

CASE REPORT



Failure to seroconvert after three doses of inactivated COVID-19 vaccines in a patient co-infected with HBV and HIV: A case report

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ABSTRACT

In the global context of the COVID-19 pandemic, the overall benefits of getting any COVID-19 vaccine approved by the World Health Organization for emergency use outweigh the potential risks, even in people with weakened immune systems, including people living with HIV (PLWH). At present, there are no reports of HIV/hepatitis B virus (HBV) co-infected patients receiving a booster dose of the inactivated COVID-19 vaccine. Here, we describe a patient with HIV/HBV co-infection who did not seroconvert to three doses of the inactivated COVID-19 vaccine.

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Introduction

PLWH are listed as a high-risk group experiencing more severe outcomes from COVID-19 by the Joint United Nations Program on HIV/AIDS (UNAIDS).¹ It is important for this vulnerable population to obtain optimal immunogenicity after vaccination. Due to different degrees of immunodeficiency, the antibody titers and seropositive rates of PLWH are lower than those of the healthy population after vaccination with the inactivated COVID-19 vaccine.^{2–4} The immune response to the two-dose COVID-19 vaccine is less robust against SARS-CoV-2 variants of concern, and the antibodies induced by the vaccine decline more rapidly over time and provide a shorter duration of protection in immunocompromised populations, such as PLWH.^{5,6} Therefore, PLWH should be the priority group for vaccination with a booster dose of the inactivated COVID-19 vaccine.³

Shared epidemiological risks result in PLWH having a high prevalence of HBV co-infection. Viral hepatitis caused by HBV infection is one of the most common causes of PLWH's immune function impairment,⁷ whereas HIV infection can lead to the depletion of CD4+T cell, which has a negative impact on all stages of the natural history of hepatitis B.⁸ Compared to patients with HIV-mono-infection, those who are co-infected with HIV/HBV are associated with poorer antiretroviral therapy (ART) outcomes, and their immune function is more difficult to rebuild, especially with lower rate of CD4+T cell recovery.⁹ Thus, patients with HIV/HBV co-infection generally have lower CD4+T cell counts despite receiving ART.^{8,10,11} However, the effective response to the vaccine requires CD4+T cell coordination,¹² which may result in HIV/HBV co-infected patients with poor immune response to the vaccine.¹³ Here, we present a patient with HIV/HBV co-infection

who did not obtain complete seroconversion after receiving three doses of the BBIBP-CorV vaccine.

Case presentation

A 39-year-old man was diagnosed as HIV- and HBV-positive (HBsAg+, HBsAb-, HBeAg+, HBeAb-, HBcAb+) on March 6 and 11, 2015, respectively. The patient started ART on 11 March 2015 and received routine follow-up and stable ART at the Third People's Hospital of Shenzhen. The patient has never been infected with SARS-CoV-2, and the ART drugs taken by the patient during vaccination were TAF (tenofovir alafenamide), 3TC (lamivudine) and EFV (efavirenz). The patient received two doses of the BBIBP-CorV vaccine 23 days apart in 2021 and a third dose 202 days after the second dose (Figure 1). In addition, the time of test is the same as the time of blood collection.

During the vaccination period, we used flow cytometry to analyze CD4+ and CD8+T cell counts and proportions in the peripheral blood of the patient. The patient's HIV viral load was detected using reverse transcription-polymerase chain reaction with the lowest detection limit of 50 copies/mL. During the vaccination period, the CD4+T cell count of the patient was maintained below 350 cells/ μ L, and the proportion of CD4+T cells was significantly low. CD8+T cell counts were all within the normal range, although the proportion was slightly high. The CD4+T/CD8+T cell ratio of the patient remained approximately 0.60. In addition, the patient had undetectable VL during vaccination (Table 1).

The above case, along with two PLWH with CD4+T <350 cells/ μ L and 11 PLWH with CD4+T \geq 350 cells/ μ L were recruited into our cohort study, all of whom had received three doses of

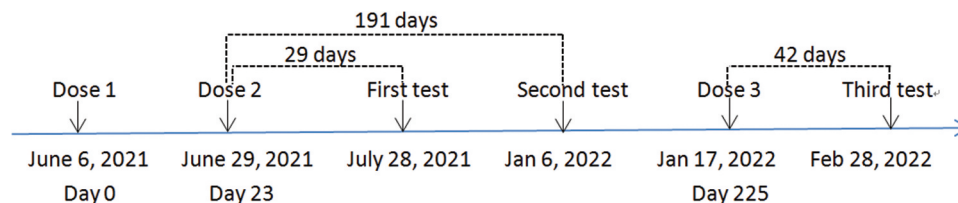


Figure 1. The HIV/HBV co-infected patient's schedule of vaccination and blood collection.

Table 1. The HIV/HBV co-infected patient's routine laboratory test results during vaccination.

