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RESEARCH ARTICLE

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Booster shot of inactivated SARS-CoV-2 vaccine induces potent immune responses in people living with HIV

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Abstract

This study aimed to investigate the immunogenicity to SARS-CoV-2 and evasive subvariants BA.4/5 in people living with HIV (PLWH) following a third booster shot of inactivated SARS-CoV-2 vaccine. We conducted a cross-sectional study in 318 PLWH and 241 healthy controls (HC) using SARS-CoV-2 immunoassays. Vaccine-induced immunological responses were compared before and after the third dose. Serum levels of IgG anti-RBD and inhibition rate of NAb were significantly elevated at the "post-third dose" sampling time compared with the pre-third dose in PLWH, but were relatively decreased in contrast with those of HCs. Induced humoral and cellular responses attenuated over time after triple-dose vaccination. The neutralizing capacity against BA.4/5 was also intensified but remained below the positive inhibition threshold. Seropositivity of SARS-CoV-2-specific antibodies in PLWH was prominently lower than that in HC. We also identified age, CD4 cell counts, time after the last vaccination, and WHO staging type of PLWH as independent factors associated with the seropositivity of antibodies. PLWH receiving booster shot of inactivated vaccines generate higher antibody responses than the second dose, but lower than that in HCs. Decreased anti-BA.4/5 responses than that of WT impede the protective effect of the third dose on Omicron prevalence.

KEYWORDS

antibodies, immune response, people with HIV, SARS-CoV-2, vaccination

Haoting Zhan, Huixia Gao, Yongmei Liu, and Xihong Zhang contributed equally to this study.

1 | INTRODUCTION

Since the onset of the COVID-19 pandemic, accumulating evidence reveals that people living with HIV (PLWH) following SARS-CoV-2 infection have been more vulnerable to severe disease and in-hospital mortality.[1,2] Increased incidence of fatal outcomes is more likely to happen in male PLWH and aged >45 years, whereas individuals on antiretroviral therapy (ART) and those with HIV viral loads of <1000 copies per ml are less prone to severe or critical disease.[3]

The efficacy of SARS-CoV-2 vaccines reduces COVID-19 severity and mortality rates by triggering robust humoral and cellular responses against the virus.[4,5] However, only a few clinical trials have focused on immunocompromised individuals because of their dysregulated host defenses. As previous studies were generated, PLWH with preserved CD4 cell counts mediated by ART mounted similar immune responses as healthy controls (HC).[6,7] After two shots of CoronaVac, the seroconversion rates of SARS-CoV-2 IgG and neutralizing antibody (NAb) positivity were higher in PLWH with CD4 counts ≥500 cells/μl than in those with CD4 counts <500 cells/μl; however, both were lower than that of HC.[8] No significant difference of antibody responses was found among PLWH subgroups stratified by CD4 lymphocytes (<350, 350–500, >500 cells/μl) at the time of vaccination, who all completed the inoculation schedule of mRNA-1273 vaccine.[7] To date, evidence is lacking on the risk factors associated with inadequate immunological landscape among PLWH.

Whether people living with HIV have decreased immunological responses toward SARS-CoV-2 vaccines remains controversial.[8–10] Waning immunoreactivity, which usually occurs at 6–8 months following vaccination, warrants an additional vaccine dose.[11,12] The advent of variants of concerns (VOCs) with increased mutations and transmissibility containing the Omicron lineage BA.4/5 drives waves of infection nowadays.[13] BA.4/5 is responsible for NAb escape and breakthrough infections even in healthy individuals who received triple doses of mRNA or adenovirus vaccine.[14,15] For CoronaVac vaccine, known for inactivated whole virus one, could neutralize 10 representative strains of SARS-CoV-2, two of which (CN1 and OS1) are closely related to the original SARS-CoV-2 strain from early 2020 (2019-nCoV-BetaCoV/Wuhan/WIV04/2019 and EPI_ISL_412973).[5] Mutated variants in the spike protein receptor binding domain (RBD) give incentives to escape from neutralizing antibodies, even in those recovered from COVID-19 infections or vaccine recipients, compromising the efficacy of the vaccination. Data on immunogenicity of inactivated COVID-19 vaccines against Omicron subvariants remains urgently needed. These alert us to assess the immune protection among immunocompromised patients including PLWH who received booster inactivated vaccination. Thus, this study aimed to investigate the immunogenicity to SARS-CoV-2 and evasive subvariants BA.4/5 in PLWH following a third booster shot of inactivated SARS-CoV-2 vaccine.

2 | MATERIALS AND METHODS

2.1 | Patients and specimen collection

The study cohort is composed of 318 PLWH from the outpatient department of the Fifth Hospital of Shijiazhuang and 241 age-matched HCs from the department of health medicine in Peking Union Medical College Hospital. The inclusion criteria of PLWH were as follows: (1) adult patients with HIV infection confirmed by Western blot analysis, (2) PLWH with detailed medical records and laboratory parameters, and (3) those who received at least the two-dose regimen of inactivated vaccine after the definite diagnosis of HIV. After excluding patients with previous SARS-CoV-2 infection fulfilling the below criteria (i) positive reverse transcription PCR results for SARS-CoV-2 on naso-oropharyngeal swabs; (ii) presence of anti-SARS-CoV-2 IgM/IgG antibodies or specific antigens; (iii) once have medical history of SARS-CoV-2 infection or recovery from SARS-CoV-2, and those who were ever administered immunosuppressive drugs or plasma replacement therapy, the remaining patients were categorized into four subgroups according to inoculation dose and duration at the time of sampling, including PLWH with the second dose of the inactivated vaccine after 14–89 days ($n = 14$), second dose of the inactivated vaccine after 180 days ($n = 51$), those with booster immunization of the third dose after 14–89 days ($n = 99$), third dose after 90–180 days ($n = 57$), and third dose after 180 days ($n = 97$). HCs were also matched with the last vaccination period. Serum samples were collected, numbered, and stored at −80°C.

For laboratory dimensions, CD4 and CD8 lymphocytes were analyzed by Flow CytoMetry on the BD FACSCanto II. White blood cell and platelet counts were measured using Sysmex XN-1000 Pure, whereas serum biochemical parameters including alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine (Cr), triglyceride, total cholesterol (TC), glucose, and total bilirubin were detected on TOSHIBA-FX8. Moreover, electronic medical records of PLWH were retrieved including age, sex, weight, height, date of a confirmed diagnosis, WHO disease staging system for HIV infection, current therapeutic regimen, and time of each inactivated vaccine dose.

The study protocol was approved by the Medical Ethics Committee of Peking Union Medical College Hospital and the Fifth Hospital of Shijiazhuang and informed consent was obtained from all the participants.

2.2 | Detection of total antibodies against SARS-CoV-2

We used the double-antigen sandwich enzyme-linked immunosorbent assay (ELISA) to determine the total antibodies against SARS-CoV-2 (Beijing Wantai Biological Pharmacy Enterprise), the reagent of which could only detect specific total antibodies (including

IgM, IgG, and IgA) targeting the RBD region of S1 subunit (antigen). A total of 100 µl of serum samples were initially added into a microwell plate coated with 2019-nCoV antigen (the RBD region of S1 subunit) and incubated at 37°C for 30 min. After washing, HRP-labeled 2019-nCoV-Ag was added to generate a complex of coated Ag-antibody–HRP-labeled Ag. Then, 50 µl of chromogenic agents A (≥ 0.3 g/L peroxide) and B (≥ 0.2 g/L HRP) was then added for coloration. The plate was read at 450 nm after 50 µl of stop solution was eventually added. The final optical density (OD) of each microwell was calculated using raw OD values minus blank OD. Additionally, 133 negative and 52 positive controls were determined, and 0.19 was selected as a threshold value using the following formula: cutoff = 0.16 + average absorbance of negative controls. The detailed information of sensitivity and specificity of total antibody test was provided in online supplementary material.

2.3 | Detection of neutralizing antibody toward SARS-CoV-2 wild type (WT) and Omicron BA.4/5 subvariant

By using competitive ELISA, the SARS-CoV-2 Surrogate Virus Neutralization Test (sVNT) assay (GenScript cPass™ SARS-CoV-2 Neutralization Antibody Detection Kit, Genscript) detected the circulating neutralizing antibodies that block the interaction between the receptor-binding domain of the viral spike glycoprotein (RBD) and human ACE2 (hACE2). According to the instructions from the manufacturer, first, the serum samples and controls were pre-incubated at 37°C for 15 min allowing the binding of NAb and HRP-RBD (antigen derived from both SARS-CoV-2 WT and Omicron BA.4/5) with a volume ratio of 1:1. Second, the mixture was transferred to capture the plate pre-coated with the hACE2 protein where the NAb-unbounded HRP-RBD was captured on the plate, whereas NAb-bound HRP-RBD remained in the supernatant and get washed. Then, after adding 100 µl of TMB and 50 µl of the stop solution, the plate was read at 450 nm where the absorbance of the sample was inversely correlated with the titers of anti-SARS-CoV-2-neutralizing antibodies. To assure the validity of the results, the OD450 values of positive (>1.0) and negative controls (<0.3) must fall within the ranges. For interpretation of the results, an inhibition rate of ≥30% was regarded to be positive in SARS-CoV-2-neutralizing antibody determination. The inhibition rate was computed as follows: Inhibition = (1−OD value of sample/OD value of negative control) × 100%. The detailed information of sensitivity and specificity of sVNT assay was provided in online supplementary material.

