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Original Article

Hepatitis B virus seroprevalence among HIV-infected patients receiving combination antiretroviral therapy three decades after universal neonatal hepatitis B immunization program in Taiwan☆

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Abbreviations: aOR, adjusted odds ratio; cART, combination antiretroviral therapy; CI, confidence interval; FTC, emtricitabine; HBV, hepatitis B virus; HCV, hepatitis C virus; LAM, lamivudine; TDF, tenofovir disoproxil fumarate.

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KEYWORDS
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Abstract *Background/purpose:* This multicenter study aimed to evaluate the seroprevalence of hepatitis B virus (HBV) and the use of combination antiretroviral therapy (cART) among patients receiving HIV care in Taiwan.
Methods: We retrospectively reviewed the medical records of HIV-infected adult patients who initiated cART at 11 designated hospitals in Taiwan between 2012 and 2016. The clinical information collected included serological profiles on HBV, hepatitis C virus (HCV), and syphilis, plasma HIV RNA load, nadir CD4 cell count, and antiretrovirals with activity against both HBV and HIV (tenofovir disoproxil fumarate [TDF], lamivudine [LAM], and emtricitabine [FTC]).
Results: We analyzed 1800 HIV-infected patients; 1742 (96.8%) were male and 794 (44.1%) were born after July, 1986, when nationwide universal neonatal HBV vaccination was implemented. HBsAg positive results were 11.6% (209/1800), which decreased significantly from 18.1% (182/1006) in those born before July 1986 to 3.4% (27/794) in those born after. In multivariable analysis, HBsAg positivity was significantly associated with age (adjusted odds ratio [aOR] 1.06, 95% confidence interval [CI] 1.05–1.08), CD4≧200 cells/μL (aOR 0.73, 95% CI 0.53–0.99), and HCV seropositivity (aOR 1.62, 95% CI 1.06–2.50). Of 209 HBV/HIV-coinfected patients, 31.1% started cART containing only LAM with anti-HBV activity, while 68.9% started cART containing TDF plus LAM or coformulated TDF/FTC.
Conclusions: The overall prevalence of HBV/HIV coinfection remained high among HIV-infected patients in Taiwan. Despite recommendations of the HIV treatment guidelines for the management of HBV infection, a substantial proportion of HIV/HBV-coinfected patients received cART containing only LAM for HBV infection.

Introduction

Hepatitis B virus (HBV) infection is a common, but serious disease that can cause acute and chronic hepatitis if left untreated, which may be followed by development of complications such as cirrhosis of the liver and hepatocellular carcinoma (HCC).[1] In 2015, the World Health Organization (WHO) estimated that a total of 257 million people were living with HBV infection, defined as being positive for hepatitis B surface antigen (HBsAg) and 887,000 died. Of the 36.7 million people living with HIV infection, an estimated 2.7 million (7.4%) had HBV coinfection.[2]

HBV transmission may occur from exposure to infectious blood or other body fluids, sexual intercourse, or sharing items such as needles, syringes, razors, toothbrushes or other sharp instruments that come in contact with blood of an infected person.[3,4] However, HBV infection can be prevented by early vaccination, or by avoiding contact with blood or other body fluids.[3,4] In 1992, the WHO recommended that national HBV vaccination programs for neonates be implemented around the world, and, by the end of 2017, the program has been implemented in more than 188 countries.[5–7] The world's first nationwide universal HBV vaccination program for infants began in Taiwan in 1986.[8] All newborns received three to four doses of recombinant or plasma-derived HBV vaccines. In addition, infants born to HBeAg-positive mothers received hepatitis B immunoglobulin within 24 h of birth.[8] The vaccination coverage rate was as high as 98.7% in 2016.[9] A recent review on the long-term effectiveness of HBV vaccination in the general population indicated that, from 1974 to 1999, the prevalence of HBsAg positivity had declined from 9.8% (pre-vaccination period) to 0.6% among the university students in Taiwan.[10] Moreover, the incidence of HCC has significantly declined among children after implementation of neonatal HBV vaccination program.[11]

After primary vaccination with a 3-dose HBV vaccine series, anti-HBs concentrations decline gradually and 15%–50% of individuals in the general population have low or undetectable concentrations of anti-HBs 5–15 years after vaccination.[12] Despite HBV vaccination, HIV-infected patients seem to have a more rapid decline in anti-HBs due to

immunodeficiency,[13–15] and HBV infection may occur among those who had received HBV vaccines at birth or during their adolescence.[16] Once chronic HBV infection occurs, HBV/HIV-coinfected patients may have faster progression to complications with cirrhosis of the liver or HCC, compared with HIV-monoinfected patients.[17,18] Therefore, using combination antiretroviral therapy (cART) containing antiretrovirals with activity against HBV could be of vital importance to maintain HBV suppression or clear HBV infection in these HBV/HIV-coinfected patients.[19]

In this study, we aimed to evaluate the seroprevalence of HBV in HIV-infected patients and to examine the use of cART containing antiretrovirals with activity against HBV in these HBV/HIV-coinfected patients.

