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Humoral immune response to inactivated COVID-19 vaccination at the 3rd month among people living with HIV

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Abstract

Background Research on the immune response to inactivated COVID-19 vaccination among people living with HIV (PLWH) is limited, especially among those with low CD4+T lymphocyte (CD4 cell) count. This prospective cohort study aimed to assess the humoral immune response to inactivated COVID-19 vaccination among PLWH compared to HIV negative controls (HNCs) and to determine the impact of CD4 cell count on vaccine response among PLWH.

Methods The neutralizing antibodies (nAbs) and the specific IgM and IgG-binding antibody responses to the inactivated COVID-19 vaccine at the third month after the second dose of inactivated COVID-19 vaccination were measured among 138 PLWH and 35 HNCs. Multivariable logistic regression and multiple linear regression models were conducted to identify factors associated with the seroconversion rate of antibodies and the magnitude of anti-SARS-CoV-2 antibody titers, respectively.

Results At the end of the third month after two doses of vaccination, the seroconversion rates of IgG were comparable between PLWH (44.9%; 95% CI 36.5–53.3%) and HNCs (60.0%; 95% CI 42.9–77.1%), respectively. The median titers and seroconversion rate of nAbs among PLWH were 0.57 (IQR: 0.30–1.11) \log_{10} BAU/mL and 29.0% (95% CI 21.3–36.8%), respectively, both lower than those in HNCs ($P < 0.05$). After adjusting for age, sex, comorbidities, and CD4 cell count, the titers and seroconversion rate of nAbs were comparable between PLWH and HNCs ($P > 0.05$). Multivariable regression analyses showed that CD4 cell count $< 200/\mu\text{L}$ was independently associated with lower titers and seroconversion rate of nAbs among PLWH ($P < 0.05$). A positive correlation was observed between the CD4 cell count and nAbs titers in PLWH (Spearman's $\rho = 0.25$, $P = 0.0034$).

Conclusion Our study concluded that the immune response to inactivated COVID-19 vaccination among PLWH was independently associated with CD4 cell count, PLWH with lower CD4 cell count showed a weaker humoral immune response, especially those with CD4 cell count $< 200/\mu\text{L}$. This finding suggests that expanding COVID-19 vaccination coverage among PLWH is impendancy. In addition, aggressive ART should be carried out for PLWH, especially for those with low CD4 cell count, to improve the immune response to vaccines.

Keywords COVID-19, Inactivated vaccine, Humoral immunity, PLWH, CD4 cell count

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Introduction

Recently, the ongoing pandemic of coronavirus disease 2019 (COVID-19) has posed a serious threat to global public health and economic development [1]. While it is noteworthy that SARS-CoV-2 infection has brought a big challenge to people living with HIV (PLWH). Studies have reported that PLWH had increased risks of more severe disease and deaths from COVID-19 [2, 3], possibly as a result of immunosuppression, higher rates of multimorbidity, unsuppressed HIV viral load (HIV-VL), and other determinants of health [4–7].

Nevertheless, limited information is available about the immune response to COVID-19 immunization in PLWH, especially in those with low CD4+ T lymphocyte (CD4 cell) count. Furthermore, the emerging immunogenicity data in PLWH were mostly focused on mRNA COVID-19 vaccines [8–11] or adenovirus vector-based vaccines [12–14], while very few studies focused on the immune response to inactivated COVID-19 vaccines. Two studies that reported the effect of inactivated COVID-19 vaccine on PLWH both had very small sample sizes [15, 16].

WIBP-CorV is an inactivated COVID-19 vaccine. An isolated SARS-CoV-2 strain (WIV-04) was cultivated in Vero cells, chemically inactivated by β -propiolactone, then mixed with an aluminium-based adjuvant [17, 18]. Phase 1 and 2 trials revealed that WIBP-CorV had a low rate of side effects and good immunogenicity [17]. The interim analysis of phase 3 clinical trials showed that the vaccine is 72.8% effective against the symptomatic COVID-19 cases and 100% against severe disease [19]. WIBP-CorV vaccine was one of the most commonly used vaccine in China.

