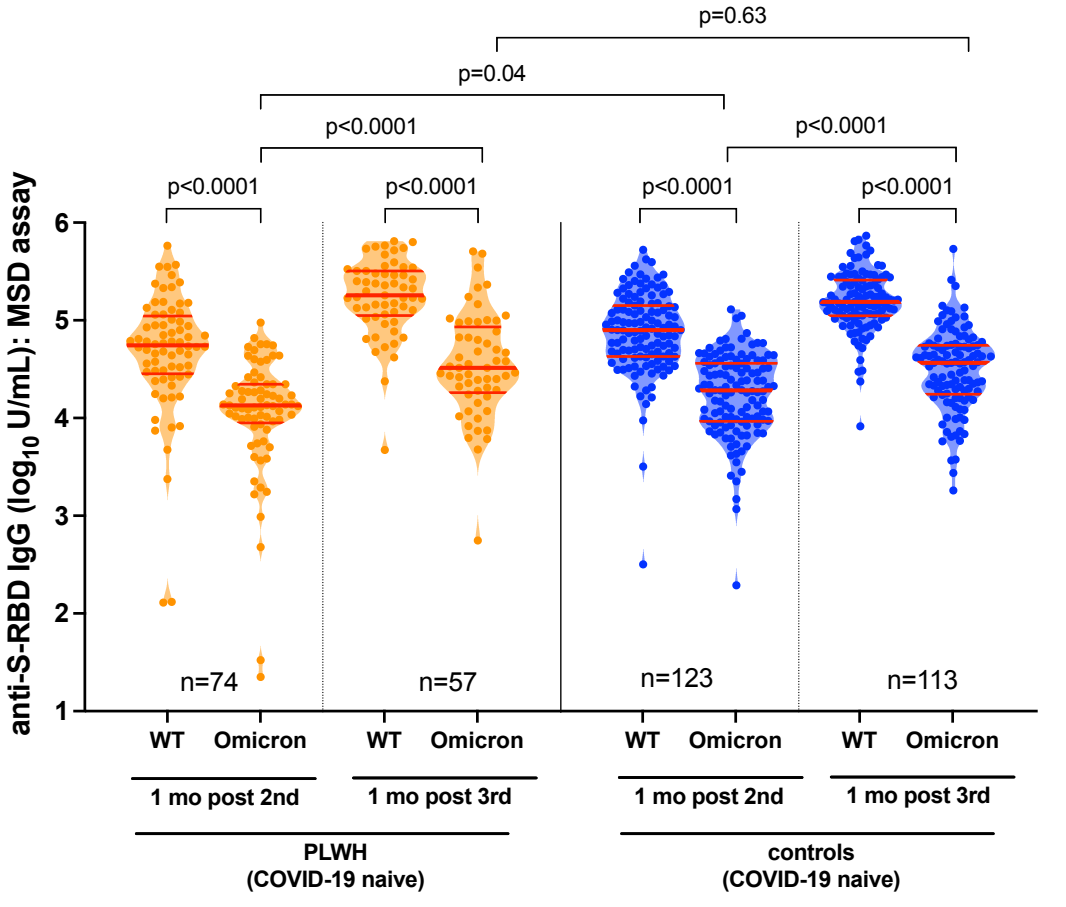
Variable[a]	anti-Omicron log_{10} Binding IgG[b]			anti-Omicron ACE2 % displacement[b]		
	Estimate	95% CI	p-value	Estimate	95% CI	p-value
HIV infection	0.36	0.14 to 0.58	**0.0017**	3.49	-8.48 to 15.47	0.57
Age (per year)	-0.0030	-0.0078 to 0.0018	0.22	0.21	-0.056 to 0.47	0.12
Male sex	-0.19	-0.36 to -0.017	**0.032**	-10.26	-19.58 to -0.94	**0.031**
White ethnicity	0.045	-0.10 to 0.19	0.55	2.05	-6.00 to 10.09	0.62
# Chronic conditions (per additional)	0.0032	-0.083 to 0.090	0.94	-1.27	-5.99 to 3.45	0.60
Dual ChAdOx1 as initial regimen (vs mixed or mRNA)	-0.14	-0.48 to 0.20	0.42	-6.80	-25.39 to 11.80	0.47
mRNA-1273 as third dose (vs BNT162b2)	0.15	0.0074 to 0.30	**0.039**	5.16	-2.80 to 13.12	0.20
Interval between 1st and 2nd dose (per day)	0.0022	-0.0016 to 0.0059	0.26	-0.044	-0.25 to 0.16	0.67
Interval between 2nd and 3rd dose (per day)	0.0036	0.0012 to 0.0060	**0.0039**	0.065	-0.067 to 0.20	0.33
Days since 3rd dose	-0.0073	-0.022 to 0.0080	0.35	0.11	-0.72 to 0.94	0.80

