Double-Dose (HBsAg 20μg) Re-Vaccination After Primary or Secondary HBV Vaccine Failure in Japanese People Living with HIV

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Backgrounds

Hepatitis B virus (HBV) co-infection remains a major concern for people living with HIV (PLWH), yet response rates to HBV vaccination are suboptimal in this population. In Japan, universal HBV vaccination was only introduced in 2016, meaning that most Japanese adults have never received HBV vaccination. Additionally, the HBV vaccine approved in Japan (Biimugen®) contains 10μg of HBsAg and has traditionally been administered subcutaneously, a method associated with lower immunogenicity compared to intramuscular administration. Given these challenges, we evaluated the effectiveness of double-dose HBV re-vaccination (20μg HBsAg per dose) in Japanese PLWH who showed primary or secondary failure to the primary series of HBV vaccination.

Figure.1 Primary vaccination series (n = 277)
Anti-HBs antibody titer (mIU/mL)

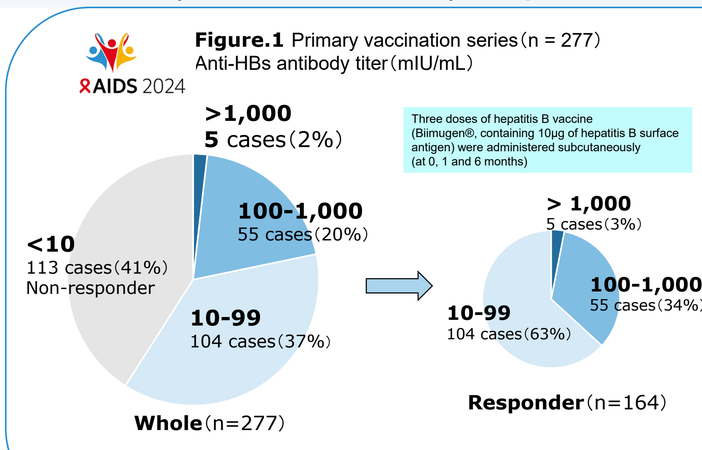
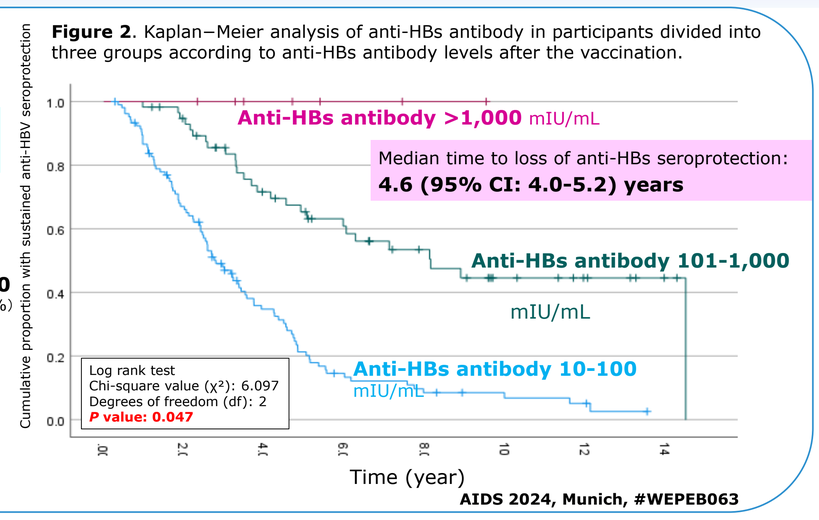


Figure 2. Kaplan–Meier analysis of anti-HBs antibody in participants divided into three groups according to anti-HBs antibody levels after the vaccination.