2.4 | Detection of IgG anti-SARS-CoV-2 spike RBD antibody

Capture sandwich ELISA (PROPRIUM Co, Ltd) was employed to detect SARS-CoV-2-neutralizing antibodies, where the SARS-CoV-2 spike RBD protein (antigen) was pre-coated onto the solid phase to form an antigen–antibody complex with IgG anti-RBD antibodies from 100 µl of the diluted serum samples or standards. Following the washing procedure and addition of HRP-conjugated anti-human IgG, an antigen–antibody–HRP complex was formed. Finally, the substrate solution TMB was then added into the microwells. Color developed proportionally to the amount of SARS-CoV-2-neutralizing antibodies, and the optical density (OD) at 450 nm was measured. The concentration (BAU/ml) of anti-RBD antibodies was calculated by standard curves formed by standards with a normal reference range of 10–1000 BAU/ml. As it was provided by manufacturer, the assay shows a performance of a specificity of 99.8%, a sensitivity of 97.8% and coefficient of variation (CV) ≦ 10%.

2.5 | Statistical analysis

For statistical purposes, normally distributed data were expressed as mean ± SD, whereas non-normally distributed data were presented as median (IQR); the normality of data distribution was assessed using the Shapiro–Wilk test. When comparing two independent groups with non-normal distributions, the nonparametric Mann–Whitney U test was used. The χ^2 test was employed to detect the difference in the positivity rate of the total antibodies against SARS-CoV-2, NAb against WT, and NAb against BA.4/5 and IgG anti-RBD antibodies. Correlations between SARS-CoV-2 antibodies and laboratory parameters were evaluated using Spearman's rank correlation coefficient test, with coefficient values >0.3 or < −0.3 considered clinically relevant. We also performed multivariate logistic regression to assess independent risk factors for PLWH, which affected the positivity of the above-mentioned antibodies after the third dose of the inactivated vaccine.

GraphPad Prism 9, IBM SPSS Statistics for Windows version 24 (IBM Corp), and R version 4.2.1 software were utilized for the statistical analyses. A p value of <0.05 was considered statistically significant.

3 | RESULTS

3.1 | Demographics and clinical characteristics of the participants

In accordance with the vaccination dose and period at the time of sampling, 318 PLWH were divided into five subgroups, including PLWH with the second dose of the inactivated vaccine after 14–89 days and after 180 days, as well as "post-third dose" PLWH after 14–89 days, after 90–180 days, and >180 days. The demographic data of PLWH were also categorized into clinical characteristics, laboratory determinations, and ART (Table 1). Overall, HCs were precisely matched by age and inoculation duration between the different subgroups of PLWH (Supporting Information: Table S1).

TABLE 1 Demographics and clinical characterization of PLWH

Category	Characteristic	2nd dose after 14–89 days	2nd dose after 180 days	3rd dose after 14–89 days*	3rd dose after 90–180 days	3rd dose after 180 days*
Clinical characteristics	Numbers	14	51	99	57	97
	Age (year)	34 [28, 49.25]	36.2 ± 9.893	35 [30,41]	34.18 ± 4.602	34 [29.5, 40]
	Gender (F/M)	2/12	6/45	7/92	3/54	6/91
	Weight (kilogram)	66.86 ± 12.44	64 [58.63, 71.5]	65 [57, 74]	66 [60, 73.25]	65 [60, 72]
	Height (centimeter)	171.1 ± 5.816	172.5 ± 6.76	172.3 ± 6.096	173 ± 6.199	172 [170, 177]
	Duration of HIV(day)	1798 ± 1140	1153 [404, 2231]	1680 [926, 2463]	2089 ± 964.4	1845 [1006, 2660]
	WHO disease staging system					
	Stage I	11 (78.57%)	40 (78.43%)	71 (71.72%)	46 (80.70%)	79 (81.44%)
	Stage II	1 (7.14%)	1 (1.96%)	3 (3.03%)	2 (3.51%)	4 (4.12%)
	Stage III	0 (0.00%)	1 (1.96%)	5 (5.05%)	1 (1.75%)	13 (13.40%)
	Stage IV	2 (14.29%)	9 (17.65%)	19 (19.19%)	8 (14.04%)	0 (0.00%)
	Period of last vacciation at the time of sampling (day)	54 ± 25.59	269 [223, 331]	70 [44, 80]	118 [103.5, 139.5]	219 [202.5, 240]
	Period of first vacciation and confirmed diagnosis (day)	1680 ± 1152	1115 [383, 2210]	1446 [681, 2229]	1865 ± 964.4	1637 [796.5, 2433]
Laboratory determinations	CD4 lymphocyte count (cells/μl)	533.6 ± 220.4	534.9 ± 214	482 [355, 700]	553 [410, 667]	461 [307, 602.5]
	CD8 lymphocyte count (cells/μl)	874.9 ± 371.5	688 [575, 927.5]	694 [501, 1074]	660 [532, 946.5]	638 [474, 834]
	HIV virus load (C/ml)	171 ± 553.9	0 [0, 0]	0 [0, 0]	0 [0, 0]	0 [0, 0]
	WBC counts (10^9/L)	6.815 ± 1.727	6.04 [4.93, 7.425]	5.81 [4.948, 7.003]	5.97 [4.83, 7.36]	5.55 [4.89, 6.52]
	Platelet counts (10^9/L)	250.2 ± 67.71	249.3 ± 57.47	244 [209.3, 281.3]	246 [220, 294]	228 [203, 265]
	Hb (g/L)	158.2 ± 14.57	158 [147.8, 167.5]	162 [148.8, 168]	164.1 ± 13.05	159 [151, 167]
	Cr (μmol/L)	75.65 ± 15.08	68.5 [59.43, 77.65]	70.28 ± 11.8	71.31 ± 11.75	73 [66.7,82.7]
	TG (mmol/L)	2.182 ± 1.441	1.475 [0.88, 2.865]	1.52 [1.095, 2.363]	1.68 [1.05, 2.45]	1.28 [0.98, 2.15]
	TC (mmol/L)	4.778 ± 0.8972	4.835 [4.008, 5.398]	4.655 [4.035, 5.598]	4.74 ± 0.81	4.25 [3.76, 4.91]
	GLU (mmol/L)	5.373 ± 0.5867	5.42 [5.108, 5.89]	5.32 [4.968, 5.838]	5.47 [5.02, 5.99]	5.65 [5.32, 5.98]
	ALT (U/L)	25.37 ± 10.68	27.65 [19.68, 39.8]	27.75 [19.38, 46.55]	31 [21.6, 46.2]	27.2 [19.5, 39.3]
	AST (U/L)	20.69 ± 4.356	21.2 [17.75, 25.1]	22.25 [17.9, 27.85]	22 [18.5, 28.5]	20.4 [16.3, 27.8]
	TBil (μmol/L)	7.7 [5.7, 10.3]	8.35 [6.45, 11.5]	8.6 [6.775, 10.73]	8.4 [6.6, 10.45]	8.9 [6.8, 11.4]
Antiretroviral therapy	3TC/DTG		1 (1.96%)	4 (4.04%)	1 (1.75%)	1 (1.03%)
	3TC/DTG + TDF + LPV/r			1 (1.01%)		
	3TC + ABC + LPV/r			1 (1.01%)	1 (1.75%)	
	3TC + DTG		1 (1.96%)			1 (1.03%)
	3TC + DTG + TDF	1 (7.14%)	3 (5.88%)		1 (1.75%)	2 (2.06%)
	3TC + EFV + TDF	7 (50.0%)	30 (58.82%)	63 (63.64%)	38 (66.67%)	57 (58.76%)
	3TC + LPV/r			2 (2.02%)		1 (1.03%)
	3TC + NVP + TDF			2 (2.02%)		3 (3.09%)

TABLE 1 (Continued)

Category	Characteristic	2nd dose after 14–89 days	2nd dose after 180 days	3rd dose after 14–89 days*	3rd dose after 90–180 days	3rd dose after 180 days*
	3TC + TDF + LPV/r	4 (28.57%)	1 (1.96%)	3 (3.03%)	3 (5.26%)	8 (8.25%)
	AZT/3TC + DTG					1 (1.03%)
	AZT/3TC + EFV	1 (7.14%)	8 (15.69%)	8 (8.08%)	8 (14.04%)	15 (15.46%)
	AZT/3TC + LPV/r		1 (1.96%)	6 (6.06%)	2 (3.51%)	
	AZT/3TC + NVP	1 (7.14%)	3 (5.88%)	4 (4.04%)	3 (5.26%)	4 (4.12%)
	AZT + LPV/r			1 (1.01%)		
	BIC/FTC/TAF			2 (2.02%)		
	EVG/c/FTC/TAF		2 (3.92%)	1 (1.01%)		3 (3.09%)
	DTG/ABC/3TC		1 (1.96%)			

Abbreviations: 3TC, Lamivudin; ABC, Abacavir; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AZT, Azidothymidine; BIC, Bictegravir; Cr, creatinine; DTG, Dolutegravir; EFV, Efavirenz; EVG/c, Elvitegravir/Cobicistat; FTC, Emtricitabine; GLU, glucose; Hb, hemoglobin; LPV/r, Ritonavir-boosted lopinavir; NVP, Nevirapine; TAF, Tenofovir Alafenamide; TBil, total bilirubin; TC, total cholesterol; TDF, TG, triglyceride.

*One patient has lost part of his medical record.

3.2 | Total antibodies against SARS-CoV-2 and IgG anti-RBD antibodies are boosted at the "post-third dose" visit in PLWH

After 180 days of the second dose, serum levels of total antibodies against SARS-CoV-2 were significantly lower in the PLWH group than in the HCs (1.092[0.373, 3.187] vs. 3.125[1.298, 3.407], $p = 0.0004$). Similar conditions occurred in those who received the third dose after 180 days (3.361[3.25, 3.437] vs. 3.439[3.342, 3.568], $p = 0.0007$) (Figure 1A and Supporting Information: Table S2). As regards dynamic changes after each vaccine dose in PLWH (Figure 1B), we observed a dramatic decrement of total antibodies 180 days after the second dose (2nd dose after 180 days: 1.092[0.373, 3.187] vs. 2nd dose after 14–89 days: 3.204[2.521, 3.253], $p = 0.0337$) and obvious increment at "post-third dose" (2nd dose after 180 days: 1.092[0.373, 3.187] vs. 3rd dose after 14–89 days: 3.423[3.177, 3.49], $p < 0.0001$). When PLWH were stratified into three subgroups (CD4 < 200 cells/μl, 200 cells/μl ≦ CD4 ≦ 350 cells/μl, and CD4 > 350 cells/μl) based on CD4 lymphocyte counts,[16] we compared levels of total antibodies toward SARS-CoV-2 in different vaccination series, and no discrepancies were found between these subgroups (Figure 1C and Supporting Information: Figure S1A). The seropositivity of the total antibodies against SARS-CoV-2 after the booster dose of the inactivated vaccine was comparable between PLWH and HCs (98.81% vs. 98.91%, $p = 0.7145$) (Figure 1D).