Indicator	Reference range	March 3, 2021	June 8, 2021	October 25, 2021	January 6, 2022
CD4+T cell count (cells/ μ L)	500–1600	309	327	313	313
CD4+T ratio (%)	34–52	24.6	26.4	23.3	24.2
CD8+T cell count (cells/ μ L)	320–1250	492	523	519	529
CD8+T ratio (%)	21–39	39.2	42.3	38.6	40.9
CD4+T/CD8+T (-)	1.4–2.0	0.63	0.63	0.60	0.59
HIV VL (copies/mL)*	–	<50	<50	<50	<50

*The lower limit of detection is 50 copies/mL.

the BBIBP-CorV vaccine (Sinopharm, 4 μ g/0.5 mL) successively. Peripheral venous blood was collected from the participants at 28 ± 7 days and 180 ± 20 days after the second dose and at 35 ± 7 days after the third dose. Magnetic particle chemiluminescence kits (Shengxiang Biotechnology, Changsha, China) were used to detect specific S-RBD-IgG antibodies in blood samples. The participants' antibody levels were tested once at each time point, whereas we tested the case's antibody level twice at 42 days after the third dose. The test result was expressed as the ratio of the sample luminescence value (S) to the cutoff (CO) (S/CO value), the S/CO value indirectly reflected the antibody level, and an S/CO value ≥ 1 was defined as S-RBD-IgG antibody seropositivity. Twenty-nine days after two doses of the BBIBP-CorV vaccine, the S-RBD-IgG antibody S/CO value of the case was 0.13; 42 days after the third dose, the case's S-RBD-IgG antibody S/CO values of two tests were 0.39 and 0.44 (mean 0.42), respectively, suggesting that the patient failed to seroconvert after vaccination (Figure 2).

Two PLWH with CD4+T <350 cells/ μ L had successful seroconversion not only 28 days after receiving two doses of the BBIBP-CorV vaccine but also 35 days after receiving the third dose, although one PLWH had low antibody levels after receiving the third dose of the BBIBP-CorV vaccine. Among the 11 PLWH with CD4+T ≥ 350 cells/ μ L, 2 of them failed to seroconvert after receiving two doses of BBIBP-CorV vaccine; however, all of them succeeded to seroconvert after receiving the third dose of the BBIBP-CorV vaccine, and the S/CO value of the S-RBD-IgG antibody increased significantly from 4.05 ± 3.60 at 28 days after the second dose to 21.57 ± 12.65 at 35 days after the third dose ($p < .001$) (Figure 2).

Discussion

The immunogenicity of inactivated COVID-19 vaccines in immunocompromised populations, such as PLWH, has received

extensive attention. To date, there are very few preliminary reports on the early efficacy of PLWH after receiving the third dose of inactivated COVID-19 vaccine,¹⁴ while the effectiveness of PLWH vaccination with the third dose of inactivated COVID-19 vaccine still lacks research.

The level of immunogenicity induced by the vaccine in PLWH is related to their CD4+T cell counts and VL.¹⁵ The CD4+T cell count, which was considered as an indicator of the PLWH immune status,¹⁶ was significantly associated with reduced humoral responses of PLWH to a variety of vaccines, including inactivated COVID-19,^{2,3} hepatitis A virus,¹⁷ and pneumococcal vaccine.¹⁸ ART can permanently suppress HIV to an undetectable level in plasma, usually rebuilds the immune function of PLWH and restores its CD4+T cell count, improving the immune responses of PLWH after vaccination.¹⁹ This patient received stable ART and his VL was well suppressed. However, the recovery of his CD4+T cell counts was poor due to co-infection with HBV, and the CD4+T cell count remained below 350 cells/ μ L constantly. In addition, the CD4+T/CD8+T ratio of this patient remained approximately 0.60, and the CD4+T/CD8+T ratio was also significantly associated with reduced humoral response of PLWH to the vaccine.¹⁷ A previous study noted that compared with PLWH with a CD4+T/CD8+T ratio of 0.6–1.0 or a ratio >1.0, the BBIBP-CorV vaccine induced lower antibody level in PLWH with a CD4+T/CD8+T ratio of <0.6.²⁰ These may be related to the fact that the patient failed to seroconvert not only after receiving two doses of the BBIBP-CorV vaccine but also after receiving the third dose of the vaccine.

In our cohort, two PLWH with CD4+T count ≥ 350 cells/ μ L did not seroconvert to two doses of the BBIBP-CorV vaccine. However, they not only succeeded in seroconversion after receiving the third dose of the vaccine but also showed a significant increase in the S-RBD-IgG antibody level. This suggests that they are not really “non responders” and their immune memory has been established, therefore the repeated antigen stimulation may be required. It is also worth noting that one PLWH with CD4+T <350 cells/ μ L had low antibody levels after receiving the third dose of the BBIBP-CorV vaccine, which may not have been enough to provide him with immunity against SARS-CoV-2. Strategies such as higher antigen titer per dose of vaccine or increased doses for repeated stimulation, should be studied to improve the immune response of the PLWH population after vaccination, especially in PLWH with low CD4+T cell counts due to HBV infection or other reasons.