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Methods

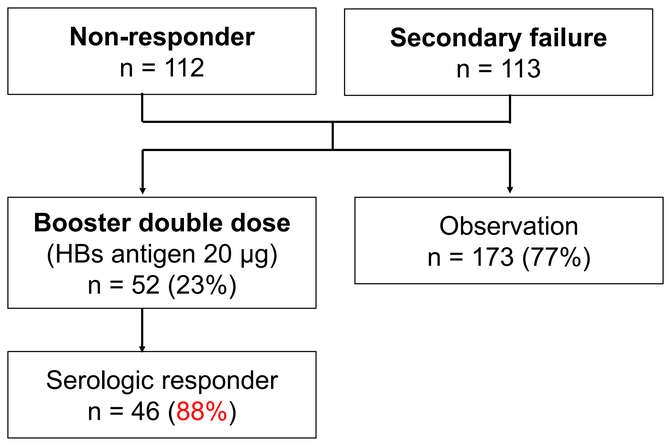


Figure 3. Flow chart of the HBV double-dose revaccination program participants.

Between 2004 and 2016, we administered an HBV vaccination program to 277 PLWH without HBV immunity at our hospital. The primary vaccination regimen consisted of three doses of **10μg HBsAg (Biimugen®)** administered subcutaneously at 0, 1, and 6 months. Among these participants, 164 (59.2%) showed a serological response (anti-HBs ≥ 10 mIU/mL), while the remaining 112 (40.8%) were classified as primary non-responders. Additionally, 113 participants initially achieved an adequate response (anti-HBs ≥ 10 mIU/mL) but later experienced a decline in antibody levels to <10 mIU/mL during follow-up, meeting the definition of secondary failure. Both primary and secondary failures were offered a **double-dose (20μg) re-vaccination regimen**, administered subcutaneously at the same intervals (0, 1, and 6 months). Serological responses were assessed immediately post-re-vaccination and during long-term follow-up to evaluate response durability and factors influencing vaccine effectiveness.

Double-dose revaccination (Biimugen®, 20μg, 0, 1 and 6 months, subcutaneously) was proposed for participants with primary failure (n=112) and secondary failure (n=113). We performed a retrospective analysis of those who received re-vaccination.
Seroprotection was defined as anti-HBs ≧ 10 mIU/mL. The durability of anti-HBV seroprotection was assessed by measuring antibody titers at least twice after the vaccination.

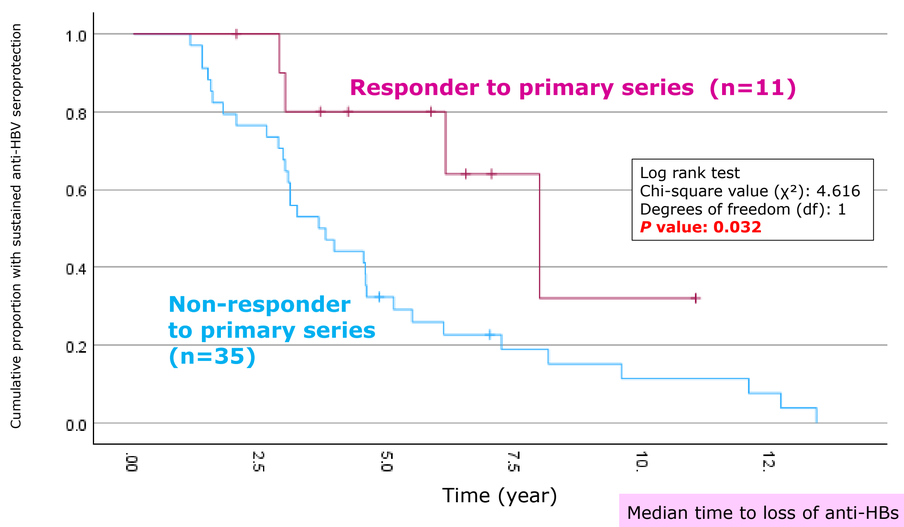
Results

Table 1. Baseline characteristics of the participants.