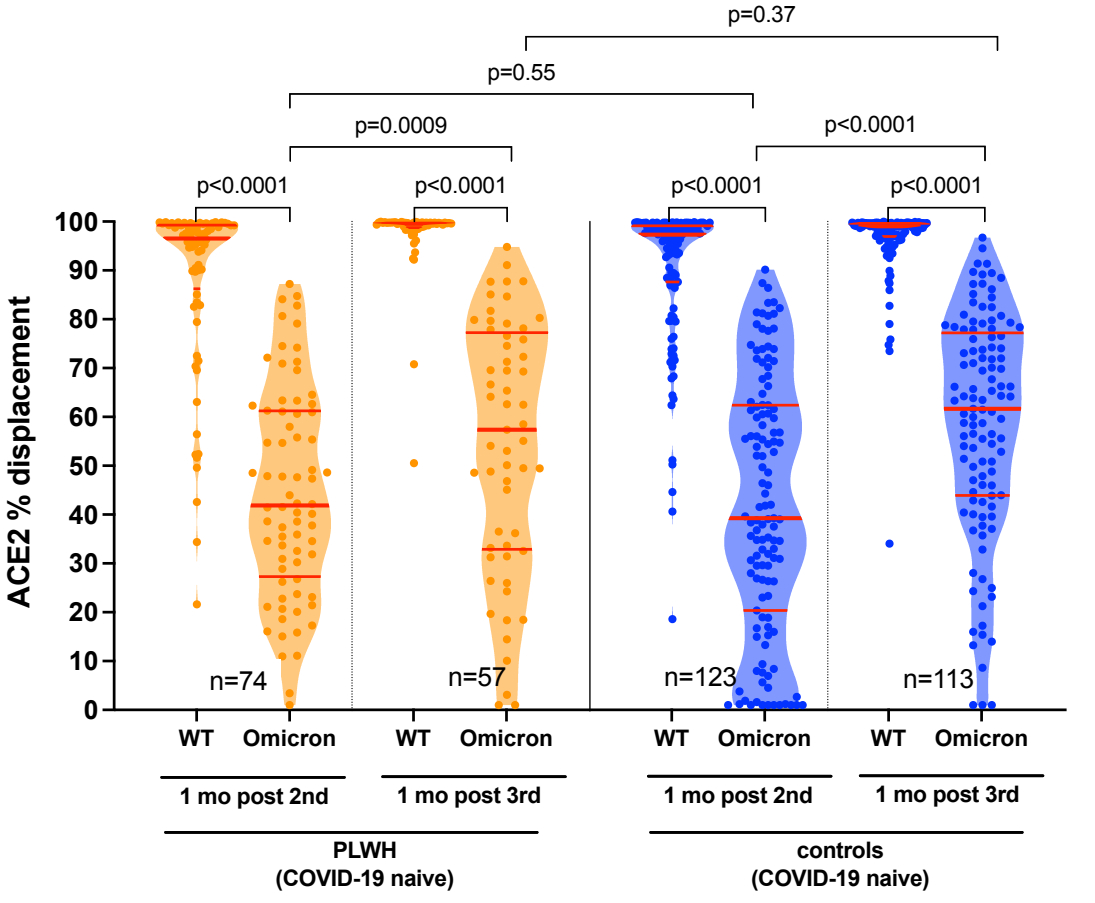
[a] Analysis was restricted to participants with no evidence of prior COVID-19

