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Factors associated with isolated anti-hepatitis B core antibody in HIV-positive patients: impact of compromised immunity

H.-Y. Sun,[1] H.-C. Lee,[2] C.-E. Liu,[3] C.-L. Yang,[4] S.-C. Su,[5] W.-C. Ko,[2] C.-Y. Lin,[4] J.-J. Tsai,[6] W.-W. Wong,[7] M.-W. Ho,[8] S.-H. Cheng,[9] Y.-H. Lin,[10] W.-J. Miao[11] and C.-C. Hung[1] [1]*Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan;* [2]*Department of Internal Medicine, National Cheng-Kung University Hospital, Tainan, Taiwan;* [3]*Department of Internal Medicine, Chang-Hua Christian Hospital, Chang-Hua, Taiwan;* [4]*Department of Internal Medicine, National Taiwan University Hospital Yun-Lin Branch, Yun-Lin County, Taiwan;* [5]*Department of Internal Medicine, MacKay Memorial Hospital, Hsin-Chu, Taiwan;* [6]*Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan;* [7]*Branch of Disease Control, Taipei City Hospital, Taipei, Taiwan;* [8]*Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan;* [9]*Department of Internal Medicine, Department of Health, Taoyuan Hospital, Taoyuan, Taiwan;* [10]*Department of Internal Medicine, Veterans General Hospital, Taichung, Taiwan; and* [11]*Department of Internal Medicine, Mennonite Christian Hospital, Hwa-Lien, Taiwan*

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SUMMARY. In regions that are hyperendemic for chronic hepatitis B virus (HBV) infection, prevalence of and risk factors associated with isolated anti-hepatitis B core antibody (anti-HBc) in HIV-positive patients are less well described. HIV-positive patients who were tested for hepatitis B surface antigen (HBsAg), anti-hepatitis B surface antibody (anti-HBs) and anti-HBc at designated hospitals for HIV care in Taiwan were included for analysis. HBV DNA was detected by real-time polymerase chain reaction in patients with and without isolated anti-HBc. Of 2351 HIV-positive patients, 450 (19.1%) were HBsAg positive, 411 (17.5%) were anti-HBc positive alone and 963 (41.0%) for both anti-HBs and anti-HBc. Compared with patients who were positive for both anti-HBs and anti-HBc, patients with isolated anti-HBc were older, less likely to have anti-hepatitis C virus antibody (anti-HCV), had lower CD4 lymphocyte counts and higher plasma HIV RNA loads. Older age (adjusted odds ratio, 1.029; 95% confidence interval, 1.015–1.043) and CD4 <100 cells/μL (adjusted odds ratio, 1.524; 95% confidence interval, 1.025–2.265) were independently associated with isolated anti-HBc by logistic regression, while presence of anti-HCV and injecting drug use were not. HBV DNA was detectable in 8.3% of 277 patients with isolated anti-HBc and 14.3% of 56 patients with both anti-HBs and anti-HBc (P = 0.160). In a country hyperendemic for HBV infection, HIV-positive patients at older age and with CD4 <100 cells/μL were more likely to have isolated anti-HBc, suggesting that compromised immunity plays a role in the presence of this marker.

Keywords: anti-hepatitis B surface antibody, anti-hepatitis C virus antibody, hepatitis B surface antigen, hepatitis B virus, HIV infection, isolated anti-hepatitis B core antibody, occult hepatitis B virus infection.

INTRODUCTION

Despite an uncommon serological pattern in the general population, isolated anti-hepatitis B virus (HBV) core antibody (anti-HBc), defined as positive anti-HBc with both negative HBV surface antigen (HBsAg) and anti-HBV surface antibody (anti-HBs), is frequently observed in HIV-positive patients [1,2]. Nevertheless, the clinical significance and implications of isolated anti-HBc detection remain not well defined in the HIV-positive population. It has been shown that isolated anti-HBc is not associated with progression from AIDS or HIV diagnosis to death or with increased risk of liver disease or liver-related deaths [3]. Additionally, hepatitis C virus (HCV) infection and injecting drug use have been identified as risk factors associated with the presence of isolated anti-HBc in HIV-positive patients [3–9]. However, we previously found that HIV-positive patients with isolated anti-HBc at baseline had a significantly shorter survival than those with positive anti-HBs at baseline [10]; furthermore, patients with isolated anti-HBc at baseline, who

Abbreviations: anti-HBc, anti-hepatitis B core antibody; anti-HBs, anti-hepatitis B surface antibody; HAART, highly active antiretroviral therapy; HBsAg, HBV surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; IDU, injecting drug users.

