# Isolated Antibody to Hepatitis B Core Antigen in HIV-1 Infected Patients and a Pilot Study of Vaccination to Determine the Anamnestic Response

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***Background:*** *Isolated antibody to hepatitis B core antigen (anti-HBc) is frequently found in HIV-infected patients. The present study aimed to determine the prevalence and risk factors of isolated anti-HBc and the anamnestic response to hepatitis B vaccination in this population.*
***Material and Method:*** *HIV-infected patients who visited Ramathibodi Hospital in May 2006 were included to test hepatitis B serology. Subjects with isolated anti-HBc were given hepatitis B vaccine and tested for anti-HBs.*
***Results:*** *Of 140 patients, 28 (20%) had isolated anti-HBc. From multivariate analysis, IVDU (OR 30.8, $p < 0.001$) and anti-HCV seropositive (OR 6.7, $p = 0.002$) were independent risk factors for isolated anti-HBc. Two from 28 (7%) patients who received vaccine had a response to vaccination.*
***Conclusion:*** *Prevalence of isolated anti-HBc among Thai HIV-infected patients was 20%. Risk factors of isolated anti-HBc were IVDU and anti-HCV seropositive. Anamnestic response to hepatitis B vaccination was low. Further study with strategies to improve the response of vaccination is needed.*

***Keywords:*** *Anti-HBc, HBV, Hepatitis B, HIV, Vaccination*

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Hepatitis B virus (HBV) infection is a common co-infection in HIV-1 infected patients with 70-90% of HIV-1 infected individuals having evidence of past or active infection with HBV[1-3]. The course of acute HBV infection may be modified in the presence of HIV with lower incidence of icteric illness and a higher HBV carriage rate of about 25% compared with about 5% in those uninfected with HIV[4,5]. In chronic infection, markers of HBV replication appear to be influenced by HIV infection. There is a trend toward lower rate of clearance of the hepatitis B "e" antigen (HBeAg) and HBV DNA as well as a significant increase in the serum HBV DNA viral load[6,7]. Symptomatic reactivation and loss of anti-HBs is uncommon in HIV-1 infected individuals[3,4]. Asymptomatic reactivation or reinfection occurs frequently in patients who develop AIDS, leading to a significantly higher prevalence of seropositive for hepatitis B surface antigen (HBsAg)[4].

Standard guidelines for HIV care recommends that all HIV-1 infected individuals should be tested for HBV infection in part to determine which individuals should receive vaccination for HBV[8]. However, isolated antibody to hepatitis B core antigen (anti-HBc) is frequently found in HIV-1 infected patients and it is difficult to determine the significance. Isolated anti-HBc may represent either 1) resolved HBV infection with loss of antibody to hepatitis B surface antigen (anti-HBs), 2) occult chronic HBV infection with levels of HBsAg below the limits of detection, or 3) a false positive test result of anti-HBc.

From previous studies in the United States and Europe, the prevalence of isolated anti-HBc varies from 14 to 45% and positive test for HCV antibody is a significant risk factor[9-12]. These findings suggest that HCV co-infection is common in HIV-1 infected patients

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with isolated anti-HBc. HCV co-infection might suppress antibody production or even viral replication, thus leading to the persistent anti-HBc positive state but negative for HBsAg and anti-HBs[10]. Vaccination in isolated anti-HBc in non HIV-infected patients had an anamnestic response 41.6%[13]. Unfortunately, vaccination in HIV-1 infected patients had such a response in only 24%[14]. Although HBV infection is generally more common in Asian populations, there is no data regarding the prevalence of isolated anti-HBc and response to vaccination in Asian HIV-1 infected population. The present study aimed to determine the prevalence and associated risk factors of isolated anti-HBc in HIV-1 infected patients and the anamnestic response to hepatitis B vaccination in this population.

## Material and Method

HIV-1 infected patients who visited the Infectious Diseases Clinic in Ramathibodi Hospital in May 2006 were included in the present study. This study was approved by the Ethics Committee of the Faculty of Medicine Ramathibodi Hospital. Patients were informed and gave their consents. All subjects had undergone blood testing for HBsAg (Architect i2000 SR, ELISA, Abbott Laboratories, USA), anti-HBs and anti-HBc (Vitros ECi, chemiluminescence based ELISA, Johnson & Johnson, USA). Patients were defined as "isolated antibody to hepatitis B core antigen (isolated anti-HBc) if the results of HBsAg and anti-HBs antibody were negative and anti-HBc antibody was positive. These subjects with isolated anti-HBc were given one dose of 20- g recombinant hepatitis B vaccine (Hepavax-Gene , Greencross Vaccine Corp., Korea) by intramuscular injection. At the time of vaccination, the subjects' HIV-1 RNA levels (Amplicor HIV-1 Monitor test, Roche Molecular Diagnostics, USA), anti-HCV antibody testing (Architect i2000 SR, ELISA, Abbott Laboratories, USA), and CD4 cell counts by flow-cytometry method were measured. Patients' demographics and characteristics such as age, gender, risk of HIV acquisition and history of AIDS defining illness and intravenous drug use (IVDU) were also collected. Anti-HBs antibody was tested again one month after hepatitis B vaccination. If the titer of anti-HBs was greater than 10 mIU/ml, it was considered that there was an anamnestic response.