IgG anti-SARS-CoV-2 spike RBD antibodies were measured by ELISA, which support an increased response post-booster shot after 14–89 days, but significantly decreased when >180 days in PLWH (2nd dose after 180 days: 0[0, 11.03] BAU/ml vs. 3rd dose after 14–89 days: 337.7[97.66, 694] BAU/ml vs. 3rd dose after 180 days: 108.1[34.73, 330.1] BAU/ml, $p < 0.0001$ and $p < 0.0001$, respectively) (Figure 2A,B, Supporting Information: Table S2). Concentrations of IgG anti-RBD in PLWH were always inferior to those in HCs at pre- and post-third dose time of sampling (2nd dose after 180 days: 0[0, 11.03] vs. 54.85[1.773, 133.1] BAU/ml, $p < 0.0001$; 3rd dose after 14–89 days: 337.7[97.66, 694] vs. 638.8[568.6, 797.7] BAU/ml, $p < 0.0001$; 3rd dose after 90–180 days: 248.2[123.1, 431.3] vs. 558.1[358.9, 612.1] BAU/ml, $p < 0.0001$; 3rd dose after 180 days: 108.1[34.73, 330.1] vs. 274.9[151.9, 622.6] BAU/ml, $p = 0.0001$) (Figure 2A). Additionally, PLWH with well-controlled CD4 counts hold a relatively higher magnitude of IgG anti-RBD post-third dose after 180 days when the efficacy of the booster dose was gradually wearing off (Figure 2C), but not in other time points (Supporting Information: Figure S1B). The proportion of IgG anti-RBD seropositivity was prominently lower in PLWH than in HC (89.33% vs. 99.45%, $p < 0.0001$) (Figure 2D).

3.3 | Waning VOC humoral responses following booster vaccination in both PLWH and HC

The effects of booster inoculation on neutralizing antibodies to SARS-CoV-2 WT were presented as the inhibition rate (%), which varied in PLWH and HCs (3rd dose after 14–89 days: 59.98[33.54, 89.53] vs. 91.69[74.33, 96.96], $p < 0.0001$; 3rd dose after 90–180 days: 47.13[21.74, 79.03] vs. 72.86[48.47, 93.74], $p = 0.0047$; 3rd dose after 180 days: 14.04[3.212, 54.97] vs. 48.24[21.11, 90.3], $p = 0.0001$) (Figure 3A and Supporting Information: Table S2). In PLWH, analyses of serum "post-third dose" samples revealed an apparent elevation of the inhibition rate (%) of NAb on WT, but significantly declined each day after triple injection (3rd dose after 14–89 days: 59.98[33.54, 89.53] vs. 3rd dose after 90–180 days: 47.13[21.74, 79.03] vs. 3rd dose after 180 days: 14.04[3.212, 54.97], $p = 0.0491$ and $p < 0.0001$, respectively) (Figure 3B). Noteworthy, we also uncovered an increased potency of NAb to WT in PLWH with a

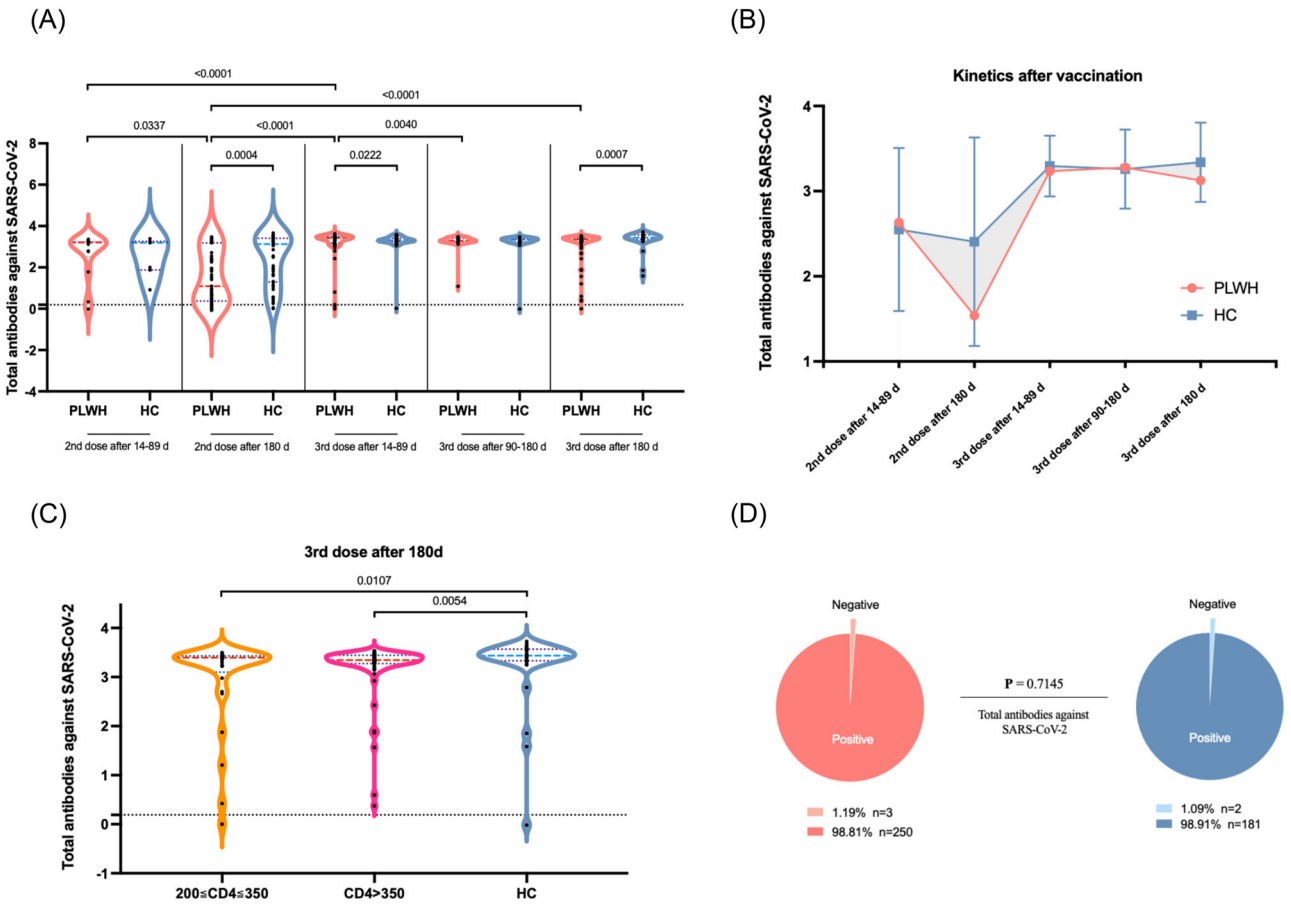

FIGURE 1 Total antibodies against SARS-CoV-2 are boosted following third dose of inactivated SARS-CoV-2 vaccines among PLWH. (A) Levels of total antibodies against SARS-CoV-2 (OD value) in PLWH and HC subjects at pre- and post- booster (third) dose of inactivated vaccine. (B) Kinetics of total antibodies responses against SARS-CoV-2 before and after triple dose injection. (C) Comparison of total antibody levels against SARS-CoV-2 among PLWH classified by CD4 cell counts (CD4 < 200 cells/μl, 200 cells/μl ≦ CD4 ≦ 350 cells/μl, CD4 > 350 cells/μl) and HC. PLWH with lower CD4 counts <200 cells/μl were not visualized due to small sample size at post third dose after 180 days. (D) Seropositivity of total antibodies against SARS-CoV-2 in PLWH (red) comparing with HC (blue). Optical Density (OD) values above 0.19 were regarded as positive.

CD4 cell count of >350 cells/μl (Figure 3C). Moreover, the positivity of NAb against WT was quite different in PLWH from that in HC (61.66% vs. 86.89%, $p < 0.0001$) (Figure 3D).

Moreover, we evaluated the magnitude of humoral responses to Omicron BA.4/5 variants (most prevalent VOCs nowadays) after the third dose. The waning tendency of NAb against BA.4/5 at pre- and post-third dose visits (2nd dose after 180 days: 12.54[10.12, 15.97] vs.3rd dose after 14–89 days: 22.05[9.528, 38.83] vs. 3rd dose after 90–180 days: 12.47[6.095, 21.38] vs. 3rd dose after 180 days: 5.68[−0.1171, 13.33], $p = 0.0010$, $p = 0.0088$ and $p = 0.0005$, respectively) was found in PLWH and HC (Figure 4C and Supporting Information: Table S2). Both the inhibition rate and NAb seropositivity toward BA.4/5 after the third dose were prominently decreased in PLWH in contrast to HCs (Figure 4A,D, Supporting Information: Table S2). No difference was discovered among PLWH subgroups stratified by CD4 cell counts (Figure 4C and Supporting Information: Figure S1C).