Correspondence: Chien-Ching Hung, Department of Internal Medicine, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei 100, Taiwan. E-mail: hcc0401@ntu.edu.tw

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subsequently developed anti-HBs had significantly higher likelihood to have improved immunity and control of HIV replication than those with persistent isolated anti-HBc [10]. Our findings suggested immunosuppression is associated with the presence of isolated anti-HBc.

The inconsistency between our study and others may be attributed to the fact that our patients were much more immunocompromised than the patients in other studies in terms of CD4 counts [5,9–11]. Additionally, the majority of the aforementioned studies were conducted in countries with low HBV endemicity where HIV, HBV and HCV share the same transmission routes [3,5–9]. It is not known whether these observations remain valid in countries with higher HBV endemicity, where most of HBV infection occurs via vertical transmission or in early childhood [12–14].

Thus, in this study, we aimed to assess the prevalence of and risk factors associated with isolated anti-HBc in HIV-positive patients in a region with an estimated seroprevalence of HBV infection of 17.3% in the general and 19.8% in HIV-positive population [15,16]. We hypothesized that declining immunity may play a role in the presence of isolated anti-HBc. In addition, we reviewed all published studies that investigated isolated anti-HBc in HIV-infected patients with an attempt to assess the factors associated with isolated anti-HBc in study populations with different prevalence of HBV or HCV infection.

MATERIALS AND METHODS

Study population

From 1984 to 2008, a total of 17 428 cases of HIV infection were reported to the Taiwan Centers for Disease Control through several active and passive surveillance systems for HIV around the island [17]. Before 2004, the majority of HIV infection occurred through sexual transmission, with men who have sex with men (MSM) accounting for the largest proportion (48.2%), followed by heterosexuals (39.9%) [16]. However, an outbreak of HIV infection occurred among injecting drug users (IDU) through sharing needles and heroin diluents since 2003, and IDU accounted for two-thirds of all cases of newly diagnosed HIV infection in 2005 and 2006 [18]. After implementation of a harm reduction program in late 2005, continued and significant reduction in the incidence of HIV infection was observed among IDU after 2006, and sexual transmission became once again the most common route for HIV transmission [17]. HIV-infected patients in Taiwan are provided with free medical care at designated hospitals by the government of Taiwan, including highly active antiretroviral therapy (HAART) that was introduced on 1 April 1997 [18]. It was estimated that 70% of HIV-infected patients sought HIV-related care, and more than 40% had received HAART after the diagnosis of HIV infection was made [18].

In this study, we retrospectively reviewed medical records of patients aged 15 years or greater, who were newly diagnosed with HIV infection and sought HIV care at designated hospitals around Taiwan between January 2004 and March 2008. A computerized data collection form was used to extract their demographics and clinical data, which included date of birth, gender, HIV exposure route, baseline CD4 counts and plasma HIV RNA loads and results of anti-HCV, HBsAg, anti-HBs, anti-HBc and plasma HBV DNA loads at baseline, if available. HBV DNA was determined from archived serum samples obtained from all patients at baseline and from patients who tested positive for HBs antigenemia or isolated anti-HBc in subsequent visits [10]. The Institutional Review Board of the hospitals approved the study and waived the need of informed consent.

Laboratory investigations

Hepatitis B surface antigen, anti-HBs and anti-HBc were determined with the use of enzyme immunoassays (Abbott Laboratories, Abbott Park, IL, USA). Anti-HBs titers equal to or >10 mIU/mL were reported as positive, while those <10 mIU/mL as non-reactive. Anti-HCV was determined with the use of a third-generation enzyme immunoassay (Ax SYM HCV III; Abbott Laboratories, North Chicago, IL, USA). The HBV DNA level was quantified among archived blood samples using a real-time polymerase chain reaction (PCR) using a LighterCycler (Roche Molecular Biochemicals, Indianapolis, IN, USA), in accordance with the manufacturer's instructions. The laboratory staff were blinded to the HBV serostatus of the patients. The detection limit of HBV DNA was estimated to be 1000 copies/mL. Plasma HIV RNA loads were quantified using RT-PCR (Roche Amplicor, version 1.5; Roche Diagnostics, Branchburg, NJ, USA) with a lower detection limit of 400 (2.60 $\log_{10}$) copies/mL, and CD4 counts were determined using FACFlow (BD FACS Calibur; Becton Dickinson, San Jose, CA, USA).