Patient characteristics	All participants (n=52)	Responders (n=46, 88%)	Non-responders (n=6)	*P* value
Age（year）	37 [30-41]	37 [30-41]	37 [31-39]	0.989
Sex（male:female）	52:0	46:0	6:0	-
Body weight (kg)	75 [66-82]	74 [66-81]	78 [61-89]	0.812
Body mass index	24.2 [22.0-27.7]	24.2 [22.1-27.6]	24.5 [20.5-29.1]	1.000
Active smoker	29（56%）	25 (54%)	4 (67%)	0.453
Positive HCV antibody	2（4%）	2（4%）	0	0.812
CD4 cell count（cells/μL）	448 [330-572]	424 [327-552]	622 [462-815]	0.685
CD4/CD8 ratio	0.68 [0.42-0.87]	0.68 [0.42-0.90]	0.64 [0.38-0.73]	0.645
ART	**36（69%）**	**35（70%）**	**1（17%）**	**0.013**
HIV-RNA				
HIV-RNA < 400 copies/mL	37（72%）	34 (74%)	3 (50%)	0.224
HIV-RNA < 50 copies/mL	33（63%）	31 (67%)	2 (33%)	0.121
Responder to primary HBV vaccination series	11 (21%)	11 (24%)	0	0.221

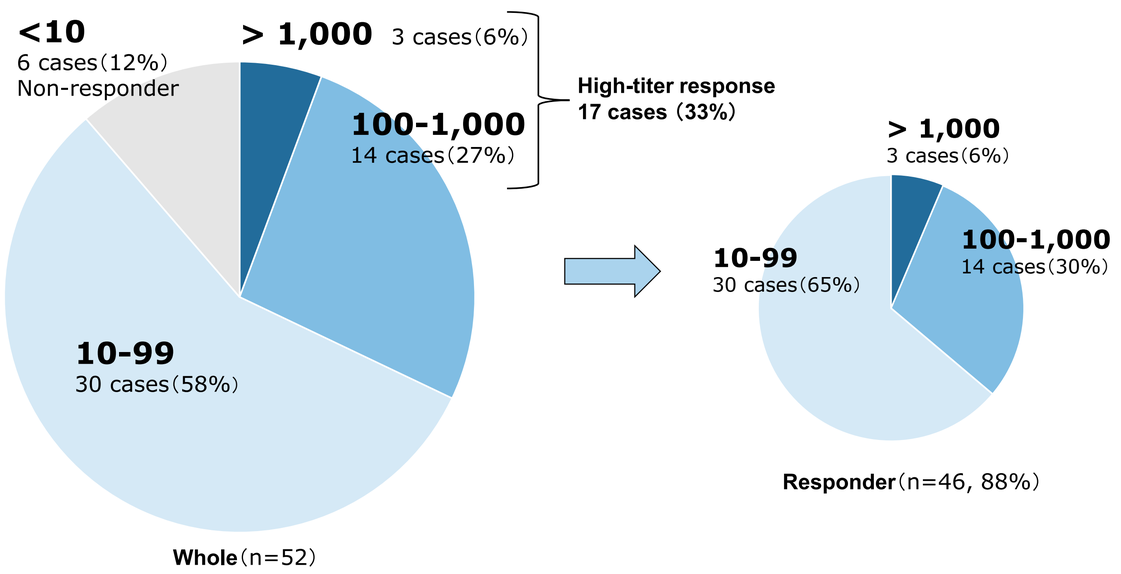
Values are expressed as medians [IQR] or as numbers (%)

Figure 4. Kaplan–Meier analysis of the durability of anti-HBV seroprotection anti-HBs antibody in participants divided into three groups according to anti-HBs antibody levels after the vaccination. (n=46)



Median time to loss of anti-HBs seroprotection:
4.5 (95% CI: 3.4-5.6) years

Figure 4. Secondary double-dose vaccination series (n = 52)
Anti-HBs antibody titer (mIU/mL)



