Seroprevalence of Chronic Hepatitis B Virus Infection Among Taiwanese Human Immunodeficiency Virus Type 1–Positive Persons in the Era of Nationwide Hepatitis B Vaccination

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OBJECTIVES: **We aimed to assess the impact of nationwide hepatitis B virus (HBV) vaccination program on the seroprevalence of HBV infection among human immunodeficiency virus (HIV)–positive persons in a country where most HBV exposure occurs during the perinatal period or in early childhood.**

METHODS: **Data on HBV surface antigen (HBsAg), anti-HBV surface (anti-HBs), anti-HBV core (anti-HBc), and anti-hepatitis C virus (anti-HCV) antibody were retrospectively collected from 3,164 HIV-positive and 2,594 HIV-negative persons between 2004 and 2007. Comparisons of serological markers of HBV and HCV were made between HIV-positive and -negative adults born before and after the implementation of the HBV vaccination program in Taiwan in July 1984.**

RESULTS: **Compared with HIV-negative persons, the adjusted odds ratio for HBsAg seropositivity was 1.100 (95% confidence interval, 0.921–1.315) among HIV-positive persons. Although the seroprevalence of anti-HCV antibody remained similar between HIV-positive persons born before and those born after 1984, the seroprevalence of HBsAg declined from 20.3 to 3.3% in HIV-positive persons ($P<0.001$) and from 15.5 to 8.5% in HIV-negative persons ($P<0.001$). Despite the high seroprevalence of anti-HCV antibody (97.1%) in HIV-positive injecting drug users (IDUs), there was no statistically significant difference in the seroprevalence of HBsAg (5.6% vs. 8.5%, $P=0.75$) or anti-HBc antibody (40.7% vs. 27.9%, $P=0.14$) between HIV-positive IDUs and HIV-negative persons who were born after 1984.**

CONCLUSIONS: **Our study showed a significant decline of seroprevalence of HBV infection among both HIV-negative and -positive persons who were born in the era of the nationwide HBV vaccination in Taiwan.**

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INTRODUCTION

Prevalence of chronic hepatitis B virus (HBV) infection is higher in human immunodeficiency virus (HIV)-positive population than in HIV-negative population, because these two viruses share the same transmission routes (1–3). However, the predominant routes of HIV and HBV transmission, in different geographic regions, might influence the extent to which HBV seroprevalence differs between HIV-positive and -negative populations. In regions with a low HBV endemicity, sexual exposure and injecting drug use are the two major routes for HBV and HIV transmissions. HIV and HBV infections may occur concurrently when people engage themselves in high-risk behaviors. In the regions of Africa and Asia where HBV endemicity is high, most HBV exposure occurs during perinatal period or in early childhood (4); people develop either chronic hepatitis B infection or immunity against HBV long before the HIV infection occurs. Thus, exposure to HBV (5,6) and prevalence of chronic HBV infection (7–10) were similar between HIV-positive and -negative persons in these regions.

Highly active antiretroviral therapy (HAART) has successfully prolonged the survival of HIV-positive persons (11,12), and HAART containing lamivudine and/or tenofovir provides additional virological benefits in terms of suppression of HBV replication. Nevertheless, persons with HIV and HBV coinfection remain at significantly higher risks for all-cause and liver-related mortality than those without coinfection (1,2,13,14). Thus, HBV vaccination is recommended for persons at risk for, or having, a diagnosis of HIV infection who remain susceptible to HBV transmission (15). However, HIV-positive persons receiving HBV vaccination had lower response rates than HIV-negative persons (16–21). In addition, HIV-positive persons also had lower levels and variable persistence of protective anti-HBV surface (anti-HBs) antibody titers. Furthermore, on a population level, benefits of nationwide or targeted HBV vaccination have seldom been evaluated in high-risk populations, such as HIV-positive persons or injecting drug users (IDUs) (22).

Before implementation of the nationwide universal HBV vaccination program in Taiwan in July 1984, as many as 15% of adults were chronic HBV carriers, and vertical transmission had been the main route of HBV infection (23–25). Although the long-term immunogenicity and efficacy of universal HBV vaccination among persons born after 1984 has been documented (26–33), the impact of this nationwide HBV vaccination program on high-risk populations, such as HIV-positive persons and IDUs, remains unknown. Thus, this study aimed to compare the seroprevalence of HBV surface antigen (HBsAg) between HIV-positive persons of different transmission routes and HIV-negative persons who were born before and between those persons who were born after July 1984, when the nationwide HBV vaccination program was implemented in Taiwan.

