Prevalence, Risk Factors, and Impact of Isolated Antibody to Hepatitis B Core Antigen and Occult Hepatitis B Virus Infection in HIV-1–Infected Pregnant Women

Woottichai Khamduang,[1,2,3] Nicole Ngo-Giang-Huong,[1,2,4] Catherine Gaudy-Graffin,[3] Gonzague Jourdain,[1,2,4] Weerapong Suwankornsakul,[5] Tapnarong Jarupanich,[6] Veeradate Chalermpolprapa,[7] Sirisak Nanta,[8] Noossara Puarattana-aroonkorn,[9] Sakchai Tonmat,[10] Marc Lallemant,[1,2,4] Alain Goudeau,[3] and Wasna Sirirungsi,[1] for the Program for HIV Prevention and Treatment (PHPT-2) group[a]

[1]Faculty of Associated Medical Sciences, Chiang Mai University, and [2]Institut de Recherche pour le Développement UMI 174/Programs for HIV Prevention and Treatment, Chiang Mai, Thailand; [3]INSERM U966, CHU Tours, Faculté de Médecine, Université François-Rabelais, Tours, France; [4]Department of Immunology and Infectious Diseases, Harvard School of Public Health, Boston, Massachusetts; [5]Rayong Hospital, Rayong, [6]Hat Yai Hospital, Songkhla, [7]Nakhonpathom Hospital, Nakhonpathom, [8]Mae Sai Hospital, Chiangrai, [9]Nong Khai Hospital, Nong Khai, and [10]Mahasarakam Hospital, Mahasarakam, Thailand

Background. Prevalence and risk factors for isolated antibody to hepatitis B core antigen (anti-HBc) and occult hepatitis B virus (HBV) infection are not well known in human immunodeficiency virus type 1 (HIV-1)–infected pregnant women. It is unclear if women with occult infections are at risk of transmitting HBV to their infants.

Methods. HIV-1–infected and HBV surface antigen (HBsAg)–negative pregnant women were tested for antibody to HBsAg (anti-HBs) and anti-HBc using enzyme immunoassay. Women with isolated anti-HBc were assessed for occult HBV infection, defined as HBV DNA levels >15 IU/mL, using the Abbott RealTime HBV DNA assay. Infants born to women with isolated anti-HBc and detectable HBV DNA were tested at 4 months of age for HBV DNA. Logistic regression analysis was used to identify factors associated with isolated anti-HBc and occult HBV infection.

Results. Among 1812 HIV-infected pregnant women, 1682 were HBsAg negative. Fourteen percent (95% confidence interval [CI], 12%–15%) of HBsAg-negative women had an isolated anti-HBc that was independently associated with low CD4 count, age >35 years, birth in northern Thailand, and positive anti–hepatitis C virus serology. Occult HBV infection was identified in 24% (95% CI, 18%–30%) of women with isolated anti-HBc, representing 2.6% (95% CI, 1.9%–3.5%) of HIV-1–infected pregnant women, and was inversely associated with HIV RNA levels. None of the women with isolated anti-HBc and occult HBV infection transmitted HBV to their infants.

Conclusions. HIV-1–infected pregnant women with isolated anti-HBc and occult HBV infection have very low HBV DNA levels and are thus at very low risk to transmit HBV to their infants.

Keywords. HIV-1–infected pregnant women; isolated anti-HBc; occult HBV infection; perinatal transmission.

Over the past decade, individuals with isolated antibody to hepatitis B core antigen (anti-HBc) serology (ie, anti-HBc positive in the absence of detectable hepatitis B surface antigen [HBsAg] and hepatitis B surface antibody [anti-HBs]) have drawn much attention to their management because they are potentially infectious. Indeed, transmission of hepatitis B virus (HBV) from isolated anti-HBc individuals has been reported following sexual contact [1], blood transfusion [2], organ transplantation [3], or during the perinatal

period [4]. Furthermore, immunosuppressed patients with isolated anti-HBc can reactivate HBV replication following therapies or infectious diseases [5]. The clinical significance of this serology pattern remains unclear. Although the majority of individuals with this serology pattern present with normal liver enzyme levels and no sign of liver disease, it has been observed in patients presenting with cirrhosis and hepatocellular carcinoma [6, 7] and has been associated with a significantly shorter survival in patients infected with human immunodeficiency virus (HIV) as compared to those with anti-HBs antibody [8]. Moreover, the Multicenter AIDS Cohort Study reported a 3.6-fold increased risk of non-AIDS-related deaths in HIV-infected men with isolated anti-HBc compared to those without HBV infection [9]. The prevalence of isolated anti-HBc varies according to that of chronic HBV infection in the population; the rate among blood donors ranges between 1% and 4% [1, 10] in countries with low chronic HBV infection prevalence and between 1%–21% in high chronic HBV infection prevalence countries [11–13]. Higher isolated anti-HBc prevalence, ranging between 17% and 81%, has been found among HIV-infected [14–18] or hepatitis C virus (HCV)–infected individuals [19] and injection drug users [18, 20]. Individuals with isolated anti-HBc represent a heterogeneous population that comprises individuals who had completely cleared HBV infection but lost their anti-HBs antibody and those with occult HBV infection defined by the presence of HBV DNA in their serum and/or liver without detectable HBsAg, irrespective of other HBV serological markers [21]. The latter may present higher risk of transmission and liver disease progression.