Previously, another published study of our team based on PLWH and HIV negative controls (HNCs) who finished 70 days' follow-up showed that early humoral immune response to the inactivated COVID-19 vaccine was weaker and delayed among the PLWH than that among HNCs. But it has not discussed the risk factors associated with the humoral immune response in PLWH and HNCs because of limited sample size [20]. This study aimed to fill this gap by comparing the humoral immune response induced by the inactivated COVID-19 vaccine between PLWH and HNCs, and determining the impact of CD4 cell count on vaccine response in PLWH.

Materials and methods

Study participants and design

The study was conducted from March to October 2021. A total of 138 PLWH and 35 HNCs who received two doses of inactivated COVID-19 vaccine (Sinopharm, WIBP-CorV, 4 μ g/0.5 mL, WIV04 strain, Wuhan Institute of Biological Products Co. Ltd) with an interval of 28 days were enrolled in our study. The inclusion criteria for

PLWH included the following: (1) age \geq 18 years old; (2) confirmed HIV infection by HIV-1/2 Western blot assay. Exclusion criteria included the following: (1) presence of severe hearing loss, impaired vision, or intellectual disability observed by the interviewers; or (2) a history of SARS-CoV-2 infection (via serological and nucleic acid test), major psychiatric illness (schizophrenia or bipolar disorder) or neurocognitive impairment; the HNCs shared the first inclusion criteria and both exclusion criteria with PLWH. HNCs were recruited from the physical examination center in Zhongnan Hospital of Wuhan University. Written informed consent was obtained from each participant before screening for eligibility. 138 PLWH and 35 HNCs completed immunizations with inactivated COVID-19 vaccine at respective community hospitals and scheduled visits within the prescribed time. Blood samples were collected at baseline (before the first dose vaccination) and the 3rd month after the second dose of COVID-19 vaccination. Data on demographic information, including age, sex, and comorbidities (i.e., hypertension, diabetes mellitus, hyperlipidemia, cancer, chronic cardiovascular and lung, liver, or kidney diseases) were collected from all participants through an electronic questionnaire before vaccination. Clinical and laboratory data regarding the HIV status of PLWH were obtained from the China National HIV/AIDS Comprehensive Response Information Management System (CRIMS). The CD4 cell count of the PLWH and HNCs were tested with the blood samples at baseline.

Immunogenicity assessments

The primary humoral immunogenicity outcomes included the neutralizing antibodies (nAbs) and the specific IgM and IgG-binding antibody response to the COVID-19 vaccine, measured at baseline and 3rd months after the participants were fully present vaccinated with inactivated COVID-19 vaccination. An in-house SARS-CoV-2 nAbs assay kit by surrogate virus neutralization test (Livzon Diagnostics Inc., Zhuhai, China) was used to determine the serum titers of nAbs against the spike protein receptor-binding domain (RBD) according to the manufacturers' instructions. In brief, SARS-CoV-2 surrogate virus neutralization test detects total immunodominant neutralizing antibodies targeting the viral spike (S) protein receptor-binding domain in an isotype- and species-independent manner. This rapid test is based on antibody-mediated blockade of the interaction between the angiotensin-converting enzyme 2 (ACE2) receptor protein and the receptor-binding domain [21], a positive response is defined as \geq 10BAU/mL. The semi-quantitative of total specific IgM and IgG antibodies were detected using an in-house-developed ELISA kits (Livzon Diagnostics Inc., Zhuhai, China), which used

the recombinant nucleocapsid (N) and RBD antigen of SARS-CoV-2 as coating antigen, following the instruction manual. Positive responses of IgM and IgG were defined as ≥ 0.15 EU/mL and 0.18 EU/mL, respectively. The qualitative of specific IgM or IgG antibodies was detected using an in-house-developed colloidal gold kit (Livzon Diagnostics Inc., Zhuhai, China), following the instruction manual. We defined seroconversion of antibodies as a change from baseline seronegative to seropositive.