The primary objective of the present study was to determine the prevalence rate of isolated anti-HBc in HIV-1 infected patients. The secondary objectives of interest were to determine the associated risk factors of isolated anti-HBc and the rate of anamnestic response to hepatitis B vaccination in HIV-1 infected patients with isolated anti-HBc. Data were described using mean $\pm$ standard deviation (SD) (or median and range where appropriate) and frequency (%) for continuous and categorical variables, respectively. Chi-square test (or Fisher's exact test where appropriate) was used to assess the association between categorical variables and isolated anti-HBc. Student t test was used to compare means and Mann-Whitney u test was used to compare medians between groups for continuous variables. Univariate analysis and multivariate analysis of potential risk factors where appropriated to find out the association with isolated anti-HBc. All analyses were performed using SPSS version 13. A *p* value less than 0.05 was considered to have statistically significant difference.

## Results

There were 140 patients with a mean age of 38.1 years and 59.3% were male. Table 1 summarizes the demographics and baseline clinical characteristics

**Table 1.** Clinical characteristics of 140 HIV-1 infected patients who had been tested for hepatitis B serology

| Characteristic | Number of patients (%) |
|---|---|
| Age, years, mean $\pm$ SD | 38.1 $\pm$ 8.1 |
| Gender | |
| Male | 83 (59.3) |
| Female | 57 (40.7) |
| Risk of HIV acquisition | |
| Sexual transmission | 129 (92.1) |
| Intravenous drug user | 7 (5.0) |
| Sexual transmission and intravenous drug user | 4 (2.9) |
| History of AIDS defining illness | |
| Yes | 74 (52.9) |
| No | 66 (47.1) |
| HCV infection status (n = 134) | |
| Positive | 16 (11.9) |
| Negative | 118 (88.1) |
| History of intravenous drug use (n = 139) | |
| Yes | 11 (7.9) |
| No | 128 (92.1) |
| Antiretroviral therapy | |
| Yes | 112 (80) |
| No | 28 (20) |
| $CD_4$ cell count, median cell/ l (range) | 300 (2-1371) |
| Plasma HIV RNA, copies/ml (n = 129) | |
| < 50 | 101 (78.3) |
| $\geq$ 50 | 28 (21.7) |

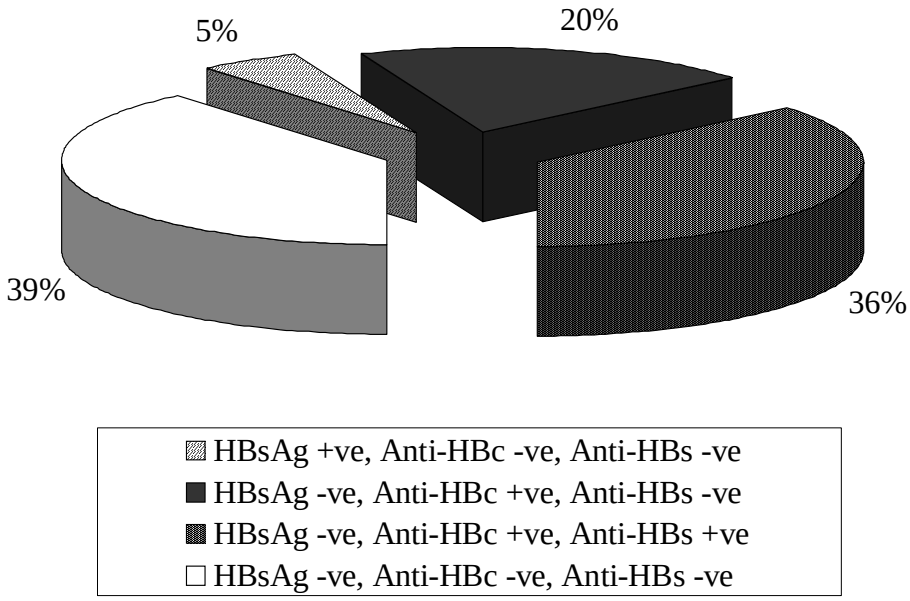


**Fig. 1** Hepatitis B serology of 140 HIV-1 infected patients who had been tested for hepatitis B serology

of all study patients. Of 140 patients, 28 (20%) had isolated anti-HBc and had undergone hepatitis B vaccination. The other groups of patients i.e. patients with negative results to all hepatitis B serology, patients with positive anti-HBs with or without positive anti-HBc and patients with positive HBsAg only are shown in Fig. 1.