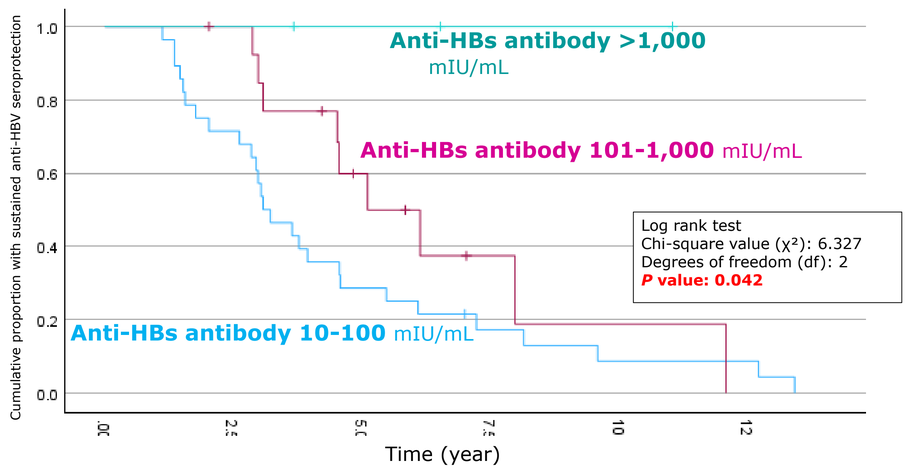


Table 2. FactorsUnivariate and multivariate regression analysis for factors associated with the earlier loss of seroprotection after the initial series of HB vaccination.(n = 46)

	Univariate regression analysis			multivariate regression analysis		
factors	**Hazard ratio**	**95%CI**	***p* value**	**Hazard ratio**	**95%CI**	***p* value**
Age (per 1 year increase)	0.992	0.974-1.010	0.381			
Body weight (per 1 kg increase)	1.026	0.997-1.056	0.083	1.028	0.996-1.060	0.084
Antiretroviral therapy	1.073	0.516-2.234	0.850			
CD4 (per 1 /μL increase)	0.999	0.997-1.002	0.585			
VL<50	1.980	0.917-4.276	0.082	2.057	0.862-4.908	0.104
Responder to primary HBV vaccination series	0.335	0.117-0.956	**0.041**	0.483	0.125-1.869	0.483
HBs antibody titer > 100	0.437	0.204-0.940	**0.034**	0.493	0.180-1.355	0.170

Discussion

Table 3. Summary of HBV Vaccine Revaccination Studies in People Living with HIV(Only studies with ≥100 participants included)

Author(Country)	Study design	n	HBV Vaccine	Schedule	Outcomes	Factors associated with better response
de Vries-Sluijs[1] (Netherlands)	prospective open study	144	HBVaxPro®	3 doses	Seroprotection: 51.4%	Female sex, age <40, undetectable VL
Rey D[2] (France)	RCT	132	Engerix-B®	3 doses	67% (20 μg) vs 74% (40 μg); no significant difference	Double dose
Chatkittikunwong G[3] (Thailand)	Retrospective	210	Recombinant (unspecified)	3 doses	70% (standard) vs 97% (double)	Double dose, CD4 >450, age <40
Khaimova R[4] (United States)	Retrospective	127	Heplisav-B®	2 doses	86.6% achieved seroprotection	CpG-adjuvanted vaccine highly effective
Schnittman SR[5] (United States)	Retrospective	233	Heplisav-B®	2 doses	Overall SPR 81%; 84% in prior non-responders	CpG-adjuvanted vaccine highly effective

Limitation

- Small sample size, single-center study
- Retrospective design and lack of standardized testing for long-term immunity
- Heterogeneity in participant characteristics
- ✓ We included non-responders and participants with secondary failure, which makes the interpretation confusing.

Conclusion

- Double-dose re-vaccination significantly improves initial serological response. However, the durability of immunity remains a challenge, with a high proportion of patients losing seroprotection within a few years.
- Further studies should explore predictors of sustained immunity and evaluate whether modified vaccination schedules could enhance serological protection in this population.

Acknowledgement

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References

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