Among HIV-infected patients, prevalence of occult HBV infection ranges between 0% and 89%, with most studies reporting HBV DNA values of <1000 IU/mL [22], and is much higher among individuals with isolated anti-HBc [23]. However, there are still very limited data on occult HBV infection in HIV-infected pregnant women and its impact on HBV transmission to their infants.

In this study, we assessed the prevalence and risk factors for isolated anti-HBc and occult HBV infection among a large number of HIV type 1 (HIV-1)–infected pregnant women in Thailand and evaluated the risk of HBV transmission to their infants.

MATERIALS AND METHODS

Study Population

The study population was derived from HIV-1–infected pregnant women who participated between 2001 and 2003 in a clinical trial conducted in Thailand that investigated the efficacy of zidovudine plus single-dose nevirapine to prevent mother-to-child transmission of HIV-1 (PHPT-2 [ClinicalTrials.gov identifier: NCT00398684]) [24]. Demographic, clinical, and biological

data were collected before enrollment and during the study. Maternal and infant blood samples were collected at entry and during study and plasma/sera were stored frozen. Only HBsAg-negative women were included in this study, which was approved by the Ethics Committee of the Faculty of Associated Medical Sciences, Chiang Mai University.

Analysis of HBV Infection Markers

Women were screened for HBsAg using an enzyme immunoassay of 250 pg/mL sensitivity (DiaSorin ETI-MAK-2, Salluggia, Italy). HBsAg-negative women were tested for anti-HBc (Monolisa anti-HBc PLUS) and anti-HBs (Monolisa anti-HBs PLUS, Bio-Rad Laboratories, Marnes La Coquette, France). Women positive for both anti-HBc and anti-HBs antibodies were considered as having resolved HBV infection; those with only anti-HBc were considered as having acquired HBV infection; those positive for anti-HBs only were considered as having received hepatitis B vaccine; and those negative for both anti-HBc and anti-HBs antibodies were considered as having not acquired HBV infection.

Women with isolated anti-HBc had HBV DNA quantified using the Abbott RealTime HBV DNA assay (Abbott France, Rungis, France; lower limit of detection of 15 IU/mL or 1.18 $\log_{10}$ IU/mL) and HBsAg verified using an HBsAg test kit of 50 pg/mL sensitivity (Monolisa HBsAg Ultra, Bio-Rad Laboratories) and able to detect up to 30 additional mutations on HBsAg proteins.

Infants born to women with isolated anti-HBc and detectable HBV DNA were tested at 4 months of age for HBV DNA using the Abbott RealTime HBV DNA assay. Children were followed up until 12 months of age.

HBV Sequencing

HBV sequencing was performed for women with detectable HBV DNA. HBV DNA was extracted from women's plasma using the automatic sample extraction system (Abbott M2000sp, Rungis, France). Ten microliters of HBV DNA extract was used as the template for nested polymerase chain reaction (PCR). Published primers were used to amplify HBV surface/polymerase region (nucleotide position 251 to 1058) [25]. Amplicons were sequenced using the BigDye Terminator Mix V. 1.1 (Applied Biosystems, Foster City, California) and the ABI PRISM 3100 Genetic Analyzer, and sequencing data were analyzed using the software Bioedit (version 7.0.9.0).

Statistical Analysis

Characteristics of women including age at enrollment, region of birth, prior pregnancies, alanine aminotransferase (ALT) level, white blood cells, lymphocytes, CD4+ and CD8+ T-cell counts, and the presence of antibodies against syphilis and hepatitis C virus were described using number and percentage for

categorical data and median with interquartile range (IQR) for continuous data. Univariate analyses were performed using logistic regression analysis to identify risk factors for having isolated anti-HBc or occult HBV infection. Continuous variables were transformed into categorical variables using common cutoff values. For multivariate analysis, all factors with a P value <.20 identified by univariate analysis were then introduced into the forward stepwise logistic regression model, to investigate independent risk factors associated with isolated anti-HBc serology or occult HBV infection. All data analyses were performed using Stata version 10.1 software (StataCorp, College Station, Texas). Differences were considered statistically significant if the P value was ≤.05.

RESULTS

Characteristics of Study Population

Of 1812 HIV-1–infected pregnant women, 1752 were found to be HBsAg-negative, of whom 1682 (96.0%) had sufficient samples to be included in this study (Figure 1). Baseline characteristics of HBsAg-negative women are described in Table 1. At enrollment, the median age was 26 years, median ALT level was normal, median HIV RNA load was 4.03 $\log_{10}$ copies/mL, and median CD4$^+$ and CD8$^+$ T-cell counts were 378 cells/µL and 915 cells/µL, respectively. One percent of women were anti–syphilis antibody positive and 5% were anti-HCV positive (Table 1). Women who were not included in this study because of insufficient samples had similar baseline characteristics: age of enrollment, ALT level, CD4$^+$ and CD8$^+$ T-cell counts, and HIV RNA load (data not shown).