The univariate analysis of clinical characteristics of patients with or without isolated anti-HBc is shown in Table 2. Patients with isolated anti-HBc were more likely to have a history of IVDU (25% vs 3.6%, p = 0.001) and anti-HCV seropositive (32.1% vs 6.6%, p = 0.001). In a multivariate model, history of IVDU and anti-HCV seropositive were independently associated with isolated anti-HBc (adjusted odd ratio (OR), 30.8, p < 0.001 and OR 6.7, p = 0.002, respectively; Table 3). CD4 cell count, antiretroviral therapy and HIV RNA level were not associated with isolated anti-HBc.

Among 28 patients with isolated anti-HBc and received hepatitis B vaccine, only two patients (7%) had a response to vaccination with anti-HBs antibody titer of 24 and greater than 1000 mIU/ml. These two patients had a high CD4 cell count (> 800 cell/ l, Fig. 2) and an undetectable HIV RNA (< 50 copies/ml).

**Table 2.** Univariate analysis of potential risk factors associated with isolated anti-HBc in HIV-1 infected patients

| Characteristics or variables | Isolated anti-HBc | | p-value |
|---|---|---|---|
| | Yes (n = 28) | No (n = 112) | |
| Age, years, mean ± SD | 40.0 ± 6.5 | 37.6 ± 8.4 | 0.135 |
| Male gender, number (%) | 21 (75.0) | 62 (55.4) | 0.084 |
| History of intravenous drug use | 7 (25.0) | 4 (3.6) | 0.001 |
| History of AIDS defining illness | 16 (57.1) | 58 (51.8) | 0.675 |
| Positive anti-HCV antibody | 9 (32.1) | 7/101 (6.6) | 0.001 |
| Antiretroviral therapy | 21 (75.0) | 91 (81.3) | 0.440 |
| CD4 cell count, cell/ l, median (range) | 248 (7-932) | 312 (2-1371) | 0.277 |
| Subjects with HIV-1 RNA < 50 copies/ml, number (%) | 22 (78.6) | 79 (70.5) | 0.484 |

**Table 3.** Multivariate analysis of potential risk factors associated with isolated anti-HBc in HIV-1 infected patients

| Factors | Adjusted OR (95%CI) | p-value |
|---|---|---|
| History of intravenous drug use | 30.79 (3.45-274.68) | <0.001 |
| Positive anti-HCV antibody | 6.70 (2.12-21.15) | 0.002 |
| CD4 cell count | 1.00 (0.99-1.02) | 0.556 |
| Antiretroviral therapy | 0.87 (0.29-2.58) | 0.823 |

