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 Omicron-specific 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.

KEY WORDS: 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], vaccination is expected to benefit this group. While two-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], reported generally strong immune responses to two-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 cells/mm^3 [22, 25-27].

VaccineBut, vaccine-induced antibody responses decline over time, which can increase SARS-CoV-2 infection risk [30-32], particularly with the more transmissible Omicron variant [33-37]. Though immune response durability following two-dose COVID-19 vaccination has been examined among PLWH participants of 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 and Omicron SARS-CoV-2 variants up to one month post-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 health care 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 [ACD] for the remainder) were collected before vaccination; one month after the first dose; one, three and six months post-second dose; and one month post-third dose. Here, we extend our previous study [29] to include all post-second-dose, and the one month post-third dose, study visits. A cohort flowchart is shown in **Supplemental Figure 1**.

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 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 $\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. Binding antibodies were measured using two commercial 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 report results in arbitrary Units/mL. 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 also quantified using the V-plex SARS-CoV-2 (IgG) Panel 22 ELISA kit (Meso Scale Diagnostics) on a Meso QuickPlex SQ120 instrument. This assay quantifies both wild-type-

and Omicron-specific IgG. Sera were diluted 1:10000, allowing a broader dynamic range than the Roche assay. Results are 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. This represents a higher throughput approach to estimate potential virus neutralizing activity, and is commonly used as a surrogate for this function [42]. 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. As described previously [29], viral stock was adjusted to 50 $TCID_{50}$/200 µl in the presence of serial two-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 (CPE) in 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 defined as below the limit of quantification (BLOQ).

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 post-second dose, we used multiple logistic regression due to the high proportion of results BLOQ. Variables included HIV infection (controls as reference group), age (per year), sex at birth (female as reference), ethnicity (non-white 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 (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 (ACD as reference). 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 two-tailed, with $p<0.05$ considered statistically significant. Analyses were conducted using Prism v9.2.0 (GraphPad).

RESULTS

Cohort characteristics

As described previously [29], all PLWH had suppressed plasma HIV loads on therapy (**Table 1**). Recent and nadir CD4+ T-cell counts were a median 715 cells/mm^3 (Interquartile Range [IQR] 545-943; range 130-1800) and a median 280 cells/mm^3 (IQR 123-490; range <10-1010), respectively. PLWH and controls were broadly similar in age and the number of chronic conditions, but the PLWH group included more males and white ethnicity. Because the majority of controls were health care workers who were vaccinated prior to 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 days versus 58 for PLWH), as those vaccinated earlier in Canada's campaign waited up to 112 days between doses due to initially limited vaccine supply [43]. Fewer controls received dual ChAdOx1 vaccines as their initial regimen (<1%; compared to 8% of PLWH), as initially only mRNA vaccines were available in Canada. Vaccine timing also indirectly influenced post-vaccination SARS-CoV-2 infection incidence. While a comparable number of PLWH (8%) and controls (10%) were anti-N seropositive at study entry, a larger proportion of PLWH (18%) experienced post-vaccination infections compared to controls (9%). This is unlikely due to increased infection susceptibility, but rather because the first Omicron "wave" occurred

just prior to 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. Third doses began to be offered in BC 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 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 six 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 dose recommendations also differed by risk group: 100 mcg was recommended for adults aged ≥70 years and PLWH meeting any priority criterion, whereas the standard 50 mcg booster was recommended for all other adults.

Binding antibody responses

Initial responses to two-dose vaccination in this cohort have been described previously [29]. Briefly, 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**). Only two participants were non-responders: one PLWH with non-HIV-related immunodeficiency, and one >80 year old control participant with three chronic conditions. By three months following the second dose, antibody concentrations had declined 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). HIV infection however did not remain significantly associated with antibody concentrations at these two time points after controlling for sociodemographic, health- and vaccine-related variables (HIV-related estimates and p-values shown in **Table 2**; full models shown in **Supplemental Table 1**).

Rather, older age, a greater number of 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 six months after the second dose, anti-RBD 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 no effect of HIV infection on antibody concentrations remained after multivariable correction (p=0.64; **Table 2**; full model in **Supplemental Table S2**). 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, as 13 controls aged ≥ 70 years did not contribute samples at this time point as they had already received third doses as per BC's age-based rollout, and a further 25 participants aged ≥ 65 years contributed this sample early due to imminently scheduled third doses. Prior COVID-19 was also associated with superior antibody concentrations at this time point, though 11 recent infections (red dots in **Figure 1A**) influenced this result.