METHODS

Study populations

By the end of 2007, there were 15,011 reported cases of HIV infection in Taiwan through several active and passive surveillance systems for HIV around the island (34). With a population of 23 million in Taiwan, the HIV seroprevalence rate among adults aged 15–49 years was estimated as 0.07% in 2003; the HIV seroprevalence among pregnant women was 15.7 per 100,000 in an universal HIV testing among 198,034 pregnant women in 2006. Perinatal transmission of HIV was diagnosed in 25 newborns as of 2007, and HIV infection was diagnosed in 46 persons aged <15 years over the two decades of HIV epidemic. 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%) (34). However, an outbreak of HIV infection occurred among IDUs by sharing needles and heroin diluents since 2003, and IDUs accounted for two-thirds of all cases of newly diagnosed HIV infection in 2005 and 2006 (34,35).

In this study, we retrospectively reviewed medical records of 4,176 HIV-positive persons aged >15 years who sought medical care for HIV infection between 2004 and 2007 at designated hospitals in Taiwan. HIV infection was diagnosed by the detection of anti-HIV antibody using ELISA or particle agglutination and confirmed by western blot test. Control group consisted of 2,594 consecutive HIV-negative persons aged >15 years who sought health check-up at the same designated hospitals during the same study years.

A computerized data collection form was used to extract their demographic and clinical data, which included birth date, sex, HIV transmission route, baseline CD4+ lymphocyte count, and plasma HIV RNA load, and test results of anti-hepatitis C virus (anti-HCV) antibody, HBsAg, anti-HBs antibody, and anti-HBV core (anti-HBc) antibody at baseline. The Institutional Review Board of the hospitals approved the study and waived the need for informed consent.

HBV vaccination program in Taiwan

In July 1984, the Taiwan government launched the nationwide universal HBV vaccination program (25). The program was initially implemented to vaccinate newborns of HBsAg-positive mothers in July 1984, and subsequently extended to cover all newborns after July 1986 (25). It was further extended to cover susceptible preschool children, school children, teenagers, and then adults from July 1987 to 1990. Since 1991, the vaccination records of school children aged 7 years were checked, and those children who were not vaccinated or incompletely vaccinated were given catch-up HBV vaccination (25,26). Therefore, persons born between January 1982 and June 1984 might have the chance to receive catch-up HBV vaccination in their childhood. The coverage rate of the nationwide HBV vaccination program was estimated to be 86.9–98.0% (26).

Laboratory investigations

HBsAg, anti-HBs antibody, and anti-HBc antibody were determined with the use of enzyme immunoassay (Abbott Laboratories, Abbott Park, IL). Antibodies to HCV were determined with the use of a third-generation enzyme immunoassay (Ax SYM HCV III; Abbott Laboratories, North Chicago, IL). Plasma HIV RNA load was quantified using reverse transcription-PCR (Roche Amplicor, COBAS AMPLICOR MONITOR version 1.5; Roche Diagnostics, Branchburg, NJ) with a lower detection limit of 400 (2.60 $\log_{10}$) copies/ml, and CD4 counts were determined using FACFlow (BD FACSCalibur Flow Cytometer; Becton Dickinson, San Jose, CA).

Statistical analysis

All statistical analyses were performed using SPSS software version 15.0 (SPSS Inc., Chicago, IL). Categorical variables were compared using χ^2 or Fisher's exact test, whereas non-categorical variables were compared using Mann–Whitney *U*-test. A multiple logistic regression model was built to identify independent variables associated with the seropositivity of anti-HCV antibody, HBsAg, anti-HBs, and anti-HBc antibody. All tests were two-tailed and a *P* value <0.05 was considered significant.