Methods

Study setting and population

This retrospective cohort study was conducted at 11 designated hospitals for HIV care around Taiwan.[20] Because the neonatal HBV vaccination program started in 1984 and was expanded to include all newborns after July 1986,[8] we divided the included patients into 2 groups: patients born in the universal neonatal vaccination era (in or after 1986) and those born in the pre-vaccination era.

HIV care, including cART and monitoring of CD4 lymphocyte count and plasma HIV RNA load (PVL), is provided free-of-charge to HIV-infected Taiwanese nationals according to the national HIV treatment guidelines,[20] in which serological investigations for HBV and hepatitis C virus (HCV) are recommended at baseline.[21,22] For those without immunity against HBV, vaccination is advised by following the Adult Committee on Immunization Practice (ACIP) of the Taiwan Centers for Disease Control. Serological tests for HCV are recommended to be performed once annually or when the risk of HCV transmission is high, particularly after diagnosis of syphilis or other sexually transmitted infections (STIs).[23]

The national HIV treatment guidelines had raised the CD4 cell count threshold for cART initiation from 350 to 500 cells/mm^3 in September 2013, which was further revised to treat all HIV-infected patients irrespective of CD4 cell count in June 2016.[24,25] Because of the concerns about increasing medical expenditure and budgetary constraints, Taiwan CDC implemented regulations on the regimens of cART to be initiated in antiretroviral-naive patients and, between 1 June 2012 and 31 May 2016, antiretroviral-naive patients were recommended to start cART with the preferred regimens of non-nucleoside reverse-transcriptase inhibitor (nNRTI) plus 2 NRTIs. After 1 June 2016, the preferred regimens have been changed to 3 single-tablet regimens, including coformulated efavirenz/emtricitabine (FTC)/tenofovir disproxil fumarate (TDF), rilpivirine/emtricitabine/TDF, and dolutegravir/abacavir/lamivudine (LAM). TDF and coformulated TDF/FTC were not available for HIV treatment in Taiwan until 2011 and 2015, respectively.[25] For the patients testing positive for HBsAg, TDF-containing cART is recommended as it has been shown to be effective in HBV/HIV-coinfected patients with or without HBV resistance to LAM.[26]

We reviewed the medical records of HIV-infected adult patients initiating cART to collect information on the demographic and clinical characteristics from 1 June 2012 to 31 May 2016. The data collected included birth date, sex, HIV transmission route, baseline HBsAg, anti-HBs, antibody to hepatitis B core antigen (anti-HBc), anti-HCV antibody, rapid plasma reagin (RPR) titer, baseline PVL, and nadir CD4 count. All of the laboratory tests were performed at each participating hospital by following the standard procedures of the manufacturers.[21,22,27] The patients were categorized into five groups according to their age: 20–24, 25–29, 30–34, 35–39, and 40 years or greater. Hence, the first 2 groups were born in the HBV vaccination era and the latter 3 in the pre-vaccination era (Table 1). We further divided the included patients into 2 categories according to the cART regimens they were receiving: (1) cART containing LAM only and (2) cART containing TDF and LAM or coformulated TDF and FTC.

Definitions

We defined all-negative HBV serology as being negative for HBsAg, anti-HBs and anti-HBc; vaccination-type serology as being positive only for anti-HBs due to HBV vaccination; past infection as being negative for HBsAg but positive for both anti-HBs and anti-HBc; HBV infection as being positive for HBsAg and negative for anti-HBs; and isolated anti-HBc positivity as being positive only for anti-HBc. HCV infection was defined as being seropositive for HCV.

Ethics

This was designed as a retrospective study by collecting the relevant data for analysis. Identification of the included patients was removed and data were analyzed anonymously. The study was approved by the Research Ethics Committee or Institutional Review Board of each participating hospital and the necessity for informed consent was waived.