Literature review

Studies for the review were identified through searches of PubMed up to March 2009 by cross-referencing the key words 'isolated anti-hepatitis B core antibody' or 'anti-hepatitis B core antibody alone' and 'HIV' or 'AIDS'. Studies reporting prevalence of isolated anti-HBc or risk factors associated with isolated anti-HBc in HIV-positive populations were included for analysis. Bibliographies of original articles were manually reviewed for additional studies.

Statistical analysis

All statistical analyses were performed using SPSS software version 16.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were compared using chi-square or Fisher's exact test, whereas non-categorical variables were compared using

Student's *t*-test or Mann–Whitney *U*-test. A multiple logistic regression model was built to identify independent factors associated with isolated anti-HBc. Correlation coefficients for correlation between two prevalences were calculated by Spearman's rho. All tests were two-tailed and a *P* value < 0.05 was considered significant.

RESULTS

During the 4-year study period, 4273 HIV-positive patients sought HIV care at the designated hospitals, and 2351 (55.0%) of them were tested for all the three HBV markers as part of routine care: HBsAg, anti-HBs and anti-HBc. Compared with 1922 patients (45.0%) who were not tested for all the three HBV markers, patients who were tested were older (39.9 *vs* 38.9 years, $P = 0.003$), had lower mean CD4 counts (282.6 *vs* 354.7 cells/μL, $P \leq 0.001$) and higher mean plasma HIV RNA loads (4.52 *vs* 4.30 $\log_{10}$ copies/mL, $P \leq 0.001$) and were less likely to be IDU (35.0% *vs* 52.7%, $P \leq 0.001$) or have positive anti-HCV (39.1% *vs* 47.4%, $P \leq 0.001$).

Of the 2351 patients tested for all three HBV markers, 450 (19.1%) were positive for HBsAg, 411 (17.5%) for isolated anti-HBc and 963 (41.0%) for both anti-HBs and anti-HBc. In addition, 2161 of these 2351 patients were also tested for anti-HCV, and 845 (39.1%) had positive results. The present analysis included 411 patients with isolated anti-HBc and 963 patients positive for both anti-HBs and anti-HBc. Their demographic and clinical characteristics are shown in Table 1. Persons with isolated anti-HBc were older, less likely to have positive anti-HCV and more likely to have lower CD4 counts and higher plasma HIV RNA loads than patients positive for both anti-HBs and anti-HBc (Table 1). No significant differences were observed between the two groups in terms of gender or routes of HIV exposure (Table 1). In multiple logistic regression, factors independently associated with isolated anti-HBc were older age (adjusted odds ratio, 1.029; 95% confidence interval (CI), 1.015–1.043; $P < 0.001$) and a CD4 count <100 cells/μL (adjusted odds ratio, 1.524; 95% CI 1.025–2.265; $P = 0.037$), but not anti-HCV presence or injection drug use (Table 2).

Baseline HBV DNA levels were available in a total of 333 patients, including 277 patients (67.4%, 277/411) with isolated anti-HBc and 56 patients (5.8%, 56/963) positive for both anti-HBs and anti-HBc. Compared with patients without baseline HBV DNA data, these patients were older (mean, 43.5 *vs* 40.2 years, $P < 0.001$), less likely to be IDU (24.1% *vs* 42.2%, $P < 0.001$) or to have HCV infection (29.2% *vs* 46.1%, $P < 0.001$) and had lower CD4 counts (mean, 218 *vs* 306 cells/μL, $P < 0.001$) and higher plasma HIV RNA loads (mean, 4.73 *vs* 4.42 $\log_{10}$ copies/mL, $P < 0.001$).

