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Persistence of Protective Hepatitis B Surface Antibody Titers after Successful Double-Dose Hepatitis B Virus Rescue Vaccination in HIV-Infected Patients

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Background/Aims: To assess the durability of protective hepatitis B surface antibody (anti-HBs) titers in HIV-infected patients who responded to double-dose hepatitis B virus (HBV) rescue vaccination. **Methods:** A retrospective chart review was performed for HIV-infected patients who received the double-dose HBV rescue vaccination at 0-, 1-, and 2-month intervals after they had failed conventional HBV vaccination series. A protective antibody response was defined as an anti-HBs titer ≥10 mIU/mL. **Results:** Of 54 HIV-infected patients who received a double-dose HBV rescue vaccination, 44 patients (81.5%) had a positive response and achieved protective anti-HB titers. Of the 44 patients who developed protective anti-HB titers, 33 patients received an evaluation of their anti-HB titers 12 months later. Of the 33 patients, 19 (57.6%) had persistent protective anti-HB titers (persistent responders, PR), and 14 patients (42.4%) lost their protective anti-HB titers (nonpersistent responders, NPR). There were significantly more patients who had an undetectable HIV viral load (<50 copies/mL) at baseline and follow-up in the PR group (11/19, 57.9%) than in the NPR group (3/14, 21.4%, p=0.036). Logistic regression analysis showed that an undetectable HIV viral load at baseline and follow-up (odds ratio, 12.973; 95% confidence interval, 1.189 to 141.515; p=0.036) was associated with PR. **Conclusions:** Protective anti-HB titers may decrease over time after successful double-dose HBV rescue vaccination in HIV-infected patients. HIV viral load suppression could improve the persistence of anti-HB titers. **(Gut Liver 2012;6:86-91)**

Key Words: HIV; Hepatitis B virus; Double dose HBV rescue vaccination

INTRODUCTION

Co-infection with HIV and hepatitis B virus (HBV) is common; in the Western world, chronic HBV infection has been found in 6% to 14% among HIV-positive patients.[1,2] Chronic co-infection with HBV and HIV can lead to increased rates of liver-related morbidity (cirrhosis, hepatocellular carcinoma) and mortality.[3,4] Prevention of HBV infection is therefore essentially important in the setting of HIV-infection. The success rate of HBV vaccine, however, is much lower in HIV-infected patients as compared with healthy immunocompetent individuals. 90% to 95% of healthy adult individuals develop protective anti-HBV antibody, whereas only 20% to 70% of the HIV-infected patients develop protective anti-HBV antibody after a conventional standard dose of HBV vaccination at 0-1-6 monthly intervals.[5] Contributing factors associated with nonresponsiveness to HBV vaccination in HIV-infected patients include ongoing HIV-viremia, impaired humoral and cellular immunity, HCV co-infection, and increasing age.[6-10] The most effective strategy for maximizing HBV-vaccine response in HIV-infected patients remains unknown. Administering doubled HBV vaccine dose, i.e., from 20 to 40 μg, has been tried in several studies with improved overall success rates of 36.6% to 89.5%.[11-15] In our experience, double-dose HBV rescue vaccination (40 μg HBV vaccination at 0-1-2 monthly intervals) achieved more than 80% seroconversion rates in HIV-infected patients who had failed to respond with conventional standard dose HBV vaccination (20 μg HBV vaccination at 0-1-6 monthly intervals with or without additional 20 μg HBV booster vaccination).[16] Also, it is important to point out that HIV co-infection decreases hepatitis B surface antibody (anti-HBs) persistence in naturally infected

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and conventionally vaccinated individuals.[17,18] Few data exist to assess the persistence of protective anti-HBs titers after successful double-dose HBV rescue vaccination in the setting of HIV-infection. We reviewed anti-HBs titers a year later in HIV-infected patients who had responded to double-dose HBV rescue vaccination.

MATERIALS AND METHODS

A retrospective medical-chart review study was conducted in our center. HIV-infected patients who had failed to develop protective anti-HBs after three or more standard conventional dose HBV vaccine (20 μg HBV vaccination at 0-1-6 monthly intervals with or without additional 20 μg HBV booster vaccination) were identified and were given double-dose HBV rescue vaccination, (40 μg –20 μg/mL in each deltoid–) (Recombivax HB® (Merck & Co., Inc., Whitehouse Station, NJ, USA) at 0-1-2 monthly intervals. The vaccination schedule was based on a previous study, in which 0-1-2 monthly intervals of standard dose recombinant HBV vaccination resulted in a faster and also identical seroconversion rate to the standard dose recombinant HBV vaccination at 0-1-6 monthly intervals.[19] Patients who developed protective anti-HBs titers of ≥10 mIU/mL after double-dose HBV rescue vaccination were classified as double-dose HBV rescue vaccination responders. These patients had anti-HBs titers assessment 12 months later.