Statistical analysis

We used SPSS for Windows Version 22.0 (SPSS Inc., Chicago, IL, USA) to analyze the data and applied the Chi-square or Fisher's exact test to compare categorical variables. Mann–Whitney U-test was used to analyze non-categorical variables. In logistic regression analysis, we examined the associations between HBsAg seropositivity with demographics (age and sex), behaviors (sexual orientation and people who inject drugs [PWID]), CD4 count, PVL, syphilis, anti-HCV positivity, and cART. Multivariate logistic regression models were applied to factors with p-value less than 0.05 found in univariate analysis. The results of the multivariate logistic models were expressed as adjusted odds ratios (aOR) with 95% confidence intervals (95% CI). Statistical significance was defined as a p-value less than 0.05 and all tests were two-tailed.

Table 1 Clinical characteristics of the included HIV-infected patients according to age group.

	All patients n (%)	Group I 20—24 years	Group II 25—29 years	Group III 30—34 years	Group IV 35—39 years	Group V 40 years	*p* value
All patients, N	1800	364	430	402	230	374	
Male gender, n (%)	1742 (96.8)	361 (99.2)	424 (98.6)	384 (95.5)	220 (95.7)	353 (94.4)	a **, b, c*,d*, e**
Risk, n (%)							
Heterosexuals	122 (6.8)	13 (3.6)	15 (3.5)	17 (4.2)	19 (8.3)	58 (15.5)	a **, b, c**, d**, e**
MSM	1514 (84.1)	350 (96.2)	411 (95.6)	356 (88.6)	173 (75.2)	224 (59.9)	
PWID	164 (9.1)	1 (0.3)	4 (0.9)	29 (7.2)	38 (16.5)	92 (24.6)	
CD4 <200 cells/mm^3, n (%)	648 (36.0)	91 (25.0)	123 (28.6)	144 (35.8)	91 (8.3)	199 (53.2)	a **, b, c*, d**, e**
PVL >100,000 copies/mL, n (%)	719 (39.9)	141 (38.7)	154 (35.8)	162 (40.3)	95 (41.3)	167 (44.7)	a, b, c, d, e
cART containing antiretrovirals with anti-HBV activity, n (%)							a **, b, c*, d**, e**
LAM only[f]	1071 (59.5)	252 (69.2)	274 (63.7)	233 (59.0)	110 (47.8)	202 (54.0)	
Dual HBV-active regimens[g]	729 (40.5)	112 (30.8)	156 (36.3)	169 (41.0)	120 (52.2)	172 (46.0)	
HBV serologic markers, n (%)							a **, b**, c**, d**, e**
All-negative	511 (28.4)	186 (51.1)	157 (36.5)	79 (19.7)	32 (13.9)	57 (15.2)	
Vaccination-type	645 (35.8)	137 (37.6)	200 (46.5)	178 (44.3)	72 (31.3)	58 (15.5)	
Past infection	335 (18.6)	24 (6.6)	49 (11.4)	71 (17.7)	61 (26.5)	130 (34.8)	
HBV infection	209 (11.6)	9 (2.5)	18 (4.2)	60 (14.9)	46 (20.0)	76 (20.3)	
Isolated anti-HBc positivity	100 (5.6)	8 (2.2)	6 (1.4)	14 (3.5)	19 (8.3)	53 (14.2)	
RPR titer ≥4, n (%)	292 (16.2)	53 (14.6)	85 (19.8)	68 (16.9)	28 (12.2)	58 (15.5)	a, b, c, d, e
RPR titer <4, n (%)	1508 (83.8)	311 (85.4)	345 (80.2)	334 (83.1)	202 (87.8)	316 (84.5)	
Anti-HCV-positive, n (%)	220 (12.2)	19 (5.3)	22 (5.1)	49 (12.2)	41 (17.8)	89 (23.8)	a **, b, c*, d**, e**
Anti-HCV-negative, n (%)	1576 (87.8)	342 (94.7)	408 (94.9)	353 (87.8)	188 (82.1)	285 (76.2)	

[a] Comparison among the five age groups.
[b] Comparison between Groups I and II.
[c] Comparison between Groups I and III.
[d] Comparison between Groups I and IV.
[e] Comparison between Groups I and V.
[f] Only LAM regimens: LAM, or zidovudine/LAM, or abacavir/LAM.
[g] Dual HBV-active regimens: tenofovir disoproxil fumarate with emtricitabine or LAM.

p value: *, P < 0. 01; **, P < 0.001.