RESULTS

During the study period, 4,176 HIV-positive persons sought HIV care at the designated hospitals and 3,164 (75. 8%) tested for HBsAg were enrolled to evaluate the impact of universal HBV vaccination on the seroprevalence of HBsAg. Compared with the 1,012 (24.2%) HIV-positive persons who did not receive tests for HBsAg, those receiving the tests were older, had acquired HIV infection through sexual transmission, had a lower median CD4 count, and a higher median plasma HIV RNA load (data not shown). Among the enrolled HIV-positive persons, 1,170 (37.0%) identified themselves as MSM, 505 (16.0%) as heterosexuals, 1,109 (35.1%) as IDUs, and 380 (11.9%) had unknown risk factors. As multiple comparisons showed no differences of seroprevalence of HBsAg and anti-HCV antibody between MSM and heterosexuals (data not shown), they were analyzed together as sexual transmission group.

The demographic and clinical characteristics of 3,164 HIV-positive and 2,594 HIV-negative persons are shown in **Table 1**. Here, of the HIV-positive persons, 3,034 and 91 were born before and after the implementation of the nationwide HBV vaccination program in July 1984, respectively; the respective number was 1,737 and 857 for HIV-negative persons. Among HIV-positive persons, IDUs were younger and had higher CD4 counts and lower plasma HIV RNA loads than the sexual transmission group, because most of the IDUs who were infected with HIV in Taiwan were detected between 2003 and 2006 (**Table 1**) (35).

Comparisons of overall seroprevalence of HBsAg, anti-HBs antibody, and anti-HBc antibody between HIV-positive and -negative persons

Overall, HIV-positive persons had a significantly higher seroprevalence of HBsAg (19.8% vs. 13.2%, $P<0.001$) and anti-HBc antibody (77.7% vs. 57.5%, $P<0.001$) than HIV-negative persons, whereas the seroprevalence of anti-HBs antibody was lower in HIV-positive persons (56.0% vs. 61.9%, $P<0.001$) (**Table 1**). However, the difference in the seroprevalence of HBsAg was caused by the enrollment of more HIV-negative persons who were aged <25 years than HIV-positive persons (36.2% vs. 5.1%). The seroprevalences of HBsAg of different age groups are shown in **Figure 1** (**Supplementary Tables 1–3** online). After adjustment for age, sex, and being born after July 1984, the odds ratio for HBsAg seropositivity among HIV-positive persons compared with HIV-negative persons was 1.100 (95% confidence interval (CI), 0.921–1.315).

Similarly, HIV-positive persons in the sexual transmission group did not have a higher risk for HBsAg seropositivity than HIV-negative persons after adjustment (adjusted odds ratio, 1.170; 95% CI, 0.957–1.431), and neither did IDUs compared with HIV-negative persons (adjusted odds ratio, 1.152; 95% CI, 0.911–1.456). Nevertheless, compared with HIV-negative persons, HIV-positive persons in the sexual transmission group were less likely to have positive anti-HBs antibody and more likely to have positive anti-HBc antibody with adjusted odds ratio of 0.703 (95% CI, 0.601–0.823) and 1.515 (95% CI, 1.255–1.828), respectively. On the other hand, IDUs had a higher risk for positive anti-HBc antibody (adjusted odds ratio, 2.924; 95% CI, 2.319–3.685), but a similar risk for positive anti-HBs antibody (adjusted odds ratio, 1.021; 95% CI, 0.841–1.239) compared with HIV-negative persons.

Comparisons of overall seroprevalence of anti-HCV antibody, HBsAg, anti-HBs, anti-HBc antibody between HIV-positive persons in the sexual transmission group and IDUs

Compared with the HIV-positive persons in the sexual transmission group, IDUs had a significantly higher seroprevalence of anti-HCV antibody (96.8% vs. 6.4%, $P<0.001$), anti-HBc antibody (82.1% vs. 76.0%, $P=0.001$), and anti-HBs antibody (61.6% vs. 53.3%, $P<0.001$); however, seroprevalence of HBsAg was similar between the two groups (20.1% vs. 20.1%, $P=0.994$) (**Table 1**). After adjustment for age, sex, being born after July 1984, CD4, and log plasma HIV RNA load, the respective adjusted odds ratio for HBsAg, anti-HBs, and anti-HBc antibody in IDUs compared with the sexual transmission group was 1.198 (95% CI, 0.944–1.521), 1.111 (95% CI, 0.902–1.367), and 1.811 (95% CI, 1.394–2.353), respectively. Here, of note, the higher the CD4 count, the higher the seroprevalence of anti-HBs antibody (odds ratio, 1.001; 95% CI 1.000–1.001; $P<0.001$), but not that of HBsAg (odds ratio, 1.000; 95% CI 0.999–1.000; $P=0.51$), and anti-HBc antibody (odds ratio, 1.000; 95% CI 0.999–1.000; $P=0.16$) (**Supplementary Table 4**).