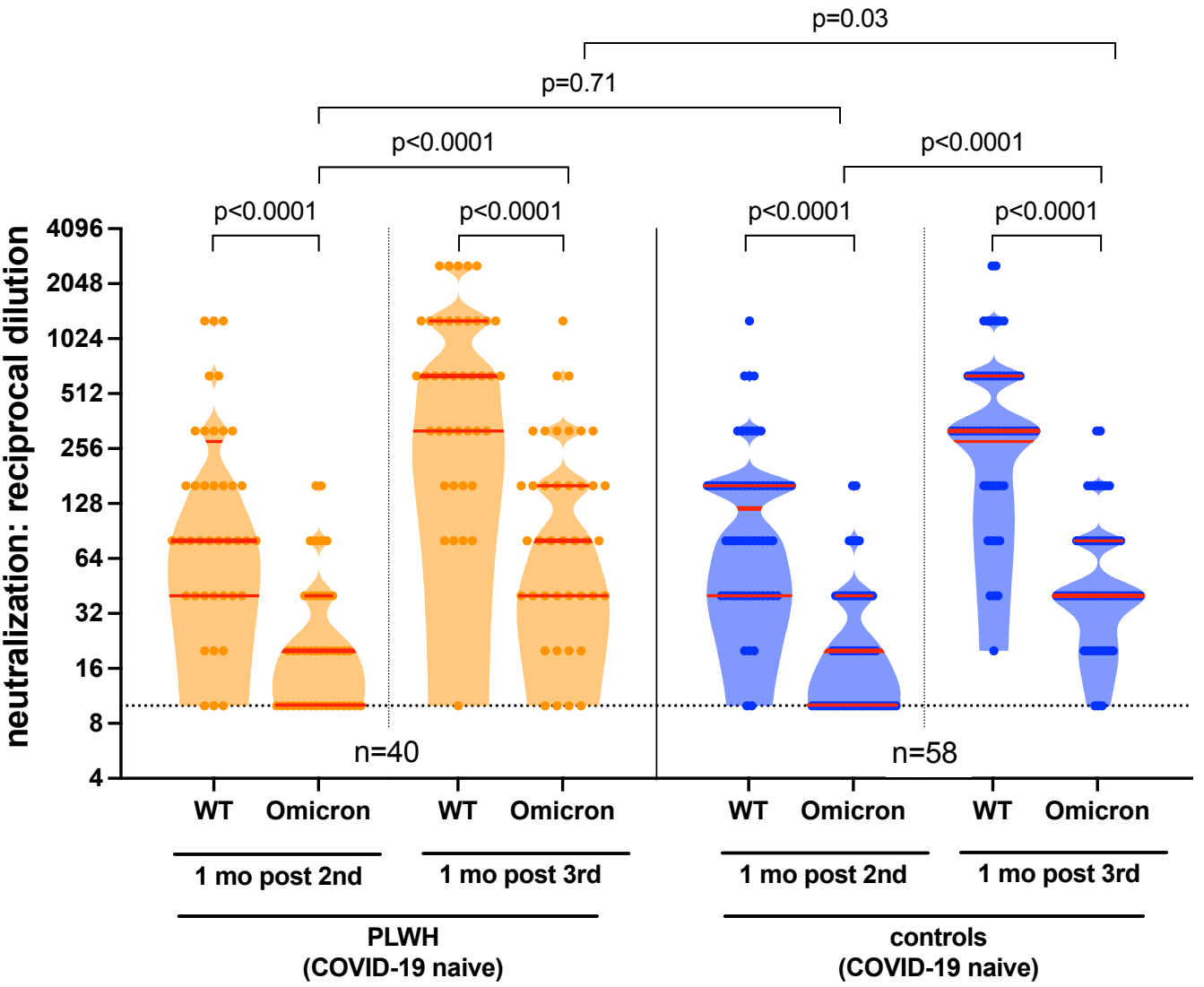
[b] Both immunogenicity measures were quantified in serum using the Meso Scale Diagnostics V-Plex assay (panel 22) which features wild-type and Omicron S-RBD.


a
<0.0001
<0.0001
0.18
0.08
<0.0001
0.54
0.028
0.001
<0.0001
0.43
0.04
0.0001
0.0021
0.83
ULOQ
LLOD
Anti-RBD Ab conc (log10 U/mL): Elecsys assay
5
4
3
2
1
0
-1
n=89 134 25 88 129 27 46 117 35 59 110 41
PLWH
Controls
COVID
1 mo after 2nd
3 mo after 2nd
6 mo after 2nd
1 mo after 3rd
b
ULOQ
PLWH (n=43)
controls (n=104)
Anti-RBD Ab conc (U/mL): Elecsys assay
25000
20000
15000
10000
5000
0
0
50
100
150
200
days after 2nd dose
c
p=0.023
estimated antibody half-life
500
160
140
120
100
80
60
40
20
0
n=43
104
PLWH
Controls


<0.0001
<0.0001
<0.0001
<0.0001
<0.0001
<0.0001
0.007
0.0002
<0.0001
0.09
0.06
0.23
0.07
0.0006
virus neutralization: reciprocal dilution
4096
2048
1024
512
256
128
64
32
16
8
4
ULOQ
LLOQ
n=88
130
25
88
129
27
45
117
35
56
107
26
PLWH
Controls
COVID
1 mo after 2nd
3 mo after 2nd
6 mo after 2nd
1 mo after 3rd


p=0.63
p=0.04
p<0.0001
p<0.0001
p<0.0001
p<0.0001
p<0.0001
p<0.0001
anti-S-RBD IgG (log10 U/mL): MSD assay
6
5
4
3
2
1
n=74
n=57
n=123
n=113
WT
Omicron
WT
Omicron
WT
Omicron
WT
Omicron
1 mo post 2nd
1 mo post 3rd
1 mo post 2nd
1 mo post 3rd
PLWH
(COVID-19 naive)
controls
(COVID-19 naive)