Statistical analysis

Categorical variables were presented as n (%) and compared using the Chi-square test or Fisher's exact test. Continuous variables with normal distribution were presented as mean (standard deviation [SD]) and compared using t-test or ANOVA analysis, while continuous variables with abnormal distribution were expressed as median (interquartile range [IQR]) and compared using Mann–Whitney U test. Multivariable logistic regression models with 2-sided 95% confidence intervals were conducted to identify factors associated with the seroconversion rate of antibodies. Multiple linear regression was employed to identify factors associated with the magnitude of anti-SARS-CoV-2 antibody titers. Analyses were

conducted using SPSS software, version 26.0 (IBM SPSS Inc), and GraphPad Prism 8 for Mac OS X (GraphPad Software, San Diego, CA, USA). A two-sided $p < 0.05$ was considered statistically significant.

Results

Study participants

Characteristics of the 138 PLWH and 35 HNCs were shown in Table 1. PLWH and HNCs were similar in age and comorbidities but differed in proportion of male ($P < 0.001$). The median (IQR) age of PLWH was 38 (31–49) years old, and 88.4% were males. 91.3% of the PLWH were receiving ART and 107 (77.5%) had a HIV VL < 50 copies/mL. The CD4 cell count in PLWH was significantly lower than that in HNCs [495 (IQR: 320–646) vs. 666 (IQR: 534–800)/ μ L, $P < 0.001$].

Binding-antibody responses to COVID-19 vaccination

At the end of third month after two doses of vaccination, the seroconversion rates of IgM in PLWH and HNCs were 3.6% (95% CI 0.5–6.8%) and 2.9% (95% CI 0–8.7%), respectively, while no significant difference between the two groups was observed. No significant difference was also found in seroconversion rates of IgG between PLWH

Table 1 Characteristics of the PLWH (n = 138) and HNCs (n = 35) in Wuhan, China, 2021

Characteristics	PLWH (n = 138)	HNCs (n = 35)	Statistics	P
Age in years, median (IQR)	38 (31–49)	33 (29–44)	2.56	0.08
Men, No. (%)	16 (88.4)	17 (48.6)	28.06	< 0.001
Comorbidities (%)	17 (12.3)	2 (5.7)	–	0.26
CD4 cell count/ μ L, median (IQR)	495 (320–646)	666 (534–800)	4.12	< 0.001
CD4 cell count (/ μ L)				
< 200	18	0		
200–500	52	4		
≥ 500	68	31	18.04	< 0.001
Receiving ART, n (%)	126 (91.3)	–		
ART regimens				
No	12 (8.7)	–		
NNRTIs (NVP/EFV)	102 (73.9)	–		
INSTIs (EVG/DTG)	14 (10.1)	–		
PIs (LPV/r)	10 (7.3)	–		
HIV VL < 50 copies/mL	107 (77.5)			
IgM, n (%)	5 (3.6)	1 (2.9)	–*	1.00
IgG, n (%)	62 (44.9)	21 (60.0)		0.11
nAbs, n (%)	40 (29.0)	17 (48.6)	4.85	0.03
IgM titers, GMT (95% CI)	0.016 (0.014–0.020)	0.018 (0.013–0.024)	1.18	0.24
IgG titers, GMT (95% CI)	0.10 (0.074–0.13)	0.21 (0.14–0.32)	1.97	0.049
Log ₁₀ nAbs titers, median (IQR)	0.57 (0.30–1.11)	0.91 (0.64–1.26)	2.46	0.01

NNRTIs: nonnucleoside reverse transcriptase inhibitors; INSTIs: integrase inhibitors; PIs: protein inhibitors; NVP: nevirapine; EFV: efavirenz; EVG: elvitegravir; DTG: dolutegravir; LPV/r: lopinavir/ritonavir

*No statistics are computed because Fisher exact method was used

(44.9%; 95% CI 36.5–53.3%) and HNCs (60.0%; 95% CI 42.9–77.1%). After adjusting for age, sex, comorbidities, and CD4 cell count, IgG seroconversion rates were comparable between PLWH and HNCs.