By comparing the effects of NAb in blocking infection toward SARS-CoV-2 WT and VOC (BA.4/5), we observed decreased inhibition rates of BA.4/5 than that of WT at the third dose after 14–89 days (22.05[9.528, 38.83] vs. 59.98[33.54, 89.53], $p < 0.0001$), 90–180 days (12.47[6.095, 21.38] vs. 47.13[21.74, 79.03], $p < 0.0001$) and >180 days (5.68[−0.1171, 13.33] vs. 14.04[3.212, 54.97], $p = 0.0003$) in PLWH, which was in accord with HC (Figure 5 and Supporting Information: Table S2). However, booster vaccination could not invigorate the neutralization ability on BA.4/5, and the inhibition rate remained low, which was evidently <30% in PLWH.

3.4 | Correlation of the vaccination period and magnitude of SARS-CoV-2 antibodies after the third dose

To further explore the association of antibody responses with clinical and laboratory parameters, we conducted Spearman's correlation analyses (Figure 6A). Generally, a robust and significant

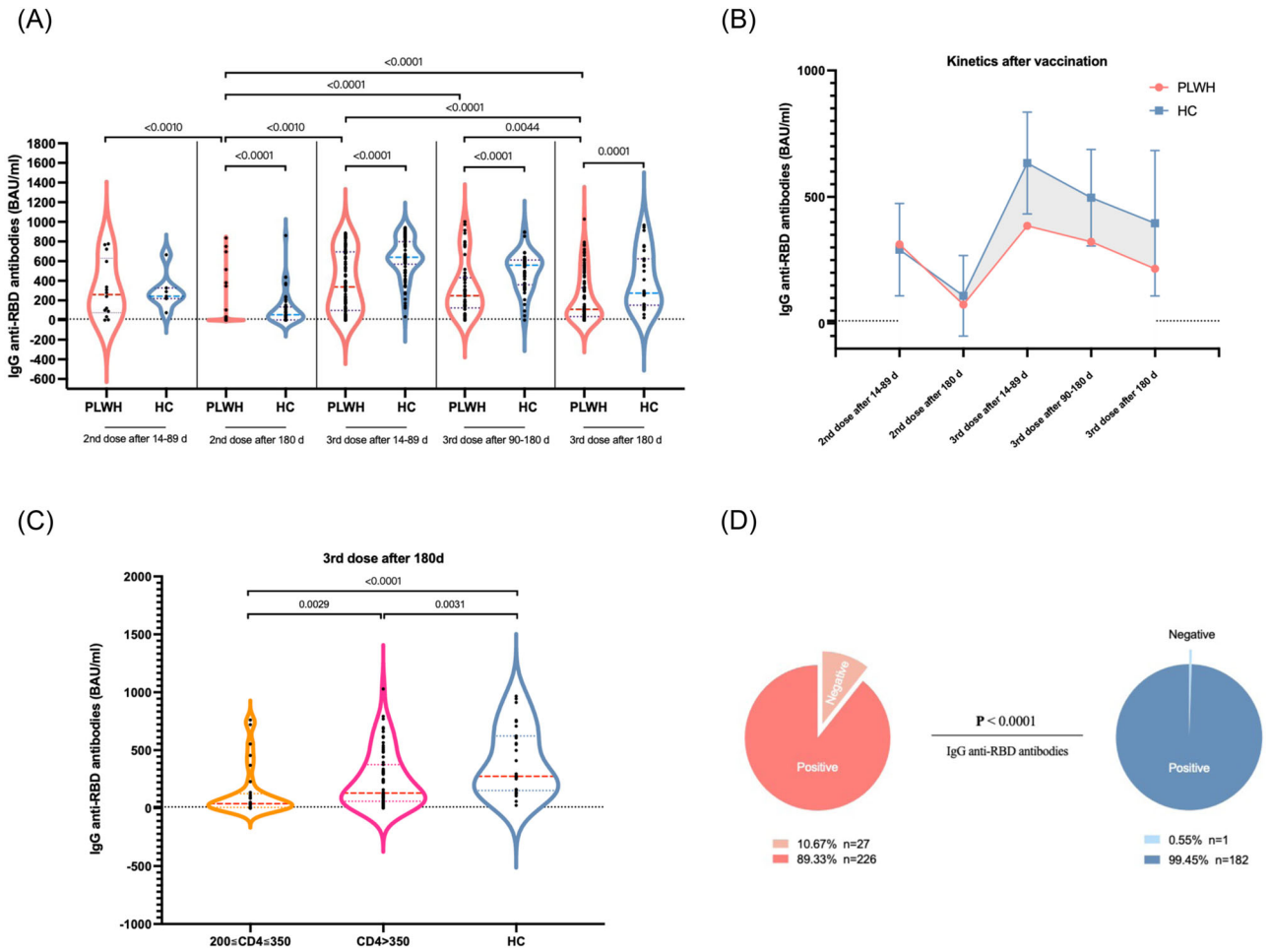

FIGURE 2 IgG anti-RBD antibodies are increased after third dose of inactivated SARS-CoV-2 vaccines among PLWH. (A) Concentrations (BAU/ml) of IgG anti-RBD antibodies in PLWH and HC subjects at pre- and post-booster (third) dose of inactivated vaccine. (B) Kinetics of IgG anti-RBD antibodies before and after triple dose injection. (C) Comparison of IgG anti-RBD antibodies among PLWH classified by CD4 cell counts (CD4 < 200 cells/μl, 200 cells/μl ≦ CD4 ≦ 350 cells/μl, CD4 > 350 cells/μl) and HC. PLWH with lower CD4 counts <200 cells/μl were not visualized due to small sample size at post third dose after 180 days. (D) Seropositivity of IgG anti-RBD antibodies in PLWH (red) comparing with HC (blue). Concentrations among 10–1000 BAU/ml were regarded as positive.

correlation was found between IgG anti-RBD and NAb against WT ($r = 0.8366$, $p < 0.0001$), IgG anti-RBD and NAb against BA.4/5 ($r = 0.7082$, $p = 0.0010$), NAb against WT and NAb against BA.4/5 ($r = 0.7683$, $p = 0.0001$) (Figure 6C and Supporting Information: Table S3). These phenomena are in parallel with the excellent correlation between anti-spike binding titers and NAb.[17] Simultaneously, the inhibition rates of NAb against WT ($r = -0.3882$, $p = 0.0137$), NAb against BA.4/5 ($r = -0.4031$, $p = 0.0070$), and magnitude of IgG anti-RBD ($r = -0.2327$, $p = 0.0429$) were negatively related with time after the third dose (Figure 6D and Supporting Information: Table S3). The heatmap of SARS-CoV-2-specific antibodies similarly indicated that in PLWH, humoral responses toward vaccination would gradually diminish with time (Figure 6B), especially at 180-day post-second and third doses. For the "post-third dose" PLWH, flow cytometry results revealing an upregulation of NK cells and a down-regulation of B cells have also verified this speculation (Supporting Information: Figure S2).

3.5 | Risk factors associated with the seropositivity of SARS-CoV-2 antibodies

We exploited multivariate logistic analyses to investigate independent factors that influence the seropositivity of SARS-CoV-2-specific antibodies in PLWH who received triple doses of inactivated vaccines. The characteristics of PLWH were divided into three categories: clinical information, laboratory determinations, and ART records (Table 1). Then, three dimensions of PLWH were included to the logistic regression models step by step, containing adjusted Model 1 (intake clinical information), adjusted Model 2 (intake clinical information and laboratory determinations), and adjusted Model 3 (intake clinical information, laboratory determinations, and ART records) (Table 2).

We uncovered that age (OR = 0.964, $p = 0.048$) and time after the last vaccine dose (OR = 0.990, $p < 0.001$) were associated with NAb seropositivity against WT in adjusted Model 1. When