We next assessed temporal reductions in antibody concentrations after two vaccine doses (**Figure 1B)**. Assuming exponential decay, and restricting the analysis to COVID-19-naive participants with a complete post-second-dose longitudinal series with no values above the assay upper limit of quantification (ULOQ), we estimated antibody half-lives to be a median of 53 [IQR 47-70] days in PLWH versus a median of 59 [IQR 51-75] days in controls (p=0.023, **Figure 1C**). This difference however did not remain significant after multivariable correction (p=0.63; **Table 2;** full model in **Supplemental Table S2**).

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<0.0001 for both PLWH and controls), to a median of 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

(between-group p=0.83), values that were comparable to those in participants with prior COVID-19 (**Figure 1A**). Multivariable analyses were not performed as nearly 50% of values were >ULOQ.

Consistent with our previous observations at one and three months post-second vaccine dose [29], we observed no significant relationship between most recent or nadir CD4+ T-cell count and antibody concentrations either six months post-second dose or one month post-third dose in PLWH (**Supplementary Figure 2**). We also observed no significant relationship between these CD4 parameters and antibody half-life post-second dose (Spearman $\rho \leq 0.16$, $p \geq 0.3$; not shown).

Viral neutralization

One month post-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 confirmed no association between HIV infection and neutralization at these time points (HIV-related estimates in **Table 2**; full model in **Supplemental Table 1**). Rather, older age, a higher number of chronic conditions and dual ChAdOx1 vaccination was associated with weaker neutralization at one or both of these time points , while prior COVID-19 was associated with stronger neutralization. By six months post-second dose, neutralization had declined to BLOQ in 52% of COVID-19-naive participants, to a median reciprocal dilution of 20 [IQR BLOQ-40] in PLWH and a median of 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 confirmed no association between HIV infection and neutralization at this time point (HIV-related estimates in **Table 2**; full model in **Supplemental 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 four-fold 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, **Table 2**; full model in **Supplemental Table 4**). Rather, having received mRNA-1273 as a third dose and having prior COVID-19 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 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 2**). 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).

HumoralOmicron-specific responses

To estimate the extent to which a third vaccine dose boosts protection against the now-dominant Omicron variant, we compared peak wild-type- and Omicron-specific responses one month post-second and -third doses using a platform that simultaneously quantifies responses to both antigens (Meso Scale Diagnostics V-plex assay; see methods). To avoid confounding by infection-induced immunity, we restricted this analysis to COVID-19-naive individuals. For both PLWH and controls, Omicron-specific anti-RBD serum IgG concentrations were on average ~0.6 $\log_{10}$ U/mL lower than wild-type-specific ones 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 post-second-dose levels in both groups (within-group comparisons p<0.0001). One month post-second dose, anti-Omicron IgG concentrations were a median 4.13 [IQR 3.95-4.35] $\log_{10}$ U/mL in PLWH and a

median of 4.28 [IQR 3.97-4.56] log_{10} U/mL in controls (p=0.06). After three doses however, 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 post-third dose identified HIV infection as being associated with an adjusted 0.36 log_{10} U/mL *higher* Omicron-specific IgG concentration (p=0.0017, **Table 2**; full model in **Supplemental Table 5**). Having received mRNA-1273 for the third dose, and a longer interval between second and third doses, were also significantly associated with higher Omicron-specific anti-RBD IgG responses, while male sex was associated with lower responses. We also confirmed that total wild-type specific anti-RBD antibody concentrations (measured by the Roche Elecsys assay in **Figure 1**) and total wild-type specific anti-RBD IgG concentrations (measured by Meso Scale Diagnostics assay in **Figure 3**) correlated strongly as expected (**Supplemental Figure S3**).

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 wild-type- and Omicron-specific activities in PLWH were 97% versus 42%, respectively, at this time). The third dose nevertheless universally boosted Omicron-specific responses to above second-dose levels (all within-group comparisons p≤0.0009), with median Omicron-specific activity in PLWH rising from 42% after two doses to 57% after three (p=0.0009). Omicron-specific ACE2 % displacement activities were comparable between groups at both time points: one month post-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 post-third dose (p=0.37). Multivariable analyses confirmed no association between HIV infection and Omicron-specific ACE2 displacement activity after

three doses (p=0.57, **Table 2**; full model in **Supplemental Table 5**). After three doses, we observed a weak inverse relationship between nadir CD4+ T-cell count and Omicron-specific ACE2 % displacement (Spearman ρ= -0.3; p=0.02), but no relationship between other CD4+ T-cell count measures and Omicron-specific responses (**Supplemental Figure 2)**.

