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**Abstract**

# Serological response to one intradermal or intramuscular hepatitis B virus vaccine booster dose in human immunodeficiency virus-infected nonresponders to standard vaccination

**Purpose:** Hepatitis B virus (HBV) vaccination is recommended for all human immunodeficiency virus (HIV)-infected patients without HBV immunity. However, serological response to standard HBV vaccination is frequently suboptimal in this population and the appropriate strategy for revaccination of HIV-infected nonresponders remained controversial. We aimed to determine the serological response to one booster dose of HBV vaccine given by intradermal (ID) or intramuscular (IM) route in HIV-positive nonresponders to standard HBV vaccination. **Materials and Methods:** In this study, 42 HIV-infected nonresponders were enrolled. We randomized them to receive either 10 µg (0.5 mL) for ID (20 cases) or 20 µg (1 mL) for IM (22 cases) administration of HBV vaccine as a one booster dose. After 1 month, anti-HBs titer was checked in all cases. A protective antibody response (seroconversion) defined as an anti-HBs titer  $\geq 10$  IU/L. **Results:** Seroconversion was observed in 47.6% of subjects after 1 ID dose. A total of 30% showed antibody titers above 100 IU/L. Except one case, all responders had  $CD4^+ > 200$  cells/mm<sup>3</sup>. Mean anti-HBs titer was  $146.5 \pm 246$  IU/L. After the one IM booster dose, seroconversion was observed in 50% of cases. A total of 36.3% of subjects had anti-HBs  $\geq 100$  IU/L. All responders had  $CD4^+ > 200$  cells/mm<sup>3</sup>, except one case. Mean anti-HBs titer was  $416.4 \pm 765.6$  IU/L. Responders showed significantly higher  $CD4^+$  cell counts, in

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comparison to nonresponders ( $P < 0.001$ ). **Conclusions:** One booster dose administered IM or ID to HIV-infected nonresponders resulted in similar rates of seroconversion, overall response rate 50%. However, higher anti-HBs titers observed more frequently in IM group.

**Key words:** Booster dose, hepatitis B virus vaccination, human immunodeficiency virus, intradermal, intramuscular, nonresponder

## INTRODUCTION

Because Human Immunodeficiency Virus (HIV) and hepatitis B virus (HBV) share similar routes of transmission, HIV/HBV coinfection rate is considerable (6.3-9.7%).<sup>[1-3]</sup> This coinfection is associated with higher HBV viremia, HBV reactivation, chronic HBV infection, cirrhosis and eight fold increase in liver-related mortality.<sup>[3,4]</sup> In addition, HBV also can affect HIV treatment as a result of hepatotoxicity of antiretroviral medicine.<sup>[5]</sup> Therefore, HBV vaccine is highly recommended to all asymptomatic HIV-infected patients without immunity to HBV according to current guideline.<sup>[6-8]</sup>

HIV-infected individuals have suboptimal response to HBV vaccine with immunogenicity rates varying from 17.5% to 72%.<sup>[9-11]</sup> High CD4<sup>+</sup> cell counts and low HIV viremia are important factors associated with proper hepatitis B vaccine response.<sup>[12]</sup>

It is not clear how nonresponders to HBV vaccine should be managed. Common practice is to administer a second course of three doses of intramuscular vaccine, but this approach has variable success.<sup>[13]</sup> Previous studies suggested that modification of the standard HBV vaccination schedule such as administering additional doses or doubling the standard antigen dose, or both, may be effective in increasing vaccine response.<sup>[11,14]</sup> An alternate approach is intradermal administration (ID) of HBV vaccine which facilitates the exposure of antigen to antigen-presenting cells, dendritic cells, and macrophages.<sup>[15-18]</sup>

However, few studies are performed in the setting of HBV revaccination schedules in HIV-infected nonresponders and the appropriate strategy in this population remains controversial.<sup>[11,17,19]</sup> Therefore, we aimed to determine the serological response to one booster dose of HBV vaccine given randomly by ID or intramuscular (IM) in two groups of HIV-infected patients who failed to response to standard HBV vaccination.

## MATERIALS AND METHODS

In this study, 42 HIV-infected patient who attend to triangular clinics (sexually transmitted infections, HIV/

AIDS, drug abuse) and failed to respond to standard three doses of IM HBV vaccination [anti-HBs titers  $< 10$  IU/L by enzyme-linked immunosorbent assay (ELISA) assay] were enrolled from January to September 2012. Duration between the standard HBV vaccination and booster dose was between 1 to 2 years. This project was approved by Arak University of Medical Sciences Ethical Committee and informed consent was obtained from patients prior to their enrollment. A questionnaire that gathered characteristic and laboratory data was completed by clinicians.