HBV Serology Profile Among HBsAg-Negative, HIV-1–Infected Pregnant Women

Of 1682 HBsAg-negative women, 553 (33%; 95% CI, 31%–35%) had markers of resolved HBV infection (anti-HBc and anti-HBs positive), 229 (14%; 95% CI, 12%–15%) had marker of exposure to HBV (isolated anti-HBc), 68 (4%; 95% CI, 3%–5%) had marker of hepatitis B vaccine (anti-HBs positive only), and 832 (49%; 95% CI, 47%–52%) had no markers of exposure to HBV (anti-HBc and anti-HBs negative).

The prevalence of isolated anti-HBc antibodies differed according to the region of birth; the highest rate, 22%, was found in women born in the northern region of Thailand, whereas the lowest rate, 4%, was found in the southern region (Table 2). The rate of isolated anti-HBc in HIV-1–infected pregnant women increased with their age (Figure 2).

Factors Associated With Isolated Anti-HBc

Among all parameters analyzed, univariate analysis showed that age >35 years, birth in northern region, white blood cell count <7500 cells/µL, lymphocyte count <1000 cells/µL, CD4$^+$ T-cell count <350 cells/µL, and HCV infection were significantly associated with isolated anti-HBc serology in HIV-1–infected pregnant women (Table 3). After adjustment on all significant parameters, factors independently associated with isolated anti-HBc were age >35 years (adjusted odds ratio [AOR], 1.8; P = .029); birth in northern region (AOR, 1.8; P < .001); absolute CD4$^+$ cell count <350 cells/µL (AOR, 1.5; P = .02) and, much more significant, CD4$^+$ cell count <200 cells/µL (AOR, 2.8; P < .001); and exposure to HCV (AOR, 2.6; P = .001) (Table 3).

Prevalence of Occult HBV Infection Among HIV-1–Infected Pregnant Women With Isolated Anti-HBc

We first verified the absence of HBsAg in all women with isolated anti-HBc using a different HBsAg test kit. Of 228 women with available samples, 12 (5%) tested positive for HBsAg with the new test kit. Samples of all but 1 woman showed a low signal-to-cutoff ratio, ranging from 1.02 to 2.79 (median, 1.4 [IQR, 1.1–2.0]). Women with discrepant HBsAg results were then excluded from further analysis.

Among all 216 HIV-1–infected pregnant women with confirmed isolated anti-HBc serology, 200 had a sample available for HBV DNA quantification. All 200 women had HBV DNA <1000 IU/mL; 153 had HBV DNA below the limit of detection (15 IU/mL), 44 had HBV DNA level between 15–100 IU/mL, and 3 had HBV DNA between 101 and 1000 IU/mL. The prevalence of occult HBV infection among women with isolated anti-HBc was thus 23.5% (47/200; 95% CI, 18%–30%). Of 47 women with detectable HBV DNA (>15 IU/mL), 2 had successful HBV sequencing: one (16 IU/mL HBV DNA level) had sS117I, sT118K, and sR160K mutations (GenBank accession number: JX402002), and the other (117 IU/mL HBV DNA) had no S gene mutation (GenBank accession number: JX402003).

Factors Associated With Occult HBV Infection in HIV-1–Infected Pregnant Women With Isolated Anti-HBc Serology

Among all parameters analyzed, only HIV RNA level was inversely associated with occult HBV infection in HIV-1–infected pregnant women having isolated anti-HBc serological pattern (AOR, 0.2; P = .013; Table 4).

Assessment of HBV Infection in Infants Born to Mothers With Occult HBV Infection

We assessed HBV infection in infants born to 47 mothers with detectable HBV DNA (>15 IU/mL) at enrollment. No HBV DNA was detected in any of their infants at 4 months of age.

DISCUSSION

This is the first detailed analysis of HBV serologic markers among a large number of HIV-1–pregnant women. We have analyzed 3 variables associated with isolated anti-HBc profile
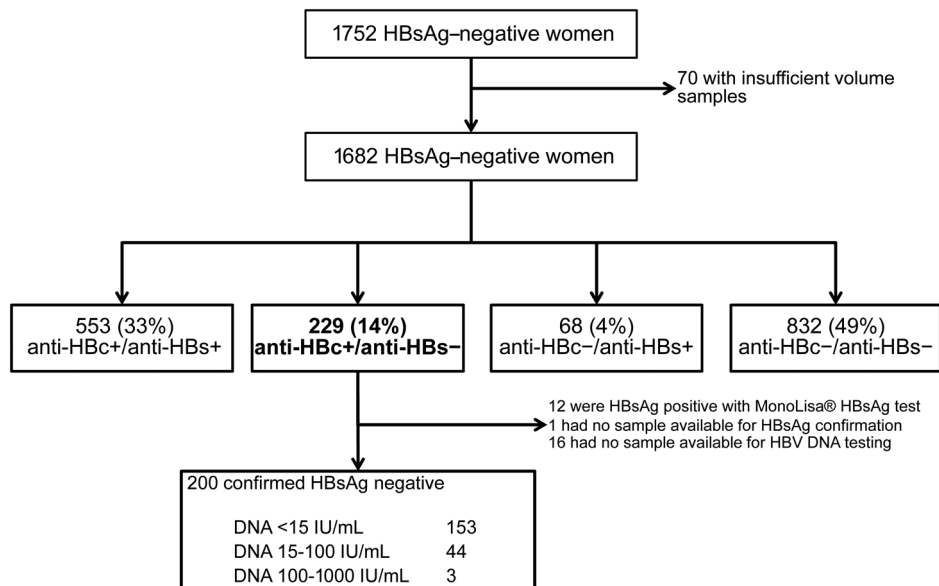
```
                    ┌─────────────────────────┐
                    │ 1752 HBsAg–negative women │
                    └─────────────────────────┘
                                 │        → 70 with insufficient volume
                                 │            samples
                    ┌─────────────────────────┐
                    │ 1682 HBsAg–negative women │
                    └─────────────────────────┘
```

| 553 (33%) anti-HBc+/anti-HBs+ | **229 (14%) anti-HBc+/anti-HBs−** | 68 (4%) anti-HBc−/anti-HBs+ | 832 (49%) anti-HBc−/anti-HBs− |

