

**Original Research Report****Percentage of Hepatitis B Virus Infection among People Living with HIV (PLWH) and Antibody Titer after Vaccination: Single-Center Retrospective Study**Koko SHIBUTANI<sup>1</sup>, Emilie Louise Akiko MATSUMOTO-TAKAHASHI<sup>2</sup> and Nobuyoshi MORI<sup>1</sup><sup>1</sup> Division of Infectious Diseases, St. Luke's International Hospital,<sup>2</sup> Graduate School of Public Health, St. Luke's International University

**Background** : People living with HIV (PLWH) are often complicated with hepatitis B, and hepatitis B infection status is usually checked at the initial medical examination. There are few data on rates of hepatitis B vaccination among PLWH in Japan, or changes in antibody titers after vaccination. In addition, it has been reported from Western countries that hepatitis B antibody titers are difficult to increase in PLWH even after vaccination, but there are few data on this in Japan.

**Methods** : We calculated the percentage of hepatitis B infection status among PLWH attending our hospital and charted the trends of HBs antibody titer in patients who had been vaccinated against hepatitis B among those uninfected with hepatitis B. Descriptive statistics were conducted.

**Results** : Among 134 PLWH attending our hospital, 64 (47.8%) were already infected and 70 (52.2%) were uninfected. Among the uninfected patients, 42 (60.0%) were vaccinated against hepatitis B. The mean ages of patients with and without antibody titer increase after vaccination (responder and non-responder) were  $36.3 \pm 9.25$  and  $42.6 \pm 10.8$  years (mean  $\pm$  SD), respectively, and 96.4% and 85.7% of them were male, respectively. The mean HIV-RNA levels at the time of vaccination were  $13.2 \pm 10.1$  and  $11.4 \pm 22.8$  copies/mL, respectively (mean  $\pm$  SD,  $p=0.73$ ), and the mean of absolute numbers of CD4-positive lymphocytes were  $560.4 \pm 187.5/\mu\text{L}$  and  $494.5 \pm 125.3/\mu\text{L}$ , respectively (mean  $\pm$  SD,  $p=0.33$ ). The responder rate was 28 (66.7%), 25 (89.3%) responded to the first series of vaccination and 3 (10.7%) to the second series of vaccination.

**Discussion** : About half of the PLWH in our hospital who were uninfected with hepatitis B were vaccinated. It is said that PLWH are less likely to develop antibody titer to the vaccine than people without HIV. Sixty-six point seven percent of PLWH responded to the hepatitis B vaccine in our hospital, but 10.7% of them responded in the second series and 33.3% of them were non-responder. The importance of follow-up of antibody titers after vaccination and the second series of vaccinations in case of non-responders is suggested.

**Key words** : HIV infection, hepatitis B infection, hepatitis B vaccination

*The Journal of AIDS Research* 27 : 64–68, 2025

**Background**

HIV and HBV (hepatitis B virus) are often diagnosed simultaneously due to their similar route of transmission. People living with HIV (PLWH) in Japan are mostly men who have sex with men (MSM), and co-infection of HBV and HIV or previous HBV infection is common. The rate

of chronic HBV infection in PLWH is estimated to be about 8%<sup>1,2)</sup>, but the rate of co-infection varies from country to country and region to region. In sub-Saharan countries, perinatal horizontal transmission is a problem, while in developed countries, most cases are transmitted through sexual intercourse or injection needles of illicit drugs. However, the above data are on a national or regional basis, and data on the rate of co-infection of HIV and HBV in Japan are limited.

HBV vaccination is recommended worldwide for PLWH who are not infected with HBV or isolated anti-HBc, due to the risk of its transmission and concerns

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Received June 12, 2024 ; Accepted December 3, 2024

about the transition to chronic infection<sup>3)</sup>. In addition, with the approval of Dovato (lamivudine and dolutegravir) in 2020 and intramuscular cabotegravir and rilpivirine in 2022 in Japan, HBV prevention will become increasingly important as more patients are treated with two-drug regimens. However, in Japan, HBV vaccination in PLWH is not covered by insurance and is therefore paid for out-of-pocket, and vaccination rates are not consistent. In addition, it is known that HBs-antibody is unlikely to elevate among PLWH after HBV vaccination<sup>4,5)</sup>, or that even if antibody titer increases, the titer decreases over time<sup>6,7)</sup>. The HBV vaccination coverage among PLWH in Japan and the trends in their antibody titers are currently unknown.