Comparisons of seroprevalence of HBsAg and anti-HBc antibody in HIV-negative and -positive persons who were born before and after July 1984

After the implementation of the nationwide HBV vaccination, the seroprevalence of HBsAg declined significantly

Table 1. Comparisons of demographic and clinical characteristics between HIV-positive persons with different risks for HBV infection and HIV-negative persons

	All HIV-positive persons	Sexual transmission group	IDUs	HIV-negative persons	*P* value[a]	*P* value[b]	*P* value[c]	*P* value[d]
Number of persons	3,164	1,675 (53.0)	1,109 (35.1)	2,594	—	—	—	—
Male, *n* (%)	2,911 (92.0)	1,553 (92.7)	1,018 (91.8)	1,800 (69.4)	<0.001	<0.001	<0.001	0.370
Median age (range) (years)	37 (16–95)	39 (16–95)	35 (16–73)	38, 16–94	0.020	<0.001	0.043	<0.001
Age groups, n *(%)*								
<24 years	160 (5.1)	73 (4.4)	57 (5.1)	938 (36.2)	<0.001	<0.001	<0.001	<0.001
25–34 years	1,092 (34.5)	479 (28.6)	497 (44.8)	291 (11.2)				
35–44 years	1,106 (35.0)	606 (36.2)	380 (34.3)	261 (10.1)				
45–54 years	472 (14.9)	267 (15.9)	153 (13.8)	378 (14.6)				
>55 years	295 (9.3)	212 (12.7)	22 (2.0)	726 (28.0)				
Unknown	39 (1.2)	38 (2.3)	0 (0)	0 (0)				
Born after 1 July 1984, *n* (%)	91 (2.9)	38 (2.3)	36 (3.2)	857 (33.0)	<0.001	<0.001	<0.001	0.142
Median CD4 (range), cells/μl (3,034)[e]	288 (0–2,760)	137 (0–1,202)	402 (1–1,943)	NA	—	—	—	<0.001
<100 cells/μl, *n* (%)	852 (28.1)	733 (45.1)	24 (2.3)	NA	—	—	—	<0.001
<200 cells/μl	1,142 (37.6)	948 (58.3)	59 (5.6)	NA	—	—	—	<0.001
Median PVL (range) log_{10} copies/ml (2,752)[e]	4.6 (1.7–7.2)	5.1 (1.7–7.2)	4.2 (1.7–6.0)	NA	—	—	—	<0.001
>5 log_{10} copies/ml, *n* (%)	939 (34.1)	711 (52.5)	106 (10.1)	NA	—	—	—	<0.001
Positive HBsAg, *n*/*N* (%)	628/3,164 (19.8)	337/1,675 (20.1)	223/1,109 (20.1)	342 (13.2)	<0.001	<0.001	<0.001	0.994
Positive anti-HBs antibody, *n*/*N* (%)	1,512/2,698 (56.0)	832/1,561 (53.3)	551/894 (61.6)	1,606 (61.9)	<0.001	<0.001	0.882	<0.001
Positive anti-HBc antibody, *n*/*N* (%)	1,906/2,454 (77.7)	1,036/1,363 (76.0)	716/872 (82.1)	1,491 (57.5)	<0.001	<0.001	<0.001	0.001
Positive anti-HCV antibody, *n*/*N* (%)	1,227/2,912 (42.1)	97/1,504 (6.4)	1,035/1,069 (96.8)	NA	—	—	—	<0.001

IDUs, injecting drug users; NA, not applicable; *n*, number of persons with positive results; *N*, number of persons with data available; PVL, plasma HIV RNA load.
[a]Total HIV-positive persons vs. HIV-negative persons; [b]sexual transmission group vs. HIV-negative persons; [c]IDUs vs. HIV-negative persons; [d]sexual transmission group vs. IDUs; [e]number of patients with data available.