p=0.37
p=0.55
p=0.0009
p<0.0001
p<0.0001
p<0.0001
p<0.0001
p<0.0001
ACE2 % displacement
100
90
80
70
60
50
40
30
20
10
0
n=74
n=57
n=123
n=113
WT
Omicron
WT
Omicron
WT
Omicron
WT
Omicron
1 mo post 2nd
1 mo post 3rd
1 mo post 2nd
1 mo post 3rd
PLWH
(COVID-19 naive)
controls
(COVID-19 naive)


p=0.03
p=0.71
p<0.0001
p<0.0001
p<0.0001
p<0.0001
p<0.0001
neutralization: reciprocal dilution
4096
2048
1024
512
256
128
64
32
16
8
4
n=40
n=58
WT
Omicron
WT
Omicron
WT
Omicron
WT
Omicron
1 mo post 2nd
1 mo post 3rd
1 mo post 2nd
1 mo post 3rd
PLWH
(COVID-19 naive)
controls
(COVID-19 naive)

Supplemental Table 1: Multivariable analyses of the relationship between sociodemographic, health and vaccine-related variables on immunogenicity measures one and three months following the second vaccine dose

Immunogenicity outcome	Variable	Time point					
		1 month after 2nd dose			3 months after 2nd dose		
		Estimate	95% CI	p-value	Estimate	95% CI	p-value
Log_{10} anti-RBD Abs[a]	HIV infection	-0.017	-0.18 to 0.14	0.83	-0.13	-0.27 to 0.019	0.088
	Age (per year)	-0.0057	-0.0098 to -0.0017	**0.0053**	-0.0035	-0.0072 to 0.000079	0.055
	Male sex	-0.016	-0.16 to 0.13	0.82	0.028	-0.10 to 0.16	0.68
	White ethnicity	0.053	-0.078 to 0.18	0.43	0.048	-0.069 to 0.17	0.42
	# Chronic conditions (per additional)	-0.11	-0.19 to -0.030	**0.0072**	-0.086	-0.16 to -0.012	**0.022**
	Dual ChAdOx1 as initial regimen	-0.63	-0.97 to -0.29	**0.0003**	-0.70	-1.00 to -0.40	**<0.0001**
	Interval btw 1st and 2nd doses (per day)	0.0036	0.00039 to 0.0069	**0.028**	0.0037	0.00085 to 0.0066	**0.011**
	Days since second dose	-0.0018	-0.024 to 0.020	0.87	0.0061	-0.010 to 0.022	0.46
	Prior COVID-19	0.063	-0.13 to 0.26	0.53	0.14	-0.030 to 0.31	0.10
Viral neutralization[b]	HIV infection	0.20	-0.47 to 0.86	0.56	-0.063	-0.74 to 0.62	0.86
	Age (per year)	-0.018	-0.030 to -0.0050	**0.0064**	-0.012	-0.025 to 0.00051	0.059
	Male sex	-0.39	-0.84 to 0.055	0.086	-0.12	-0.59 to 0.34	0.60
	White ethnicity	-0.21	-0.61 to 0.18	0.29	-0.19	-0.60 to 0.21	0.36
	# Chronic conditions (per additional)	-0.29	-0.53 to -0.041	**0.022**	-0.15	-0.41 to 0.10	0.23
	Dual ChAdOx1 as initial regimen	-1.39	-2.41 to -0.37	**0.0077**	-1.57	-2.60 to -0.53	**0.0032**
	Interval btw 1st and 2nd doses (per day)	0.0073	-0.0038 to 0.018	0.2	0.00067	-0.010 to 0.012	0.91
	Days since second dose	-0.0061	-0.073 to 0.060	0.86	-0.029	-0.084 to 0.027	0.31
	EDTA as anticoagulant[c]	0.85	0.091 to 1.61	**0.028**	0.58	-0.20 to 1.35	0.14
	Prior COVID-19	1.15	0.56 to 1.75	**0.0002**	1.65	1.06 to 2.24	**<0.0001**

[a]quantified using the Roche Elecsys anti-S assay

[b]for viral neutralization, reciprocal plasma dilutions were log_2 transformed prior to multivariable analysis.

[c]Neutralization assays were performed using plasma, so the analysis also corrects for the anticoagulant used, with ACD as the reference category. Analyses of anti-RBD concentration do not correct for this variable because this assay was performed on serum collected in the same tube type.