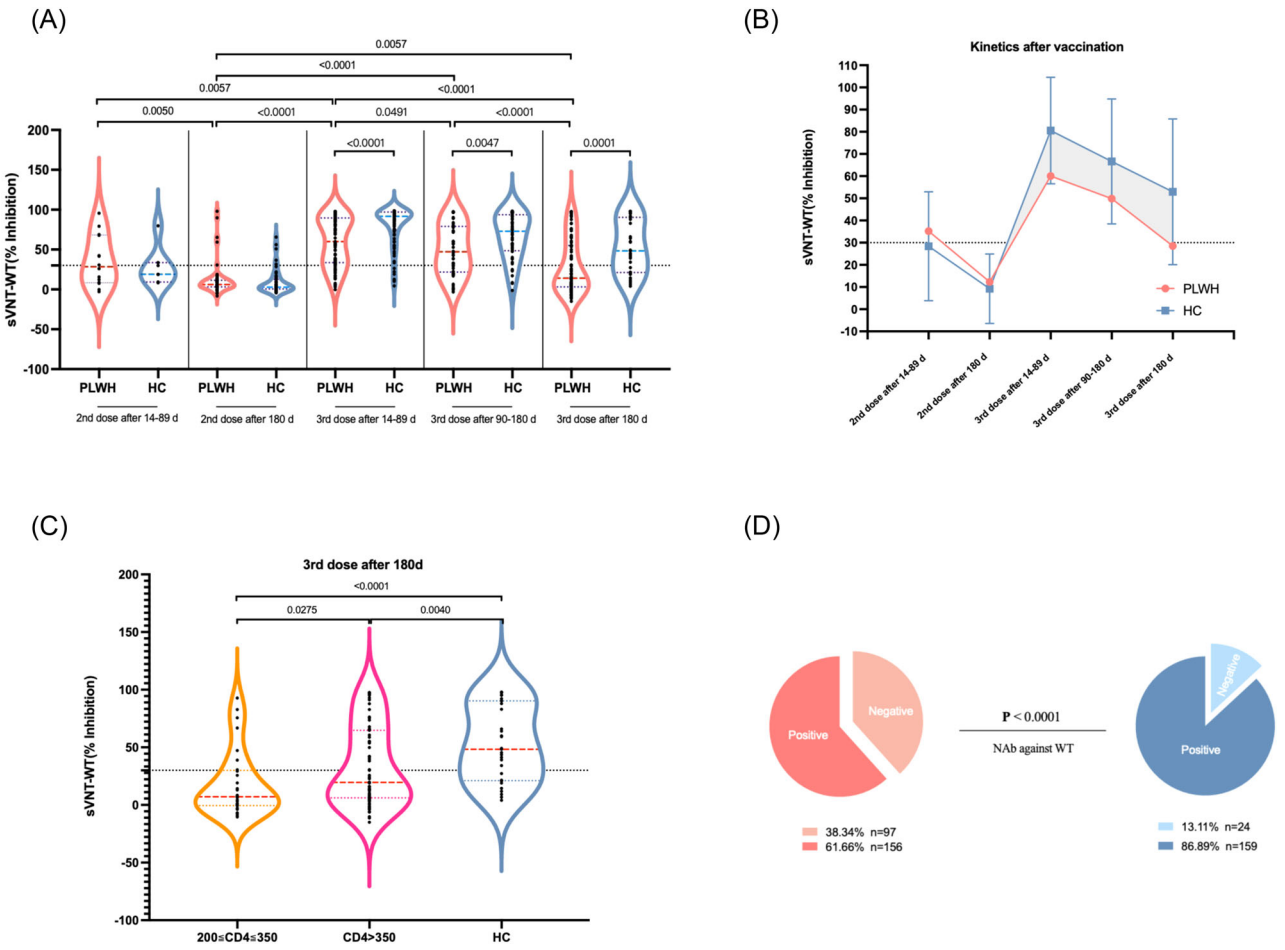

FIGURE 3 Neutralizing effect to SARS-CoV-2 wild type (WT) are elevated after triple dose of inactivated SARS-CoV-2 vaccines among PLWH. (A) Inhibition rates (%) of neutralizing antibodies against WT (NAb against WT) evaluated by SARS-CoV-2 surrogate virus neutralization test (sVNT) in PLWH and HC subjects at pre- and post- booster (third) dose of inactivated vaccine. (B) Kinetics of NAb inhibition function against WT before and after triple dose injection. (C) Comparison of NAb inhibition function against WT among PLWH classified by CD4 cell counts (CD4 < 200 cells/μl, 200 cells/μl≦ CD4 ≦ 350 cells/μl, CD4 > 350 cells/μl) and HC. PLWH with lower CD4 counts <200 cells/μl were not visualized due to small sample size at post third dose after 180 days. (D) Seropositivity of NAb against WT in PLWH (red) comparing with HC (blue). Inhibition rate above 30% were regarded as positive.

introducing laboratory variables into adjusted Model 2, the adverse effect of the WHO disease staging type of PLWH emerged (OR = 1.717, p = 0.035). Age (OR = 0.914, p = 0.048), CD4 cell counts (OR = 1.002, p = 0.050), and serum Cr (OR = 1.072, p = 0.028) were also significant factors affecting positive rates of NAb against WT. As for NAb positivity against BA.4/5, age (OR = 0.946, p = 0.019) and time after the last vaccine dose (OR = 0.990, p < 0.001) were found as protective factors in adjusted Model 1, whereas age and TC were independently associated with it (Table 2).

We found the association of age (OR = 0.930, p = 0.004) and time from the first vaccine dose to confirmed diagnosis of HIV (OR = 1.000, p = 0.048) with IgG anti-RBD antibodies positivity in adjusted Model 1. After incorporating laboratory indicators into logistic Model 2, TC and AST became dominant effectors on the seropositivity of IgG anti-RBD antibodies (Table 2).

To prove the effect of age on antibody responses among PLWH who received three vaccine doses, we recruited 28 elder PLWH who received the third dose after 14–89 days, 8 who received the third dose after 90–180 days, 15 received the third dose after 180 days, with precisely matching vaccination period with younger PLWH. Moreover, age- and vaccination time-matched elder HCs were enrolled (Figure S3). We found lower levels of total antibodies against SARS-CoV-2, less inhibition rate of NAb toward WT and BA.4/5, and decreased concentrations of IgG anti-RBD antibodies in older PLWH than in younger PLWH, mostly in those 90–180 days post-third dose.

4 | DISCUSSIONS

With the higher infectivity but lower disease severity caused by Omicron variant, Chinese authorities are now rethinking of altering "dynamic zeroing policy" into "reopening in an orderly and effective manner," which could well balance socioeconomic development and minimizing confirmed or death cases of China. However, the

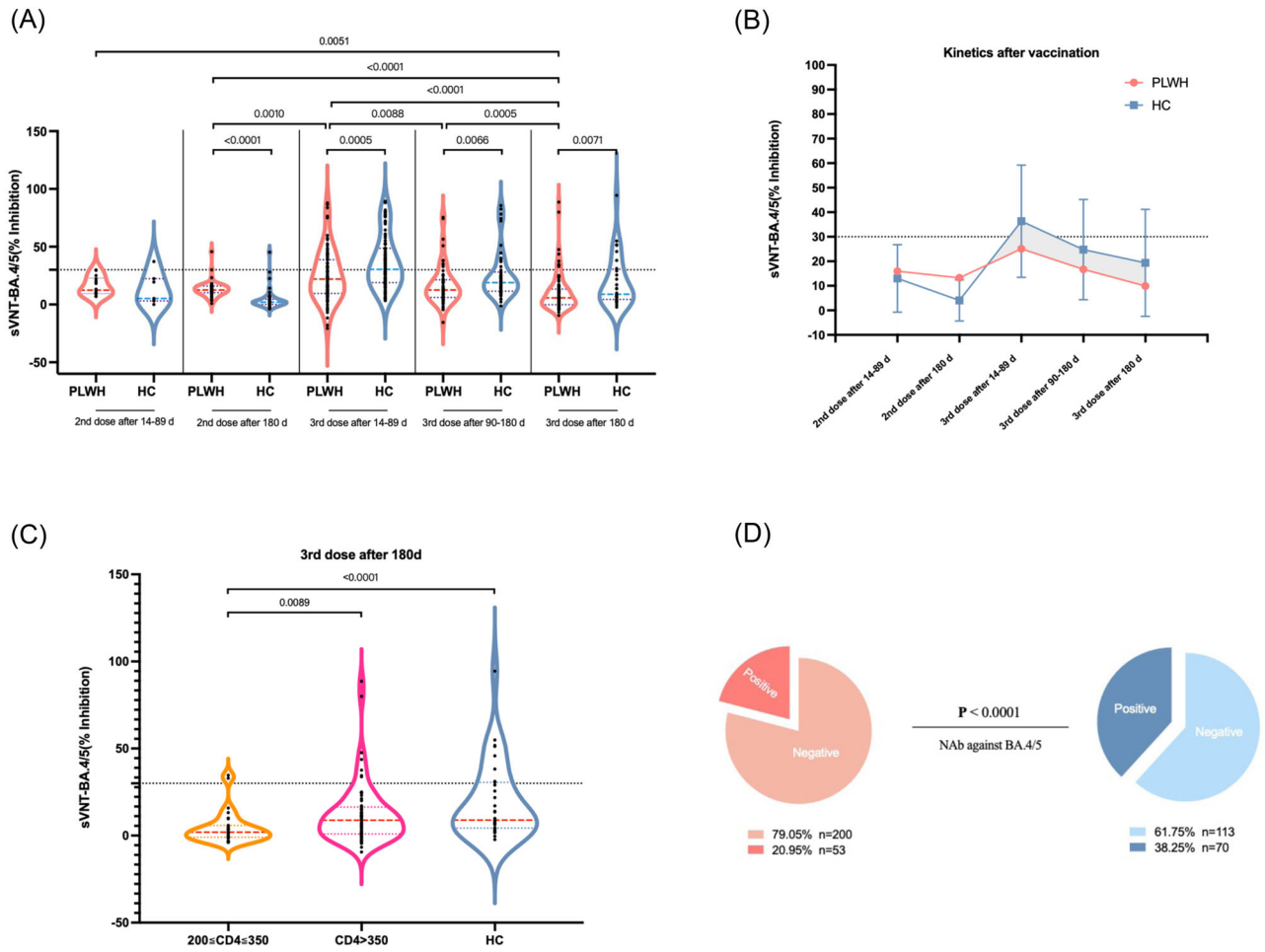

FIGURE 4 Neutralizing effect to Omicron sublineage BA.4/5 are elevated after triple dose of inactivated SARS-CoV-2 vaccines among PLWH. (A) Inhibition rates (%) of neutralizing antibodies against Omicron variants BA.4/5 (NAb against BA.4/5) evaluated by SARS-CoV-2 surrogate virus neutralization test (sVNT) in PLWH and HC subjects at pre- and post- booster (third) dose of inactivated vaccine. (B) Kinetics of NAb inhibition function to BA.4/5 before and after triple dose injection. (C) Comparison of NAb inhibition function to BA.4/5 among PLWH classified by CD4 cell counts (CD4 < 200 cells/μl, 200 cells/μl ≦ CD4 ≦ 350 cells/μl, CD4 > 350 cells/μl) and HC. PLWH with lower CD4 counts <200 cells/μl were not visualized due to small sample size at post third dose after 180 days. (D) Seropositivity of NAb towards BA.4/5 in PLWH (red) comparing with HC (blue). Inhibition rate above 30% were regarded as positive.

reopening strategy would bring health burdens on vulnerable populations. Enforcing vaccination nationwide is of significance in not only safeguarding herd immunity, but reducing risk of critical illness progression and mortality among key objects as well. Therefore, our study focusing on vaccine efficacy among immunocompromised individuals might have directive implications on current gradually loosening epidemic policy. To our knowledge, this study presents the first large cohort of PLWH focusing on immunological alterations pre- and post-booster doses of inactivated vaccines. Total antibodies against SARS-CoV-2 among PLWH were evidently downregulated compared with those in HCs 180 days after the second dose, which were subsequently enhanced to a comparable level with HCs at the post-third dose sampling time. The reassuring effect of the booster dose in strengthening humoral responses also generated in IgG anti-RBD antibodies and in neutralizing antibodies blocking the WT and Omicron BA.4/5 lineage among PLWH, although their seropositivity was significantly lower than that of HCs. However, owing to the minimal inhibition rate of NAb on BA.4/5, the third dose regimen of an inactivated vaccine appears to not be able to avoid the escape of BA.4/5 subvariants from the immune system in both PLWH and HCs.