Abbreviations: anti-HBc, anti-hepatitis B core; cART, combination antiretroviral therapy; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; LAM, Lamivudine; MSM, men who have sex with men; PVL, plasma HIV RNA load; PWID, people who inject drugs; RPR, rapid plasma reagin.

Results

Characteristics of the included patients

During the 4-year study period, 2226 HIV-infected patients who were antiretroviral-naïve and sought HIV care at the 11 participating hospitals. A total of 1800 (80.9%) HIV-infected patients were included in this study after we excluded 345 (15.5%) patients with incomplete HBV serologic data and 81 (3.6%) patients who did not initiate cART (Fig. 1). Of the 1800 patients, 1762 (96.8%) were male and 794 patients (44.1%) were born in the HBV vaccination era. The risk groups of HIV transmission included 1514 MSM (84.1%), 122 heterosexuals (6.8%), and 164 PWID (9.1%) (Table 1).

Five groups were defined according to the HBV serologic patterns: 511 (28.4%) with all-negative serologic pattern, 645 (35.8%) vaccination-type pattern, 335 (18.6%) past infection, 209 (11.6%) HBV infection, and 100 (5.6%) isolated anti-HBc positivity (Fig. 1). Compared with patients who were born in the HBV vaccination era, patients who were born in the pre-vaccination era had a significantly higher proportion of patients with CD4 count <200 cells/mm^3 (43.1% [434/1006] vs 33.0% [214/794]) (Table 1). The prevalence of patients with an RPR titer ≥ 4 were similar among the five age groups. The HCV seroprevalence, however, significantly increased with age, from 5.2% in those aged 20—24 years to 23.8% in those aged 40 years or greater (Table 1). The significant increases were likely related to the fact that the proportion of PWID increased from 0.3% (1/364) in those aged 20—24 years to 24.6% (92/374) in those aged 40 years or older.

Seroprevalence of HBV infection

HBsAg positive results were 11.6% (209/1800), which increased from 2.5% (9/364) in those aged 20—24 years to 20.3% (76/374) in those aged 40 years or older (Table 1 and Fig. 2). HIV-infected patients born in the era of universal neonatal HBV vaccination had a significantly lower HBV seroprevalence than those born in the pre-vaccination era (3.4% [27/794] vs 18.1% [182/1006], $P < 0.001$) (Table 1 and Fig. 2). The proportion of patients with all-negative HBV serological pattern fell significantly with age, from 51.1% (186/364) in those aged 20—24 years to 15.2% (57/374) in those aged 40 years or greater, so was the decline of the proportion of patients with vaccination-type serological pattern. After about 30 years of age, there was a sharper decline in the proportion of vaccination-type serological pattern, from 46.5% (200/430) in patients aged 25—29 years to 15.5% (58/374) in those aged 40 years or greater. In contrast, the prevalence of past HBV infection and isolated anti-HBc positivity increased significantly with age.

Patterns of HBV serological markers and risk groups

The serological patterns differed among different risk groups of HIV transmission (Table 2). MSM born in the pre-vaccination era had a significantly lower proportion of all-negative serological pattern compared with those born in the vaccination era (18.3% vs 47.5%, $P < 0.0001$) (Table 2). In contrast, there was no significant difference in the prevalence of vaccination-type serological pattern among MSM and heterosexuals between patients born in the pre-vaccination and those born in the vaccination era. Among