→ 12 were HBsAg positive with MonoLisa® HBsAg test
1 had no sample available for HBsAg confirmation
16 had no sample available for HBV DNA testing

200 confirmed HBsAg negative

DNA <15 IU/mL	153
DNA 15-100 IU/mL	44
DNA 100-1000 IU/mL	3

Figure 1. Overall study diagram. Abbreviations: anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to hepatitis B surface antigen; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen.

and occult HBV infection: prevalence, risk factors, and impact on perinatal transmission of HBV. Consistent with data from regions where vertical transmission of HBV has significant contribution, about half of HIV-1–infected pregnant women in

Table 1. Characteristics of HIV-1–Infected Pregnant Women Negative for Hepatitis B Surface Antigen

Characteristic	No.	Median (IQR) or No. (%)
Age at enrollment, y	1682	25.9 (22.7–29.7)
Region of birth	1682	
Central		373 (22)
Eastern		256 (15)
Northern		348 (21)
Northeastern		553 (33)
Southern		76 (5)
Western		76 (5)
Prior pregnancy	1678	1041 (62)
SGPT or ALT, IU/L	1638	15 (10–24)
WBC count, cells/µL	1652	8615 (7300–10 160)
Absolute lymphocyte count, cells/µL	1650	1805 (1430–2250)
Absolute CD4 count, cells/µL	1671	378 (245–531)
Absolute CD8 count, cells/µL	1634	915 (700–1193)
HIV RNA load, $\log_{10}$ copies/mL	1660	4.03 (3.37–4.65)
Anti-syphilis antibody positive	1649	17 (1)
Anti-HCV antibody positive	1659	75 (5)

Abbreviations: ALT, alanine aminotransferase; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range; SGPT, serum glutamic pyruvic transaminas; WBC, white blood cell.

our study showed HBV exposure markers. Fourteen percent had isolated anti-HBc. This rate is close to that observed among HIV-1–infected adults in Bangkok (20%) [20], northern areas (13%; S. Thongsawat, unpublished data), and other countries with high prevalence of chronic HBV infection [11–13].

About half of HIV-1–infected pregnant women had no HBV serological markers, indicating they are an HBV-susceptible population. Because immunization with HBV vaccine is strongly recommended for all HIV-infected individuals without immunity to HBV [26], our finding highlights the need for testing of all HIV-infected patients in order to vaccinate uninfected people who are not immune.

We identified several independent risk factors for isolated anti-HBc serological status in HIV-1–infected pregnant women: low CD4 count, age >35 years, and HCV infection. These factors have also been found in other populations, both HIV-infected [8, 22, 27] and HIV-uninfected [28]. Severe immunocompromised status, CD4 T-cell count <100 cells/µL, has been associated with loss of anti-HBs and development of isolated anti-HBc in HIV-positive patients [22]. The effect of age may be related to the progressive loss of anti-HBs producing capacity over time after resolution of HBV infection, or insufficient level of anti-HBs production [29]. We also found that being born in the northern region of Thailand was independently associated with isolated anti-HBc. Other studies have reported higher prevalence of HBsAg positivity in the northern region of Thailand as compared to the southern region [30–32], which may explain the rates of isolated anti-HBc observed

Table 2. Hepatitis B Virus Serological Status According to Region of Birth of Hepatitis B Surface Antigen–Negative Women

Status	Central	Eastern	Northern	Northeastern	Southern	Western	Total
Anti-HBc+/anti-HBs+	128 (34)	74 (29)	148 (43)	161 (29)	20 (26)	22 (29)	553 (33)
Anti-HBc+/anti-HBs−	38 (10)	31 (12)	77 (22)	69 (12)	3 (4)	11 (14)	229 (14)
Anti-HBc−/anti-HBs+	26 (7)	10 (5)	16 (5)	10 (2)	1 (1)	5 (7)	68 (4)
Anti-HBc−/anti-HBs−	181 (49)	141 (55)	107 (31)	313 (57)	52 (68)	38 (50)	832 (49)

Abbreviations: anti-HBc,antibody to hepatitis B core antigen; anti-HBs, antibody to hepatitis B surface antigen.

in our study. Our results are also consistent with other studies describing HCV infection as a main factor for isolated anti-HBc in both HIV-infected and -uninfected populations [1, 14, 17, 19, 20, 33], possibly as a result of the direct interference of HCV core protein on the synthesis of HBsAg [34, 35].