Patients were randomized into two groups. A total of 22 cases received one intramuscular injections of the standard dose 20  $\mu$ g (1 mL), and 20 individuals received one intradermal injection of 10  $\mu$ g (0.5 mL) recombinant HBV vaccine (Pasteur Institute of Iran, Tehran, Iran). One month later, a blood sample was taken for measuring hepatitis B surface antibody (anti-HBs) titer (Enzygnost, Dade Behring Marburg GmbH, Germany) by ELISA.

Hepatitis C antibody (anti-HCV) was also checked by ELISA in all samples. The used kit was Biorad, Segrate, Italy. Recombinant immunoblot assay (RIBA Innogenetics, Ghent, Belgium) was employed to confirm anti-HCV reactivity. CD4<sup>+</sup> cell counts was determined by flowcytometry and defined as cells/mm<sup>3</sup>.

### Definitions

Standard HBV vaccination includes administration of three intramuscular injections of the standard dose (20  $\mu$ g or 1 mL) of recombinant HBV vaccine at months 0, 1, and 6.

Nonresponders, defined as cases with anti-HBs titer  $< 10$  IU/L, were offered for revaccination.

Anti-HBs  $\geq 10$  IU/L was considered protective and anti-HBs  $\geq 100$  IU/L was considered fully protective.

### Statistical analysis

The Chi-square test was used with the SPSS 16 Package program for statistical analysis (Chicago, IL, USA). Data are presented as mean  $\pm$  standard deviation or, when indicated, as an absolute number and percentage.

In each group (IM, ID), individuals with adequate serological response compared with nonresponders respect to age, sex, CD4<sup>+</sup> cell counts, HCV infection, and use of antiretroviral therapy (ART).

## RESULTS

In this study 42 HIV-infected nonresponders were enrolled. The mean age of patients was  $33.3 \pm 1.08$  years. 57.1% of patients were males and 42.9% were females. The mean and median CD4<sup>+</sup> cell counts were  $454.5476 \pm 551.8$  and 267.5 cells/mm<sup>3</sup> respectively, and 31% of HIV cases had CD4<sup>+</sup>  $\leq 200$  cells/mm<sup>3</sup>. A total of 78.6% of patients received ART. Anti-HCV was positive in 38% of cases.

One IM or ID booster dose was administered to 22 and 20 HIV-infected nonresponders, respectively.

In ID group, mean CD4<sup>+</sup> cell counts of patients was  $693.9 \pm 723.6$  cells/mm<sup>3</sup>. Seroconversion was observed in 47.6% subjects after one ID dose. A total of 30% showed antibody titers above 100 IU/L, which was considered to be fully protective. Only one subject (5%) showed anti-HBs  $\geq 1000$  IU/L. From five cases with CD4<sup>+</sup>  $\leq 200$  cells/mm<sup>3</sup>, only one case responded to ID booster dose with anti-HBs titer of 35.8 IU/L. Anti-HCV was positive in 45% of ID group. Except one case, all responders had CD4<sup>+</sup>  $> 200$  cells/mm<sup>3</sup>. Mean anti-HBs titer was  $146.5 \pm 246$  IU/L.

In IM group, mean CD4<sup>+</sup> cell counts of patients was  $237 \pm 128.8$  cells/mm<sup>3</sup>. After the one IM booster dose, a protective antibody response was observed in 50% of cases. Fully protective antibody was detected in 36.3% of subjects. A total of three subjects (13.6%) showed anti-HBs  $\geq 1000$  IU/L. HCV infection was seen in 31.8% of IM group. From eight cases with CD4<sup>+</sup>  $\leq 200$  cells/mm<sup>3</sup>, only one case responded to IM booster dose (anti-HBs  $\geq 1000$  IU/L). All responders had CD4<sup>+</sup>  $> 200$  cells/mm<sup>3</sup>, except one case. Mean titer of anti-HBs was  $416.4 \pm 765.6$  IU/L.

There was not any significant difference between responders and nonresponders except for CD4<sup>+</sup> cell counts. Responders showed significantly higher CD4<sup>+</sup> cell counts, in comparison to nonresponders ( $P < 0.001$ ).

Both intramuscular and intradermal booster dose improved serological response in HIV-infected patients who failed to response to standard HBV vaccination. But there was not any significant difference in respect to anti-HBs response rate and titer between IM and ID groups. Although, IM group with lower CD4<sup>+</sup> cell counts, showed higher anti-HBs titer.

The vaccine was well-tolerated in all patients with no side effects.