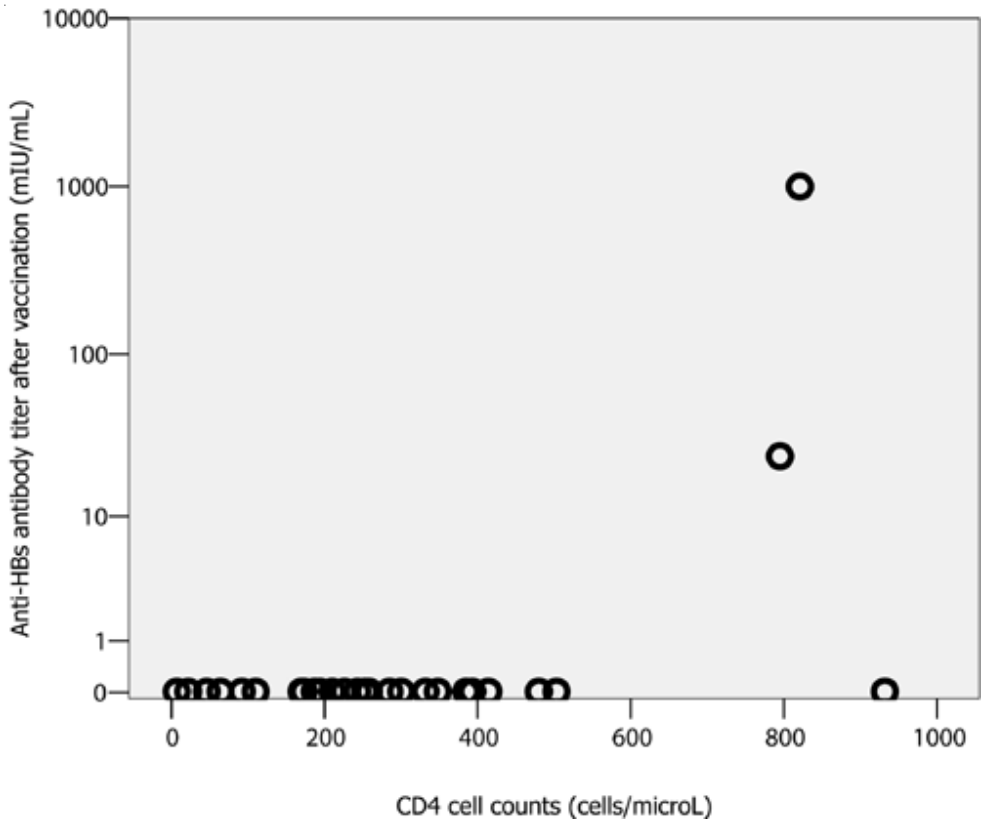


**Fig. 2** Anti-HBs antibody responses after hepatitis B vaccination and baseline CD4 cell counts in patients with isolated anti-HBc

## Discussion

The results from the present study have demonstrated that the prevalence of isolated anti-HBc among Thai HIV-1 infected patients was 20%, which is within the range of prevalence from the previous studies in Europe and the United States (14-45%)[9-12]. There are several possible explanations for the high prevalence of anti-HBc in HIV-1 infected individuals. First, subjects who have cleared HBV infection may loose detectable levels of anti-HBs antibody over time; as a result, such individuals will have isolated anti-HBc. This loss of anti-HBs antibody may be more frequent in subjects with HIV-infection because of an altered immune response. Second, the high frequency of isolated anti-HBc in HIV-1 infected individuals may reflect occult HBV infection particularly among individuals with a high risk for HBV infection, such as injection drug use (IVDU) or risky sexual behavior. Occult HBV infection in these individuals may manifest by having negative test results for HBsAg but positive results

for HBV DNA. The frequency of occult HBV infection in patients with isolated anti-HBc is controversial in which the rate varies from 0 to 60%[15]. Third, the patients were infected with mutant HBV, which cause seronegative for HBsAg[16]. Lastly, subjects with isolated anti-HBc who test negative for HBV DNA may have a false-positive test result for anti-HBc. However, this entity is uncommon; it has been reported in about 3% of patients with isolated anti-HBc[17].

The authors found that the factors significantly associated with isolated anti-HBc were history of IVDU and positive anti-HCV antibody. Gandhi et al[14] have recently described that anti-HCV positivity is associated with isolated anti-HBc. To date, the etiology of this association is still unclear. However, this association warrants it necessary to test for anti-HCV antibody in patients with isolated anti-HBc to identify HCV co-infection. Additionally, the present study also found that a history of IVDU was the significant factor associated with isolated anti-HBc. The previous study in Thailand had demonstrated that history of IVDU was associated with HCV co-infection[18]. Although these two factors can be related to one another, the results from multivariate analysis in the present study demonstrated that both factors are independently associated with isolated anti-HBc.

From the present study, anamnestic response to hepatitis B vaccination in HIV-1 infected patients with isolated anti-HBc was quite low. Gandhi et al[14] found that the anamnestic response to the first dose vaccination in HIV-1 infected patients with isolated anti-HBc was 24% (7 from 29 patients). They concluded that most of HIV-1 infected patients who had isolated anti-HBc did not have anamnestic response after vaccination. Previous studies by Ural and Findik[13] has shown that anamnestic response rate in non HIV-1 infected with isolated anti-HBc was 41.6%. Thus, HIV-1 infection may play a role on the immunologic response to hepatitis B vaccination. In the present study, HIV-1 infected patients who had a high CD4 cell count and undetectable plasma HIV RNA were likely to have anamnestic response. The authors could not determine this significance secondary to a nature of pilot study with a small sample size. Nevertheless, the data of hepatitis B vaccination in HIV-1 infected patients has demonstrated that a higher CD4 cell count and undetectable HIV RNA are associated with successful vaccination although the overall response rate is low[19,20].