## Method

A retrospective cohort of PLWH was evaluated. The patients were selected from the medical records of the division of Infectious Diseases clinic of St. Luke's International Hospital in Tokyo, Japan from January 2004 to February 2023. We evaluated all medical records of diagnosed and treated PLWH, totaling 125 individuals. The past medical history, risk of acquisition of HIV, the presence of opportunistic infections, and body mass index (BMI) were collected and analyzed, as well as information on HBV and hepatitis C virus (HCV) serology, CD4+ cell counts before vaccine, HIV viral load, HBV vaccine doses, type of HBV vaccination and antiretroviral therapy (ART). Vaccine response was considered when the patients showed an HBs-antibody level was upper than 10 mIU/mL more than one month after vaccination.

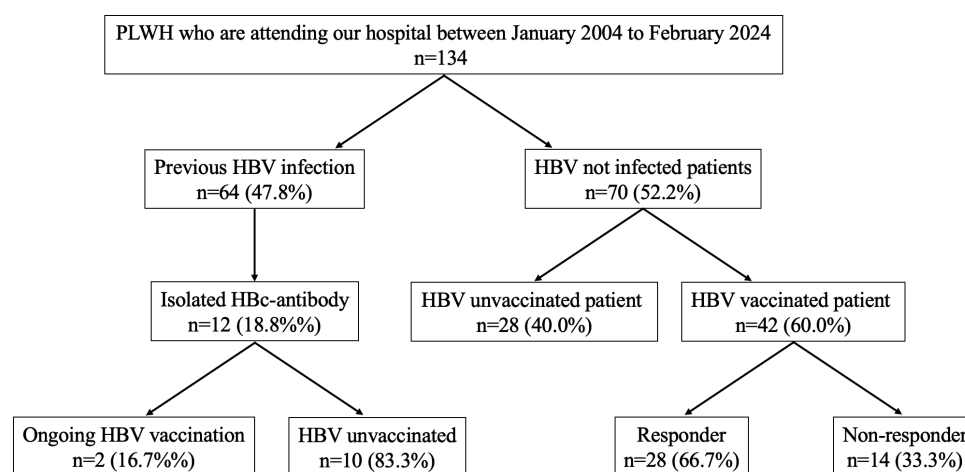
For statistical analysis, continuous variables were described as mean and standard deviation. Categorical variables were expressed as frequency and percentage. The categorical variables were compared by chi-square test or

by Fisher's exact test when appropriate, and continuous variables were compared by *t*-test. Since there were missing values for the CD4-positive T-cell counts, a *t*-test was performed by fitting the mean CD4 count value to the missing values and assuming that they were normally distributed. The findings were considered significant when  $p < 0.05$ . The data were stored in Microsoft Office Excel and analyzed using Stata version 18.0.

This study was submitted to and approved by the Ethics Committee of the St. Luke's International University, Tokyo, Japan, following the ethical precepts of the Declaration of Helsinki.

## Results

The total number of PLWH attending our hospital during the period covered was 134. Of these, 64 (47.8%) already had a history of hepatitis B (current HBV infection whose HBV-DNA or HBs-antigen is positive, and previous HBV infection whose HBe-antibody was positive) and 70 (52.2%) were uninfected with hepatitis B (whose HBs-antigen and HBe-antibody were all negative). Among these patients with previous infection of HBV, 12 patients have isolated HBe-antibody; 10 patients are not vaccinated to HBV and 2 patients are now on the first series of HBV vaccination. Of the uninfected patients, 28 (40.0%) were unvaccinated against hepatitis B and 42 (60.0%) were vaccinated. Of the vaccinated patients, 28 (66.7%) showed an increase upper than 10 mIU/mL in HBs-antibody titer more than one month after vaccination (named as "responder"), whereas 14 (33.3%) had no elevated antibody titers less than 10 mIU/mL in HBs-antibody titer more than one month after vaccination (named "non-responders"). The total number of patients and the percentage of hepatitis B infection are shown in Figure. Of the 14 non-responder patients, 13 were vaccine-refrac-



**Figure** The total number of patients and the percentage of hepatitis B infection.

HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; HBV, hepatitis B virus.

tory in the first series of vaccination and one was refractory in the second series of vaccinations.

