# Antibody Response to Hepatitis B Immunization in Infants Born to HIV-Infected Mothers

PIMOLRAT THAITHUMYANON, M.D.*,
PRAMOTE PRAISUWANNA, M.D.*,
KIAT RUXRUNGTHAM, M.D.**
SANTI PUNNAHITANANDA, M.D.*,
USA THISYAKORN, M.D. *,

**Abstract**

**Objectives :** To determine the antibody response of hepatitis B immunization begun at birth in HIV-1 exposed infants.

**Design :** Prospective, clinical trial.

**Site :** King Chulalongkorn Memorial Hospital, Bangkok, Thailand.

**Material and Method :** Seventy six infants born to HIV-1 seropositive mothers, who were not hepatitis B carriers, received three 10 microgram doses of recombinant DNA hepatitis B vaccine (Engerix B, Smith Kline, Belgium) in a 0, 1 and 6 month schedule. The first dose was given at birth. Serum hepatitis B surface antibody (Anti -HBs) was measured at age 3, 9 and 12 months. Anti-HBs levels were determined by enzyme-linked immunoassay using the commercial kits (AUSAB EIA diagnostic kits, Abbott Laboratories, Chicago, USA) Antibody titer ≥10mIU/ml was defined as seroconversion. HIV infection was diagnosed by a positive test of HIV antibody at age ≥18 months and/or by positive test of HIV polymerase chain reaction at age ≥3 months.

**Results :** There were 14 HIV-1 infected (group 1) and 62 HIV-1 non infected (group 2) infants enrolled in this study. Anti-HBs titers of group 1 infants were significantly lower than those of groups 2 infants at both 3 and 6 months after the 3rd dose of vaccine, (Mann Whitney *U* test, p=0.019 and 0.001 respectively). Ten infants in group 1 and 57 infants in group 2 had anti-HBs titer ≥10 mIU/ml. Their peak antibody titers were also noted at both 3 and 6 months after the 3rd dose of vaccine. Seroconversion rates were 71.4 per cent and 91.9 per cent in group 1 and 2 infants respectively, ($p<0.05$). Among the infants who had blood tests performed at age 12 months or 6 months after the 3rd dose of vaccine, anti-HBs titers declined in approximately 50 per cent of both groups of infants. There was a significantly higher percentage of seroconverters in group 1 who lost their protective titers than those in group 2, ($p<0.001$).

**Conclusion :** The results in this study suggested that HIV-1 infected infants have poor antibody response to hepatitis B immunization and the protection was less durable. A fourth dose of vaccine at 6 months after the 3rd dose may be necessary.

**Key word :** Anti HBs, Hepatitis B Vaccine, HIV Infected Infants, Seroconversion

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* Department of Pediatrics,
** Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

Hepatitis B is one of the major perinatal transmitted diseases with a high prevalence in South-east Asian countries. Thailand is an endemic area where the carrier rate in pregnant women is approximately 7 per cent(1). HIV-infected infants may be at increased risk of hepatitis B virus infection through perinatal transmission, exposure to HBV infected household contacts and exposure to blood products. Serious complications of hepatitis B disease include chronic hepatitis, acute fulminant hepatitis, cirrhosis and hepatic cancer. Immunization is an important public health measure to prevent this infection(2). Therefore, hepatitis B vaccine has been incorporated in the Expanded Program on Immunization (EPI) for every newborn including those born to HIV infected mothers, in Thailand, since 1992. Although, an antibody response to the vaccine has been demonstrated in children exposed to HIV infection, the response in HIV infected children is poor, ranged between 25 per cent and 41 per cent(3-7). Zuin et al(3) showed that HIV infected children developed geometric mean hepatitis B surface antibody titers (anti-HBs) lower than non infected cases, and they lost their antibodies more quickly than healthy children. However, the antibody response of HIV infected children to an immunization schedule started at birth was not conclusive. Few data are available for this group of infants. Therefore, the authors conducted a study in infants born to HIV seropositive mothers whose hepatitis B vaccinations were begun at birth, in order to determine the pattern of antibody response and the seroconversion rate of this immunization in both HIV infected and non infected infants.