A wide range (0%–89%) of occult HBV infection has been reported in HIV-infected patients with isolated anti-HBc [22]. The heterogeneity of study populations and the usage of different sensitivity and specificity of HBV DNA assays may account for these discrepancies. In this study, we used a highly sensitive commercial technique to detect HBV DNA and were thus able to detect HBV DNA in 24% (47 of 200) of HIV-1–infected pregnant women with isolated anti-HBc serological profile. These rates of occult HBV infection are within the range found in isolated anti-HBc blood donors (4%–24%) of high-HBV-endemic areas such as India, Taiwan, Japan, and Sardinia [36]. When considering the whole population of HIV-1–infected pregnant women, the prevalence of isolated anti-HBc and occult HBV infection was 2.6% (47/1783; 95% CI, 1.9%–3.5%).

One intriguing observation was the inverse association between the detection of HBV DNA and HIV RNA concentrations. Unlike Lo Re et al [37] who found more frequently occult HBV infection in patients with HIV RNA >1000 copies/mL (17% in patients with a high HIV RNA level vs 4.6% in those with a low HIV RNA level, n = 179), we observed a higher rate of occult HBV infection in patients (n = 200) with low HIV RNA concentrations than in those with high HIV RNA level (42% vs 21%; *P* = .04). Possible explanations to this could be that 73% of patients in Lo Re et al's study were on highly active antiretroviral treatment, whereas in our study all women were naive to antiretroviral treatment. Further studies are needed to understand this discrepancy.

The clinical relevance of isolated anti-HBc and impact of low levels of HBV DNA in HIV-pregnant women with isolated anti-HBc are not well known. Walz et al recently reported that 7 of 105 infants born to women with isolated anti-HBc were infected with HBV, but none of the infants were positive for both HBsAg and HBV DNA. Interestingly, only 1 woman was HBV DNA positive [38]. In our study, the level of HBV DNA was <1000 IU/mL in 47 women with occult HBV infection, and none transmitted HBV to their infants.

Our study has several limitations. First, we quantified HBV DNA at only 1 time point, which may be insufficient as HBV DNA levels can fluctuate over time, depending on the phase of infection and host immune responses. However, pregnant
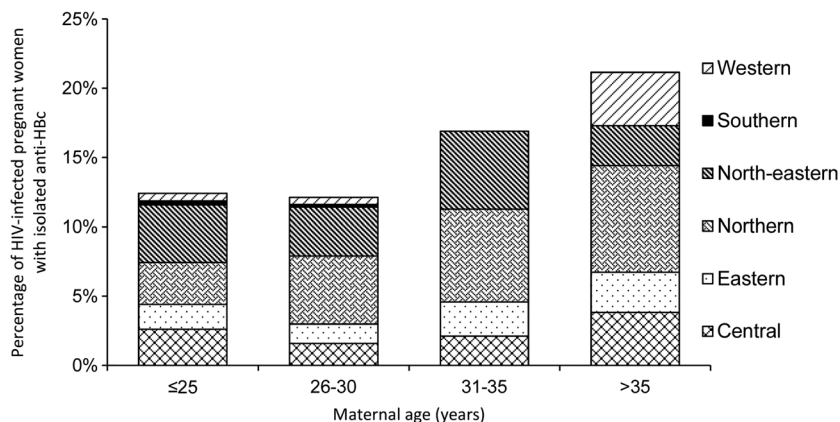

Figure 2. Age-related distribution of patients with isolated antibody to hepatitis B core antigen. Abbreviations: anti-HBc, antibody to hepatitis B core antigen; HIV, human immunodeficiency virus.

Table 3. Factors Associated With Isolated Antibody to Hepatitis B Core Antigen in HIV-1–Infected Pregnant Women