Supplemental Table 2: Multivariable analyses of the relationship between sociodemographic, health and vaccine-related variables and detectable viral neutralization activity six months following the second vaccine dose

Immunogenicity outcome	Variable	Odds Ratio	95% CI	p-value
Detectable viral neut. 6 months after 2nd dose[a]	HIV infection	0.51	0.12 to 1.77	0.32
	Age (per year)	0.98	0.96 to 1.01	0.22
	Male sex	0.68	0.29 to 1.50	0.35
	White ethnicity	0.88	0.44 to 1.78	0.73
	# Chronic conditions (per additional)	1.00	0.61 to 1.63	1.00
	Dual ChAdOx1 as initial regimen	0.19	0.0079 to 2.36	0.21
	Interval btw 1st and 2nd doses (per day)	1.01	0.99 to 1.03	0.14
	Days since second dose	1.03	0.98 to 1.09	0.24
	EDTA as anticoagulant[b]	9.31	2.41 to 44.62	**0.0023**
	Prior COVID-19	4.57	1.74 to 13.99	**0.0037**

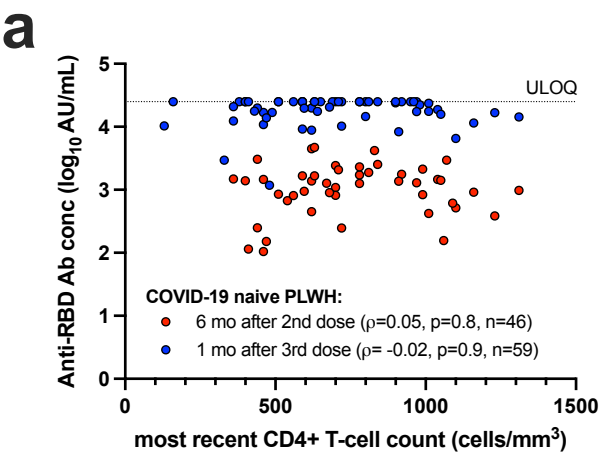
[a] Results are presented as the adjusted Odds Ratios and 95% CI of detectable viral neutralization activity at this time point, calculated using multivariable logistic regression.

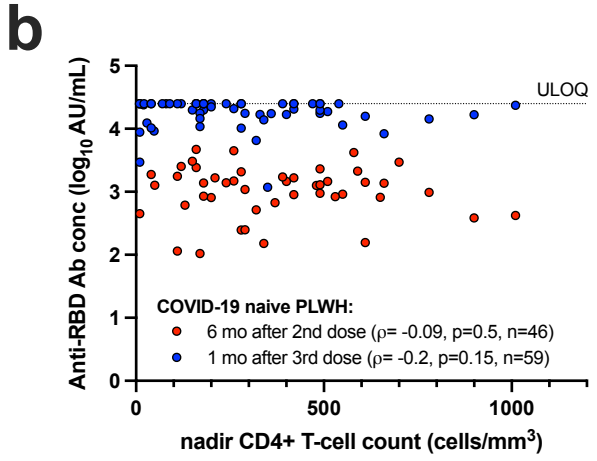
[b] Neutralization assays were performed using plasma, so the analysis also corrects for the anticoagulant used, with ACD as the reference category.

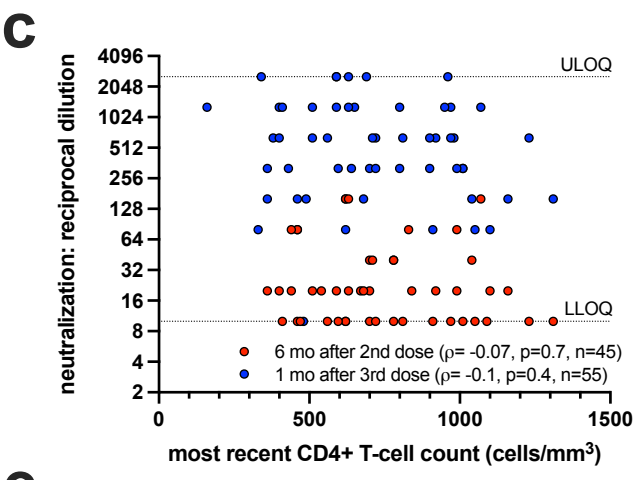
Supplemental Table 3: Multivariable analysis of the relationship between sociodemographic, health and vaccine-related variables and viral neutralization activity one month following the third vaccine dose