Information about lamivudine use was available in 76.9% (256/333) of the patients tested for serum HBV DNA. HBV DNA was determined before lamivudine use in 57.2% (115/201) of patients with isolated anti-HBc and 23.6% (13/55) of patients positive for both anti-HBs and anti-HBc ($P < 0.001$). Serum HBV DNA was detectable in 23 patients (8.3%, 23/277) with isolated anti-HBc and in eight patients (14.3%, 8/56) positive for both anti-HBs and anti-HBc ($P = 0.160$). The median HBV DNA level was significantly higher in patients positive for both anti-HBs and anti-HBc than in patients with isolated anti-HBc (4.35 *vs* 3.67 $\log_{10}$ copies/mL, $P = 0.002$). For the 23 patients with isolated anti-HBc and detectable HBV DNA, 16 had information about lamivudine use, including 10 (62.5%) receiving lamivudine before and six (37.5%) after HBV DNA determinations (median, 92.5 days; range, 30–138 days). Only one (12.5%) of the eight patients positive for both anti-HBs and anti-HBc was tested for HBV DNA before lamivudine use, and the remaining seven patients (87.5%) were tested after the initiation of treatment (median, 1253 days; range, 27–2214 days). For patients with undetectable serum HBV DNA, HBV DNA was tested after lamivudine use in 43.2% (80/185) of the patients with isolated anti-HBc (median, 71.5 days; range, 8–3236 days) and 74.5% (35/47) of patients positive for both anti-HBs and anti-HBc (median, 797 days; range, 28–2179 days).

Literature review

We identified 26 published studies that investigated the prevalence of isolated anti-HBc and its associated factors. These studies, including ours, are summarized in Table 3. The rates of occult HBV infection, defined as absence of HBsAg and detectable HBV DNA, in patients with isolated anti-HBc ranged from 0% to 89.5% (Table 3). Fourteen studies were conducted in countries of low HBV endemicity (prevalence of HBsAg below 2%) defined by the World Health Organization [19], including seven studies in the United States, four in France, one in Germany, one in the Netherlands and one in Switzerland; seven studies in countries of intermediate HBV endemicity (prevalence of HBsAg of 2–8%), including five in Spain, one in Brazil and one in Lebanon; and another six studies in countries of HBV hyperendemicity (prevalence of HBsAg > 8%), including three in Taiwan, two in Africa and one in Thailand. Including the present study, 18 studies analysed patients with all three HBV serological markers (HBsAg, anti-HBs and anti-HBc); four analysed patients negative for HBsAg and positive for anti-HBc; three analysed patients negative for both HBsAg and anti-HBs; and two analysed patients with isolated anti-HBc only (Table 3). The prevalence of HBsAg and HCV infection varied greatly in these studies, ranging from 0% to 23.6% and 1.9% to 100%, respectively. The proportions of IDU (2.9–100%) and patients receiving antiretroviral therapy (0–100%) also differed among the studies (Table 3).

The prevalence of isolated anti-HBc was 9–44.4% in patients who were tested for all three HBV markers, 23.6–61.7% in patients who tested negative for HBsAg and

Table 1 Comparisons of clinical characteristics between HIV-positive persons with and persons without isolated anti-HBc

	Isolated anti-HBc	Anti-HBs(+)/ anti-HBc(+)	*P* value
Number of persons	411	963	
Age, year, mean ± SD	43 ± 11	40 ± 11	<0.001
15–24, *n* (%)	4 (1.0)	16 (1.7)	<0.001
25–34	88 (21.4)	302 (31.4)	
35–44	155 (37.7)	387 (40.2)	
45–54	89 (21.7)	164 (17.0)	
≥55	75 (18.2)	93 (9.7)	
Male sex, *n* (%)	378 (92.0)	885 (91.9)	0.965
Number of patients with known HIV	373	903	
Exposure routes			
Sexual transmission, *n* (%)	247 (66.2)	549 (60.8)	0.069
Injecting drug use	126 (33.8)	354 (39.2)	
Positive anti-HCV	145/393 (36.9)	385/872 (44.2)	0.016
CD4 cells/μL, mean ± SD (number with data available)	247.3 ± 255.3 (400)	300.2 ± 245.4 (938)	<0.001
<100 cells/μL, *n* (%)	162 (40.5)	253 (27.0)	<0.001
<200 cells/μL	198 (49.5)	345 (36.8)	<0.001
200–350 cells/μL	83 (20.8)	235 (25.1)	
>350 cells/μL	119 (29.8)	358 (38.2)	
PVL, $\log_{10}$ copies/mL, mean ± SD (number with data available)	4.60 ± 0.99 (353)	4.45 ± 1.01 (846)	0.014
PVL >5 $\log_{10}$ copies/mL, *n* (%)	140 (39.7)	276 (32.6)	0.020
Number of patients tested for HBV DNA	277 (67.4)	56 (5.8)	<0.001
Number of patients tested positive for HBV DNA	23/277 (8.3)	8/56 (14.3)	0.160
HBV DNA load, $\log_{10}$ copies/mL, median (range)	3.67 (3.06–4.46)	4.35 (3.54–7.73)	0.002

anti-HBc, anti-hepatitis B core antibody; anti-HBs antibody, anti-hepatitis B surface antibody; HBV, hepatitis B virus; HCV, hepatitis C virus; PVL, plasma HIV RNA load; SD, standard deviation.