Numerous studies have proved the strong immune responses of two-dose vaccination in PLWH with preserved disease status on ART.[10,18] Attenuating vaccine effectiveness has been claimed within 6 months after the second dose.[19,20] Similarly, we indeed observed a dramatic decrement >180 days after the second inactivated vaccine dose. In a longitudinal cohort, a significant decrement of NAb titers was identified 8 months after the second inactivated vaccine dose,[21] which was distinctly mitigated by the triple-dose immunization regimen.[22] Thus, there exists an urgent necessity for a booster vaccination to enhance protection, especially for most-at-risk populations. Recently, Vergori et al. revealed a higher antibody response of PLWH inoculated with the third dose of COVID-19 mRNA vaccine than with the second dose.[23] From a British cohort,

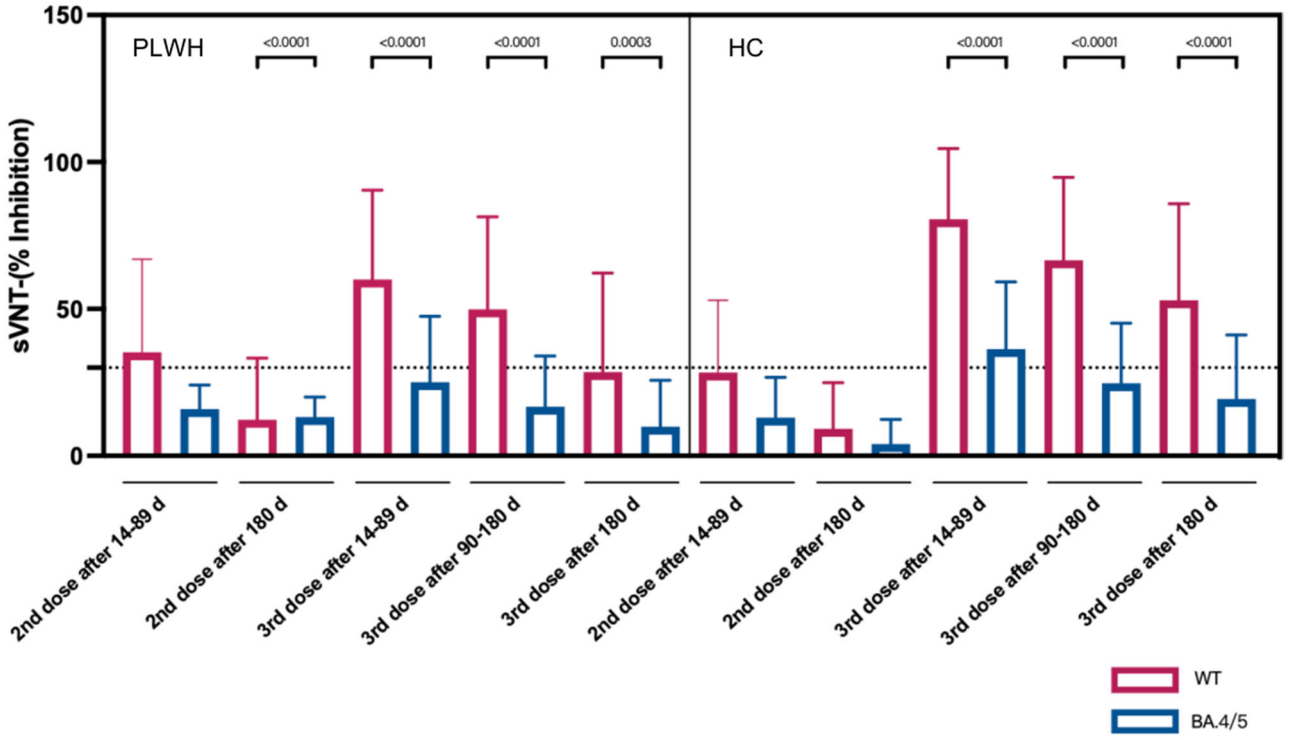

FIGURE 5 Waning humoral responses towards BA.4/5 after booster vaccination in both PLWH and HC. As it presented, inhibition functions of NAb against BA.4/5 (dark blue bar) were significantly decreased in both PLWH and HC than that against WT (purple bar). Seropositivity of NAb against BA.4/5 remained below positive threshold (30%) at all sampling time after vaccination.

53 participants with HIV who received a booster mRNA dose have shown increased B and T cell immunity.[24] An equivalent antibody concentration and a slightly higher blocking activity of NAb have been established in "post-third dose" immunogenicity among PLWH.[25] We found enhanced humoral reactivity in PLWH after the booster dose of inactivated vaccine, including IgG anti-RBD and NAb toward WT and Omicron subvariants, which were prominently inferior to HCs. The scarcity of evidence has hampered further exploration of immunological kinetics beyond the third intramuscular vaccine dose among PLWH. The booster effect of inactivated vaccines exceeded the post-second dose levels and reached its peak 14–89 days after the third dose and then decreased at a faster rate in PLWH than in HCs over time, which precisely filled this gap. Furthermore, we simultaneously revealed the time after the last vaccine dose as an independent risk factor influencing NAb positivity to both WT and Omicron BA.4/5. The durability of vaccine immunogenicity affects antibody responses in our PLWH cohort. This was consistent with the previous finding that in a randomized trial of healthy participants, the geometric mean of neutralization titers toward SARS-CoV-2 reached its peak at 14 days, diminished at 28 days, and retained 180 days after the booster dose of CoronaVac.[26]

Risk factors in PLWH also influence the serological response toward SARS-CoV-2 vaccine. For PLWH who received the second inactivated vaccine dose, those with low CD4 nadir achieved lower seroconversion rates, NAb inhibition rates, and positivity rates than PLWH with well-controlled CD4 cell counts.[8,27,28] CD4 cell counts also diversify the neutralizing function of SARS-CoV-2-specific antibodies in PLWH after triple injections of SARS-CoV-2 vaccine,[29] since the activation of CD4 T cells stimulates B cell proliferation, thus leading to NAb generation to inhibit the invasion of pathogens.[30] Our results consistently uncovered a significant improvement of IgG anti-RBD antibody titers and neutralizing rate against WT in PLWH who have 200 cells/μl ≦ CD4 ≦ 350 cells/μl than those with CD4 < 200 cells/μl 3 months after the third dose. Meanwhile, we identified CD4 cell counts and WHO disease staging type as risk factors for NAb seropositivity to WT. Moreover, we additionally found that there exists significant relationship between CD4 cell counts and total antibodies against SARS-CoV-2 ($p = 0.0096$), IgG RBD antibodies ($p = 0.0395$) and NAb towards WT ($p = 0.0124$) among PLWH, but not in HC (Supporting Information: Figure S4). From a British study recorded 54 PLWH who completed the vaccination schedule with ChAdOx1 nCoV-19,[10] they found no correlation of antibody responses and CD4 count at day 56 after completing booster vaccine. We consider that this difference from our study is attribute to the PLWH enrolled in their study were those with undetectable plasma HIV viral loads (<50 copies per ml), and CD4 counts of more than 350 cells per μL, where we did not set this restriction to our enrollment criteria. To be noticed, 24 PLWH who received two injections of inactivated SARS-CoV-2 vaccines from Yunnan,[31] presented a close association between neutralizing antibodies and levels of CD4 absolute counts ($r = 0.610$, $p = 0.002$), but no statistical