Demographic characteristics, presence of hepatitis C virus (HCV) antibody, CD4 T-cell count, HIV RNA viral load, and use of highly active antiretroviral therapy (HAART) were reviewed at baseline –the time of first double-dose HBV rescue vaccination (at 0 month out of 0-1-2 monthly interval), and at one year follow-up, 12 months after completion of the double-dose HBV rescue vaccination series. Patients who retained anti-HBs titers of ≥10 mIU/mL at one year follow-up were classified as persistent responders (PR) while patients with decreased anti-HBs titers of <10 mIU/mL were defined as nonpersisent responders (NPR).

Statistical analysis was performed using SPSS version 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Dichotomous variables were compared using Pearson χ^2 test or Fisher's exact test. For continuous variables, Mann-Whitney test was used. Multivariate analysis by logistic regression was used to determine factors associated with successful PR. Odds ratio (OR) and 95% confidence interval (CI) were calculated. A p-value less than 0.05 was considered to be statistically significant.

This study was approved by Institutional Review Board at St. Luke's-Roosevelt Medical Center, New York, NY, USA.

RESULTS

The medical records of HIV-infected patients followed in our center between January 2004 and October 2010 were reviewed. Fifty-four patients received three double-dose HBV rescue vaccine at 0-1-2 monthly intervals after failure to develop protective anti-HBs with three or more conventional standard dose HBV vaccinations. The study population consisted of 41 males (75.9%) with a median age of 45 years. Hispanics and Blacks were the predominant ethnic groups (31/54, 57.4% and 15/54, 27.8%, respectively). Homosexual men (men who have sex with men, MSM) were the major HIV-risk group, 30/54 of patients, 55.6%. Nine patients (9/54, 16.7%) had chronic HCV infection. At the start of the double-dose HBV rescue vaccination series, 49 patients (49/54, 90.7%) were on HAART. The median CD4 T-cell count was 433 cell/mm^3 (interquartile range [IQR], 328 to 645 cell/mm^3) and 20 patients (20/54, 35.7%) had CD4 T-cell count >500 cell/mm^3. The median Log_{10} HIV viral load was 1.699 (IQR, 1.699 to 2.358) and 30 patients (30/54, 53.6%) had HIV viral load <50 copies/mL. Forty-four patients (44/54, 81.5%)

Table 1. Baseline Characteristics at the First Double-Dose HBV Rescue Vaccination and Double-Dose HBV Rescue Vaccine Response Rate

Characteristic	Value
Total number of patients	54
Age median (IQR)	45 (37-50)
Sex	
Female	13 (24.1)
Male	41 (75.9)
Ethnicity	
White	8 (14.8)
Hispanic	31 (57.4)
Black	15 (27.8)
HIV risk factor	
Hetero	18 (33.3)
IVDU	6 (11.1)
MSM	30 (55.6)
Hepatitis C co-infection	
Hepatitis C positive	9 (16.7)
HAART	
On HAART	49 (90.7)
CD4 T-cell count median (IQR)	433 (328-645)
Patients with CD4 >500	20 (35.7)
Log_{10} HIV viral load median (IQR)	1.699 (1.699-2.358)
Patients with HIV viral load <50	30 (53.6)
Double dose HBV rescue vaccine responders	44 (81.5)

Values are presented as median (IQR) or number (%).
HBV, hepatitis B virus; IQR, interquartile range; Hetero, heterosexual contact; IVDU, intravenous drug abuse; MSM, men who have sex with men; HAART, highly active antiretroviral therapy; CD4 T-cell cell count cells/mm^3, HIV viral load copies/mL; Double-dose HBV rescue vaccine responders, patients who developed protective anti-HBs titers of ≥10 mIU/mL after double-dose HBV rescue vaccination.