For the difference of IgG titers between PLWH and HNCs, univariate analysis showed that the IgG titers among PLWH was significantly lower than that among HNCs, but no significantly difference was found after adjusting for age, sex, comorbidities, and CD4 cell count.

Neutralizing antibody responses to COVID-19 vaccination among PLWH and HNCs

At the end of third month after two doses of vaccination, the seroconversion rate of nAbs among PLWH was 29.0% (95% CI 21.3–36.7%), which was significantly lower than that among HNCs (48.6%; 95% CI 31.2–66.0%). The nAbs titers among PLWH [0.57 (IQR: 0.30–1.11) log₁₀ BAU/mL] was also significantly lower than that among HNCs [(median 0.91; IQR, 0.64–1.26) log₁₀ BAU/mL] (Fig. 1).

In multivariable logistic regression analysis, the people with CD4 cell count <200/μL tended to have a lower seroconversion rate of nAbs (OR: 0.09; 95% CI 0.01–0.74; P=0.03), as compared to those with CD4 cell count ≥ 500 /μL. Age, sex, comorbidities and HIV infection were not significantly associated with the seroconversion rate of nAbs (Table 2).

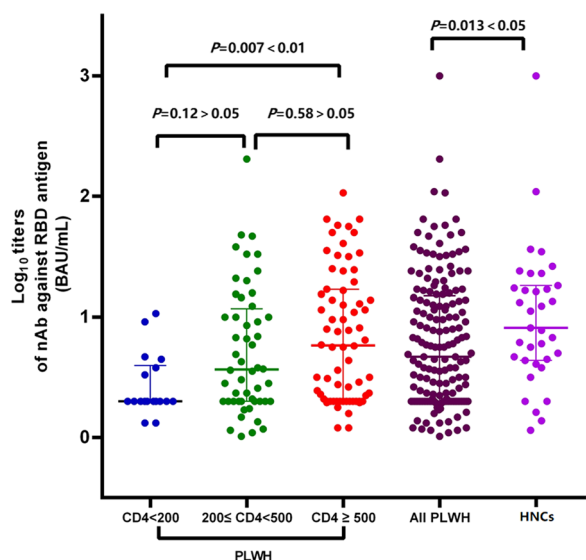


Fig. 1 nAbs titers in different groups (PLWH were divided into three groups: CD4 cell count <200/μL, CD4 cell count between 200 and 500/μL and CD4 cell count ≥ 500/μL). P < 0.05, nAbs titers in PLWH were significantly different from HNCs; P < 0.01, nAbs titers in PLWH with CD4 cell count <200/μL were differ from those in PLWH with CD4 cell count ≥ 500/μL; P > 0.05, there were no significantly difference between the groups; P-values were computed using the Mann–Whitney U-test

Table 2 Factors associated with seroconversion rates of nAbs among PLWH and HNCs in Wuhan, China, 2021 (N = 173)

Variables	Adjusted OR (95% CI)	P
Age	0.98 (0.96–1.01)	0.28
Sex		
Male	Ref	
Female	2.19 (0.87–5.51)	0.10
CD4 cell count (/μL)		
≥ 500	Ref	
200–500	0.68 (0.32–1.45)	0.32
< 200	0.89 (0.01–0.74)	0.03
Comorbidities		
No	Ref	
Yes	0.95 (0.26–3.46)	0.94
HIV infection		
No	Ref	
Yes	0.86 (0.35–2.15)	0.75

We further transformed the nAbs titers (log₁₀) and performed multivariable linear regression analysis. The results determined that nAbs titers in participants with CD4 cell count <200/μL were –0.21 log₁₀ lower than those with CD4 cell count ≥ 500/μL (P=0.012). Age, sex, comorbidities, and HIV infection were not significantly associated with the nAbs titers (Table 3).