There are limitations in the present study. First, the small sample size as a pilot study may limit the study to determine statistically the predicting factors for successful vaccination. However, the results from this pilot study can lead to the design of the study of hepatitis B vaccination in HIV1 infected patients with isolated anti-HBc, high CD4 cell count, and undetectable HIV RNA. Second, the authors did not test HBV DNA in the present study patients particularly those with isolated anti-HBc to determine the occult HBV infection secondary to the limited budget. However, the previous studies by Nunez et al and Acquitaine cohort[21-23] found that isolated anti-HBc in HIV-1 infected patients had occult HBV infection at only 0 and 0.6% respectively.

In conclusion, the prevalence of isolated anti-HBc among Thai HIV-1 infected patients was 20%. The risk factors significantly associated with isolated anti-HBc were a history of intravenous drug use and positive anti-HCV antibody. Anamnestic response to hepatitis B vaccination in Thai HIV-1 infected patients with isolated anti-HBc was quite low. Until additional data from the clinical studies is available, one-dose hepatitis B vaccination in HIV-1 infected patients with isolated anti-HBc is not recommended. A further large-scale study with strategies to improve the response of hepatitis B vaccination is needed.

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## *การมีแอนติบอดีต่อคอร์แอนติเจนตัวเดียวของไวรัสตับอักเสบบีในผู้ป่วยติดเชื้อเอชไอวีและการศึกษานำร่องถึงการให้วัคซีนเพื่อประเมิน การตอบสนองแบบที่เคยมีภูมิคุ้มกันมาก่อน*

***ยงยุทธ จงจิรวิศาล, ประยุทธ อังกูรไกรวิชญ์, สมนึก สังฆานุภาพ***

***วัตถุประสงค์:*** *การมีแอนติบอดีต่อคอร์แอนติเจนตัวเดียวของไวรัสตับอักเสบบีพบได้บ่อยในผู้ป่วยติดเชื้อเอชไอวี การศึกษานี้มีเป้าหมายที่จะประเมินความชุกและปัจจัยเสี่ยงของการมีแอนติบอดีต่อคอร์แอนติเจนตัวเดียวของไวรัสตับอักเสบบีในผู้ป่วยติดเชื้อเอชไอวีไทยและศึกษานำร่องถึงการให้วัคซีนเพื่อประเมินการตอบสนองแบบที่เคยมีภูมิคุ้มกันมาก่อนในประชากรกลุ่มนี้*

***วัสดุและวิธีการ:*** *ทำการศึกษาโดยตรวจทางซีโรโลจีต่อไวรัสตับอักเสบบีในผู้ป่วยติดเชื้อเอชไอวีที่ติดตามที่โรงพยาบาลรามาธิบดีในเดือนพฤษภาคม พ.ศ. 2549 ผู้ป่วยที่มีแอนติบอดีต่อคอร์แอนติเจนตัวเดียวของไวรัสตับอักเสบบีจะได้รับวัคซีนป้องกันตับอักเสบบี และตรวจระดับแอนติบอดีต่อเอสแอนติเจน*

***ผลการศึกษา:*** *จากจำนวนผู้ป่วย 140 ราย มี 28 ราย (ร้อยละ 20) ที่มีแอนติบอดีต่อคอร์แอนติเจนตัวเดียวของไวรัสตับอักเสบบี จากการวิเคราะห์แบบมัลติวาริเอทพบว่าประวัติการใช้ยาเสพติดฉีดเข้าเส้น (สัดส่วนออร์ด 30.8, ค่าพี < 0.001) และการมีแอนติบอดีต่อไวรัสตับอักเสบซี (สัดส่วนออร์ด 6.7, ค่าพี = 0.002) เป็นปัจจัยเสี่ยงอิสระของการมีแอนติบอดีต่อคอร์แอนติเจนตัวเดียวของไวรัสตับอักเสบบี ในผู้ป่วย 28 รายที่ได้รับวัคซีน มีเพียง 2 ราย (ร้อยละ 7) ที่ตอบสนองต่อวัคซีน*

***สรุป:*** *ความชุกของการมีแอนติบอดีต่อคอร์แอนติเจนตัวเดียวของไวรัสตับอักเสบบีในผู้ป่วยติดเชื้อเอชไอวีไทยคือร้อยละ 20 ปัจจัยเสี่ยงของการมีแอนติบอดีต่อคอร์แอนติเจนตัวเดียวของไวรัสตับอักเสบบีคือประวัติการใช้ยาเสพติดฉีดเข้าเส้นและการมีแอนติบอดีต่อไวรัสตับอักเสบซี การตอบสนองต่อวัคซีนป้องกันตับอักเสบบีแบบที่เคยมีภูมิคุ้มกันมาก่อนมีน้อย การศึกษาเพื่อหาวิธีในการให้วัคซีนที่ได้ผลกว่านี้มีความจำเป็น*