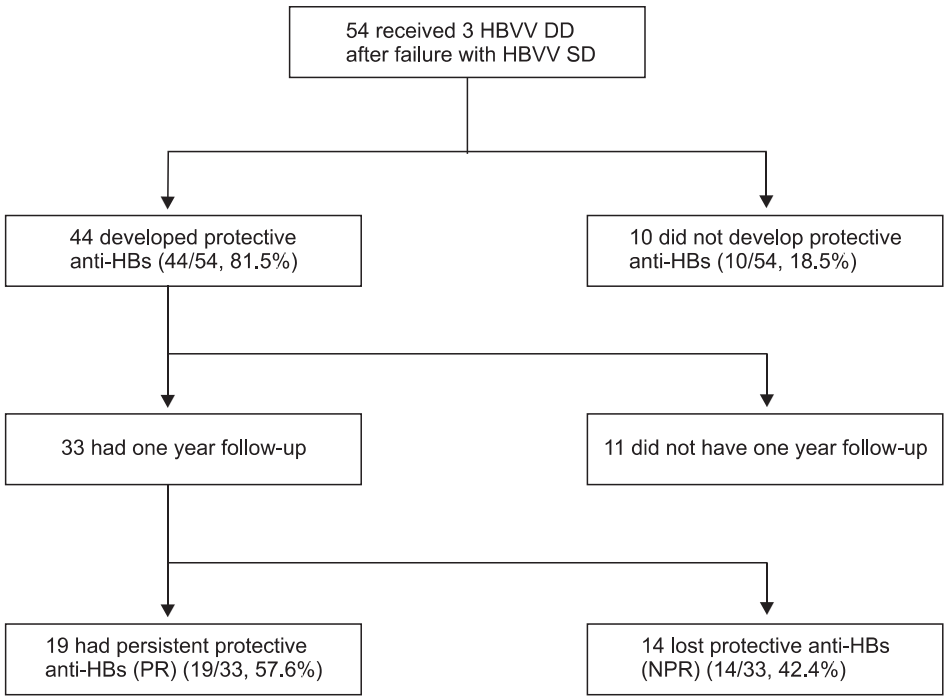

Fig. 1. Double-dose hepatitis B virus (HBV) rescue vaccination and evaluation of the durability of protective HBV surface antibody (anti-HBs) titers.
HBVV DD, double-dose hepatitis B virus rescue vaccination at 0-, 1-, and 2-month intervals; HBVV SD, standard-dose hepatitis B virus vaccination at 0-, 1-, and 6-month intervals with or without an additional standard-dose hepatitis B booster vaccination; PR, persistent responders; NPR, nonpersistent responders.

developed protective anti-HBs after completion of three double-dose HBV vaccination series (double-dose HBV rescue vaccine responders). The baseline characteristics of patients at the start of double-dose HBV rescue vaccination are shown in Table 1.

Thirty-three of 44 double-dose HBV rescue vaccine responders had follow-up evaluation at one year after the last vaccine dose. Nineteen of the 33 double-dose HBV rescue vaccine responders (19/33, 57.6%) were found to have persistent levels of protective anti-HBs ≥10 mIU/mL and they were classified as PR. Fourteen patients (14/33, 42.4%) lost their protective anti-HBs at one year follow-up were defined as NPR. These are shown in Fig. 1. We compared the PR and NPR groups and there was no significant difference in terms of median CD4 T-cell count at baseline or at follow-up. Also the proportions of patients who had CD4 T-cell count >500 cell/mm^3 both at baseline and one year follow-up were not different; 4/19, 21.1% in PR group and 3/14, 21.4% in NPR group (p=1.000). Although there was no significant difference in terms of median Log_{10} HIV viral load at baseline and follow-up between the two groups, the proportion of patients who had undetectable HIV viral load <50 copies/mL both at baseline and one year follow-up was significantly higher in PR group (11/19, 57.9%) than in NPR group (3/14, 21.4%) (p=0.036). The median of total number of overall HBV vaccinations including conventional standard dose HBV vaccine and double-dose HBV rescue vaccine was 6.0 (IQR, 6.0 to 7.0) for PR group and 6.0 (IQR, 6.0 to 6.3) for NPR group without significant difference (p=0.360) as shown in the Table 2.

A multivariate logistic regression analysis was performed using the variables of sex, HIV risk factors, presence of HCV antibody, receipt of HAART, CD4 T-cell count, and HIV viral load. Successful HIV viral load suppression defined by undetectable HIV viral load <50 copies/mL both at baseline and follow-up (OR, 12.973; 95% CI, 1.189 to 141.515; p=0.036) was found to be associated with PR among HIV-infected double-dose HBV vaccine recipients as shown in Table 3.