Then we analyzed the association between IgG and nAbs, the result showed that there were positive correlations between IgG and nAbs titers in PLWH (ρ=0.843, p < 0.001) and HNCs (ρ=0.766, p < 0.001).

Neutralizing antibody responses to COVID-19 vaccination among PLWH

At the end of third month after two doses of vaccination, the seroconversion rates of nAbs were 5.6% (95% CI 0–17.3%) in the group with CD4 cell count <200/μL, 25.0% (95% CI 12.8–37.2%) in the group with CD4 cell count between 200 and 500/μL, and 61.8% (95% CI 49.9–73.6%) in the group with CD4 cell count ≥ 500/μL,

Table 3 Factors associated with nAbs titers among PLWH and HNCs in Wuhan, China, 2021 (N = 173)

Variables	Estimate	95% CI	P
CD4 cell count in 200–500 / μL (versus CD4 ≥ 500/μL)	–0.07	–0.27 to 0.12	0.43
CD4 cell count < 200 / μL (versus CD4 ≥ 500/μL)	–0.21	–0.69 to –0.09	0.01
Age	–0.14	–0.01 to 0.001	0.07
Comorbidities (Yes vs No)	0.03	–0.23 to 0.34	0.71
HIV infection (Yes vs No)	–0.07	–0.33 to 0.15	0.45
Sex (Female vs Male)	0.09	–0.11 to 0.36	0.29

respectively. In the multivariable model, participants with CD4 cell count <200/μL tend to have a lower nAbs seroconversion rate than those with CD4 cell count ≥ 500/μL ($P=0.03$) (Table 4).

At the end of third month after two doses of vaccination, the median nAbs titers were 0.30 (IQR: 0.30–0.59) \log_{10} BAU/mL in the group with CD4 cell count <200/μL, 0.61 (IQR: 0.30–1.14) \log_{10} BAU/mL in the group with CD4 cell count between 200 and 500/μL and 0.81 (IQR: 0.35–1.24) \log_{10} BAU/mL in the group with CD4 cell count ≥ 500/μL, respectively. The nAbs titers were significantly different in three CD4 groups ($P=0.009$), while participants with lower CD4 cell count <200 /μL tend to have lower nAbs titers (Fig. 1). Multivariable linear regression analysis confirmed this finding (Table 5). There was no significant association between age, sex, comorbidities, HIV-VL, ART, and nAbs titers ($P>0.05$).

The correlation analysis between CD4 cell count and nAbs titers showed a positive correlation in PLWH (Spearman’s $\rho=0.25$, $P=0.0034$), while no significant correlation between CD4 count and nAbs titers was observed in HNCs (Spearman’s $\rho=0.03$, $P=0.86$) (Fig. 2).

Discussion

Understanding the humoral immune response induced by the inactivated COVID-19 vaccine and the impact of CD4 cell count on vaccine response in PLWH were essential in decision-making regarding future disease control and revaccination strategies. It is important to

Table 4 Factors associated with seroconversion rate of nAbs among PLWH in Wuhan, China, 2021 (N = 138)

Variables	Adjusted OR (95% CI)	P
Age	0.99 (0.96–1.03)	0.62
Sex		
Male	Ref	
Female	1.57 (0.41–6.01)	0.51
CD4 cell count (μL)		
≥ 500	Ref	
200–500	0.51 (0.21–1.19)	0.12
< 200	0.07 (0.007–0.77)	0.03
Comorbidities		
No	Ref	
Yes	0.73(0.14–3.62)	0.70
HIV VL (copies/mL)		
< 50	Ref	
≥ 50	2.51 (0.81–7.81)	0.11
ART		
No	Ref	
Yes	2.40 (0.20–28.63)	0.49