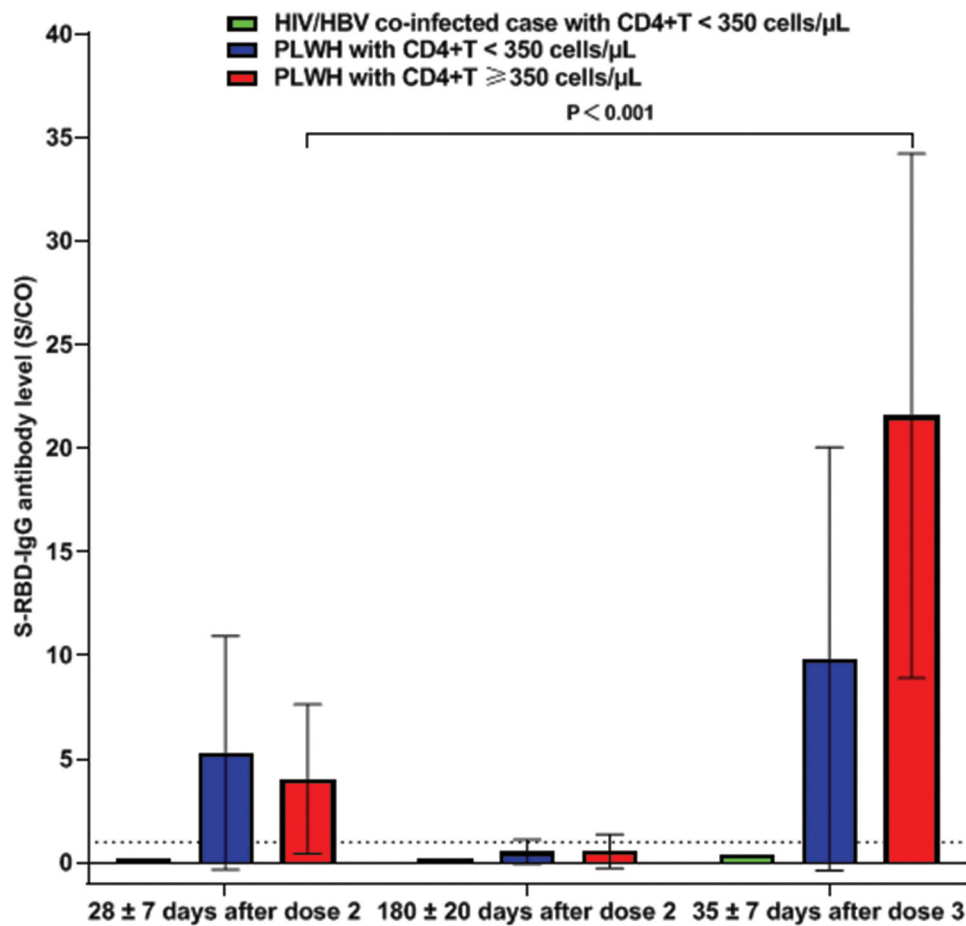


Figure 2. The S-RBD-IgG antibody levels of the participants during follow-up period.

Conclusion

In this report, we present the case of a patient with HIV/HBV co-infection who did not respond to three doses of the BBIBP-CorV vaccine. We suggest that local authorities should strengthen health education and regular HBV screening for early detection and appropriate management of PLWH. Drug therapy that can simultaneously suppress both HIV and HBV should be initiated as early as possible to improve the immune response of PLWH to conventional vaccines. For PLWH with low CD4+T cell counts who failed to seroconvert after receiving three doses of inactivated COVID-19 vaccine, it is necessary to consider appropriately higher antigen titers per dose of vaccine or increase the number of doses to stimulate repeatedly on the premise of safety; to improve the immune response of PLWH after vaccination.

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Authors' contribution

GZ and JT did the ideation, conceptualization, data collection, literature collection, writing original draft, reviewing, and editing. SF and LX did the data collection, reviewing, and editing. WX did the reviewing and editing. ZY did the ideation, reviewing and editing. GZ and JT contributed equally to this work as co-first authors. All authors critically reviewed and approved the final version of the manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The data presented in this case report are available on request from the corresponding author. The data are not publicly available according to the ethical committee decision on the conduct of this study.

Ethical approval

This study was approved by the Ethics Committee of Shenzhen Center for Disease Control and Prevention (No.QS2021070043, 10 August 2021). The patient consent to the publication of this case report.

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