## MATERIAL AND METHOD

Seventy six infants born to asymptomatic HIV-seropositive mothers were enrolled at King Chulalongkorn Memorial Hospital. All mothers were systematically screened on their first prenatal visit for hepatitis B surface antigenemia. They were not drug addicted and had no hepatitis B surface antigen. These mothers had received various kinds of prenatal antiretroviral drugs according to the protocol of each project on prevention of HIV-1 vertical transmission they had registered in. All infants were healthy at birth without congenital anomalies and had no evidence of vertical bacterial infection, based on clinical findings and appropriate culture. They did not receive immunoglobulin therapy throughout the study period. Recombinant DNA hepatitis B vaccine (Engerix B™, Smith Kline, Belgium) was given to the infants as a series of three 10 microgram doses. The first dose was administered within 12 hours after birth, and the second and third doses were given at 1 and 6 months after the first. The vaccine was administered intramuscularly in the anterolateral thigh. Venous blood was drawn from the infant at birth before vaccination at 3, 9 and 12 months of age for analysis of hepatitis B surface antibody (Anti-HBs). Serum was separated and stored at -70°C until analyses. Anti-HBs levels were determined by

enzyme-linked immunoassay with the use of commercially available kits (AUSAB EIA diagnostic kits, Abbott Laboratories, Chicago, IL, USA). Seroprotective level was defined as Anti-HBs titer ≥10 mIu/ml[8].

Infants were classified into 2 groups according to their HIV status. Infants with positive HIV-antibody in serum at ≥18 months of age and/or with at least one positive test by HIV polymerase chain reaction at 3 months or more were defined as the HIV-1 infected group (group 1). Group 2 or HIV-1 seroreverters or HIV-1 non infected infants were those with negative results of these two tests and had no AIDS defining clinical condition.

Written informed consent was obtained from the mothers or guardians. The study protocol was approved by the Ethics Committee of the Faculty of Medicine, Chulalongkorn University.

Statistical analyses were performed using SPSS FW software (SPSS Inc. Chicago, Il, USA). Comparison of the infants' birth weight was determined by Student's *t*-test. Mann-Whitney U test was used to compare the antibody response. Comparison on seroconversion rate was determined by Chi-square or Fisher exact test. P value less than 0.05 was considered as statistically significant.

## RESULTS

Of 76 studied infants, 14 were HIV-1 infected (group1) and 62 were not HIV-1 infected (group 2). All of them had received 3 doses of hepatitis B vaccine by age 6 months without any adverse effect. There were 40 boys and 36 girls, only one of them (in group 1) was premature (36 weeks gestation), the others were delivered at term. Mean ± SD of birth weight was 3,002 ± 402 gram, (range, 2,110-4,200 grams). Mean birth weight in both groups of infants were not statistically different, (3,023 ± 346 *vs* 2,998 ± 416 grams; p-value >0.05). Hepatitis B surface antibody (Anti-HBs) was determined in 45 infants at birth before 1st vaccination; one infant in group 1 and 44 infants in group 2. Anti-HBs was not detected in any of them. Anti-HBs titers of group 1 infants were significantly lower than those of group 2 infants at both 3 and 6 months after the 3rd dose of vaccine, (Mann Whitney *U*, p=0.019 and 0.001 respectively); (Table 1). Ten infants in group 1 and 57 infants in group 2 had peak anti- HBs titer ≥10 mIU/ml at 9 or 12 months of age, Four infants in group 1 and 5 infants in group 2 failed to develop protective antibodies at any time after vaccination. Therefore, seroconversion rates were 71.4 per cent and 91.9 per cent in group 1 and 2 infants respectively, (p<0.05). Among the infants who had blood tests performed at age 12 months (Table 2), anti-HBs titer declined in 4 out of 8 infants (50%) in group 1 and 27 out of 49 infants (55%) in group 2. But there were fewer infants in group 1 (1/5) with rising anti-HBs titer than those in group 2 (18/49), (p<0.05). Loss of their protective titers at age 12 months or 6 months after the 3rd dose of vaccine was noted in 3 of 5 infants in group 1 and only 2 of 45 in group 2, (p<0.001).

## DISCUSSION

The results of this study suggested that infants born to HIV-1 infected mothers had good response to the recommended dose of hepatitis B vaccine (10 microgram) when immunization was begun at birth. Seroconversion rate in HIV-1 seroreverters or non infected infants is 91.9 per cent which was consistent with previous studies in both healthy[9,10] and HIV-1 exposed infants[6,7]. Zuin et al[3] and Zuccotti et al[5] used a double dose of hepatitis B vaccine (20 microgram) and gained a higher response rate. Seroconversion rate in HIV-1 non infected children in their studies were 97 per cent and 100 per cent respectively. The authors think that for mass immunization, the scroconversion rate of the HIV-1 non infected infants in the present