Table 5 Factors associated with nAbs titers among PLWH in Wuhan, China, 2021 (N = 138)

Variables	Estimate	95% CI	P
CD4 cell count in 200–500/μL (versus CD4 ≥ 500/μL)	− 0.11	− 0.32 to 0.08	0.24
CD4 cell count <200/μL (versus CD4 ≥ 500/μL)	− 0.22	− 0.71 to − 0.02	0.04
Sex (Female vs Male)	− 0.04	− 0.38 to 0.23	0.63
Age	− 0.14	− 0.01 to 0.001	0.11
Comorbidities (Yes vs No)	− 0.01	− 0.35 to 0.32	0.94
ART (Yes vs No)	0.07	− 0.26 to 0.55	0.48
HIV VL (≥ 50 vs < 50)	0.16	− 0.05 to 0.47	0.11

ensure adequate protection against infection in the vulnerable population, especially to prevent the emerging new variants. This prospective cohort study extends the existing literatures [8–16] by providing more comprehensive evidence to assess the inactivated COVID-19 vaccine response among PLWH.

We found that PLWH and HNCs had a similar humoral immune response to the inactivated COVID-19 vaccine at the 3rd month after two doses of inactivated COVID-19 vaccination. Even though nAbs titers and seroconversion rate of nAbs in PLWH were both lower than that in HNCs, after adjusting for potential confounders, the differences disappeared. These findings are consistent with the results of other studies conducted in South Africa and UK, which suggested that the immune responses produced by the adenovirus vector-based COVID-19 vaccine among PLWH are similar to those among HNCs [12, 13]. Other studies about the immune response to mRNA COVID-19 vaccine among PLWH also reported similar humoral immune response to the healthy controls

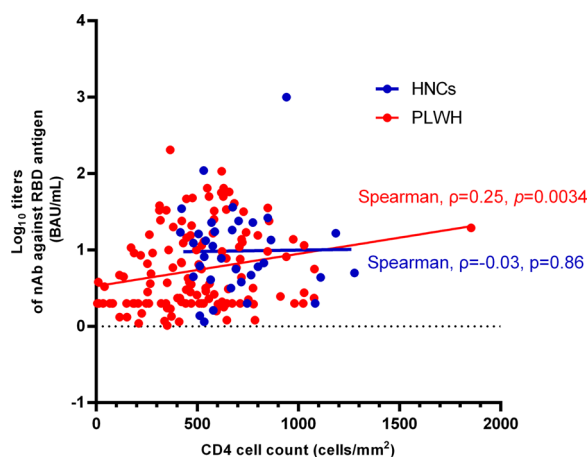


Fig. 2 Correlation between CD4 cell count and nAbs titers at the 3rd months after two doses of inactivated COVID-19 vaccination among PLWH and HNCs

[8]. The results indicate that PLWH should complete both doses of inactivated COVID-19 vaccine to achieve good protection. Studies have shown that two doses of inactivated CoronaVac vaccines offer high levels of protection against severe disease and death among all age group [22].

Several studies have shown that PLWH have lower responses to some types of vaccine, including hepatitis A, hepatitis B, and influenza vaccine. These responses are dependent on the level of CD4 cell count [23–25]. CD4 cell is pivotal in orchestrating both the humoral and cellular immune responses to vaccination and has an essential impact on antibody production [26]. Some studies also suggested that PLWH with low CD4 cell count had a poor response to the COVID-19 vaccine while PLWH with CD4 cell count in a healthy range mounted equivalent vaccine responses to those in HIV-negative people [27, 28]. Our study found a statistically lower titer and seroconversion rate of nAbs among PLWH with the CD4 cell count < 200 μ L (versus the group CD4 \geq 500/ μ L). We also found a positive correlation between CD4 cell count and nAbs titers in PLWH and CD4 cell count < 200/ μ L independently predicted lower nAbs titers. The results indicate that PLWH, especially those with CD4 cell count < 200/ μ L were still relatively vulnerable even after two doses of inactivated COVID-19 vaccination. A study on the infection forms of SARS-CoV-2 infection among PLWH showed that PLWH were more likely to be an asymptomatic carrier [29]. Prolonged SARS-CoV-2 infection in advanced PLWH with profound immunosuppression or without ART would drive SARS-CoV-2 virus evolution [30], which may be the reason that 'omicron' emerged. We should expand COVID-19 vaccination coverage and promote the uptake among the lower- and middle-income countries where the COVID-19 vaccination rates are still low [31], and especially among PLWH. Furthermore, we should strengthen the appropriate ART for PLWH, especially for those with low CD4 cell count, to increase the CD4 cell count and strengthen their immune response level to vaccines and achieve longer duration of vaccines. This is not just to prevent PLWH from SARS-CoV-2 infection but to prevent the emergence of new variants.