from 15.5% in HIV-negative persons born before 1984 to 8.5% in those born after 1984; the corresponding seroprevalence of anti-HBc antibody declined from 72.1 to 27.9% ($P<0.001$) (**Figure 2**). Similar declines were also observed among HIV-positive persons; the seroprevalence of HBsAg declined from 20.3% in HIV-positive persons born before 1984 to 3.3% in those born after 1984, and the corresponding seroprevalence of anti-HBc antibody declined from 78.9 to 30.0% ($P<0.001$) (**Figure 2**). In contrast, no change in seroprevalence of anti-HCV antibody was observed in HIV-positive persons enrolled during two different periods (42.5% (1,188/2,795) vs. 45.8% (38/83), $P=0.552$). In the sexual transmission group, no significant difference existed in the seroprevalence of anti-HCV (6.6% (95/1,437) vs. 2.9% (1/34), $P=0.614$) in the two periods, but the corresponding seroprevalence of HBsAg declined from 20.5 (327/1,599) to 0% (0/38) ($P=0.002$). With regard to IDUs, the seroprevalence of HBsAg also decreased from 20.6 (221/1,073) to 5.6% (2/36) ($P=0.027$), although the seroprevalence of anti-HCV antibody among IDUs born before and after 1984 remained as high as 96.8 (1,001/1,034) and 97.1% (34/35) ($P=1.000$), respectively.

The seroprevalence of HBV infection was compared among persons born in the following three periods: before December 1981, from January 1982 to June 1984, and after July 1984. The trends of increasing seroprevalence of anti-HBs antibody and decreasing seroprevalence of HBsAg and anti-HBc antibody, across the three periods, were clearly shown

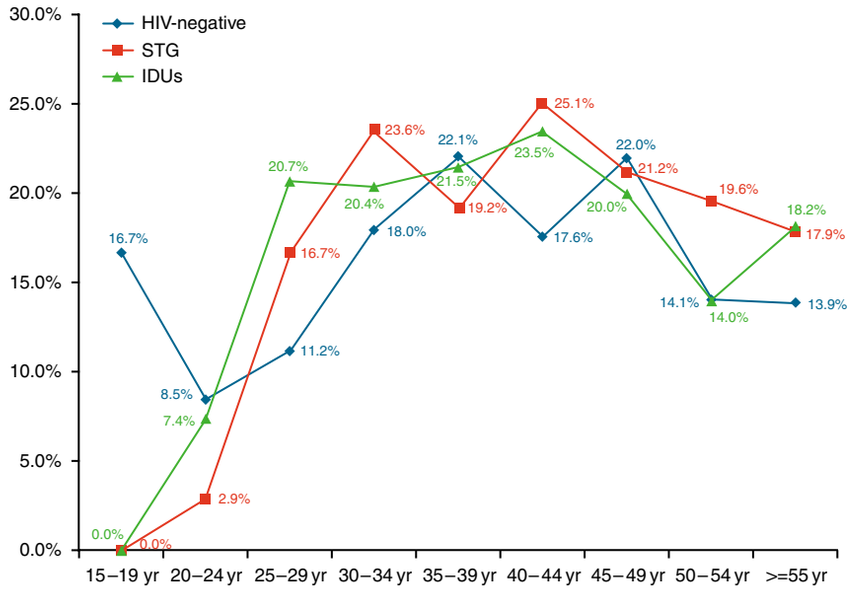

Figure 1. The seroprevalence of hepatitis B surface antigen (HBsAg) against age in HIV-positive and -negative persons. The seroprevalence of HBsAg reached the plateau at the age group of 30–34 years (yr) among HIV-negative persons and HIV-positive persons of the sexual transmission group (STG). Among the injecting drug users (IDUs), the age group to reach plateau of seroprevalence of HBsAg was 25–29 years.