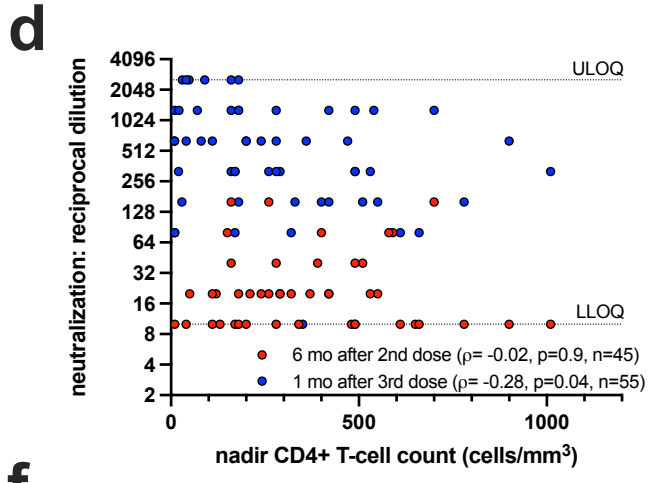
Immunogenicity outcome	Variable	Estimate	95% CI	p-value
Viral neut. (log_2) 1 mo after 3rd dose[a]	HIV infection	0.58	-0.22 to 1.37	0.15
	Age (per year)	-0.00068	-0.017 to 0.016	0.94
	Male sex	-0.047	-0.61 to 0.51	0.87
	White ethnicity	-0.27	-0.74 to 0.20	0.27
	# Chronic conditions (per additional)	-0.067	-0.35 to 0.21	0.64
	Dual ChAdOx1 as initial regimen	0.96	-0.18 to 2.10	0.099
	mRNA-1273 as third dose (vs. BNT162b2)	0.78	0.32 to 1.23	**0.0009**
	Interval between 1st and 2nd doses (per day)	-0.00095	-0.015 to 0.013	0.89
	Interval between 2nd and 3rd doses (per day)	0.0016	-0.0066 to 0.0097	0.71
	Days since 3rd dose (per day)	-0.016	-0.065 to 0.034	0.53
	EDTA as anticoagulant[b]	0.28	-0.68 to 1.25	0.56
	Prior COVID-19	0.98	0.39 to 1.57	**0.0013**

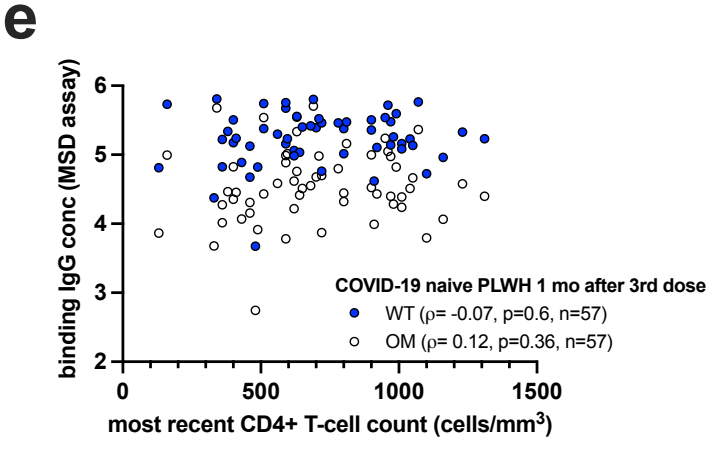
[a]for viral neutralization, reciprocal plasma dilutions were log_2 transformed prior to multivariable analysis.
[b]Neutralization assays wwere performed using plasma, so the analysis also corrects for the anticoagulant used, with ACD as the reference category.

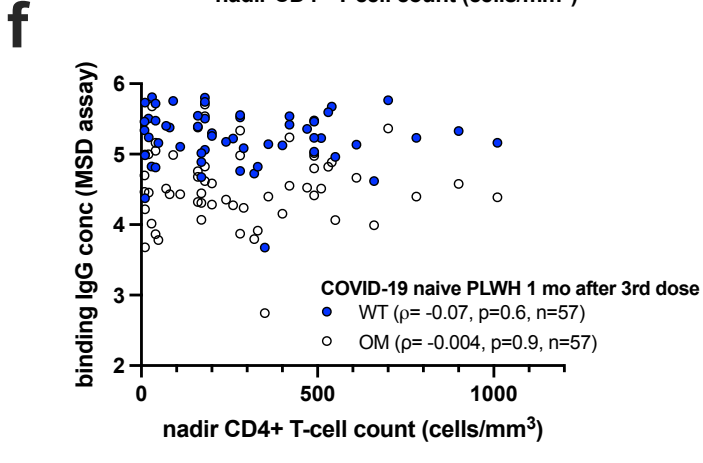

a
Anti-RBD Ab conc (log10 AU/mL)
ULOQ
COVID-19 naive PLWH:
6 mo after 2nd dose (ρ=0.05, p=0.8, n=46)
1 mo after 3rd dose (ρ= -0.02, p=0.9, n=59)
most recent CD4+ T-cell count (cells/mm3)