The vaccines used were “Bimmugen Injection” and “HEPTAVAX”, and “Twinrix” was not used. Of the 42 patients who received the HBV vaccination, 13 received “Bimmugen Injection” and 16 received “HEPTAVAX”. The remaining 13 patients received the vaccine at another hospital, so it was unknown which product they used. As for the administration route and dose of the vaccine, both were administered intramuscularly at a dose of 10 µg. All vaccinated patients received a series of three doses of 10 µg each.

The baseline characteristics of patients, backgrounds, and the univariate analysis of the two groups are shown in Table. The median age was  $36.3 \pm 9.25$  years for responders and  $42.6 \pm 10.8$  years for non-responders (mean  $\pm$  SD,  $p = 0.055$ ), with a higher proportion of males in both groups. There were no significant differences in body weight, BMI, history of hepatitis C, presence of opportunistic infection at the initial visit, and ART regimen. The mean HIV viral load at hepatitis B vaccination was  $13.2 \pm 10.1$  copies/mL for responders and  $11.4 \pm 22.8$  copies/

mL for non-responders ( $p = 0.73$ ). The mean CD-4 positive T-cell counts at hepatitis B vaccination were  $560.4 \pm 187.5/\mu\text{L}$  for responders and  $494.5 \pm 125.3/\mu\text{L}$  for non-responders ( $p = 0.33$ ). Significant differences were found for the presence of diabetes (responder 0, non-responder 3,  $p = 0.027$ ).

## Discussion

Among PLWH attending our hospital, 52.2% were uninfected with hepatitis B. Among them, 60.0% were vaccinated against hepatitis B. Among those who were vaccinated against hepatitis B, 33.3% showed no increase in HBs-antibody titer up to 10 mIU/mL more than one month after vaccination. In the univariate analysis between the responder and non-responder groups, a statistically significant difference was observed in diabetes mellitus. Although 0 patients in the responder group and 3 patients in the non-responder group had diabetes mellitus, the univariate analysis showed a statistically significant difference, suggesting that those with diabetes were less responsive to the hepatitis B vaccine. However, due to the small number, multivariate analysis could not be performed, and

**Table** Baseline characteristics and univariate analysis

		Responder <i>n</i> = 28	Non-responder <i>n</i> = 14	<i>p</i> -Value
Age, mean $\pm$ SD		36.3 $\pm$ 9.25	42.6 $\pm$ 10.8	0.055
Sex	Male	27	12	0.20
	Female	1	2	
Body weight (kg), mean $\pm$ SD		75.2 $\pm$ 17.4	68.0 $\pm$ 13.3	0.19
BMI (body mass index), mean $\pm$ SD		25.0 $\pm$ 5.23	23.6 $\pm$ 4.05	0.38
Comorbidity	Hypertension	5 (17.9)	3 (21.4)	0.78
	Diabetes mellitus	0 (0.0)	3 (21.4)	0.011
	Dyslipidemia	4 (14.3)	5 (35.7)	0.11
	Chronic kidney disease	1 (3.57)	2 (14.29)	0.20
	Malignancy	1 (3.57)	0 (0.0)	0.47
Hepatitis C co-infection		1 (3.57)	0	0.47
Opportunistic infection <sup>*1</sup>	<i>Pneumocystis jirovecii</i> pneumonitis	2 (7.14)	0	0.31
	Cytomegalo virus infection	1 (3.57)	1 (7.14)	0.61
	<i>Candida esophagitis</i>	1 (3.57)	0	0.47
	Progressive multifocal leukoencephalopathy	0	1 (7.14)	0.15
	Kaposi sarcoma	0	1 (7.14)	0.15
ART regimen	TAF/FTC+DTG	10 (35.7)	3 (21.4)	0.35
	ABC/3TC/DTG	2 (7.14)	1 (7.14)	1.00
	BIC/FTC/TAF	11 (39.3)	6 (42.9)	0.82
	TAF/FTC/DNR/cobi	1 (3.57)	1 (7.14)	0.61
HIV status	HIV-RNA viral load (copy/mL), mean $\pm$ SD <sup>*2</sup>	13.2 $\pm$ 10.1	11.4 $\pm$ 22.8	0.73
	CD4 count (/µL), mean $\pm$ SD <sup>*2</sup>	560.4 $\pm$ 187.5	494.5 $\pm$ 125.3	0.33