Finally, we assessed plasma neutralization against live wild-type and Omicron viruses at one month post-second and third doses in a subset of COVID-19-naive 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<0.0001), the third dose significantly boosted Omicron-specific neutralization above second dose levels (both within-group comparisons p<0.0001). One month post-second dose, both PLWH and controls neutralized Omicron at a median reciprocal dilution of 20 [IQR BLOQ - 40] (p=0.71). One month post-third dose, anti-Omicron neutralization increased to a median reciprocal dilution of 80 [IQR 40-160] in PLWH compared to a median 40 [IQR 40-80] in controls (p=0.03). This was consistent with the superior neutralization of wild-type virus observed in PLWH at this time point (**Figure 2**). Neutralization of wild-type and Omicron viruses correlated significantly with ACE2 displacement activities as expected (all p<0.0001, **Supplemental Figure 4**).

DISCUSSION

Our study confirms that anti-SARS-CoV-2 antibody concentrations and neutralizing activities naturally decline following two-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 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. The lack of significant difference in immune

response decline in PLWH compared to controls following two-dose vaccination is consistent with data from PLWH participants of 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 wild-type-specific ones at all times tested. Nevertheless, after three 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 three-dose vaccination (**Supplemental Table 3**). In fact, most PLWH were eligible for 100mcg 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 multi-morbidities or who have CD4+ T-cell counts <200 cells/mm^3, 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+ counts, possibly due to their eligibility for 100mcg 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 100mcg, 23% received 50mcg, and data for the remainder were unavailable, so we could not assess dose effects on vaccine responses. As 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 two and three-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.

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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 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. *Panel C*: Binding antibody half-lives following two 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 panel B. The two 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. 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 studied time point, as well as individuals who had recovered from COVID-19 at the studied time point (COVID group, black). Plasma neutralization was defined as the reciprocal of the highest plasma dilution at which vial cytopathic effect was prevented in all triplicate assay wells. Plasma samples showing neutralization in fewer than three wells at the lowest plasma dilution of 1/20 were coded as having a reciprocal dilution of 10, corresponding to the lower limit of quantification (LLOQ) in this assay. The highest dilution tested was 1/2560, which corresponds to the upper limit of quantification (ULOQ). Participants who experienced a post-vaccination infection were relocated from their original group into the COVID19 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.

Figure 3: Anti-Omicron IgG binding and ACE2 displacement activities one month after the second and third COVID-19 vaccine doses. *Panel A:* Binding IgG responses in plasma to the wild-type (WT) and Omicron (OM) spike-RBD (S-RBD), measured using the Meso Scale Diagnostics V-Plex assay, in 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 all within-group comparisons) or the Mann-Whitney U-test (for between-group comparisons) and are uncorrected

for multiple comparisons. *Panel B:* same as A, but for ACE2 displacement activity, measured using the V-plex SARS-CoV-2 (ACE2) assay, where results are reported in terms of % ACE2 displacement.

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.

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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/mm^3, median [IQR]	715 [545-943]	-
Nadir CD4+ T-cell count in cells/mm^3, 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 (%)	4 (4%)	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%)	56 of 137 (41%)
mRNA-1273	56 of 80 (70%)	81 of 137 (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%)	137 (90%)
Day of collection one month after third dose, median [IQR]	30 [30-32]	30 [29-32]

Table 2: Impact of HIV infection on humoral responses to COVID-19 vaccination: summary of estimates from multivariable analyses