DISCUSSION

Our study showed an impressive response rate, 81.5%, of double-dose HBV rescue vaccination series in HIV-infected patients who had prior not responded to conventional HBV vaccination. However, levels of protective anti-HBs titer decreased over a year. 57.6% of double-dose HBV rescue vaccine responders were noted to have persistence of protective anti-HBs titer at one-year follow-up. Our findings are consistent with a previous study in which a high serologic response rate with double-dose HBV vaccination was observed, however, 63% of the responders had persistence of protective anti-HBs titer at 12 months.[14] Also results of our study correspond with the results of earlier study by Cooper *et al*.,[15] in which 89.5% of HIV-infected patients who received double-dose HBV vaccination developed protective anti-HBs titer, and persistence of seroprotective anti-HBs titer was 60% at 24 months of follow-up. Of note, Cooper *et al*.[15] observed improved durability of the protective anti-HBs titers with the adjuvant CPG 7909 (>80% of patients at 42 to 60 months) compared to those generated by double-dose HBV vaccination without the adjuvant.

We observed that persistence of protective anti-HBs titers in HIV-infected patients at 1 year after double-dose HBV rescue vaccination was associated with HIV viral load suppression.

Table 2. Demographic and Clinical Characteristics at One-Year Follow-Up after Completion of Three Double-Dose Hepatitis B Rescue Vaccinations by Two Groups of Persistent Responders (PR) and Non-Persistent Responders (NPR)

Characteristic	PR (n=19; 19/33, 57.6%)	NPR (n=14; 14/33, 42.4%)	p-value
Age median (IQR)	42 (39–48)	47 (39–52)	0.201
Sex			0.422
Female	3 (15.8)	4 (28.6)	
Male	16 (84.2)	10 (71.4)	
Ethnicity			
White	5 (26.3)	1 (7.1)	0.209
Hispanic	11 (57.9)	6 (42.9)	0.393
Black	3 (15.8)	7 (50.0)	0.057
HIV risk factor			
Hetero	5 (26.3)	4 (28.6)	1.000
IVDU	0 (0.0)	2 (14.3)	0.172
MSM	14 (73.3)	8 (57.1)	0.459
Hepatitis C	1 (5.3)	4 (28.6)	0.138
On HAART	18 (94.7)	14 (100.0)	1.000
Total number of HBV vaccination median (IQR)	6.0 (6.0–7.0)	6.0 (6.0–6.3)	0.360
CD4 baseline	425 (333–610)	386 (290–535)	0.308
CD4 follow-up	465 (287–607)	465 (273–594)	0.855
CD4 >500	4 (21.1)	3 (21.4)	1.000
Log_{10} HIV baseline	1.699 (1.699–2.057)	1.922 (1.699–2.867)	0.103
Log_{10} HIV follow-up	1.699 (1.699–1.919)	1.766 (1.699–2.253)	0.375
HIVvl <50 copies	11 (57.9)	3 (21.4)	0.036

Values are presented as median (IQR) or number (%).
HBV, hepatitis B virus; IQR, interquartile range; Hetero, heterosexual contact; IVDU, intravenous drug abuse; MSM, men who have sex with men; HAART, highly active antiretroviral therapy; Hepatitis C, hepatitis C co-infection; total number of HBV vaccinations, includes the conventional standard-dose HBV vaccination and the double-dose HBV rescue vaccination; CD4 baseline and follow-up, CD4 T-cell cell count cells/mm^3 median (IQR) at baseline and follow-up, respectively; CD4 >500, patients who had CD4 T-cell counts at baseline >500 and at follow-up >500; Log_{10} HIV baseline and follow-up, Log_{10} HIV viral load copies/mL at baseline and follow-up, respectively; HIVvl <50 copies, patients who had HIV viral load <50 at both baseline and follow-up.

