

Efficacy and Safety of Hepatitis B Revaccination in HIV-infected Thai Children and Adolescents

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ABSTRACT

Introduction: There are limited data of efficacy and safety of recombinant hepatitis B vaccine (HBV) revaccination in HIV-infected children after immune recovery from antiretroviral therapy. Here, we reported the efficacy and safety of HBV manufactured based on purified hepatitis B surface antigen from yeast expression, *Pichia pastoris*, in HIV-infected Thai children.

Methods: HIV-infected children and adolescents, aged 5-20 years with current CD4 \geq 200 cells/mm³, HIV-RNA below 20 copies/mL, and had antiHBs < 10 mIU/mL were enrolled. The HBV were administered intramuscularly at months 0, 2, and 6. The antiHBs titer was evaluated within 6 months after completion of 3-dose HBV. The antiHBs titer \geq 10 mIU/mL was defined as protective antibody and \geq 100 mIU/mL was defined as high antibody response.

Results: Eighteen HIV-infected adolescents; median (IQR) age was 11.9 (7.3-15.1) years, nadir CD4 was 311 (154-971) cells/mm³, current CD4 cell count was 741 (583-982) cells/mm³ were enrolled. Median (IQR) time received antiretroviral therapy was 8.7 (4.8-12.0) years. After received HBV, 18 (100%) had protective antiHBs and 16 (89%) adolescents were good responders. No serious adverse event was reported.

Conclusion: HIV-infected children and adolescents in this study had a good antibody response to HBV revaccination. HIV-infected children who had immune recovery from antiretroviral therapy and suppressed HIV-RNA should be considered for HBV revaccination. (*J Infect Dis Antimicrob Agents* 2015;32:113-8.)

Keywords: hepatitis B vaccine, revaccination, HIV-infected adolescents, antiretroviral therapy, antiHBs

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INTRODUCTION

In Thailand, the routine National hepatitis B vaccine (HBV) program was launched in 1992. The recommended HBV course consists of 3 vaccinations at birth, and 2 and 6 months after birth. In general, perinatally HIV-infected children also received a course of HBV from this National HBV program. However, majority of HIV-infected children lost their protective antibody levels to hepatitis B despite history of completed HBV immunization and evidence of immune recovery on highly active antiretroviral therapy (HAART).¹

The Thai HIV guideline recommends HBV revaccination after HIV-infected children were started HAART and had immune recovery. Hepatitis B vaccine is routinely recommended in HIV-infected children via intramuscular administration (IM).² The good responses to hepatitis B re-vaccination in HAART-treated children were reported.³⁻⁵

In this study, we used a recombinant HBV manufactured based on purified hepatitis B surface antigen from yeast expression using Methylophilic yeast, *Pichia pastoris*.^{6,7} There are limited data of efficacy and safety of this recombinant HBV in HIV-infected patients. Here, we reported the efficacy and safety of HBV in HIV-infected children.

MATERIAL AND METHODS

This report included HIV-infected children and adolescents who had history of completed 3 doses of HBV. The inclusion criteria were HIV-infected children and adolescents, aged 5-20 years with current CD4 \geq 200 cells/mm³, HIV-RNA below 20 copies/mL and had no protective antibody to hepatitis B virus, which defined as antiHBs < 10 IU/mL at enrollment

The children's weight (kg), height (cm), HIV clinical classification⁸, HAART, CD4% and CD4 cell count, and

plasma HIV-RNA were reported. Plasma HIV-1 RNA was performed by the Cobas Ampliprep/Cobas AMPLICOR HIV-1 Ultrasensitive test, version 2.0 (Roche Molecular Systems, Inc., Branchburg, NJ, 08876 USA) with a level of detection of 20 copies/mL.

Hepatitis B vaccine and serologic test

The vaccine used in this study during 2013-2014 was recombinant HBV manufactured by Center for Genetic Engineering and Biotechnology (CIGB), Cuba and distributed by Pharmadica Ltd., Thailand. This HBV is a recombinant HBV which manufactured based on purified hepatitis B surface antigen from yeast expression using *Pichia pastoris*.^{6,7} Each 1 mL of vaccine contained 20 microgram of HBsAg. The doses were 10 microgram/dose for children age less than 10 years, and 20 microgram/dose for adolescent age 10 years and above. The vaccines were administered intramuscularly at months 0, 2, and 6.

AntiHBs was evaluated within 6 months after completion of 3-dose HBV. AntiHBs was measured by Microparticle Enzyme Immunoassay (MEIA), Abbott AxSYM system (Wiesbaden, Germany) at the HIV-NAT laboratory which was qualified by the external quality control program from the External Quality Assessment Scheme in Clinical immunology (EQAI), Thailand and the College of American Pathologists (CAP).

Definitions^{5,9}

- Non-responders were defined as children with antiHBs 0-10 mIU/mL.
- Protective antiHBs level or responsiveness to HBV was defined as antiHBs \geq 10 mIU/mL.
- Good responders were defined as children with antiHBs \geq 100 mIU/mL.