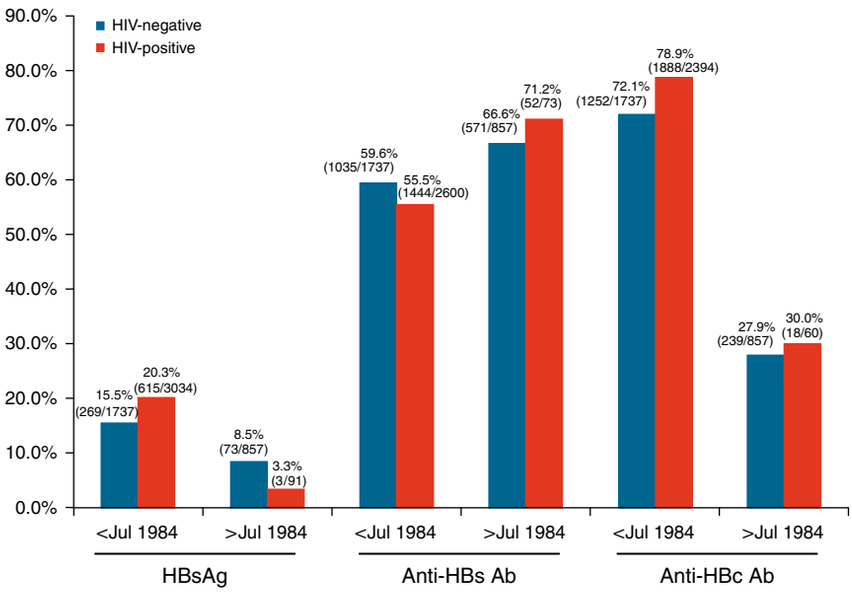

Figure 2. Comparisons of seroprevalence of HBsAg, anti-HBs antibody (anti-HBs Ab), and anti-HBc antibody (anti-HBc Ab) between HIV-positive and -negative persons born before (<July 1984) and after July 1984 (>July 1984). Although there were differences in the seroprevalence of HBsAg, anti-HBs Ab, and anti-HBc Ab between HIV-positive and -negative persons born before July 1984, similar seroprevalence of these HBV markers was observed between the two groups born after July 1984.

in both HIV-negative and -positive persons of different risk factors (**Table 2**; **Supplementary Figure 1**). In contrast, the seroprevalence of anti-HCV antibody across the three periods were similar in the HIV-positive sexual transmission group and IDUs, respectively (**Table 2**).

Comparisons of seroprevalence of HBsAg, anti-HBs, and anti-HBc antibody between HIV-positive and -negative persons born in the era of nationwide HBV vaccination

Compared with HIV-negative persons born before July 1984, HIV-positive persons born before July 1984 were more likely

Table 2. Comparison of seroprevalence of hepatitis B infection between HIV-negative and -positive persons under different HBV vaccination policies (through December 1981: no HBV vaccination; January 1982–June 1984: catch-up HBV vaccination; July 1984 and onward: universal HBV vaccination)

Birth	Through December 1981	January 1982–June 1984	July 1984 and onward
HIV-negative, n/N[a] *(%)*			
HbsAg	258/1,617 (16.0)[b,c]	11/120 (9.2)	73/857 (8.5)
Anti-HBs antibody	95/1,617 (58.8)[b,c]	84/120 (70.0)	571/857 (66.6)
Anti-HBc antibody	1,215/1,617 (75.1)[b,c]	37/120 (30.8)	239/857 (27.9)
HIV-positive, n/N[a] *(%)*			
Overall			
HBsAg	597/2,896 (20.6)[b,c]	18/138 (13.0)[b]	3/91 (3.3)
Anti-HBs antibody	1,364/2,483 (54.9)[b,c]	80/117 (68.4)	52/73 (71.2)
Anti-HBc antibody	1,834/2,285 (80.3)[b,c]	54/109 (49.5)[b]	18/60 (30.0)
Anti-HCV antibody	1,133/2,668 (42.5)	55/127 (43.3)	38/83 (45.8)
Sexual			
HBsAg	322/1,534 (21.0)[b,c]	5/65 (7.7)	0/38 (0)
Anti-HBs antibody	750/1,443 (52.0)[c]	44/61 (72.1)	22/32 (68.8)
Anti-HBc antibody	1,006/1,286 (78.2)[b,c]	26/52 (50.0)[b]	4/25 (16.0)
Anti-HCV antibody	94/1,379 (6.8)	1/58 (1.7)	1/34 (2.9)
IDUs			
HBsAg	211/1,022 (20.6)[b]	10/51 (19.6)	2/36 (5.6)
Anti-HBs antibody	500/825 (60.6)[b]	27/40 (67.5)	24/29 (82.8)
Anti-HBc antibody	685/806 (85.0)[b,c]	20/39 (51.3)	11/27 (40.7)
Anti-HCV antibody	954/985 (96.9)	47/49 (95.9)	34/35 (97.1)