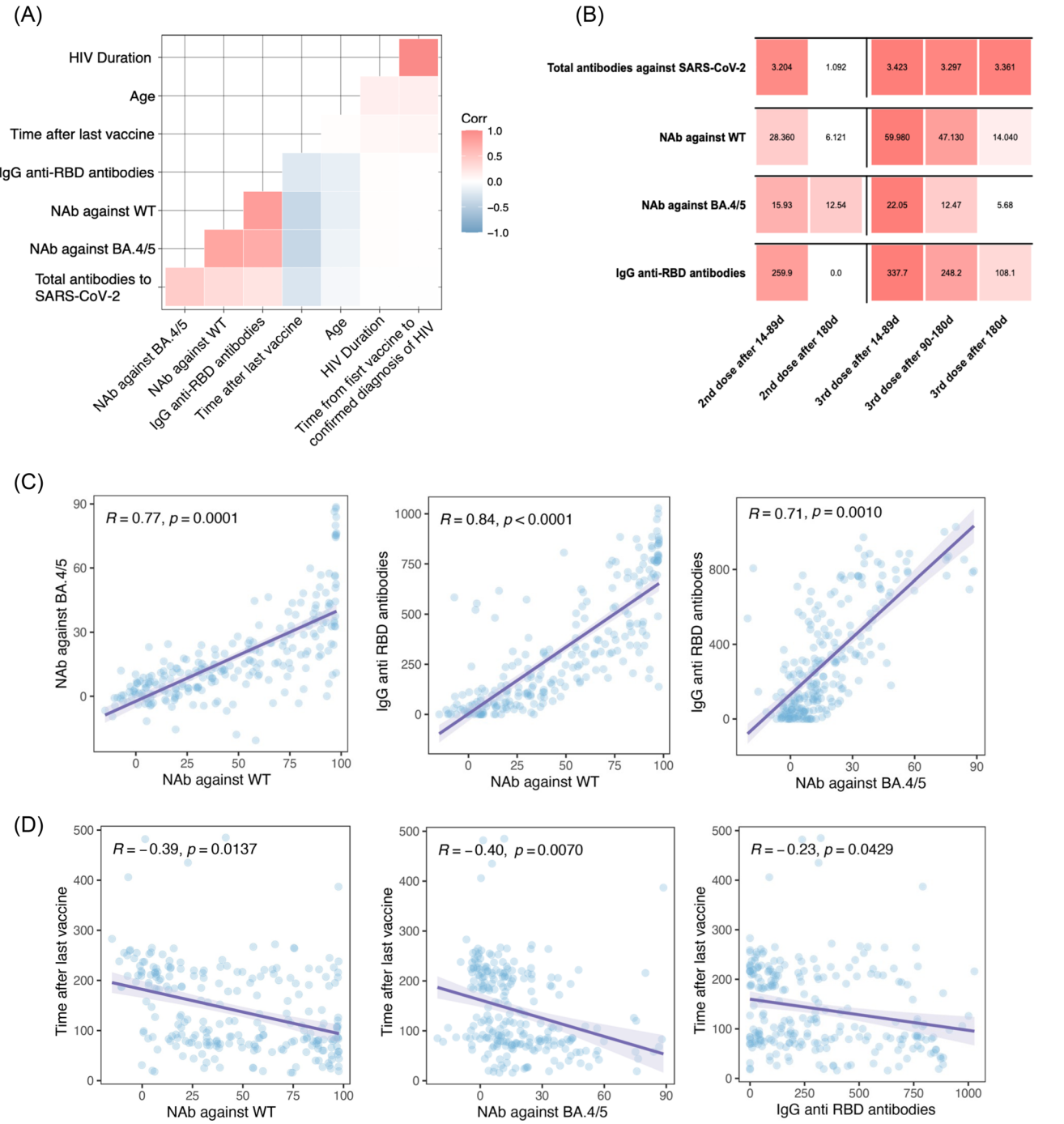

FIGURE 6 Correlation of vaccination period and the magnitude of SARS-CoV-2 antibodies after third dose. (A) Correlation heatmap visualized the association between SARS-CoV-2 antibodies and clinical characteristics among PLWH. (B) Levels of SARS-CoV-2 antibodies were increased after the booster shot of inactivated vaccine and attenuated over time after last vaccination among PLWH. Values in each block of heatmap were shown as medians. (C) Associations of NAb against WT (%), NAb against BA.4/5 (%) and IgG anti-RBD antibodies (BAU/ml). (D) Associations of NAb against WT (%), NAb against BA.4/5 (%), IgG anti-RBD antibodies titers (BAU/ml) and time after last vaccine.

correlation of CD4+ CD45RO+ memory T cells and NAbs ($p = 0.310$). Moreover, they did observe a prominently decreased expression of IL-17A and IL-4 in CD4 T cells among PLWH than HC subjects, suggesting the lower SARS-CoV-2 antibody levels might be caused by a weaker pro-inflammatory role of Th17 in vaccine-elicited memory and an impairing influence of Th2 on IgG1 production. At the same time, another cohort from Thailand containing 335 healthy subjects[32] has elucidated that CoronaVac vaccines more intend to activate Th2 (CD3+CD4+IL-4+) cells proved by the decrement of Th1/Th2 ratio after the second CoronaVac inoculation, thus no correlation was found either in T cell counts and antibody responses or in anti-RBD IgG levels and IFN-γ+ T cells. The Th2 priming immune

TABLE 2 Risk factors associated with seropositivity of SARS-CoV-2 specific antibodies in PLWH received booster inoculation

Categories		Risk factors	OR	95% CI	*p* Value
NAb against WT	Adjusted Model 1	Age	0.964	0.929–1.000	0.048
		Time after last vaccine	0.990	0.987–0.994	<0.001
	Adjusted Model 2	WHO disease staging type of PLWH	1.717	1.038–2.840	0.035
	Adjusted Model 3	Age	0.914	0.836–0.999	0.048
		CD4 counts	1.002	1.000–1.005	0.050
		Cr	1.072	1.008–1.140	0.028
NAb against BA.4/5	Adjusted Model 1	Age	0.946	0.903–0.991	0.019
		Time after last vaccine	0.990	0.986–0.995	<0.001
	Adjusted Model 2	Age	0.932	0.871–0.997	0.041
	Adjusted Model 3	TC	1.696	1.098–2.618	0.017
		Age	0.932	0.871–0.997	0.041
		TC	1.696	1.098–2.618	0.017
IgG anti-RBD antibodies	Adjusted Model 1	Age	0.930	0.885–0.977	0.004
		Time from first vaccine to confirmed diagnosis of HIV	1.000	1.000–1.001	0.048
	Adjusted Model 2	TC	5.735	1.014–32.433	0.048
		AST	0.908	0.825–1.000	0.050

Abbreviations: AST, aspartate aminotransferase; Cr, creatinine; NAb, neutralizing antibody; PLWH, people living with HIV; TC, total cholesterol.

responses triggered by CoronaVac is quite distinct from Th1-skewed environment caused by mRNA vaccines,[33] providing solid evidence for discrepant immunological reactions to different platforms of COVID-19 vaccines. For studies concentrating on cellular responses, increased magnitudes of S protein specific CD4+ and CD8+ T cell responses were found on both PLWH and HC after double doses of inactivated vaccines,[18] however, the result of which varied between studies.[34,35] Therefore, cellular responses towards different platforms of vaccination could be diversified, but CD4 T cells counts exactly play an important role in vaccine-induced specific responses among PLWH. Regrettably, due to sample volume restrictions, we were not able to furtherly analyze the exact association of SARS-CoV-2 specific CD4 cells and the corresponding antibody responses. A more integrated experiment should be conducted among PLWH after a booster inactivated COVID-19 vaccine and concentrate on cellular responses especially for Th2 cells, in forming a weakened immunological environment that attenuates the efficacy of COVID-19 vaccination.

In addition, our multivariate logistic analyses suggest age as a protective element for the positivity of NAb to WT, NAb to BA.4/5, and IgG anti-RBD antibodies. Ramasamy et al. claimed that the total IgG levels of anti-RBD and anti-spike protein antibodies gradually decreased with increasing age after 28 days of inoculation with adenovirus vector vaccine; however, after the booster dose, a similar antibody spectrum was identified regardless of age.[36] Both the neutralizing capacity and T cell reactivity were evidently lower in older people than in younger ones after the two-dose vaccination of BNT162b2.[37] It appears that the antibody profiles to vaccination prevention in older individuals respond ineffectively and decline easily owing to immunosenescence and comorbidities[38]; therefore, regular boost shots and shortened vaccine intervals might help. Intriguingly, we found AST and TC as independent factors associated with the positive proportion of NAb to BA.4/5 and IgG anti-RBD antibodies, suggesting the central function of the liver in regulating antibody production.[39,40]

Concerns regarding the efficacy on Omicron variants have emerged. The Omicron lineage BA.4/5 that evolved from BA.2 caused a wave of global infection. The great escape of neutralization on BA.4/5 compared with BA.1 and BA.2 was found among triple-dosed participants and in the serum of those who suffered breakthrough infections of BA.1.[14,15] Our study identically discovered a decreased inhibition rate of NAb toward BA.4/5 compared with that of WT and evidently lower NAb capacity on both WT and BA.4/5 in post-third dose PLWH than HCs, which was attributed to the damaged immune system by HIV invasion. Despite receiving the booster dose, PLWH still hold a lower-than-threshold inhibition rate of NAb against BA.4/5, facilitating easier evasion and breakthrough infection of Omicron sublineage because all the current vaccines utilize spike protein derived from the ancestral Wuhan virus and become less protective of the antigenic evolution of subvariants. To eliminate the transmission of new strains, a tailored vaccine for Omicron is imperative.[41] "Additional primary dose" on the vaccine

strategy for immunocompromised patients to augment COVID-19 protection has been also raised.[42]

This study has some limitations. Given the cross-sectional design, we could not access serial samples of PLWH and monitor the dynamic immunological response toward each dose of the inactivated vaccine. Although the precise matching of age and time after vaccination of each dose among PLWH and HC, there still exist gender discrepancies, this might contribute to biased understanding of our current result, which should be carefully avoid in future study designs. Antibody detection could sufficiently explain the clinical phenomena of breakthrough infections, nevertheless why these happen needs to be supported by cellular immune data. Limited blood sample volume hindered further exploration of the underlying concomitant alterations of cellular and humoral responses after the booster dose among PLWH, especially in finding correlations between SARS-CoV-2 specific CD4 T cells and corresponding antibody responses among both PLWH and HC. A larger prospective cohort to investigate cellular responses after the booster dose of inactivated vaccine and a comparison of the relative immunological reactions triggered by different platforms of SARS-CoV-2 vaccine are indispensable.

5 | CONCLUSIONS

In conclusion, the booster effect of an inactivated SARS-CoV-2 vaccine in PLWH augments antibody responses and neutralizing ability, which attenuates over postinoculation time, despite being lower than that in HCs. A decreased inhibition rate of NAb against BA.4/5 compared with WT gives rise to the possibility of breakthrough infections. Age, CD4 cell counts, and time after the third dose are dominant independent factors for the seropositivity of SARS-CoV-2-specific antibodies. Dynamic insights into immune responses and serologic antibody determinations after the booster dose should be fostered to optimize the best timing of injection and maximize the benefit of additional vaccination.