Parameter	Category	No.	Isolated Anti-HBc (%)	Univariate Analysis OR (95% CI)	P Value[a]	Multivariate Analysis OR (95% CI)	P Value[b]
Age at enrollment, y	≤25	725	90 (12)	1.0			
	26–30	569	69 (12)	1.0 (0.7–1.4)	.88		
	31–35	284	48 (17)	1.4 (1.0–2.1)	.06		
	>35	**104**	**22 (21)**	**1.9 (1.1–3.2)**	**.016**	**1.8 (1.1–2.9)**	**.029**
Region of birth	Central	373	38 (10)	1.0			
	Eastern	256	31 (12)	1.2 (.7–2.0)	.45		
	Northern	**348**	**77 (22)**	**2.5 (1.6–3.8)**	**<.001**	**1.8 (1.3–2.5)**	**<.001**
	Northeastern	553	69 (12)	1.3 (.8–1.9)	.29		
	Southern	76	3 (4)	.4 (.1–1.2)	.10	.4 (.1–1.1)	NS
	Western	76	11 (14)	1.5 (.7–3.1)	.28		
Prior pregnancy	No	637	83 (13)	1.0			
	Yes	1041	145 (14)	1.1 (.8–1.4)	.60		
ALT, IU/L	≤30	1437	190 (13)	1.0			
	31–60	168	25 (15)	1.1 (.7–1.8)	.55		
	>60	33	7 (21)	1.8 (.8–4.1)	.19		
WBC count, cells/µL	>10 000	440	44 (10)	1.0			
	7501–10 000	723	91 (13)	1.3 (.9–1.9)	.18		
	5001–7500	**442**	**78 (18)**	**1.9 (1.3–2.9)**	**.001**		
	≤5000	**47**	**10 (21)**	**2.4 (1.1–5.2)**	**.02**		
Absolute lymphocyte count, cells/µL	>2000	624	74 (12)	1.0			
	1501–2000	533	63 (12)	1.0 (.7–1.4)	.98		
	1001–1500	349	52 (15)	1.3 (.9–1.9)	.18		
	≤1000	**144**	**33 (23)**	**2.2 (1.4–3.5)**	**.001**		
Absolute CD4+ T cell count, cells/µL	>500	489	44 (9)	1.0			
	351–500	423	43 (10)	1.1 (.7–1.8)	.55		
	201–350	**446**	**65 (15)**	**1.7 (1.1–2.6)**	**.009**	**1.5 (1.1–2.2)**	**.02**
	≤200	**313**	**76 (24)**	**3.2 (2.2–4.9)**	**<.001**	**2.8 (2.0–4.0)**	**<.001**
Absolute CD8+ T-cell count, cells/µL	>1500	179	21 (12)	1.0			
	1001–1500	489	58 (12)	1.0 (.6–1.7)	.96		
	501–1000	835	119 (14)	1.3 (.8–2.1)	.38		
	≤500	131	24 (18)	1.7 (.9–3.2)	.11		
HIV RNA load, log$_{10}$ copies/µL	Undetectable	42	5 (12)	1.0			
	1.18–3.00	216	23 (11)	.9 (.3–2.5)	.81		
	3.01–4.00	552	75 (14)	1.2 (.4–3.1)	.76		
	4.01–5.00	659	85 (13)	1.1 (.4–2.9)	.85		
	>5.00	191	38 (20)	1.8 (.7–5.0)	.23		
Anti-syphilis antibody	No	1632	220 (13)	1.0			
	Yes	17	2 (12)	.9 (.2–3.8)	.84		
Anti-HCV antibody	No	1584	202 (13)	1.0			
	Yes	**75**	**23 (31)**	**3.0 (1.8–5.1)**	**<.001**	**2.6 (1.5–4.3)**	**.001**

Boldface text indicates significant values (≤.05).

Abbreviations: ALT, alanine aminotransferase; anti-HBc, antibody to hepatitis B core antigen; CI, confidence interval; HCV, hepatitis C virus; HIV-1, human immunodeficiency virus type 1; NS, not significant; OR, odds ratio; WBC, white blood cell.

[a] Logistic regression analysis was used.

[b] Multivariate logistic regression analysis was used.

women have been shown to have stable HBV DNA levels, with slight increases during late pregnancy [39], likely due to their relative immune-suppressed state. In our study, HBV DNA was measured in pregnant women during the last trimester. Our results are thus in favor of a low level of HBV replication in women with isolated anti-HBc. Second, infant HBV infection

Table 4. Factors Associated With Occult Hepatitis B Virus Infection in HIV-1–Infected Pregnant Women With Isolated Antibody to Hepatitis B Core Antigen

Parameters	Category	No.	Occult HBV Infection (%)	Univariate Analysis OR (95% CI)	P Value[a]	Multivariate Analysis OR (95% CI)	P Value[b]
Age at enrollment, y	≤25	83	20 (24)	1			
	26–30	57	12 (21)	.8 (.4–1.9)	.67		
	31–35	39	8 (21)	.8 (.3–2.1)	.66		
	>35	21	7 (33)	1.6 (.6–4.4)	.39		
Region of birth	Central	29	9 (31)	1			
	Eastern	27	4 (14)	.4 (.1–1.4)	.16		
	Northern	69	18 (26)	.8 (.3–2.0)	.62		
	Northeastern	62	16 (26)	.8 (.3–2.0)	.60		
	Southern	3	0 (0)	. . .	. . .		
	Western	10	0 (0)	. . .	. . .		
Previous pregnancy	No	75	16 (21)	1			
	Yes	124	31 (25)	1.2 (.6–2.4)	.56		
ALT, IU/L	≤30	165	42 (25)	1			
	31–60	22	2 (9)	.3 (.1–1.3)	.11		
	>60	6	2 (33)	1.5 (.3–8.3)	.67		
WBC count, cells/μL	>10 000	36	7 (19)	1			
	7501–10 000	80	17 (21)	1.1 (.4–3.0)	.82		
	5001–7500	70	20 (29)	1.7 (.6–4.4)	.31		
	≤5000	8	2 (25)	1.4 (.2–8.4)	.73		
Absolute lymphocyte count, cells/μL	>2000	62	13 (21)	1			
	1501–2000	55	16 (29)	1.5 (.7–3.6)	.31		
	1001–1500	45	13 (29)	1.5 (.6–3.7)	.35		
	≤1000	31	4 (13)	.6 (.2–1.9)	.35		
Absolute CD4^{+} T-cell count, cells/μL	>500	40	10 (25)	1			
	351–500	37	8 (22)	.8 (.3–2.4)	.73		
	201–350	54	15 (28)	1.2 (.5–2.9)	.76		
	≤200	68	14 (21)	.8 (.3–2.0)	.60		
Absolute CD8^{+} T-cell count, cells/μL	>1500	18	7 (39)	1			
	1001–1500	51	9 (18)	.3 (.1–1.0)	.07		
	501–1000	104	25 (24)	.5 (.2–1.4)	.19		
	≤500	22	5 (23)	.5 (.1–1.8)	.27		
HIV RNA load, log₁₀ copies/μL	≤ 3.00	24	10 (42)	1			
	3.01–4.00	68	18 (26)	.5 (.2–1.3)	.17	.5 (.2–1.3)	.17
	4.01–5.00	71	15 (21)	.4 (.1–1.0)	.05	.4 (.1–1.0)	.05
	> 5.00	**34**	**4 (12)**	**.2 (.05–.7)**	**.013**	**.2 (.05–.7)**	**.013**
Anti-syphilis antibody	No	191	45 (24)	1			
	Yes	2	1 (50)	3.2 (.2–53)	.41		
Anti-HCV antibody	No	174	39 (22)	1			
	Yes	22	8 (36)	2.0 (.8–5.1)	.15		