## DISCUSSION

The present study investigated the results of two routes of booster dose rechallenge in HIV-infected patients not responding to their initial vaccination. This survey showed improves in the response rate (overall 50%) after both intramuscular and intradermal booster dose of HBV vaccine. IM group with lower CD4<sup>+</sup> cell counts showed higher anti-HBs titer and a little more seroconversion rate than ID group. Overall responders showed significantly higher CD4<sup>+</sup> cell counts, in comparison to nonresponders.

There are several clinical trials regarding HBV vaccination by ID route in health care workers, hemodialysis patients, and kidney transplant recipients with suboptimal response to vaccine.<sup>[15,16,20]</sup> But few data exist regarding HBV vaccination by ID route in HIV-infected individuals. Shafran *et al.*,<sup>[17]</sup> administered 0.25 mL HBV vaccine ID every 2 weeks in four doses in HIV-infected nonresponders with history of failure to prior HBV vaccination and found 50% antibody response. In a study by Ristola *et al.*,<sup>[21]</sup> ID route induced protective immunity in 50% of six HIV-infected subjects not responding to standard IM schedule. Launay *et al.*,<sup>[14]</sup> data showed that primary HBV vaccination with 4  $\mu$ g ID for four times is significantly more efficient than the standard HBV vaccination (77% versus 65% respectively). Therefore, taken together it seems that ID route can improve seroconversion rate in HIV-infected subjects who failed to respond to primary vaccination.

Revaccination with intramuscular booster dose in HIV-infected nonresponders was investigated in some studies. Rey *et al.*,<sup>[11]</sup> data indicated that rechallenging of HIV-infected nonresponders (to initial HBV vaccination) with three additional monthly injections could be effective (77.7%). In a study conducted by Bunupuradah *et al.*,<sup>[18]</sup> on HIV-infected children which 64% of them had received HBV vaccine during infancy, only 56.1% of the ID arm had good response to vaccine compared to 82.1% in the IM arm. Besides, a study in the Netherlands showed HBV revaccination with double dose of vaccine intramuscularly at 0, 1, and 2 months was effective in 50.7% of 144 HIV-infected nonresponders.<sup>[19]</sup> Another study by Cruciani *et al.*,<sup>[22]</sup> showed response rate of 60% after primary vaccination with double dose of HBV vaccine (40  $\mu$ g or 2 mL at 0, 1, and 2 months) and higher response rate (89.2%) after 1-3 booster doses in HIV-infected patients. In a recently published study, HIV patients received four doses (40  $\mu$ g) of HBV vaccine for primary

**Table 1: Studies comparing response rates of two routes of hepatitis B virus vaccine booster regimen in human immunodeficiency virus-positive nonresponders to standard HBV vaccination**

Study ID	Route of booster administration	Response rate (%)
Shafraan <i>et al.</i> (Canada)	ID every 2 weeks in four doses	50
Ristola <i>et al.</i> (Finland)	ID in three doses	50
Rey <i>et al.</i> (France)	IM in three doses monthly	77.7
de Vries-Sluijs <i>et al.</i> (Netherlands)	Double dose of IM in three times	50.7
Han <i>et al.</i> (China)	IM in three doses	85.3

ID=Intradermal, IM=Intramuscular, HBV=Hepatitis B virus

vaccination showed high seroconversion rate 82% versus standard schedule 65%.<sup>[14]</sup> Studies comparing response rates of two routes of HBV vaccine booster regimen in HIV positive nonresponders to standard HBV vaccination was shown in Table 1.

However, the optimal HBV revaccination schedule in HIV-infected nonresponders is still a subject of controversy. Our study is the first randomized trial which evaluate one dose of ID (0.5 mL) and IM (1 mL) as a booster dose vaccination in HIV-infected patients who failed to respond to initial HBV vaccination. However, our study has some limitations. First, the number of subjects was small. Second, we did not consider the effect of HIV viral load in this study. Third, despite to randomly HBV booster vaccination, patients with lower CD4 count were placed in IM group, so we could not compare two groups and draw a definite conclusion in respect to seroconversion rate and the best approach of revaccination.

## CONCLUSION

Our study revealed that one booster dose administered IM or ID to HIV-infected nonresponders was effective and resulted in similar rates of seroconversion, overall response rate 50%. The only significant finding associated with higher response rate was CD4<sup>+</sup> ≥200 cell/mm<sup>3</sup>. Despite to limitation of our study, higher antibody titers to HBV vaccine observed more frequently in IM group. However, further studies are needed to define the best approach to increase protective antibody responses to HBV immunization in the HIV setting.

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