positive for anti-HBc and 42.3–50.0% in patients who tested negative for both HBsAg and anti-HBs (Table 3). No correlation was observed between the overall prevalence of HBsAg and that of isolated anti-HBc reported from the 18 studies that were conducted in patients who had all three HBV markers determined ($P = 0.866$ by Spearman's rho) (Fig. 1). The prevalence of isolated anti-HBc was also similar between study patients with HBsAg seroprevalence greater and less than 8% (9.0–28.3% *vs* 10.6–44.4%, $P = 0.845$ by Mann–Whitney *U*-test) (Table 3). Likewise, no correlation was noted between the prevalence of anti-HCV and that of isolated anti-HBs in these 18 studies ($P = 0.894$ by Spearman's rho) (Fig. 2).

DISCUSSION

The prevalence of isolated anti-HBc varies widely among different studies that included HIV-positive patients with diverse clinical, immunologic and demographic characteristics (Table 3). In this study consisting of an HIV-positive

Table 2 Multivariate analysis for risk factors associated with isolated anti-HBc detection in HIV-positive patients by logistic regression

Factors	Odds ratio	95% Confidence interval	*P* value
Age	1.029	1.015–1.043	<0.001
Men	0.901	0.544–1.492	0.685
IDU	1.247	0.647–2.403	0.509
HCV infection	0.782	0.420–1.454	0.436
CD4 <100 cells/μL	1.524	1.025–2.265	0.037
PVL >5 $\log_{10}$ copies/mL	0.960	0.663–1.391	0.830

IDU, injecting drug users; HCV, hepatitis C virus; PVL, plasma HIV RNA load.

population with seroprevalence of HBsAg and HCV of 19.1% and 39.1%, respectively, 17.5% of the patients had a serological pattern of isolated anti-HBc. Older age and CD4 counts <100 cells/μL were independently associated with presence of isolated anti-HBc. Contrary to what other investigators in regions of lower HBV endemicity have reported, we found that presence of anti-HCV and injecting drug use were not associated with presence of isolated anti-HBc, confirming our previous observations (Table 2) [11].

Risk factors associated with isolated anti-HBc have been assessed in 15 studies that yielded inconsistent results (Table 3). The inconsistency may be attributed to use of different comparators. For example, four studies comparing patients with isolated anti-HBc with those negative for all three markers identified HCV infection, male, older age and injecting drug use as the main risk factors [5–7,20], while in another three studies that selected patients without isolated anti-HBc as the reference group, HCV infection was reported to be the risk factor in two studies, injecting drug use in one study and low CD4 counts in another study [4,9,11]. In another six studies, patients with isolated anti-HBc were compared with patients positive for both anti-HBs and anti-HBc, and HCV infection was the risk factor in three studies, low CD4 counts (<400 cells/μL in one study and <100 cells/μL in the present study) in two, injecting drug use in one, and HCV genotype 4c/4d in one [8,21–24].

Similar to our findings, two studies also found that lower CD4 counts (<400 or <500 cells/μL) were associated with presence of isolated anti-HBc in HIV-positive patients [24,25]. Patients in most of the other studies had higher CD4 counts (median CD4 counts of 300–459 cells/μL or 62–76% of study population with CD4 counts >200 cells/μL) (Table 3), while our patients had a median CD4 count of 264 cells/μL, and 58.7% of them had CD4 counts >200 cells/μL. Loss of anti-HBs has been observed in HIV-positive patients with compromised immunity [26,27]. Because HAART can suppress HIV replication and restore immunity, patients with isolated anti-HBc may subsequently develop anti-HBs [10]; furthermore, an increase in the CD4 cell count by 100 cells/μL or greater after HAART was the only independent factor associated with the development of anti-HBs in patients with isolated anti-HBc (adjusted odds ratio, 4.65; 95% CI 1.96–11.02, $P = 0.001$) [10].The Women's Interagency HIV Study also reported that HAART use and an increase in CD4 cell count predicts the development of anti-HBs in patients with isolated anti-HBc [28]. Thus, we believe severely compromised immunity leads to subsequent loss of anti-HBs and development of isolated anti-HBc in HIV-positive patients.