Boldface text indicates significant values (≤.05).

Abbreviations: ALT, alanine aminotransferase; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV-1, human immunodeficiency virus type 1; OR, odds ratio; WBC, white blood cell.

[a] Logistic regression analysis was used.

[b] Multivariate logistic regression analysis was used.

status was determined using HBV DNA PCR at 4 months of age. Because children in the original study (prevention of mother-to-child transmission of HIV-1) were only followed up until 12 months of age, it was not possible to reliably rule out a perinatal exposure to HBV based on anti-HBc testing. Indeed, anti-HBc immunoglobulin G, a marker of exposure to HBV, is

passively transmitted through placenta to the fetus and can persist in children several months before being completely cleared at 24 months of age [40].

In conclusion, our study shows that the prevalence of HIV-1–infected pregnant women presenting with isolated anti-HBc/occult HBV infection was low (2.6%) and that women with isolated anti-HBc and occult HBV infection have very low HBV DNA levels and are thus at very low risk to transmit HBV to their infants.

Notes

References

1. Grob P, Jilg W, Bornhak H, et al. Serological pattern "anti-HBc alone": report on a workshop. J Med Virol 2000; 62:450–5.
2. Hoofnagle JH, Seeff LB, Bales ZB, Zimmerman HJ. Type B hepatitis after transfusion with blood containing antibody to hepatitis B core antigen. N Engl J Med 1978; 298:1379–83.
3. De Feo TM, Poli F, Mozzi F, Moretti MP, Scalamogna M. Risk of transmission of hepatitis B virus from anti-HBC positive cadaveric organ donors: a collaborative study. Transplant Proc 2005; 37:1238–9.
4. Descos B, Scotto J, Fayol V, et al. Anti-HBc screening for the prevention of perinatal transmission of hepatitis B virus in France. Infection 1987; 15:434–9.
5. Chamorro AJ, Casado JL, Bellido D, Moreno S. Reactivation of hepatitis B in an HIV-infected patient with antibodies against hepatitis B core antigen as the only serological marker. Eur J Clin Microbiol Infect Dis 2005; 24:492–4.
6. Jain M, Chakravarti A, Kar P. Clinical significance of isolated anti-HBc positivity in cases of chronic liver disease in New Delhi, India. J Glob Infect Dis 2009; 1:29–32.
7. Ikeda K, Kobayashi M, Someya T, et al. Occult hepatitis B virus infection increases hepatocellular carcinogenesis by eight times in patients with non-B, non-C liver cirrhosis: a cohort study. J Viral Hepat 2009; 16:437–43.
8. Sheng WH, Kao JH, Chen PJ, et al. Evolution of hepatitis B serological markers in HIV-infected patients receiving highly active antiretroviral therapy. Clin Infect Dis 2007; 45:1221–9.
9. Hoffmann CJ, Seaberg EC, Young S, et al. Hepatitis B and long-term HIV outcomes in coinfected HAART recipients. AIDS 2009; 23:1881–9.
10. Hennig H, Puchta I, Luhm J, Schlenke P, Goerg S, Kirchner H. Frequency and load of hepatitis B virus DNA in first-time blood donors with antibodies to hepatitis B core antigen. Blood 2002; 100:2637–41.
11. Asim M, Ali R, Khan LA, Husain SA, Singla R, Kar P. Significance of anti-HBc screening of blood donors and its association with occult hepatitis B virus infection: implications for blood transfusion. Indian J Med Res 2010; 132:312–7.
12. Thedja MD, Roni M, Harahap AR, Siregar NC, Ie SI, Muljono DH. Occult hepatitis B in blood donors in Indonesia: altered antigenicity of the hepatitis B virus surface protein. Hepatol Int 2010; 4:608–14.
13. Seo DH, Whang DH, Song EY, Kim HS, Park Q. Prevalence of antibodies to hepatitis B core antigen and occult hepatitis B virus infections in Korean blood donors. Transfusion 2011; 51:1840–6.
14. Gandhi RT, Wurcel A, Lee H, et al. Isolated antibody to hepatitis B core antigen in human immunodeficiency virus type-1–infected individuals. Clin Infect Dis 2003; 36:1602–5.
15. Neau D, Winnock M, Galperine T, et al. Isolated antibodies against the core antigen of hepatitis B virus in HIV-infected patients. HIV Med 2004; 5:171–3.
16. Liang SH, Chen TJ, Lee SS, et al. Risk factors of isolated antibody against core antigen of hepatitis B virus: association with HIV infection and age but not hepatitis C virus infection. J Acquir Immune Defic Syndr 2010; 54:122–8.