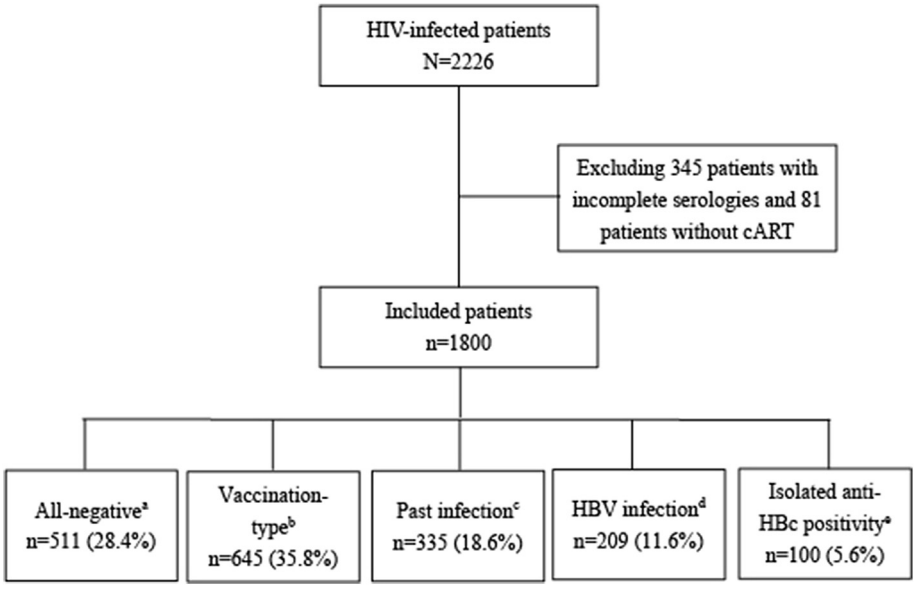

Figure 1. Study flow diagram. Abbreviations: anti-HBc, anti-hepatitis B core; cART, combined antiretroviral therapy; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen. [a] All-negative: HBsAg (−), anti-HBs(−), and anti-HBc(−); [b] Vaccination type: HBsAg (−), anti-HBs(+), and anti-HBc(−); [c] Past infection: HBsAg (−), anti-HBs(+), and anti-HBc(+); [d] HBV infection: HBsAg (+) and anti-HBs(−); [e] Isolated Anti-HBc positivity, HBsAg (−), anti-HBs(−), and anti-HBc(+).

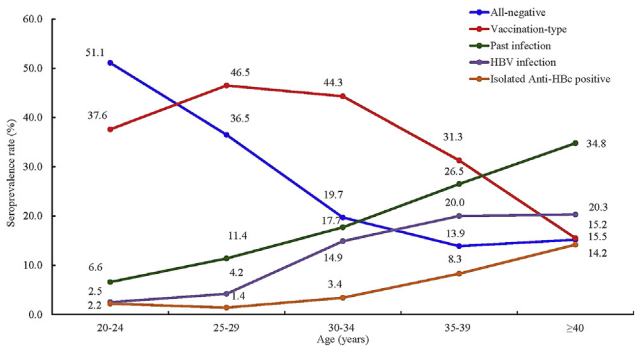

Figure 2. Trends of HBV seroprevalence in HIV-infected patients by age group. Abbreviations: Anti-HBc, anti-hepatitis B core; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen. All-negative: HBsAg (−), anti-HBs(−), and anti-HBc(−); Vaccination type: HBsAg (−), anti-HBs(+), and anti-HBc(−); Past infection: HBsAg (−), anti-HBs(+), and anti-HBc(+); HBV infection: HBsAg (+) and anti-HBs(−); Isolated anti-HBc positivity: HBsAg (−), anti-HBs(−), and anti-HBc(+).

PWID, patients born in the pre-vaccination era had a significantly lower proportion of vaccination-type serological pattern, compared with those born in the vaccination era (16.7% vs 100%, P = 0.030), though the case number was small for the latter group. With respect to past infection, there was significant difference among MSM (22.9% vs 8.2%, P < 0.0001) and heterosexual patients (32.6% vs 3.7%, P = 0.002) between those born in the pre-vaccination era and those born in the vaccination era. Among MSM, patients born in the pre-vaccination era had significantly higher proportion of HBV infection than those born in the vaccination era (16.3% vs 2.4%, P < 0.0001) (Table 2). Isolated anti-HBc positivity was significantly more prevalent in MSM patients born in the pre-vaccination era than in those born in the vaccination era (5.2% vs 1.2%, P = 0.002).

Factors associated with HBV infection

Table 3 shows associated factors with HBV infection in univariate and multivariate analyses. In multivariable analysis, compared with patients aged 20—24 years, the adjusted odds ratio (aOR) for HBV infection for those in the age group of 30—34 years, 35—39 years, and 40 years or greater was 5.82 (95% CI, 2.82—12.01), 7.12 (95% CI, 3.37—15.07) and 7.45 (95% CI, 3.61—15.34), respectively. HBsAg positivity was also significantly associated with CD4≧200 cells/mm^3 (aOR 0.73, 95% CI 0.53—0.99) and anti-HCV positivity (aOR 1.62, 95% CI 1.06—2.50).