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 Abs[a]	wild-type	1 month after 2nd dose	-0.017	-0.18 to 0.14	0.83	Supplemental Table 1
	wild-type	3 months after 2nd dose	-0.13	-0.27 to 0.019	0.088	Supplemental Table 1
	wild-type	6 months after 2nd dose	-0.036	-0.19 to 0.11	0.64	Supplemental Table 2
Antibody half-life after the 2nd dose, in days[b]	wild-type	Calculated from all post-2nd dose timepoints	6.33	-19.92 to 32.59	0.63	Supplemental Table 2
Log_2 Viral neutralization[c]	wild-type	1 month after 2nd dose	0.20	-0.47 to 0.86	0.56	Supplemental Table 1
	wild-type	3 months after 2nd dose	-0.063	-0.74 to 0.62	0.86	Supplemental Table 1
	wild-type	6 months after 2nd dose[d]	Odds Ratio = 0.51[d]	0.12 to 1.77	0.32	Supplemental Table 3
	wild-type	1 month after 3rd dose	0.58	-0.22 to 1.37	0.15	Supplemental Table 4
Omicron-specific log_{10} binding IgG[e]	Omicron	1 month after 3rd dose	0.36	0.14 to 0.58	**0.0017**	Supplemental Table 5
Omicron-specific ACE2 % displacement[e]	Omicron	1 month after 3rd dose	3.49	-8.48 to 15.47	0.57	Supplemental Table 5

This table summarizes the estimates (coefficients, or odds ratios as appropriate), 95% confidence intervals (CI) and p-values of the relationship between HIV infection and specific humoral responses to COVID-19 vaccination at the time points shown. All estimates are 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 Supplemental Tables as indicated.

[a] Quantified in serum using the Roche Elecsys anti-S assay

[b] Antibody half-lives were calculated from anti-RBD antibody concentrations from all participants with a complete longitudinal data series following the second vaccine dose, with no values above the ULOQ, and no evidence of prior COVID-19

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

[d] Results for the "6 months after 2nd dose" time point are presented as the adjusted Odds Ratios and associated 95% CI of detectable viral neutralization activity at this time point, calculated using multivariable logistic regression.

[e] Quantified in serum using the Meso Scale Diagnostics V-Plex assay (panel 22)