<sup>\*1</sup> At the initial visit. <sup>\*2</sup> At the vaccination. SD, standard deviation; ART, antiretroviral therapy; TAF, tenofovir-alafenamide; FTC, emtricitabine; DTG, dolutegravir; ABC, abacavir; 3TC, lamivudine; BIC, bictegravir; DNR, darunavir; cobi, cobicistat.

further analysis is needed to increase the number of patients.

It has been reported that HIV viremia and CD4-positive T lymphocyte counts below 350/ $\mu$ L are associated with low antibody titer increase<sup>8)</sup>. Takeuchi *et al* reported that 12 of 18 PLWH uninfected with hepatitis B received one series of hepatitis B vaccination, and antibody titers exceeding 10 mIU/mL were observed in 6 responders. The mean CD4-positive T lymphocyte count was significantly higher in responders than in non-responders<sup>9)</sup>. Nishida *et al* reported that the number of antibody acquirers among PLWH uninfected with hepatitis B after hepatitis B vaccination was 15 (43%) among 35 patients. The mean CD4-positive T lymphocyte counts of responders and non-responders by hepatitis B vaccination were not significantly different (mean values of 567/ $\text{mm}^3$  and 463/ $\text{mm}^3$ , respectively)<sup>10)</sup>. In our data, the mean CD4-positive T lymphocyte count was higher than 350/ $\mu$ L in both groups. Since the responder group has more elevated CD4-positive T lymphocytes, a significant difference was not observed between the two groups. As mentioned earlier, data on vaccine responsiveness among PLWH in Japan are scarce, our results could not help supporting the hypothesis that vaccine responsiveness is better in patients with higher CD4 counts.

There is a report that the responsiveness to the vaccine differs depending on HCV status<sup>11)</sup>, but in our case, there was only one HCV co-infection case, so it was difficult to make a comparative study.

Of the 14 non-responders, one patient was still non-responsive to the second series of HBV vaccine. The patient was 56 years old at the second series of HBV vaccination, and the BMI was 20.1. The CD4-positive T-cell count was 603.3/ $\mu$ L and the HIV viral load was  $2.3 \times 10^1$  copies/mL. The patient has been in good control of HIV infection, but the age tended to be higher than the median for non-responder patients and has diabetes mellitus. The BMI of the patient was average.

A variety of sociologic factors, such as alcohol, tobacco, and illegal injection drugs, and injection site (deltoid or gluteal) are relevant to poor response to vaccination<sup>9)</sup>. These data were not extracted in this study, it was impossible to evaluate these sociologic factors about vaccine antibody titers.

One of the reasons why antibody titers of the hepatitis B vaccine do not increase easily is the amount of antigen contained in the vaccine approved in Japan. The amount of HBs antigen in “Engerix-B”, which is approved in Europe and the United States, is 20 mcg per dose<sup>12)</sup>, whereas that in “Bimmugen Injection” and “HEPTAVAX”, which are most used in Japan, is 10 mcg per dose. Since there are 2 out of 10 (20%) cases in which antibody titers do not increase even after the second series, we may consider increasing the dose in these cases. However, this practice