Types of cART prescribed

Table 4 shows the types of cART prescribed for all included patients. We found that 59.5% (1071) of the patients initiated cART containing with only LAM with activity against HBV and 40.5% (729) initiated HBV-active agents with TDF plus LAM or coformulated TDF/FTC (Table 4). Of note, 65.6% (335/511) patients with all-negative serological pattern initiated cART containing only LAM with activity for HBV and 34.4% (176/511) initiated cART regimens containing TDF plus LAM or FTC (P = 0.001) (Table 4). Of the 209 patients with HBV infection, 31.1% (65) started cART containing only LAM for HBV and 68.9% (144) started cART containing TDF plus LAM or TDF/FTC (Table 4). The proportion of patients with using dual HBV-active regimens (TDF plus LAM or TDF/FTC) increased significantly with age, from 30.8% in patients aged 20—24 years to 46.0% in those aged 40 years. (P < 0.001) (Table 1). In multivariate analysis, patients with HBV infection were more likely to initiate cART containing dual HBV-active antiretroviral agents with TDF plus LAM or TDF/FTC (aOR, 3.63, 95% CI 2.61—5.06) compared with those without HBV infection (Table 4).

Discussion

In this multicenter cross-sectional study conducted in Taiwan where universal neonatal HBV vaccination was implemented in mid-1986, we found that the prevalence of HBV infection has significantly declined in the HIV-infected patients who were born in the era of HBV vaccination, regardless of risks for HIV transmission. Despite HBV vaccination at birth, a significant proportion of those born in the era of HBV vaccination have lost seroprotection, 51.1% and 36.5% in those aged 20—24 and 25—29 years, respectively. While national and international HIV treatment guidelines recommend cART containing dual anti-HBV antiretrovirals for HIV/HBV-coinfected patients, a substantial proportion (31.1%, 65/209) of HBV/HIV-coinfected patients received cART lacking dual anti-HBV antiretrovirals in this country with a hyperendemicity of HBV infection.

Our study showed that, despite the decline of HBV seroprevalence to 3.4% among the HIV-infected patients across all risk groups who were born in the vaccination era, the seroprevalence of HBV infection among HIV-positive patients remained 4 times higher than that observed in a recent study of university students (0.6%) within the same age group in Taiwan.[10] Moreover, 9.2% of those patients aged 20—29 years had a serological pattern consistent with past HBV infection and an elevated RPR titer was noted in 18% of HIV-infected MSM. These data suggest that the risk behaviors for HIV transmission and syphilis may also increase the risk for HBV transmission.

Given the fact that a high proportion of the patients in our study who were born in the vaccination era had lost seroprotection against HBV infection, HBV revaccination should be advised and provided to these patients with waned immunity. There are concerns about lower serological responses to HBV vaccination among HIV-infected patients. A recent study revealed that increases in HBV vaccine doses or intradermal administration of HBV vaccine could improve vaccine efficacy and durability.[28] Among the HIV-positive Taiwanese patients born in the HBV vaccination era, the serological response rate after 3 doses of HBV revaccination could reach 74.0% and the rate of high-titer response (anti- HBs titre ≥100 mIU/mL) was 46.0%.[16] Follow-up of HBV serological markers is needed because the serological responses to HBV vaccination could wane

Table 2 Comparisons of HBV markers, syphilis, and anti-HCV positivity among HIV-infected patients of different risk groups.

	MSM n = 1514			Heterosexuals n = 122			PWID n = 164		
	Pre-Vaccination era[a] n = 853	Vaccination era[b] n = 661	*p* value	Pre-Vaccination era n = 95	Vaccination era n = 27	*p* value	Pre-Vaccination era n = 162	Vaccination era n = 2	*p* value
All-negative, n (%)	156 (18.3)	314 (47.5)	<0.0001	16 (16.8)	13 (85.2)	0.001	12 (7.4)	0	>0.99
Vaccination-type, n (%)	319 (37.4)	263 (24.7)	0.343	23 (24.2)	11 (40.7)	0.091	27 (16.7)	2 (100)	0.030
Past infection, n (%)	195 (22.9)	54 (8.2)	<0.0001	31 (32.6)	1 (3.7)	0.002	54 (33.3)	0	>0.99
HBV infection, n (%)	139 (16.3)	16 (2.4)	<0.0001	17 (17.9)	2 (7.4)	0.185	35 (21.6)	0	>0.99
Isolated anti-HBc Positivity, n (%)	44 (5.2)	14 (1.2)	0.002	8 (8.4)	0	0.197	34 (21.0)	0	>0.99
Male, n (%)	853 (100)	661 (100)	>0.99	58 (61.2)	20 (74.1)	0.214	149 (92.0)	1 (50)	0.164
RPR titer ≥4, n (%)	150 (17.6)	120 (18.2)	0.774	4 (4.2)	5 (18.5)	0.025	13 (8.0)	0	>0.99
Anti-HCV positivity, n (%)	45 (5.3)	31 (4.7)	0.615	17 (17.9)	2 (7.4)	0.239	123 (75.9)	2 (100)	>0.99

[a] Pre-vaccination era: born in or before 1985.
[b] Vaccination era: born in or after 1986 when universal infant hepatitis B immunization program was implemented.
Abbreviations: anti-HBc, anti-hepatitis B core; HBV, hepatitis B virus; HCV, hepatitis C virus; MSM, men who have sex with men; PWID, people who inject drugs; RPR, rapid plasma reagin.