This study has several limitations. First, the sample size of HNCs was relatively small. Studies with larger sample size will be more conducive to identify individuals who are particularly vulnerable to the impact of SARS-CoV-2 infection and develop targeted vaccination interventions. Second, imbalance existed in the sex distribution of PLWH, which may lead to some bias in our results. However, a previous study found the responses to inactivated COVID-19 vaccination had

no significant differences between male and female, which may mitigate some of the sex imbalance in this study [19]. Third, the T-cell responses against the inactivated COVID-19 vaccines weren't investigated in our study. Long-term follow-up for PLWH with inactivated COVID-19 vaccination will be performed in our further study, and the durability and quality of humoral and cellular responses of inactivated COVID-19 vaccines will be evaluated.

In conclusion, our study indicated that PLWH with lower CD4 cell count showed a weaker humoral immune response to inactivated COVID-19 vaccination, especially those with CD4 cell count < 200 μ L. Additional measures against COVID-19 are needed for PLWH who have low CD4 cell count.

Abbreviations

PLWH	People living with HIV
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
COVID-19	Coronavirus disease 2019
HNCs	HIV negative controls
nAbs	The neutralizing antibodies
CRIMS	China National HIV/AIDS Comprehensive Response Information Management System
RBD	Spike protein receptor-binding domain
ACE2	Angiotensin-converting enzyme 2
SD	Standard deviation
IQR	Interquartile range
NNRTIs	Nonnucleoside reverse transcriptase inhibitors
INSTIs	Integrase inhibitors
PIs	Protein inhibitors
NVP	Nevirapine
EFV	Efavirenz
EVG	Elvitegravir
DTG	Dolutegravir
LPV/r	Lopinavir/ritonavir

Acknowledgements

Not applicable.

Author contributions

KL and WT participated in the inception of the idea of this manuscript with lead roles in conducting the study; SW, SZ and FM involved in the data analysis and drafting of the manuscript; SW, SZ and FM involved in data collection and interpretation; MW, WG, JL, ZX and ZZ participated in discussion section. All authors read and approved the final manuscript.

Funding

This work was supported by the National Nature Science Foundation of China (81903371), NIMH (R34MH119963), the National Science and Technology Major Project (2018ZX10101-001-003), Special Found on Prevention and Control of New Coronary Pneumonia in Guangdong Universities (2020KZDZX1047), Medical Science and Technology Innovation Platform Support Project of Zhongnan Hospital, Wuhan University (PTXM2020008), Science and Technology Innovation Cultivation Fund of Zhongnan Hospital, Wuhan University (cxpy2017043), Medical Science Advancement Program (Basic Medical Sciences) of Wuhan University (TFJC2018004) and the Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences (2020-PT320-004).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was reviewed and approved by the Research and Ethics Committee of Zhongnan Hospital (2020079K-1). All the procedures were performed in accordance with the Declaration of Helsinki, and the patient's confidentiality was maintained throughout the investigation. All individuals provided their written informed consent to participate in this study.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest.

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Received: 12 June 2022 Accepted: 3 January 2023

Published online: 20 January 2023

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