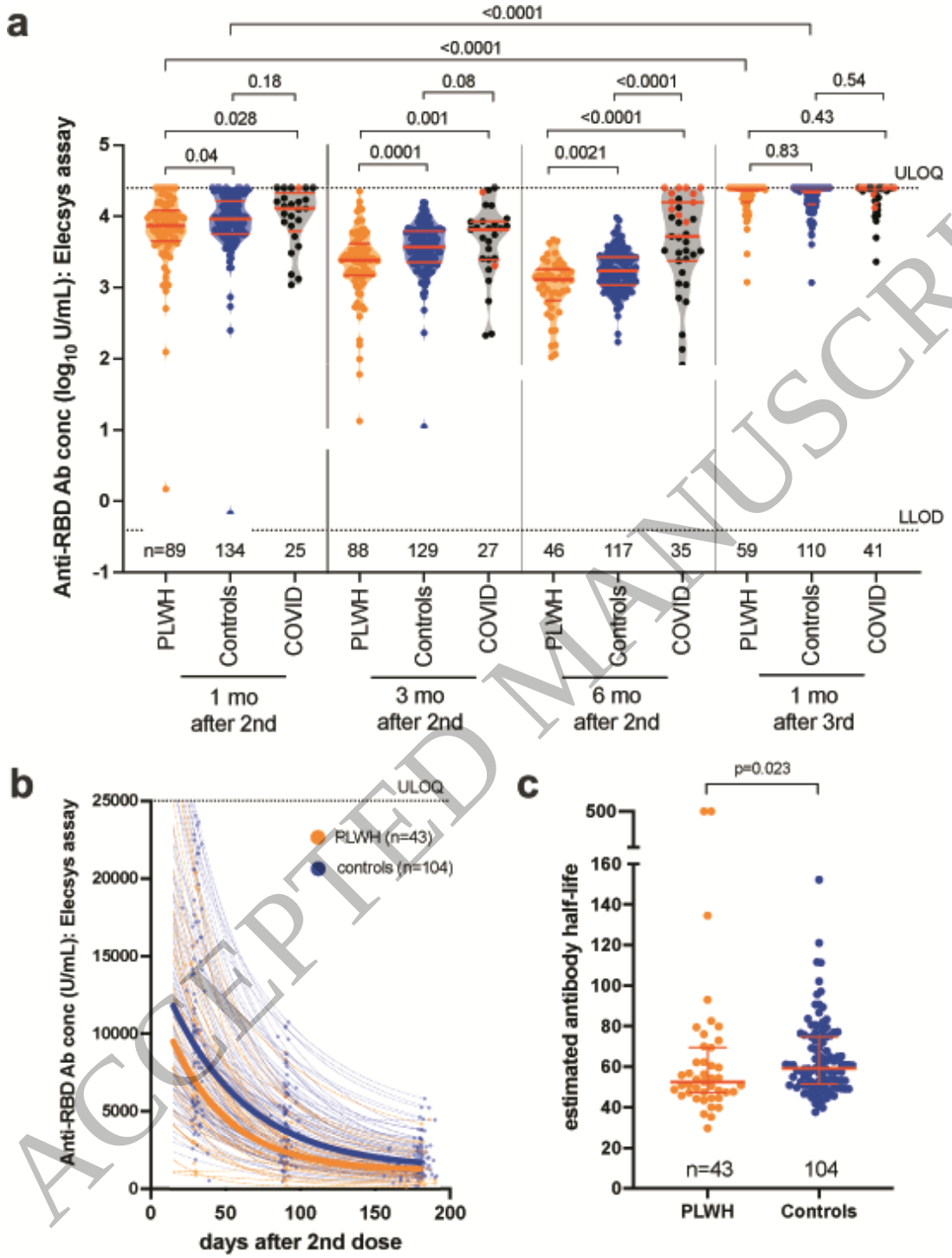

Figure 1
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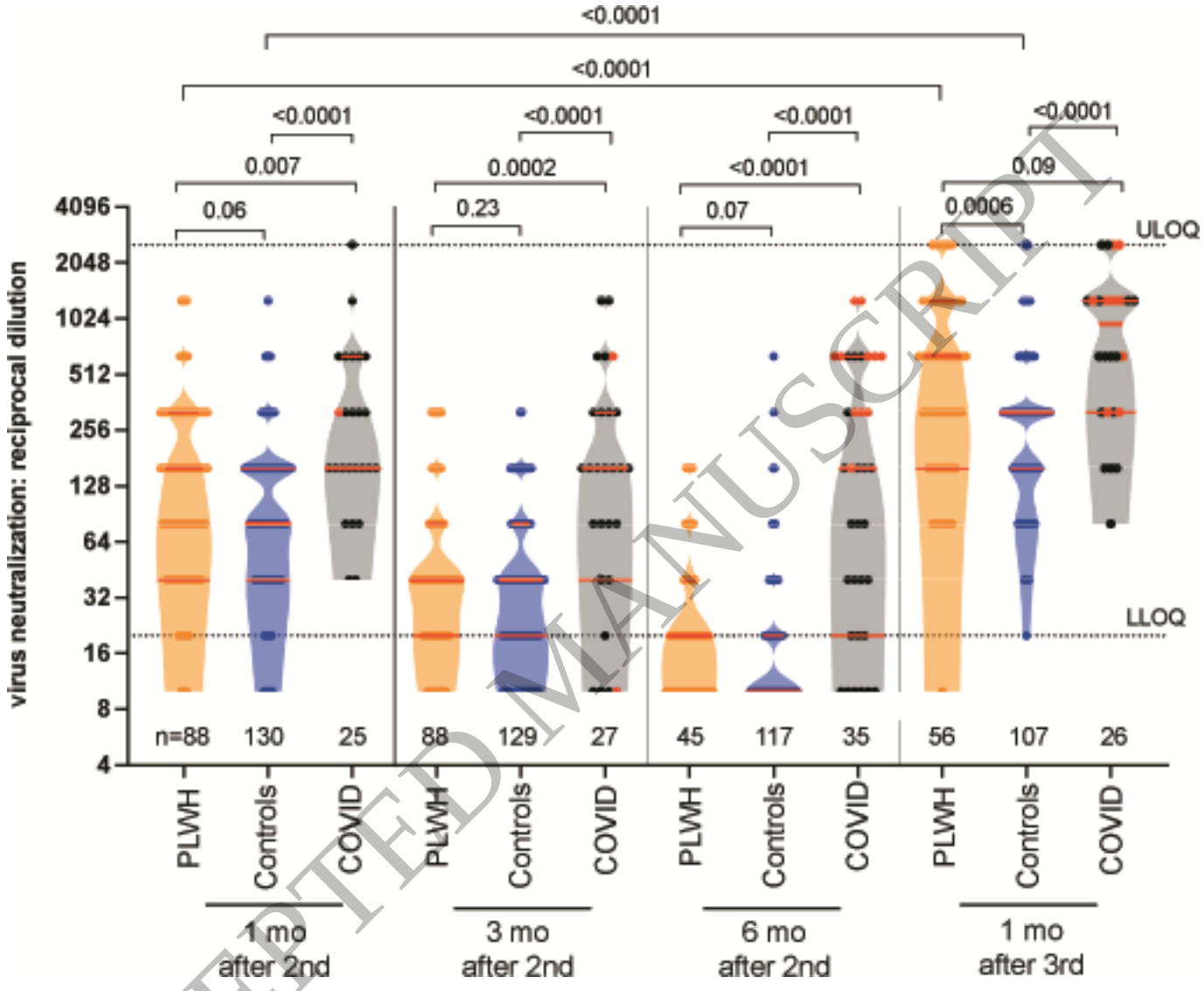