AUTHOR CONTRIBUTIONS

Yongzhe Li and Erhei Dai conceived and designed the research. Haoting Zhan extracted data, performed software analyses, and visualized graphs and tables. Haoting Zhan wrote and revised the paper. Haoting Zhan, Yongmei Liu, Xiaomeng Li, and Haolong Li performed the experiments. Huixia Gao and Xihong Zhang provided the clinical samples and data of participants. Clinical specialists Lijing Wang, Chen Li, Beilei Li, and Yuling Wang diagnosed HIV patients and provided professional consultant to this paper. All authors are accountable for all aspects of the study, and attest to the accuracy and integrity of the results. All authors have read and approved the final manuscript as submitted.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was approved by the Medical Ethics Committee of Peking Union Medical College Hospital (JS-2156 and I-22PJ147) and the Fifth Hospital of Shijiazhuang (2022-019-1).

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REFERENCES

1. Bhaskaran K, Rentsch CT, MacKenna B, et al. HIV infection and COVID-19 death: a population-based cohort analysis of UK primary care data and linked national death registrations within the OpenSAFELY platform. *Lancet HIV*. 2021;8(1):e24-e32.
2. Mirzaei H, McFarland W, Karamouzian M, Sharifi H. COVID-19 among people living with HIV: a systematic review. *AIDS Behav*. 2021;25(1):85-92.
3. Bertagnolio S, Thwin SS, Silva R, et al. Clinical features of, and risk factors for, severe or fatal COVID-19 among people living with HIV admitted to hospital: analysis of data from the WHO global clinical platform of COVID-19. *Lancet HIV*. 2022;9(7):e486-e495.
4. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med*. 2020;383(27):2603-2615.
5. Gao Q, Bao L, Mao H, et al. Development of an inactivated vaccine candidate for SARS-CoV-2. *Science*. 2020;369(6499):77-81.
6. Snyman J, Hwa SH, Krause R, et al. Similar antibody responses against severe acute respiratory syndrome coronavirus 2 in individuals living without and with human immunodeficiency virus on antiretroviral therapy during the first South African infection wave. *Clin Infect Dis*. 2022;75(1):e249-e256.
7. Lombardi A, Butta GM, Donnici L, et al. Anti-spike antibodies and neutralising antibody activity in people living with HIV vaccinated with COVID-19 mRNA-1273 vaccine: a prospective single-centre cohort study. *Lancet Reg Health Eur*. 2022;13:100287.
8. Netto LC, Ibrahim KY, Picone CM, et al. Safety and immunogenicity of CoronaVac in people living with HIV: a prospective cohort study. *Lancet HIV*. 2022;9(5):e323-e331.
9. Spinelli MA, Lynch KL, Yun C, et al. SARS-CoV-2 seroprevalence, and IgG concentration and pseudovirus neutralising antibody titres after infection, compared by HIV status: a matched case-control observational study. *Lancet HIV*. 2021;8(6):e334-e341.
10. Frater J, Ewer KJ, Ogbe A, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 in HIV infection: a single-arm substudy of a phase 2/3 clinical trial. *Lancet HIV*. 2021;8(8):e474-e485.
11. Pegu A, O'Connell SE, Schmidt SD, et al. Durability of mRNA-1273 vaccine-induced antibodies against SARS-CoV-2 variants. *Science*. 2021;373(6561):1372-1377.

12. Widge AT, Rouphael NG, Jackson LA, et al. Durability of responses after SARS-CoV-2 mRNA-1273 vaccination. *N Engl J Med*. 2021;384(1):80-82.
13. Dejnirattisai W, Huo J, Zhou D, et al. SARS-CoV-2 Omicron-B.1.1.529 leads to widespread escape from neutralizing antibody responses. *Cell*. 2022;185(3):467-484.
14. Tuekprakhon A, Nutalai R, Dijokaite-Guraliuc A, et al. Antibody escape of SARS-CoV-2 omicron BA.4 and BA.5 from vaccine and BA.1 serum. *Cell*. 2022;185(14):2422-2433.
15. Wang Q, Guo Y, Iketani S, et al. Antibody evasion by SARS-CoV-2 Omicron subvariants BA.2.12.1, BA.4 and BA.5. *Nature*. 2022;608(7923):603-608.
16. Corma-Gómez A, Fernández-Fuertes M, García E, et al. Severe immunosuppression is related to poorer immunogenicity to SARS-CoV-2 vaccines among people living with HIV. *Clin Microbiol Infect*. 2022;28(11):1492-1498.
17. Feng S, Phillips DJ, White T, et al. Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection. *Nature Med*. 2021;27(11):2032-2040.
18. Feng Y, Zhang Y, He Z, et al. Immunogenicity of an inactivated SARS-CoV-2 vaccine in people living with HIV-1: a non-randomized cohort study. *EClinicalMedicine*. 2022;43:101226.
19. Goldberg Y, Mandel M, Bar-On YM, et al. Waning immunity after the BNT162b2 vaccine in Israel. *N Engl J Med*. 2021;385(24):e85.
20. Levin EG, Lustig Y, Cohen C, et al. Waning immune humoral response to BNT162b2 Covid-19 vaccine over 6 months. *N Engl J Med*. 2021;385(24):e84.
21. Hensley KS, Jongkees MJ, Geers D, et al. Immunogenicity and reactogenicity of SARS-CoV-2 vaccines in people living with HIV in the Netherlands: a nationwide prospective cohort study. *PLoS Med*. 2022;19(10):e1003979.
22. Yue L, Xie T, Yang T, et al. A third booster dose may be necessary to mitigate neutralizing antibody fading after inoculation with two doses of an inactivated SARS-CoV-2 vaccine. *J Med Virol*. 2022;94(1):35-38.
23. Vergori A, Cozzi Lepri A, Cicalini S, et al. Immunogenicity to COVID-19 mRNA vaccine third dose in people living with HIV. *Nat Commun*. 2022;13(1):4922.
24. Fidler S, Fox J, Tipoe T, et al. Booster vaccination against SARS-CoV-2 induces potent immune responses in people with HIV. *Clin Infect Dis*. 2022:ciac796. doi:10.1093/cid/ciac796
25. Lapointe HR, Mwimanzi F, Cheung PK, et al. People with HIV receiving suppressive antiretroviral therapy show typical antibody durability after dual COVID-19 vaccination, and strong third dose responses. *medRxiv*. 2022:jiac229. doi:10.1093/infdis/jiac229
26. Zhang Y, Ma X, Yan G, et al. Immunogenicity, durability, and safety of an mRNA and three platform-based COVID-19 vaccines as a third dose following two doses of CoronaVac in China: a randomised, double-blinded, placebo-controlled, phase 2 trial. *EClinicalMedicine*. 2022;54:101680.
27. Noe S, Ochana N, Wiese C, et al. Humoral response to SARS-CoV-2 vaccines in people living with HIV. *Infection*. 2022;50(3):617-623.
28. Haidar G, Agha M, Bilderback A, et al. Prospective evaluation of coronavirus disease 2019 (COVID-19) vaccine responses across a broad spectrum of immunocompromising conditions: the COVID-19 vaccination in the immunocompromised study (COVICS). *Clin Infect Dis*. 2022;75(1):e630-e644.
29. Vergori A, Cozzi-Lepri A, Matusali G, et al. SARS-CoV-2 omicron variant neutralization after third dose vaccination in PLWH. *Viruses*. 2022;14(8):1710.
30. Chen J, Liu X, Zhang X, et al. Decline in neutralising antibody responses, but sustained T-cell immunity, in COVID-19 patients at 7 months post-infection. *Clin Transl Immunol*. 2021;10(7):e1319.
31. Lv Z, Li Q, Feng Z, et al. Inactivated SARS-CoV-2 vaccines elicit immunogenicity and T-cell responses in people living with HIV. *Int Immunopharmacol*. 2022;102:108383.
32. Phoksawat W, Nithichanon A, Lerdsamran H, et al. Phenotypic and functional changes of T cell subsets after CoronaVac vaccination. *Vaccine*. 2022;40(48):6963-6970.
33. Sahin U, Muik A, Derhovanessian E, et al. COVID-19 vaccine BNT162b1 elicits human antibody and T(H)1 T cell responses. *Nature*. 2020;586(7830):594-599.
34. Morrocchi E, Pighi C, Pascucci GR, et al. Perinatally human immunodeficiency virus-infected adolescents and young adults demonstrate distinct BNT162b2 messenger RNA coronavirus disease 2019 vaccine immunogenicity. *Clin Infect Dis*. 2022;75(suppl_1):S51-S60.
35. Moussaoui ME, Desmecht S, Tashkeev A, et al. Reduced T-cell response following a third dose of SARS-CoV-2 vaccine in infection-naïve people living with HIV. *J Infect*. 2022;85(6):702-769.
36. Ramasamy MN, Minassian AM, Ewer KJ, et al. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. *ancet*. 2020;396(10267):1979-1993.
37. Tober-Lau P, Schwarz T, Vanshylla K, et al. Long-term immunogenicity of BNT162b2 vaccination in older people and younger health-care workers. *Lancet Respir Med*. 2021;9(11):e104-e105.
38. Ciabattini A, Nardini C, Santoro F, Garagnani P, Franceschi C, Medaglini D. Vaccination in the elderly: The challenge of immune changes with aging. *Sem Immunol*. 2018;40:83-94.
39. James BH, Papakyriacou P, Gardener MJ, Gliddon L, Weston CJ, Lalor PF. The contribution of liver sinusoidal endothelial cells to clearance of therapeutic antibody. *Front Physiol*. 2022;12:753833.
40. Heymann F, Tacke F. Immunology in the liver—from homeostasis to disease. *Nat Rev Gastroenterol Hepatol*. 2016;13(2):88-110.
41. Gagne M, Moliva JI, Foulds KE, et al. mRNA-1273 or mRNA-Omicron boost in vaccinated macaques elicits similar B cell expansion, neutralizing responses, and protection from Omicron. *Cell*. 2022;185(9):1556-1571.
42. Connolly CM, Paik JJ. SARS-CoV-2 vaccination in the immunocompromised host. *J Allergy Clin Immunol*. 2022;150(1):56-58.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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