HBV, hepatitis B virus; HBc, HBV core; HBs, HBV surface; HBsAg, HBV surface antigen; HCV, hepatitis C virus; IDUs, injecting drug users.
[a]*n*/*N*: number of persons with positive results/number of persons with data available; [b]compared with persons born in or after July 1984, $P<0.05$; [c]comparison between persons born before 1982 and January 1982–June 1984, $P<0.05$.

to have positive anti-HBc antibody (adjusted odds ratio, 1.817; 95% CI, 1.525–2.164) and less likely to have positive anti-HBs antibody (adjusted odds ratio, 0.775; 95% CI, 0.669–0.898) after adjustment for age and sex, but the risk for HBsAg positivity was similar between the two groups with an adjusted odds ratio of 1.138 (95% CI, 0.946–1.368). However, in the era of nationwide HBV vaccination, there were no statistically significant differences between HIV-positive and -negative persons with respect to the overall seroprevalence of HBsAg (3.3% vs. 8.5%, $P=0.08$), anti-HBs antibody (71.2% vs. 66.6%, $P=0.42$), and anti-HBc antibody (30.0% vs. 27.9%, $P=0.73$) (**Figure 2**).

For persons born during January 1982–June 1984, who might have received catch-up HBV vaccination in their childhood, there were no statistically significant differences with regard to the seroprevalence of HBsAg (13.0% vs. 9.2%) and anti-HBs antibody (68.4% vs. 70.0%) between HIV-positive and -negative persons, except for a higher seroprevalence of anti-HBc antibody in HIV-positive persons (49.5% vs. 30.8%, $P=0.004$) (**Table 2**). However, after adjustment for age and sex, HIV-positive persons born during this period did not have a higher risk for positive anti-HBc antibody than HIV-negative persons (adjusted odds ratio, 1.717; 95% CI, 0.922–3.198).

After implementation of the nationwide HBV vaccination, the comparisons between HIV-positive sexual transmission group and HIV-negative persons were similar with respect to the seroprevalence of HBsAg (0% (0/38) vs. 8.5% (73/857), $P=0.115$), anti-HBs antibody (68.8% (22/32) vs. 66.6% (571/857), $P=0.80$), and anti-HBc antibody (16.0% (4/25) vs. 27.9% (239/857), $P=0.19$). Although the seroprevalence of anti-HCV antibody was as high as 97.1% (34/35) in HIV-positive IDUs born after July 1984, no statistically significant differences were observed in the seroprevalence of HBsAg (5.6% (2/36) vs. 8.5% (73/857), $P=0.75$), anti-HBs antibody (82.8% (24/29) vs. 66.6% (571/857), $P=0.07$), and anti-HBc antibody (40.7% (11/27) vs. 27.9% (239/857), $P=0.14$) between IDUs and HIV-negative persons.

DISCUSSION

In this study that was conducted in a country of HBV hyperendemicity, we show that HIV-positive and -negative persons had a similar risk for HBsAg sero-positivity, because most exposure to HBV that results in either development of anti-HBs antibody or chronic carriers of HBV in Taiwan before the implementation of the nationwide HBV vaccination program, occurred during perinatal period or in early childhood, long before HIV infection occurs. This finding is in contrast to what has been observed in countries of low HBV endemicity in which most HBV and HIV infections occur in young adulthood or adulthood, because the risk of becoming chronic carriers of HBV after exposure to HBV in adulthood is estimated to be <5%, which is significantly lower than that after exposure to HBV in the perinatal period (90%) (36).