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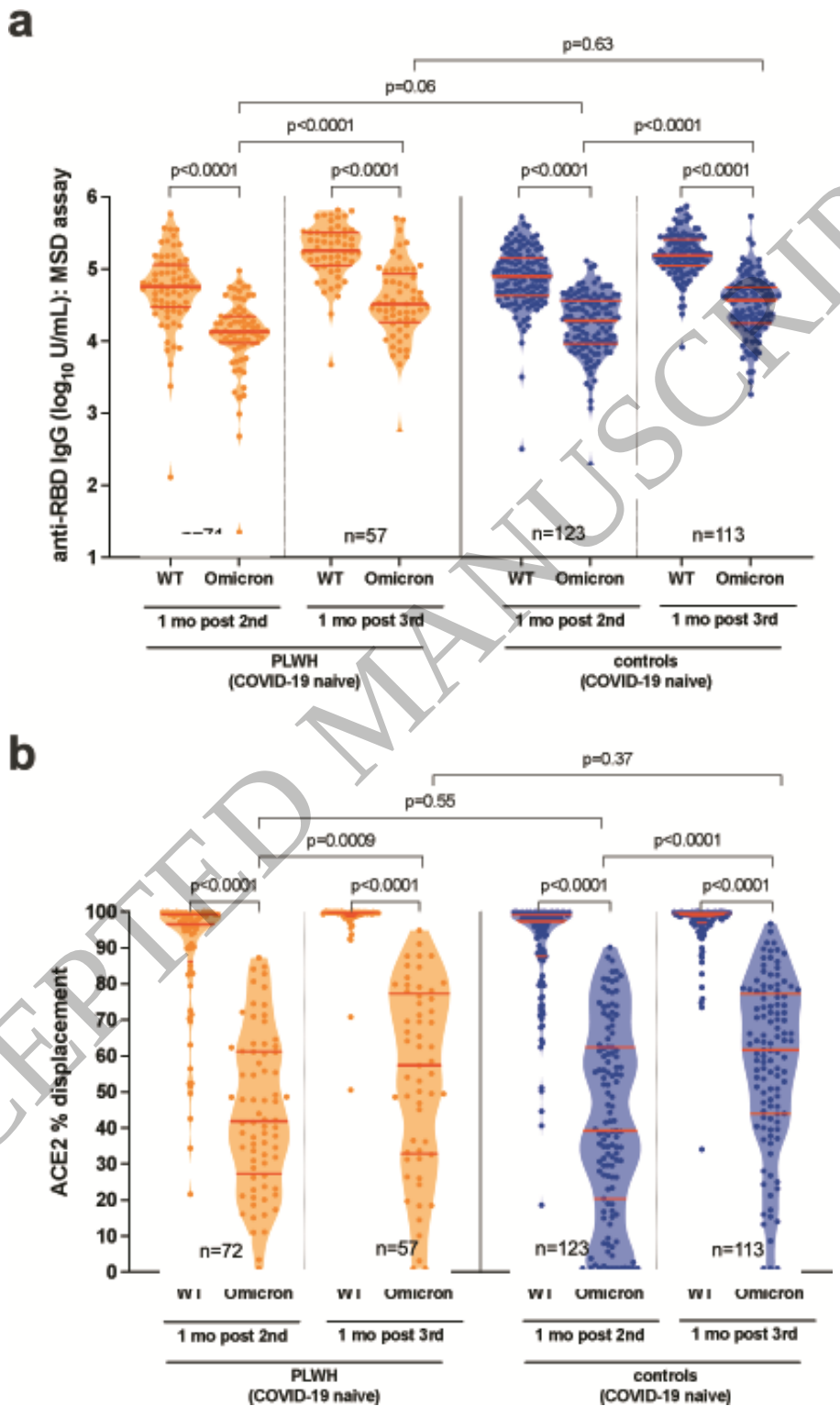