Few studies have addressed the association between age and isolated anti-HBc. In an unselected population in Germany, the prevalence of isolated anti-HBc was highest in persons aged 71–80 years (22.7%) and lowest in persons aged 1–30 years (9.4%) [29]. Like our observations, one study reported HIV-positive patients with isolated anti-HBc were older than those tested negative for all three HBV markers (mean 36.8 *vs* 34.3 years, $P = 0.026$) [20]. Because anti-HBs titers decline with age [30], it is not unexpected to observe that older age was associated with isolated anti-HBc. This further suggests factors associated with declining immunity, such as old age or low CD4 counts, also contribute to the presence of isolated anti-HBc.

Many studies reported HCV infection and injecting drug use were risk factors for presence of isolated anti-HBc in HIV-positive patients (Table 3). It is believed that presence of isolated anti-HBc is the result of suppression of HBV replication and gene expression by HCV coinfection, and injecting drug use is the main risk factor for HCV infection [31–34]. However, in the present study with IDU accounting for 35% of the study population, presence of anti-HCV was not a risk factor for isolated anti-HBc. Most of the studies reporting HCV infection as the risk factor for isolated anti-HBc were conducted in countries where HBV, HCV and HIV share the same transmission routes, such as the United States, Spain and France and their HBsAg prevalence was 5.1–11.7% (Table 3). However, our study was conducted in a country with high HBV endemicity, where the majority of HBV infection occurs in the perinatal period or early childhood, long before HCV and HIV infection occurs in adulthood [13–15,35]. It remains to be studied whether the different sequences or transmission routes of infection by these viruses could explain the differences between our study and others.

The rates of occult HBV infection ranged from 0% to 89.5%, in HIV-positive patients with isolated anti-HBc (Table 3). Heterogeneity of the study populations, receipt of antiretroviral therapy with anti-HBV activity and different sensitivity and specificity of HBV DNA assays used may account for these discrepancies. In the present study, serum HBV DNA was detected in 8.3% of our patients with isolated anti-HBc. Despite the fact that a significantly higher proportion of patients positive for both anti-HBs and anti-HBc had received lamivudine before HBV DNA determination, HBV DNA were still detected in 14.3% of

Table 3 Summarized data of published studies of HIV-positive patients with isolated anti-HBc

Reference	Pt. No.	HBV markers	HCV	IDU	ART	CD4 >200	HBsAg	Isolated	Viremia/ isolated	Comparator	Risk
Studies in countries with high HBV endemicity											
Present study	2351	3 HBV markers tested	39.1%	35.0%	NA	58.7%	19.1%	17.5%	8.3%	Anti-HBs(+)/ anti-HBc(+)	Age, CD4 <100
[10]	633	3 HBV markers tested	8.5%	4.1%	NA	41.1%	18.8%	28.3%	7.3%	NA	
[11]	416	3 HBV markers tested	9.1%	2.9%	83.2%	29.0%	23.6%	27.2%	NA	Not isolated anti-HBc	Low CD4
[4]	140	3 HBV markers tested	11.9%	7.9%	80.0%	300*	5.0%	20.0%	NA	Not isolated anti-HBc	IDU, HCV
[44]	502	3 HBV markers tested	2.3%	NA	NA	49†	4.8%	10.6%	88.4%	NA	
[45]	167	3 HBV markers tested	1.9%	NA	NA	NA	16.2%	9.0%	33.3%	NA	
Studies in countries with intermediate HBV endemicity											
[46]	170	3 HBV markers tested	NA	8.2%	68.0%	62%	8.2%	24.1%	10.0%	NA	
[47]	101	3 HBV markers tested	NA	8.9%	NA	NA	6.9%	23.8%	83.3%	NA	
[21]	348	3 HBV markers tested	NA	NA	NA	434, 459*	4.0%	15.8%	0%	Anti-HBs(+)/ anti-HBc(+)	Younger, HCV
[22]	94	HBsAg(−)/anti-HBc(+)	100%	NA	NA	309, 375†	0%	61.7%	NA	Anti-HBs(+)/ anti-HBc(+)	HCV genotype 4c/4d
[23]	104	HBsAg(−)/anti-HBc(+)	70%	NA	NA	309, 375†	NA	45.2%	NA	Anti-HBs(+)/ anti-HBc(+)	HCV
[25]	388	3 HBV markers tested	NA	100%	NA	368*	7.2%	33.0%	NA	CD4 <500 *vs* ≥500	CD4 <500
[24]	18	3 HBV markers tested	NA	100%	NA	322, 635*	0%	44.4%	NA	Anti-HBs(+)/ anti-HBc(+)	Low CD4
Studies in countries with low HBV endemicity											
[3]	1346	3 HBV markers tested	26.6%	19.8%	72.6%	65%	11.7%	15.1%	3.3%	Anti-HBs(+)/ anti-HBc(±)	Black, IDU, HCV
[48]	1606	3 HBV markers tested	NA	NA	NA	NA	2.9%	14.8%	NA	NA	
[41]	240	3 HBV markers tested	NA	16.0%	0%	28.8%	7.1%	15.8%	10.5%	NA	
[6]	97	HBsAg(−)/anti-HBs(−)	36.5%	37.0%	70.1%	435, 437†	0%	45.4%	NA	All negative	HCV, men
[7]	84	HBsAg(−)/anti-HBs(−)	41.7%	NA	75.0%	431, 445†	0%	50.0%	2.4%	All negative	HCV
[5]	142	HBsAg(−)/anti-HBs(−)	41.5%	42.0%	59.0%	335, 368†	0%	42.3%	NA	All negative	HCV
[20]	257	3 HBV markers tested	NA	71.0%	NA	368, 432, 343†	5.1%	43.6%	NA	All negative HBsAg(+) or anti-HBs(+)	Older, IDU, HCV None