Table 3 Factors associated with hepatitis B virus infection in multiple logistic regression analysis.

Demographic and characteristics	Patients n (%)	HBsAg		Univariate analysis	Multivariate analysis[a]
		Negative	Positive	OR (95% CI)	aOR (95% CI)
All patient (n=)	1800 (100)	1591 (88.4)	209 (11.6)		
Gender					
Female	58 (3.2)	55 (3.5)	3 (1.4)	1.00	
Male	1742 (96.8)	1536 (96.5)	206 (98.6)	2.46 (0.76–7.93)	
Age, (mean ± SD), years		31.8 (9.3)	38.1 (9.5)	1.06 (1.05–1.08) **	
20–24	364 (20.2)	355 (22.3)	9 (4.3)	1.00	1.00
25–29	430 (23.9)	412 (25.9)	18 (8.6)	1.72 (0.77–3.88)	1.59 (0.70–3.61)
30–34	402 (22.3)	342 (21.5)	60 (28.7)	6.92 (3.38–14.16) **	5.82 (2.82–12.01) **
35–39	230 (12.8)	184 (11.6)	46 (22.0)	9.86 (4.72–20.59) **	7.12 (3.37–15.07) **
≥40	374 (20.8)	298 (18.7)	76 (36.4)	10.06 (4.96–20.42) **	7.45 (3.61–15.34) **
Risk group					
Heterosexuals	122 (6.8)	103 (6.5)	19 (9.1)	1.00	
MSM	1514 (84.1)	1359 (85.4)	155 (74.2)	0.62 (0.37–1.04)	
PWID	164 (9.1)	129 (8.1)	35 (16.7)	1.47 (0.80–2.72)	
CD4 <200 cells/mm^3	648 (36.0)	547 (34.4)	101 (48.3)	1.00	1.00
CD4 ≧200 cells/mm^3	1152 (64.0)	1044 (65.6)	108 (51.7)	0.56 (0.42–0.75) **	0.73 (0.53–0.99) *
PVL <100,000 copies/mL	1081 (60.1)	958 (60.2)	123 (58.9)	1.00	
PVL ≧100,000 copies/mL	719 (39.9)	633 (39.8)	86 (41.1)	1.06 (0.79–1.42)	
RPR titer <4	1508 (83.8)	1337 (84.0)	171 (81.8)	1.00	
RPR titer ≧4	292 (16.2)	254 (16.0)	38 (18.2)	1.17 (0.80–1.70)	
Anti-HCV-negative	1576 (87.8)	1403 (88.4)	173 (82.8)	1.00	1.00
Anti-HCV-positive	220 (12.2)	184 (11.6)	36 (17.2)	1.59 (1.07–2.35) *	1.62 (1.06–2.50) *
Use of antiretrovirals					
Only LAM regimens[b]	1071 (59.5)	1006 (63.2)	65 (31.1)	1.00	1.00
Dual HBV-active regimens[c]	729 (40.5)	585 (36.8)	144 (68.9)	3.81 (2.79–5.20) **	3.63 (2.61–5.06) **

[a] Adjusted odds ratios controlled for age, CD4 counts, anti-HCV antibody, and antiretrovirals use.
[b] Only LAM regimens: LAM, or zidovudine/LAM, or abacavir/LAM.
[c] Dual HBV-active regimens: tenofovir disoproxil fumarate with emtricitabine or LAM.
p value: *, P < 0.05; **, P < 0. 001.
Abbreviations: aOR, adjusted odds ratios; CI, confidence interval; FTC, emtricitabine; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; LAM, lamivudine; MSM, men who have sex with men; OR, odds ratios; PVL, plasma HIV RNA load; PWID, people who inject drugs; RPR, rapid plasma reagin; SD, standard deviation.

Table 4 The types of antiretroviral regimens initiated among HIV-infected patients. (N = 1800).