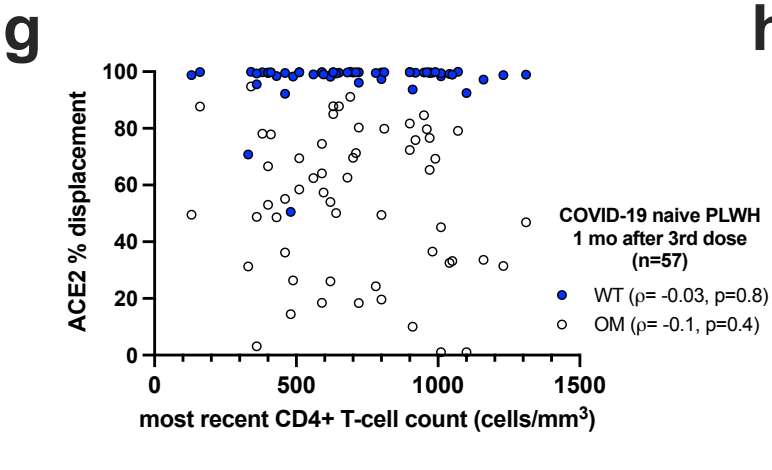

b
Anti-RBD Ab conc (log10 AU/mL)
ULOQ
COVID-19 naive PLWH:
6 mo after 2nd dose (ρ= -0.09, p=0.5, n=46)
1 mo after 3rd dose (ρ= -0.2, p=0.15, n=59)
nadir CD4+ T-cell count (cells/mm3)

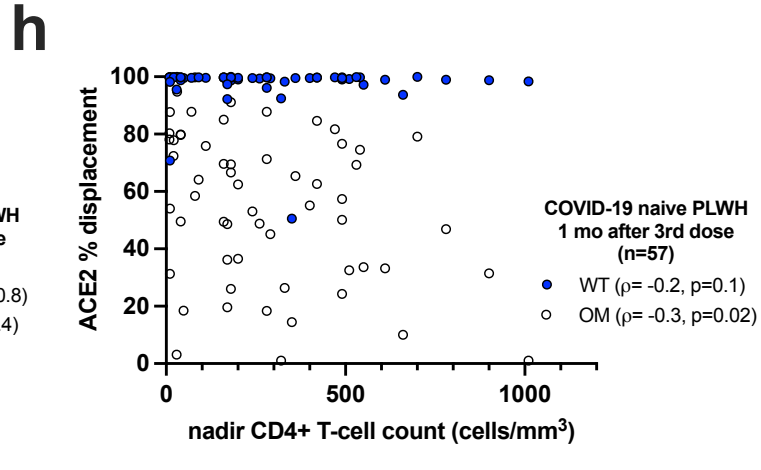

c
neutralization: reciprocal dilution
ULOQ
LLOQ
6 mo after 2nd dose (ρ= -0.07, p=0.7, n=45)
1 mo after 3rd dose (ρ= -0.1, p=0.4, n=55)
most recent CD4+ T-cell count (cells/mm3)