Table 3 (Continued)

Reference	Pt. No.	HBV markers	HCV	IDU	ART	CD4 >200	HBsAg	Isolated	Viremia/ isolated	Comparator	Risk
[48]	191	HBsAg(−)/anti-HBc(+)	13.8%	NA	0%	316†	0%	23.6%	11.1%	NA	
[49]	1123	3 HBV markers tested	52.6%	41.9%	100%	76%	NA	14.2%	0.6%	NA	
[8]	2185	3 HBV markers tested	34.8%	30.1%	NA	70%	6.7%	17.0%	NA	HBsAg(+) Anti-HBs(+)/ anti-HBc(+)	Younger, IDU, HCV IDU, HCV
[50]	30	Isolated anti-HBc	43.3%	NA	100%	90%	0%	100.0%	36.7%	NA	
[9]	240	3 HBV markers tested	23.8%	18.3%	97.5%	457†	8.3%	17.5%	35.0%	Not isolated anti-HBc	HCV
[51]	313	HBsAg(−)/anti-HBc(+)	32.7%	NA	NA	NA	0%	28.1%	3.3%	NA	
[40]	57	Isolated anti-HBc	57.9%	52.6%	NA	310*	0%	100.0%	89.5%	NA	

Note: High HBV endemicity is defined as HBsAg prevalence of ≥8%, intermediate HBV endemicity as HBsAg prevalence of 2–8% and low HBV endemicity as HBsAg prevalence of <2% [19]; Pt No. = number of study patients; HBV markers = HBV markers of study populations; HCV = percentage of study patients with hepatitis C virus infection; IDU = percentage of injecting drug users in the study population; ART = percentage of study patients receiving antiretroviral therapy; CD4 >200 = percentage of patients with CD4 counts >200 cells/μL (*median CD4 counts of one or two patient groups in the studies; †mean CD4 counts of one, two or three patient groups in the studies); Isolated = percentage of study patients with isolated anti-hepatitis B core antibody; viremia/isolated = percentage of detectable hepatitis B virus DNA in patients with isolated anti-hepatitis B core antibody; complete = with 3 HBV markers tested, including hepatitis B surface antigen (HBsAg), anti-hepatitis B surface antibody (anti-HBs) and anti-hepatitis B core antibody (anti-HBc); NA = not available; comparator = reference groups for assessment of risk factors associated with isolated anti-HBc; risk = risk factors associated with anti-HBc.