HBV coinfection not only increases the risk for hepatotoxicity of antiretroviral therapy (37), but also for chronic hepatic complications, such as cirrhosis of the liver and hepatocellular carcinoma, in HIV-positive persons (13). Indeed, liver-related death has become the leading cause of death in the era of HAART (1,14). Early HAART often contains only lamivudine, which also possesses activity against HBV; the risk for emergence of HBV resistant to lamivudine is higher those who are HIV-positive persons than those who are HIV-negative (38). Therefore, the high prevalence of chronic HBV infection among HIV-positive persons would become a challenge to long-term success in the management of HIV infection in Taiwan, where sequential introduction of antiretroviral agents with anti-HBV activity may encourage the emergence of HBV resistance to currently available antiretroviral agents.

Seroprevalence of HBV infection has declined substantially in the general population after the implementation of the universal HBV vaccination program in Taiwan (26–33). Likewise, we also showed that receipt of HBV vaccination at birth or childhood also benefits the persons who may subsequently engage themselves in high-risk behaviors for HIV transmission in their adolescence or adulthood (**Table 2** and **Figure 2**). Regardless of risk behaviors, the overall seroprevalence of HBsAg decreased from 20.3% in HIV-positive persons born before July 1984 to 3.3% in those born after, and that of anti-HBc antibody decreased from 78.9 to 30.0%. Similar declines of seroprevalence of HBsAg were observed in both the sexual transmission group and IDUs. The declines could be attributed to the implementation of the universal HBV vaccination program that targeted newborns and children and shorter duration of exposure to HBV in those persons who were born after 1984 than their counterparts who were born before 1984. However, the latter argument is not supported by our findings that seroprevalence of anti-HCV antibody, which was significantly higher in IDUs than the sexual transmission group, remained similar among IDUs who were born in the three different observation periods (before December 1981, from January 1982 to June 1984, and after July 1984). This suggests that the risks of exposure to HBV or HCV among the susceptible persons who are also at high risk for HIV transmission are similar among different birth cohorts in Taiwan.

Despite similar risk for HBsAg seropositivity, HIV-positive persons born before July 1984 did have a higher risk for positive anti-HBc antibody than HIV-negative persons born before July 1984 did. As high-risk behaviors increase the exposure to HBV in HIV-positive persons who might not acquire HBV during childhood, it is not surprising that the seroprevalence of anti-HBc antibody is higher in HIV-positive persons, especially in IDUs, than in HIV-negative persons (**Table 1**). In addition, we found that seroprevalence of anti-HBs antibody was higher in those persons with higher CD4 counts (odds ratio, 1.001; 95% CI 1.000–1.001; $P<0.001$), which may explain why HIV-positive persons in the sexual transmission group, who had significantly lower CD4 counts, had lower seroprevalence of anti-HBs antibody than IDUs and HIV-negative persons (**Table 1**).

There are several limitations in this study and interpretation of the results should be cautious. First, the number of HIV-positive persons who were born after 1984 is small, because prevalence of HIV infection remains very low in the age groups of 15–25 years in Taiwan (34), and continued surveillance is needed when more persons born after 1984 are likely to engage in high-risk activities for HIV transmission in the years to come. Second, the cross-sectional study design precludes us from determining whether the anti-HBs antibody may change over the ensuing years in those HIV-positive persons having undergone HBV vaccination who may or may not receive HAART. This may raise a concern with respect to potential risk of breakthrough HBV infection in those persons with declining anti-HBs antibody titers who develop progressive immunosuppression without receiving HAART or immunologic failure after HAART. Third, in this study, we were not able to identify specifically the HBV vaccination status and the date of vaccination of each person. However, given the high coverage rate of the nationwide HBV vaccination program (86.9–98.0%) (26) and several catch-up programs of HBV vaccination in the subsequent years after 1984 (25,26), it is quite likely that HIV-positive and -negative persons who were born after 1984 received HBV vaccination at birth or in the childhood.

In conclusion, we show that the nationwide HBV vaccination in Taiwan is associated with significant reduction of HBsAg prevalence in HIV-positive persons who were born after July 1984, regardless of the transmission routes of HIV infection.

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CONFLICT OF INTEREST

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

✓ The impact of the nationwide hepatitis B virus (HBV) vaccination program on the seroprevalence of HBV infection in HIV-positive persons is unknown.

WHAT IS NEW HERE

✓ A nationwide HBV vaccination program significantly reduces the seroprevalence of HBV infection in HIV-positive persons.

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