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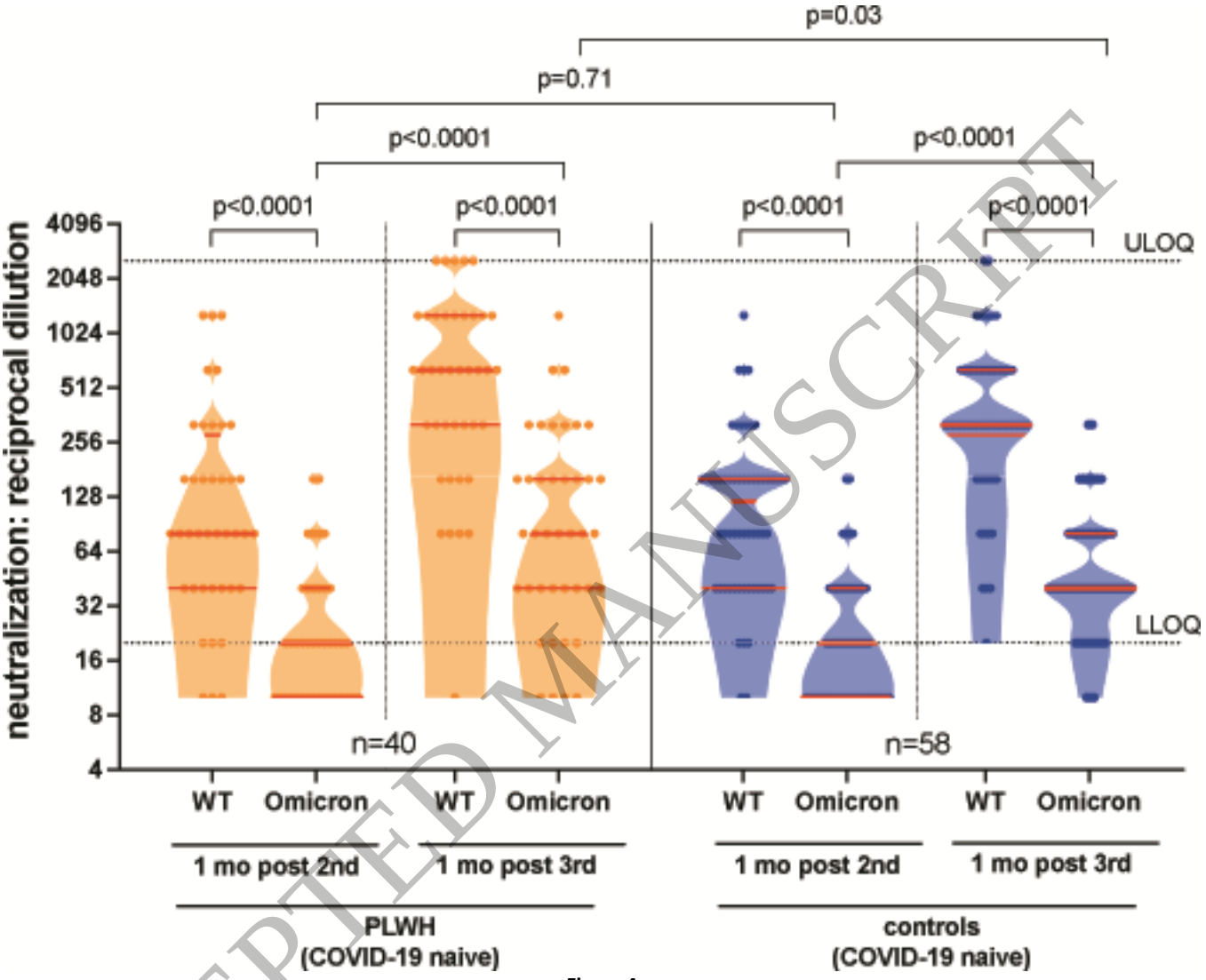

Figure 4
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