17. Gandhi RT, Wurcel A, McGovern B, et al. Low prevalence of ongoing hepatitis B viremia in HIV-positive individuals with isolated antibody to hepatitis B core antigen. J Acquir Immune Defic Syndr 2003; 34:439–41.

18. French AL, Operskalski E, Peters M, et al. Isolated hepatitis B core antibody is associated with HIV and ongoing but not resolved hepatitis C virus infection in a cohort of US women. J Infect Dis 2007; 195:1437–42.

19. Cacciola I, Pollicino T, Squadrito G, Cerenzia G, Orlando ME, Raimondo G. Occult hepatitis B virus infection in patients with chronic hepatitis C liver disease. N Engl J Med 1999; 341:22–6.

20. Jongjirawisan Y, Ungulkraiwit P, Sungkanuparph S. Isolated antibody to hepatitis B core antigen in HIV-1 infected patients and a pilot study of vaccination to determine the anamnestic response. J Med Assoc Thai 2006; 89:2028–34.

21. Allain JP. Occult hepatitis B virus infection: implications in transfusion. Vox Sang 2004; 86:83–91.

22. Sun HY, Lee HC, Liu CE, et al. Factors associated with isolated anti-hepatitis B core antibody in HIV-positive patients: impact of compromised immunity. J Viral Hepat 2010; 17:578–87.

23. Filippini P, Coppola N, Pisapia R, et al. Impact of occult hepatitis B virus infection in HIV patients naive for antiretroviral therapy. AIDS 2006; 20:1253–60.

24. Lallemant M, Jourdain G, Le Coeur S, et al. Single-dose perinatal nevirapine plus standard zidovudine to prevent mother-to-child transmission of HIV-1 in Thailand. N Engl J Med 2004; 351:217–28.

25. Villeneuve JP, Durantel D, Durantel S, et al. Selection of a hepatitis B virus strain resistant to adefovir in a liver transplantation patient. J Hepatol 2003; 39:1085–9.

26. Kaplan JE, Benson C, Holmes KH, Brooks JT, Pau A, Masur H. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR Recomm Rep 2009; 58:1–207; quiz CE201–204.

27. Laukamm-Josten U, Muller O, Bienzle U, Feldmeier H, Uy A, Guggenmoos-Holzmann I. Decline of naturally acquired antibodies to hepatitis B surface antigen in HIV-1 infected homosexual men. AIDS 1988; 2:400–1.

28. Manzini P, Girotto M, Borsotti R, et al. Italian blood donors with anti-HBc and occult hepatitis B virus infection. Haematologica 2007; 92:1664–70.

29. Ponde RA, Cardoso DD, Ferro MO. The underlying mechanisms for the 'anti-HBc alone' serological profile. Arch Virol 2010; 155: 149–58.

30. Poovorawan Y, Theamboonlers A, Vimolket T, et al. Impact of hepatitis B immunisation as part of the EPI. Vaccine 2000; 19:943–9.

31. Louisirirotchanakul S, Myint KS, Srimee B, et al. The prevalence of viral hepatitis among the Hmong people of northern Thailand. Southeast Asian J Trop Med Public Health 2002; 33:837–44.

32. Pradutkanchana S, Nasongkla K, Pradutkanchana J, Heembai U. A ten-year trend of the prevalence of hepatitis B surface antigen in pregnant women at Songklanagarind hospital. J Infect Dis Antimicrob Agents 2005; 22:111–4.

33. Berger A, Doerr HW, Rabenau HF, Weber B. High frequency of HCV infection in individuals with isolated antibody to hepatitis B core antigen. Intervirology 2000; 43:71–6.

34. Chen SY, Kao CF, Chen CM, et al. Mechanisms for inhibition of hepatitis B virus gene expression and replication by hepatitis C virus core protein. J Biol Chem 2003; 278:591–607.

35. Schuttler CG, Fiedler N, Schmidt K, Repp R, Gerlich WH, Schaefer S. Suppression of hepatitis B virus enhancer 1 and 2 by hepatitis C virus core protein. J Hepatol 2002; 37:855–62.

36. Allain JP. Occult hepatitis B virus infection. Transfus Clin Biol 2004; 11:18–25.

37. Lo Re V 3rd, Frank I, Gross R, et al. Prevalence, risk factors, and outcomes for occult hepatitis B virus infection among HIV-infected patients. J Acquir Immune Defic Syndr 2007; 44:315–20.

38. Walz A, Wirth S, Hucke J, Gerner P. Vertical transmission of hepatitis B virus (HBV) from mothers negative for HBV surface antigen and positive for antibody to HBV core antigen. J Infect Dis 2009; 200: 1227–31.

39. Soderstrom A, Norkrans G, Lindh M. Hepatitis B virus DNA during pregnancy and post partum: aspects on vertical transmission. Scand J Infect Dis 2003; 35:814–9.

40. Wang JS, Chen H, Zhu QR. Transformation of hepatitis B serologic markers in babies born to hepatitis B surface antigen positive mothers. World J Gastroenterol 2005; 11:3582–5.