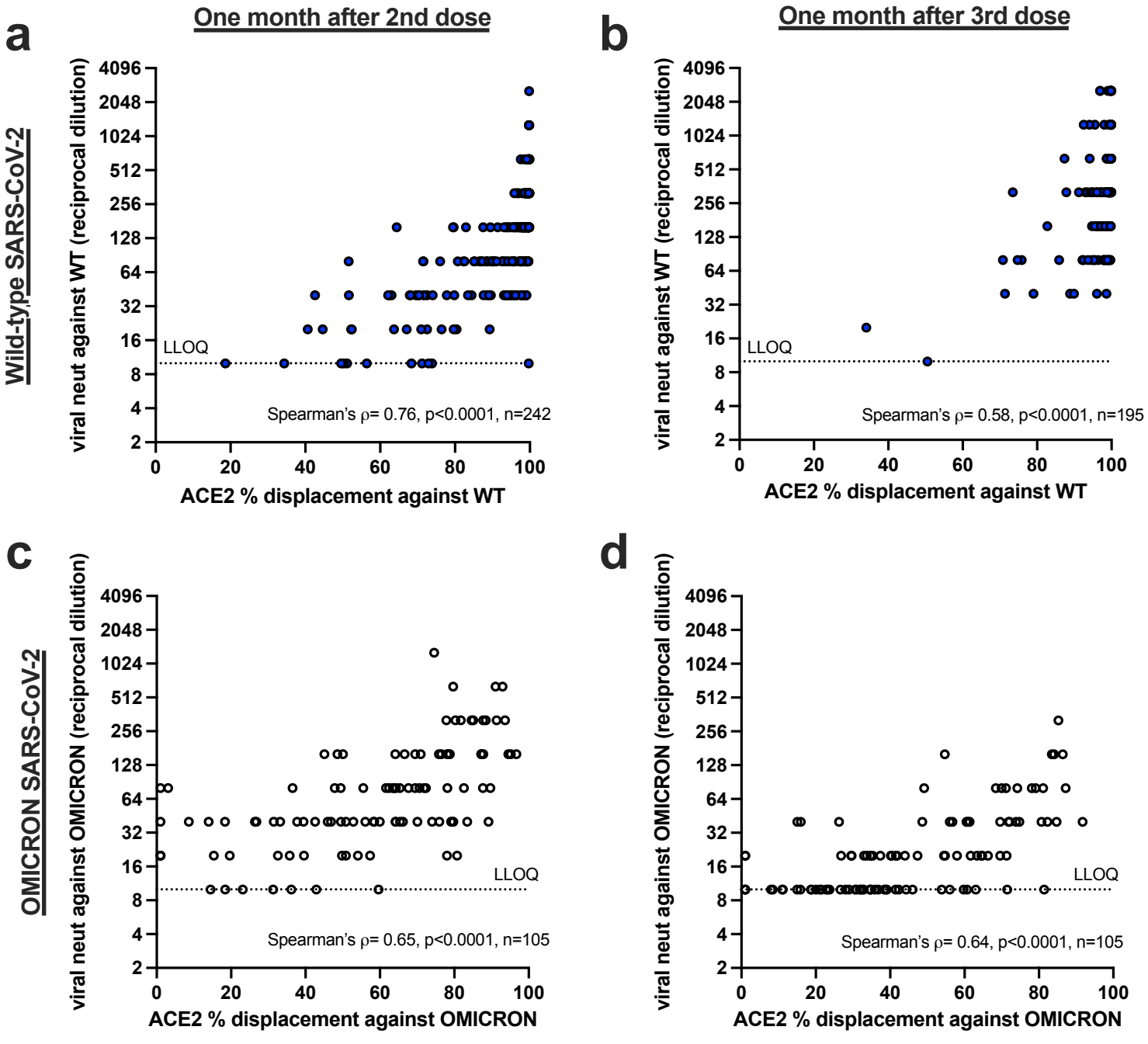

d
neutralization: reciprocal dilution
ULOQ
LLOQ
6 mo after 2nd dose (ρ= -0.02, p=0.9, n=45)
1 mo after 3rd dose (ρ= -0.28, p=0.04, n=55)
nadir CD4+ T-cell count (cells/mm3)


e
binding IgG conc (MSD assay)
COVID-19 naive PLWH 1 mo after 3rd dose
WT (ρ= -0.07, p=0.6, n=57)
OM (ρ= 0.12, p=0.36, n=57)
most recent CD4+ T-cell count (cells/mm3)


f
binding IgG conc (MSD assay)
COVID-19 naive PLWH 1 mo after 3rd dose
WT (ρ= -0.07, p=0.6, n=57)
OM (ρ= -0.004, p=0.9, n=57)
nadir CD4+ T-cell count (cells/mm3)


g
ACE2 % displacement
COVID-19 naive PLWH
1 mo after 3rd dose
(n=57)
WT (ρ= -0.03, p=0.8)
OM (ρ= -0.1, p=0.4)
most recent CD4+ T-cell count (cells/mm3)


h
ACE2 % displacement
COVID-19 naive PLWH
1 mo after 3rd dose
(n=57)
WT (ρ= -0.2, p=0.1)
OM (ρ= -0.3, p=0.02)
nadir CD4+ T-cell count (cells/mm3)


a
One month after 2nd dose
Wild-type SARS-CoV-2
viral neut against WT (reciprocal dilution)
4096
2048
1024
512
256
128
64
32
16
8
4
2
LLOQ
Spearman's ρ= 0.76, p<0.0001, n=242
0
20
40
60
80
100
ACE2 % displacement against WT
b
One month after 3rd dose
viral neut against WT (reciprocal dilution)
LLOQ
Spearman's ρ= 0.58, p<0.0001, n=195
ACE2 % displacement against WT
c
OMICRON SARS-CoV-2
viral neut against OMICRON (reciprocal dilution)
LLOQ
Spearman's ρ= 0.65, p<0.0001, n=105
ACE2 % displacement against OMICRON
d
viral neut against OMICRON (reciprocal dilution)
LLOQ
Spearman's ρ= 0.64, p<0.0001, n=105
ACE2 % displacement against OMICRON