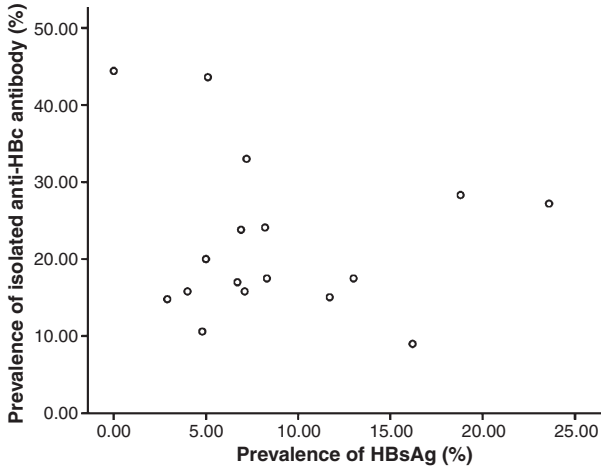

Fig. 1 Correlation between the overall prevalence of HBsAg and that of isolated anti-HBc from studies with available data. No correlation was observed between the two prevalences (P = 0.866 by Spearman's rho).

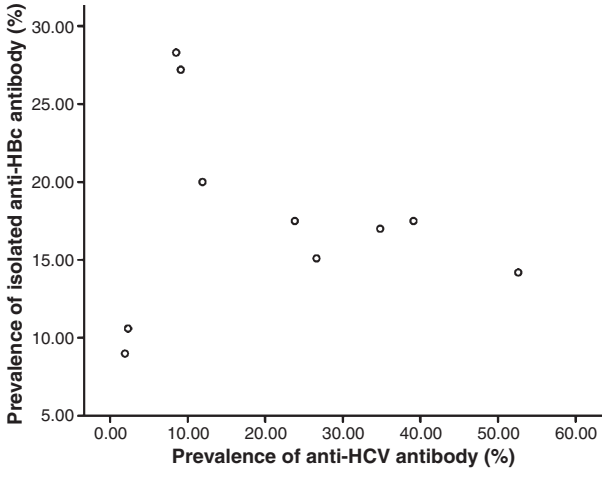

Fig. 2 Correlation between the overall prevalence of anti-HCV and that of isolated anti-HBc from the studies with available data. No correlation was observed between the two prevalence (P = 0.894 by Spearman's rho).

these patients, and their HBV DNA levels were higher than the levels of patients with isolated anti-HBc. Likewise, HBV DNA has also been detected in patients with anti-HBs in other studies [36–38]. One study reported 41% (7/17) of HIV-positive patients with occult HBV infection had anti-HBs or 7% (7/101) of patients positive for anti-HBs had occult HBV infection [38]. The authors suggest the presence of anti-HBs does not rule out occult HBV infection [38]. Although occult HBV infection can cause transmission of HBV and development of chronic liver disease or hepatocellular carcinoma in HIV-negative populations [39], the clinical significance of occult HBV infection with regard to hepatic events in HIV-positive patients is less clear [38,40–42].

Several limitations deserve to be acknowledged. First, given the retrospective study design, we included only patients who had determinations of all three HBV markers to assess factors associated with isolated anti-HBc and patients who had archived blood samples at baseline for determinations of HBV DNA; those patients differed in several demographic and clinical characteristics from those who were not included for analysis, which warrants caution in interpretation of our data. Second, the result of isolated anti-HBc may be false-positive depending on the anti-HBc test employed [5,29]. In this study, we did not repeat tests for isolated anti-HBc to rule out false positivity. Third, given the low and fluctuating HBV DNA levels in the serum, the real-time PCR with a detection limit of 1000 copies/mL employed in the present study might not be sensitive enough to detect HBV DNA in some of the patients. Fourth, only 5.8% of patients positive for both anti-HBs and anti-HBc were tested for serum HBV DNA, which limits our interpretation and further analysis of their association. Fifth, because approximately 20% of people clear HCV after infection, use of anti-HCV to define HCV infection in this study is likely to underestimate the actual prevalence of HCV infection. Sixth, the retrospective and cross-sectional study design may preclude us from assessing the clinical relevance of isolated anti-HBc and occult HBV infection in this population. Lastly, we were not able to exclude the possibility that isolated anti-HBc can be observed in the interval between the loss of HBsAg and the appearance of anti-HBs (a resolving acute HBV infection) [43], although it was infrequently seen in the HIV-infected adults in Taiwan [13,14].

In summary, isolated anti-HBc was present in 17.5% of HIV-positive patients in whom HBsAg seroprevalence was as high as 19.1%. Presence of isolated anti-HBc was associated with older age and severe immunosuppression with CD4 <100 cells/μL, suggesting compromised immunity may play a role. Review of the literature did not demonstrate good correlation between prevalence of isolated anti-HBc and prevalence of HBV or HCV coinfection.

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CONFLICT OF INTEREST

All authors, no conflicts.

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