**Table 1. HBs-antibody response in infants born to HIV-infected mothers.**

| Age (months) | Group 1 | | | Group 2 | | | P-value (Mann-Whitney *U*) |
|---|---|---|---|---|---|---|---|
| | N | Median titers (mIU/ml) | Range | N | Median titers (mIU/ml) | Range | |
| 3 (2 months after second dose) | 4 | 26.6 | 0-52.0 | 48 | 18.6 | 0-2,471.3 | >0.05 |
| 9 (3 months after third dose) | 12 | 27.8 | 0-382.3 | 50 | 241.6 | 0-8,056.6 | <0.05 |
| 12 (6 months after third dose) | 9 | 0.3 | 0-662.3 | 49 | 123.7 | 0-3,481.3 | <0.005 |

**Table 2. Outcome of hepatitis B immunization in infants born to HIV-infected mothers at 12 months of age.**

| Outcome | Group 1 | | Group 2 | | P-value ($\chi^2$) |
|---|---|---|---|---|---|
| | No. of infants | % | No. of infants | % | |
| Total seroconversion rate | 10/14 | 71.4 | 57/62 | 91.9 | <0.05 |
| Decreased anti- HBs titer | 4/8 | 50 | 27/49 | 55 | NS |
| Increased anti- HBs titer | 1/8 | 12.5 | 18/49 | 36.7 | <0.05 |
| Lost protective titer | 3/5 | 60 | 2/45 | 4.4 | <0.001 |

study should be acceptable. An increased dose of vaccine for every infant born to an HIV-1 infected mother may not be necessary.

For HIV-1 infected infants, the seroconversion rate in the present study (71.4%) was higher than other studies using a similar dose of vaccine (25%-41%)[4-7]. This is probably due to a lack of uniformity in the mean age of the infants and stage of HIV-1 infection in those studies. Diamante et al [4] reported a response rate of 25 per cent (6 out of 24) among HIV-infected children with the first vaccine dose administered at a mean age of 47 months. Rutstein et al[6] started the first dose at a mean age of 3.1 months and found a response rate of 36 per cent (5 of 14). Arrazola et al[7] found that 7 of 17 (41%) infected infants responded to the vaccine with the first dose given between less than 1 month and 32 months. The authors believe that the better response in our infants could be due to starting immunization before the infant's immune system has been damaged by the HIV disease. However, they did not respond to the vaccine as well as the non infected HIV-1 infants. Their magnitude of response was also significantly less than the non infected ones.

Most of the previous studies did not measure serial anti-HBs titers as was done in the present study. They measured the immune response at various times after the 3rd dose vaccination. So the peak of protective antibody level could not be determined. Three out of 5 infants (60%) in the HIV-1 infected group who were seroconverted, lost their antibody response at age 12 months compared to 2 of 45 infants (4.4%) in non infected HIV-1 group. It indicates that HIV-1 infected infants have suboptimal response to hepatitis B vaccine and their protective antibodies are less durable. A fourth dose of vaccine at age 12 months or 6 months after the 3rd dose may be necessary for these infants to prolong protection against hepatitis B infection. Some authors have suggested that after immunization with hepatitis B vaccine, some children might have an undetectable level of antibody but if hepatitis B infection should occur in these individuals, they would have sub-clinical infection without detectable hepatitis B surface antigen and the infection could be diagnosed only by the demonstration of antibody to hepatitis B core antigen (anti-HBc) or by a rise in anti-HBs titer[11-13]. Kohn et al[14] suggested that if the serologic testing of non-responders was performed more than 18 months after the last vaccine dose, they might not need to have a booster vaccine because these non responders might already have had initial high antibody titers which declined over time. Jack et al[15] assessed the level of vaccine-induced hepatitis B surface antibody in Gambian children and found that there was no absolute level of protection against infection but all children who attained a peak antibody response to vaccination of $\geq$10 mIU/ml were protected against carriage status of HBs antigen. The decline in the proportion of children who were surface antibody positive was marked after year four[15]. However, further studies are needed to determine the optimal vaccine dose and vaccination schedule to protect HIV-1 infected infants against hepatitis B infection.