is not covered by insurance. In addition to the issue of vaccine dosage, HBV vaccination is not covered by health insurance in Japan and is treated as a self-pay service. As a result, patients who can afford it can get vaccinated against HBV, however, patients who cannot afford it cannot get the vaccine. Even within Japan, there are disparities in economic circumstances from region to region, and the current situation is that the HBV vaccine cannot be equally administered to patients who have not been infected with HBV or patients with isolated HBc-antibody. Given these backgrounds in Japan, it is difficult to equally vaccinate against HBV, and the titer of HBs-antibody in PLWH does not increase easily, so in such patients, if there is a risk of being particularly susceptible to HBV infection, it is necessary to be careful when selecting anti-retroviral regimen. More specifically, PLWH who did not respond to HBV vaccination or cannot access to HBV vaccination should be prescribed with tenofovir-containing regimen not a 2-drug regimen or intramuscular rilpivirine and cabotegravir regimen.

## Conclusion

About half of the PLWH attending our hospital were uninfected with hepatitis B. Among them, hepatitis B vaccination coverage was 60.0%. Antibody titers increased in 66.7% of the patients after vaccination, but there were cases in which antibody titers did not increase even after two series of vaccination. As two-drug antiretroviral regimens are becoming more common in Japan, in non-responders who continue to engage in HBV risk behaviors and who are not already treated with an HBV-active ART regimen, clinicians should consider the anti-retroviral regimen carefully.

**Conflict of Interest (COI):** There is no conflict of interest to disclose.

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## HIV 患者における B 型肝炎ウイルス感染の割合と、 ワクチン接種後の抗体価の推移

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**背景:** HIV 感染者は B 型肝炎を合併することが多く, 初診時に B 型肝炎の感染状況を確認するのが一般的である。日本における HIV 患者の B 型肝炎ワクチン接種率やワクチン接種後の抗体価の変化に関するデータは少ない。また, HIV 患者ではワクチン接種後も B 型肝炎抗体価が上昇しにくいことが欧米からの報告で知られているが, 本邦のデータは少ない。

**方法:** 当院に通院中の HIV 患者における B 型肝炎感染状況をカルテレビューで抽出し, B 型肝炎未感染者における B 型肝炎ワクチン接種者の HBs 抗体価の推移について記述統計を行った。

**結果:** 当院通院中の HIV 感染者 134 例中, B 型肝炎既感染者は 64 例 (47.8%), 未感染者は 70 例 (52.2%) であった。B 型肝炎ワクチン接種後に抗体価が上昇した患者 (Responder) と上昇しなかった患者 (Non-responder) の平均年齢はそれぞれ  $36.3 \pm 9.25$  歳と  $42.6 \pm 10.8$  歳 (平均  $\pm$  SD) であり, それぞれ 96.4% と 85.7% が男性であった。ワクチン接種時の HIV-RNA 量の平均はそれぞれ  $13.2 \pm 10.1$  copies/mL,  $11.4 \pm 22.8$  copies/mL (平均  $\pm$  SD,  $p=0.73$ ), CD4 陽性リンパ球絶対数の平均はそれぞれ  $560.4 \pm 187.5/\mu\text{L}$ ,  $494.5 \pm 125.3/\mu\text{L}$  (平均  $\pm$  SD,  $p=0.33$ ) であった。ワクチン接種後に抗体価上昇がみられたのは 28 例 (66.7%) であり, 1 回目の接種で反応がみられたのが 25 例 (89.3%), 2 回目の接種で反応がみられたのが 3 例 (10.7%) であった。

**考察:** 当院では, B 型肝炎に感染していない HIV 患者の約半数が B 型肝炎ワクチン接種を受けていた。HIV 感染者は HIV 未感染者に比べてワクチンに対する抗体価が上昇しにくいといわれている。当院では HIV 感染者の 66.7% が B 型肝炎ワクチンに反応し抗体価上昇がみられたが, 1 シリーズ目では抗体価が上昇せず 2 シリーズ目で反応したのが 10.7% であり, 33.3% はワクチンに対する反応性がみられなかった。B 型肝炎ワクチン接種後の抗体価の経過観察, 非反応者に対する 2 回目の接種の重要性が示唆された。

**キーワード:** HIV 感染症, B 型肝炎, B 型肝炎ワクチン