Table 3. Logistic Regression of Variables Associated with Persistent Responders (PR) at One-Year Follow-Up after Completion of Three Double-Dose Hepatitis B Rescue Vaccinations

Variable	OR (95% CI)	p-value
Sex		
Female (ref)		
Male	11.329 (0.054–2392.338)	0.374
HIV risk factor		
Hetero (ref)		
IVDU	0.000 (0.000- .)	0.999
MSM	0.541 (0.004–72.406)	0.806
Hepatitis C co-infection		
Hepatitis C positive (ref)		
No hepatitis C	25.933 (0.977–688.251)	0.052
HAART		
No HAART (ref)		
On HAART	0.000 (0.000- .)	1.000
CD4 T-cell count		
CD4 ≤500 (ref)		
CD4 >500	0.387 (0.047–3.179)	0.377
HIV viral load		
HIV viral load >50 (ref)		
HIV viral load <50	12.973 (1.189–141.515)	0.036

OR, odds ratio; CI, confidence interval; IQR, interquartile range; Hetero, heterosexual contact; IVDU, intravenous drug abuse; MSM, men who have sex with men; HAART, highly active antiretroviral therapy; CD4 ≤500, patients who had CD4 T-cell count ≤500 either at baseline or follow-up; CD4 >500, patients who had CD4 T-cell count >500 both at baseline and follow-up; HIV viral load >50, patients who had detectable HIV viral load >50 either at baseline or follow-up; HIV viral load <50, patients who had undetectable HIV viral load <50 both at baseline and follow-up.

Furthermore our logistic regression analysis supports the role of HIV suppression as an important predictor of persistent anti-HBs titers. Previous studies have also demonstrated that development of anti-HBs responses following HBV vaccination of HIV-infected patients was associated with undetectable HIV viral load.[6,20] Lower hepatitis B-specific memory B-cell responses, altered B-cell and memory B-cell phenotypes, and reduced memory B-cell proliferative capacity were observed in HIV viremic patients following HBV vaccination.[21] Increased regulatory T cells in HIV-infected patients were found to be associated with nonresponse to HBV vaccine.[22] In addition, an expansion of regulatory T cells has been reported in HIV-infected patients with high HIV viral load.[23] Our results in conjuncture with aforementioned literature further support the notion that maintaining optimal HIV load suppression after double-dose HBV rescue vaccination may play a critical role in persistence of protective anti-HBs titers.

The long-term protective effect of HBV vaccine in HIV-infected patients remains unknown. A recent multicenter observational cohort study of 11,632 person-years of follow-up demonstrated that HIV-infected patients who had achieved a response to HBV vaccine with protective anti-HBs titers ≥10 mIU/mL had a 50% reduced risk of HBV infection compared to those with nonresponse to HBV vaccine. Of the patients with an initial positive HBV vaccine response, risk of HBV infection was

not different between those with waning or persistent vaccine responses. It is also interesting that of those vaccine responders who had developed acute HBV infection, none of them developed chronic HBV infection, suggesting benefit from positive response from HBV vaccination for at least 7 years of follow-up.[24] Also long-term memory B cells specific for hepatitis B surface antigen were found in HIV-infected patients with serum anti-HBs titer less than 10 mIU/mL.[25] Therefore, there could be still some benefit for protection against HBV infection even if protective levels of anti-HBs titers may decrease after successful response to double-dose HBV rescue vaccination in HIV-infected patients.

Our study has limitations, however, mostly stemming from its small sample size and its retrospective nature. Eleven of 44 double-dose HBV rescue vaccine responders were not available for one year follow-up evaluation, which might have affected assessment of the durability of persistent protective anti-HBs titers in double-dose HBV rescue vaccine responders. Although factors such as the level of CD4 T-cell count,[26] HAART,[27] and MSM[28] were shown to be associated with HBV vaccine response in HIV-infected patients, our study did not show significant association between these factors and persistence of protective anti-HBs titers. This might reflect one of limitations based on the small sample size due to retrospective nature, not true absence of association. Nonetheless, our cohort of patients might well represent urban HIV-infected patients with access to HIV care in the developed world such as the United States. Therefore, this study results should be of assistance to manage HBV vaccination in urban HIV-infected patients in the developed world.

In conclusion, double-dose HBV rescue vaccination in HIV-infected patients has demonstrated a higher seroconversion rate of protective anti-HBs titers. Protective levels of anti-HBs titers may decrease over time after successful double-dose HBV rescue vaccination. Optimizing HIV viral load suppression could improve the persistence of protective anti-HBs titers. Achieving protective levels of anti-HBs titers in HIV-infected patients, even if protective levels of anti-HBs titers are decreased, might conceivably provide important protection against chronic HBV infection, and double-dose HBV rescue vaccination should be considered in HIV-infected patients who never responded to conventional or booster HBV vaccination series. Further studies involving a larger number of patients are needed to define the best strategies for improving immune response to HBV vaccination in HIV-infected patients.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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