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# การตอบสนองทางภูมิคุ้มกันภายหลังฉีดวัคซีนป้องกันโรคตับอักเสบจากไวรัส บี ในทารกที่เกิดจากมารดาติดเชื้อเอ็ชไอวี

*พิมลรัตน์ ไทยธรรมยานนท์, พ.บ.*, สันติ ปุณณะหิตานนท์, พ.บ.*, ปราโมทย์ ไพรสุวรรณา, พ.บ.*, อุษา ทิสยากร, พ.บ.*, เกียรติ รักษ์รุ่งธรรม, พ.บ.***

งานวิจัยนี้ศึกษาผลการตอบสนองทางภูมิคุ้มกันต่อการฉีดวัคซีนป้องกันโรคตับอักเสบจากไวรัส บี จำนวน 3 เข็ม ในทารกเกิดจากมารดาติดเชื้อเอ็ชไอวีในโรงพยาบาลจุฬาลงกรณ์ โดยเริ่มให้ตั้งแต่แรกเกิด อายุ 1 และ 6 เดือน ด้วยวัคซีนชนิด recombinant DNA (Engerix B, Smith Kline, Belgium) ขนาดยา 10 ไมโครกรัม เพื่อเปรียบเทียบระดับภูมิคุ้มกันระหว่างทารกที่ไม่ติดเชื้อและทารกที่ติดเชื้อเอ็ชไอวีจากมารดา ตรวจวัดระดับภูมิคุ้มกันเมื่ออายุ 3, 9, 12 เดือนด้วยวิธี enzyme linked immunoassay โดยใช้ชุดตรวจ AUSAB EIA diagnostic kit (Abbott Laboratories, Chicago, USA) ระดับภูมิคุ้มกัน ≥10 หน่วยสากล/ลิตร เป็นระดับป้องกันโรคได้ (seroconversion) การวินิจฉัยว่าทารกติดเชื้อเอ็ชไอวีกระทำเมื่อผลตรวจ HIV antibody ในเลือดเมื่ออายุ ≥18 เดือนเป็นบวกและ/หรือผลตรวจ HIV polymerase chain reaction ในเลือดเป็นบวกเมื่ออายุ ≥3 เดือน ผลการศึกษาพบว่า จากจำนวนทารก 76 คน ที่มารดาไม่เป็นพาหะของโรคตับอักเสบจากไวรัสบี มี 14 คน ติดเชื้อเอ็ชไอวี (กลุ่ม 1) 62 คน ไม่ติดเชื้อเอ็ชไอวี (กลุ่ม 2) ทารกกลุ่ม 1 สร้างภูมิคุ้มกันได้ในระดับต่ำกว่าทารกกลุ่ม 2 อย่างมีนัยสำคัญทางสถิติที่ 3 และ 6 เดือนหลังฉีดวัคซีนเข็มที่ 3 (Mann-Whitney *U*, p=0.019 และ 0.001 ตามลำดับ) ทารก 57 จาก 62 คน (91.9%) ในกลุ่ม 2 มีระดับภูมิคุ้มกันที่ป้องกันโรคได้ (seroconversion) เมื่อเปรียบเทียบกับทารกในกลุ่ม 1 ที่มีเพียง 10 ใน 14 คน (71.4%) ซึ่งต่างกันอย่างมีนัยสำคัญทางสถิติ (p<0.05) ประมาณครึ่งหนึ่งของจำนวน ทารกในทั้ง 2 กลุ่มมีระดับภูมิคุ้มกันลดลงเมื่ออายุ 1 ปีและอัตราส่วนทารกกลุ่ม 1 ที่สูญเสียระดับภูมิคุ้มกันที่ป้องกันโรคได้มีมากกว่าทารกกลุ่ม 2 อย่างมีนัยสำคัญทางสถิติ (p<0.001) สรุปได้ว่าทารกที่ติดเชื้อเอ็ชไอวีตอบสนองต่อวัคซีนโรคตับอักเสบไวรัสบีไม่ดีเท่าทารกที่ไม่ติดเชื้อและสูญเสียระดับภูมิคุ้มกันที่ป้องกันโรคได้มากกว่า

**คำสำคัญ** : ระดับภูมิคุ้มกัน, วัคซีนป้องกันโรคตับอักเสบจากไวรัส บี, ทารกติดเชื้อเอ็ชไอวี, การตอบสนองต่อวัคซีน

**พิมลรัตน์ ไทยธรรมยานนท์, สันติ ปุณณะหิตานนท์, ปราโมทย์ ไพรสุวรรณา, อุษา ทิสยากร, เกียรติ รักษ์รุ่งธรรม**
**จดหมายเหตุทางแพทย์ ฯ 2545; 85: 277-282**

* ภาควิชากุมารเวชศาสตร์,
** ภาควิชาอายุรศาสตร์, คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย, กรุงเทพ ฯ 10330