Characteristics	Only LAM regimens[a] n = 1071 (59.5%)	Dual HBV-active regimens[b] n = 729 (40.5%)	*p* value
Age, (mean ± SD), years	31.7 (9.4)	33.8 (9.6)	<0.001
≦1986, n (%)	613 (57.2)	497 (68.2)	<0.001
HBV serologic markers, n (%)			<0.001
All-negative	335 (31.3)	176 (24.1)	0.001
Vaccination-type	399 (37.3)	246 (33.7)	0.127
Past infection	207 (19.3)	128 (17.6)	0.344
HBV infection	65 (6.1)	144 (19.8)	<0.001
Isolated anti-HBc positivity	65 (6.1)	35 (4.8)	0.249
CD4 <200 cells/mm^3, n (%)	372 (34.7)	276 (37.9)	0.175
PVL >100,000 copies/mL, n (%)	418 (39.0)	301 (41.3)	0.336
RPR titer ≥4, n (%)	170 (15.9)	122 (11.4)	0.626
Anti-HCV-positive, n (%)	170 (15.9)	50 (6.9)	<0.001

[a] Only LAM regimens: LAM, or zidovudine/LAM, or abacavir/LAM.
[b] Dual HBV-active regimens: Tenofovir disoproxil fumarate with emtricitabine or LAM.
Abbreviations: anti-HBc, anti-hepatitis B core; HBV, hepatitis B virus; HCV, hepatitis C virus; LAM, lamivudine; PVL, plasma HIV RNA load; RPR, rapid plasma reagin; SD, standard deviation.

and breakthrough of HBV infections may occur in patients with cART.[13,16]

Currently, guidelines for antiretroviral therapy-naive patients recommend that cART regimens contain TAF or TDF with FTC or LAM.[29] In the current study, only 34.4% (176/511) HIV-positive patients with all-negative HBV serological pattern and 68.9% (144/209) with chronic HBV patients initiated cART containing TDF with FTC or LAM. Several studies have demonstrated protective effect against HBV infection with the use of cART containing HBV-active antiretroviral agents among HIV-infected patients.[30–32] Gatanaga et al. demonstrated the use of LAM- and TDF-containing cART could reduce the risk of incident HBV infection by nearly 90%.[30] While more long-term follow-up investigations are warranted, concurrent use of TAF or TDF plus LAM or FTC in the cART and HBV revaccination are likely to confer even higher protection against HBV transmission in our HIV-infected patients with lost seroprotection against HBV in this area with a hyper-endemicity of HBV infection.[33,34]

For patients with HIV/HBV coinfection, TAF or TDF plus LAM or FTC are recommended to provide durable HBV suppression and prevent emergence of HBV resistance.[29–32] Recent studies also showed that introduction of TDF into clinical use has reduced the survival difference used to be observed in the pre-TDF era, when HIV/HBV-coinfected patients had significantly higher rates of all-cause mortality and liver decompensation than HIV-monoinfected patients.[35–37] Our results suggested that the adherence to the HIV treatment guidelines for HIV/HBV coinfection among the HIV-treating physicians was suboptimal (only LAM-containing regimens), which might have been attributed to the regulations on cART prescription in Taiwan during the study period, in which NRTIs with a lower price (zidovudine/LAM) were recommended to be used with nNRTI despite the use of TDF plus LAM or FTC has been recommended for HIV/HBV-coinfected patients. These findings highlight the need for providing information, education, and communication to health care providers when treatment guidelines are to be revised and implemented.

Our study has several limitations. First, it was a retrospective study. We were not able to document whether patients had received HBV booster vaccinations before or after the diagnosis of HIV infection was made. Second, 84.1% of the patients in this study were MSM. Hence, the data may not be generalizable to all HIV-infected patients or female patients with HIV infection. Third, due to the cross-sectional study design, we were not able to provide information on the outcome of HIV/HBV-coinfected patients who received cART containing only LAM for HBV, nor were we able to have data on the incidence rate of HBV infection among those HIV-infected patients with all-negative serologic pattern.

In conclusion, we found that, 30 year after implementation of universal neonatal HBV immunization program, the prevalence of HBV infection has significantly declined among HIV-infected patients in Taiwan. Efforts in promoting HBV revaccination among the HIV-infected patients without seroprotective antibody titers and use of cART containing antiretrovirals with dual activity against HIV and HBV (such as TAF, TDF with FTC or LAM) are needed in this country of higher endemicity for HBV infection.

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Other authors declare no conflict of interests.

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