This study was conducted at HIV-NAT, the Thai

Red Cross AIDS Research Centre, Bangkok, Thailand in children who enrolled in the HIV-NAT 015 pediatric study¹⁰; (Clinicaltrials.gov identification number NCT00476606). All caregivers signed written informed consent

Statistical analysis: Data were summarized by median and interquartile range (IQR), geometric mean and (95% confidence interval), mean and standard deviation (SD), or proportions as appropriate. All analyses were undertaken using STATA 11.1 (StataCorp. 2009. Stata Statistical Software: Release 10. College Station, TX: StataCorp LP).

RESULTS

Eighteen HIV-infected children were included in this report. The median (IQR) nadir CD4 was 311 (154-971) cells/mm³. Number of children with CDC (Center for Diseases Control and prevention) classification N:A:B:C were 6:4:4:4. None had history of active opportunistic infection at enrolment. All children were on HAART; 10 used lopinavir/ritonavir-based regimens, 6 used nevirapine-based regimen, and 2 used efavirenz-based regimen. Number of children using the first-line, and second-line antiretroviral therapy was 13, and 5 children, respectively. Median (IQR) time received antiretroviral therapy before the first dose of HBVV was 8.7 (4.8-12.0) years. Median (IQR) duration of HIV-RNA < 50 copies/mL before the first dose of HBVV was 2.7 years (0.5-5.4) years. The median (IQR) current CD4 cell count was 741 (583-982) cells/mm³ (Table 1).

Immunogenicity of hepatitis B vaccination

All 18 children completed 3 doses of HBV and the scheduled antiHBs testing. The median (IQR)

interval of antiHBs testing after 3-dose of HBVV 123 (92-148) days. The geometric mean and median of antiHBs are shown in Table 2. All children had protective antiHBs. The total proportion of children who were good responders (antiHBs titer \geq 100 mIU/mL) was 16 (89%).

Safety of HBVV among HIV-infected children and adolescents

During the study, there were no deaths, progression of CDC clinical classification, fever, systematic adverse events, or serious adverse events related to HBVV. All children had HIV-RNA < 20 copies/mL with median (IQR) CD4 of 734 (663-1,012) cells/mm³ at their last visit in this study.

DISCUSSION

All children in this study had protective antiHBs antibody and no serious adverse reaction. From the previous publications have shown 70-92% of having protective antiHBs antibody to HBVV re-vaccination in HIV-infected children after immune recovery from HAART.^{3,11,12} Rate of having protective antiHBs antibody in our study was higher than the previous publications^{3,11,12} is explained by all of the children used HAART, had high CD4 and undetectable HIV-RNA. The significantly associated factors for higher antiHBs titers in HIV-infected children were HAART use, higher CD4, and undetectable plasma HIV-RNA at time of HBVV.^{3,11,12}

From the previous reports, 1-24% of HIV-infected children who had completed hepatitis B vaccination during infancy had hepatitis B protective antibody.^{1,4,11,13} Therefore, among HIV-infected children who had immune recovery, CD4% \geq 15%, with undetectable HIV-RNA, should be considered for HBVV revaccination.

Table 1. Demographic characteristics of 18 HIV-infected children and adolescents.

Baseline characteristics	Total N=18
Mean (SD) age, years	11.7 (4.4)
Median (IQR) age, years	11.9 (7.3-15.1)
% female	61%
Mean (SD) weight, kilograms	34.4 (14.2)
Median (IQR) weight, kilograms	32.9 (19.4-50.0)
Mean (SD) height, centimeters	138.8 (19.8)
Median (IQR) height, centimeters	142.5 (120-155)
Number of children CDC classification N: A: B: C	6:4:4:4
Number of children using antiretroviral	
Lopinavir/ritonavir: nevirapine: efavirenz	10:6:2
Lamivudine: zidovudine: tenofovir disoproxil fumarate: abacavir: stavudine	18:10:5:1:1
Mean (SD) current CD4%	29.7 (6.1)
Median (IQR) current CD4%	29 (26-33)
Mean (SD) current CD4 count (cells/mm ³)	796 (313)
Median (IQR) current CD4 count (cells/mm ³)	741 (583-982)

CDC classification: Center for Diseases Control and prevention classification

Table 2. Antibody response to hepatitis B vaccine in HIV-infected children and adolescents after receiving hepatitis B vaccine revaccination.

	N=18
Geometric mean (95% confidence interval); mIU/mL	427.1 (225.9-807.5)
Median (IQR); mIU/mL	971.6 (225-1,000)
Proportion of children with protective antiHBs (≥ 10 mIU/mL) (%)	18 (100%)
Proportion of children who were good responders (≥ 100 mIU/mL) (%)	16 (89%)

We have several study limitations as 1) our study had limited number of children and adolescents, 2) we did not have the medical record of vaccination history during infancy of participants so we can't know exactly that all of participants completely received HBV vaccination. However, all of our

children in this study were born after the Thai government implemented universal HBV program, therefore, we assumed that all received HBV revaccination in our study, 3) we did not collect data of pain score.

Lao-Araya et al. reported 71% of HIV-infected

Thai children had protective antiHBs level at three years after the HBVV revaccination.¹⁴ The future study is to explore durability of antiHBs in these children.

In conclusion, our study showed that HIV-infected children and adolescents without severe immune suppression and suppressed HIV-RNA had a high antibody response to a recombinant HBVV from *Pichia pastoris* expression system. All had protective antiHBs titers. Hepatitis B re-vaccination should be considered for HIV-infected children and adolescents particularly after they have achieved immune recovery from HAART.

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