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ORIGINAL ARTICLE

Anti-HIV seropositivity was related to HBsAg seropositivity among injecting drug users in Taiwan

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Abstract In Taiwan, the number of new cases of human immunodeficiency virus (HIV) infection via drug injection has been increasing since 2003. Due to HIV and hepatitis B virus (HBV) having similar transmission routes, HBV and HIV infections among injecting drug users (IDUs) has become an important public health issue. The aim of this study was explore the prevalence of HBV infection among IDUs with and without HIV infection, and examine whether HIV infection is associated with HBV infection among IDUs in Southern Taiwan. We enrolled 566 IDUs, including 87 anti-HBV positive IDUs and 479 anti-HBV negative IDUs, and also analyzed the results of liver function tests, HBV DNA, anti-HIV, HIV RNA, and CD4 cell count. The results showed that the prevalence of HBV infection among IDUs was 15.4%. The prevalence of hepatitis B surface antigen (HBsAg) was higher among individuals born before 1985 (15.9% vs. 4.0%), but this was not significant. Anti-HIV seropositivity was related to HBsAg seropositivity [odds ratio (OR) = 2.47, 95% confidence interval = 1.26—4.82, $p = 0.008$). Anti-HCV and anti-HIV were risk factors for abnormal alanine aminotransferase (ALT; OR = 2.11, 95% confidence interval = 1.005—4.42, $p = 0.048$ and OR = 1.47, 95% confidence interval = 1.02—2.10, $p = 0.04$, respectively), and HBsAg was not a factor related to abnormal ALT. In conclusion, the prevalence of HBV infection was similar in the general population and in IDUs, and due to anti-HIV seropositivity being significantly related to HBsAg seropositivity, HBV infection among IDUs is still important. We suggest that for IDUs, HBsAg should be monitored closely.

Introduction

The hepatitis B virus (HBV) and the human immunodeficiency virus (HIV) are global viral infectious diseases. Previous studies have reported that persons with chronic HBV infection number approximately 240 million [1] and HIV infections total approximately 36.9 million [2], and there may be 3 to 6 million HIV-infected people coinfected with chronic HBV [3]. These two viruses contribute to deaths from diseases worldwide [4], and are viewed as important public health issues in Taiwan. Before 1984, vertical transmission of HBV was the main reason for the high prevalence of hepatitis B surface antigen (HBsAg) seropositivity; therefore effecting a decrease in the vertical transmission of HBV is important in order to reduce the spread of HBV infection. After a mass vaccination program against HBV infection was initiated in 1984, the prevalence gradually decreased [5].

HBV and HIV share common routes of transmission, especially blood-borne transmission, such as injecting drug use, etc. [6]. Injecting drug use is a very important cause of HBV infection worldwide [7]. A previous study reported that injecting drug users (IDUs) have higher prevalences of HBV and HIV infections than non-IDUs [8], and so the risk of coinfection with HBV and HIV is higher in IDUs.

In Taiwan, new cases of HIV infection via injecting drug use have been increasing since 2003, and this transmission route has been one of the most important routes of transmission of HIV since 2005 [9]. Regarding HBV, 40—50% of chronic hepatitis B (CHB) cases are due to perinatal mother-to-infant transmission, and the remainder is due to horizontal transmission [10,11]. Taiwan is an area of high prevalence of HBsAg, the prevalence of HBsAg in the general population being 15—20% [12]. In addition, HBsAg is detected in 5—15% of HIV-infected persons globally [13].

Previous studies have mentioned that HIV infection is associated with failure to seroconvert following acute infection and a greater risk of developing chronic hepatitis B infection as compared with HIV seronegative persons [14—16]. Among HIV-infected persons with chronic HBV infection (e.g., persistent detection of HBsAg), progressive liver fibrosis, cirrhosis, end stage liver disease (ESLD) and hepatocellular carcinoma (HCC) can occur [17—19]. Similarly, HBV negatively impacting on HIV outcomes was also reported [20]. Because HBV and HIV coinfection is an important public health issue, especially among IDUs, the aim of this study was to explore the prevalence of HBV infection among IDUs, and examine whether HIV infection is associated with HBV infection among IDUs in Taiwan.

Materials and methods

Participants

We enrolled IDUs from three prisons and Kaohsiung Medical University Chung-Ho Memorial Hospital from March 2008 to June 2010. We excluded persons with severe liver, renal, or other systemic disease, such as decompensated hepatic failure, renal failure, any malignant disease, or severe heart failure, etc. Finally, we enrolled 566 IDUs, including 479 anti-HBV negative IDUs and 87 anti-HBV positive IDUs. The study was approved by the ethics committee of Kaohsiung Medical University Hospital. Signed informed consent was obtained from all participants.

Laboratory data

We measured the levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), HBsAg, HBV DNA,

anti-HIV antibody, HIV RNA viral load, CD4 cell count and anti-hepatitis C virus (HCV) antibody. HBsAg was examined by enzyme immunoassay (EIA; Abbott Laboratories, North Chicago, IL, USA), and quantitative HBV DNA was performed by the Roche Cobas Apliprep/Cobas Taqman HBV Test (Roche Molecular System, Roche, Branchburg, USA). Anti-HCV antibody was detected using a third-generation, commercially-available enzyme-linked immunosorbent assay kit (AxSYM 3.0; Abbott Laboratories, Chicago, IL, USA). Anti-HIV antibody assay (SERODIA-HIV; Fujirebio, Tokyo, Japan) was performed as per the manufacturer's instructions. HIV viral loads were quantified using an RT-PCR assay (COBAS Amplicor, version 1.5; Roche Diagnostics, Branchburg, NJ, USA), and CD4 counts were determined using a flow cytometer (BD FACSCalibur; Becton Dickinson, San Jose, CA, USA).

Statistical analysis

The statistical tests employed in this study were Student *t*-test, the χ^2 test, the Mann-Whitney U test, and one-way ANOVA. In addition, multivariate analysis was used for estimating the odds ratios (ORs) and 95% confidence intervals. All of these tests were two-sided, and the significance levels were set at $\alpha = 0.05$. The procedures were performed using the SPSS 19th edition statistical package (SPSS Inc., Chicago, IL, USA).

Results

In this study, 566 IDUs were enrolled. Males were dominant (71.7%), and most of the participants in this study were born before 1985 (95.6%). The prevalences of HBsAg seropositivity, anti-HIV, and anti-HCV were 15.4%, 53.2% and 91.3%, respectively (Table 1). In addition, the prevalences of HBsAg among IDUs without and with HIV infection were 11.3% (30/265) and 18.9% (57/301), respectively, and significant difference was also noted ($p = 0.01$; not shown in the table).

Table 2 shows the data for IDUs born before and after 1985. Sex, HIV RNA level, anti-HCV, and whether HCV RNA was detectable or not differed significantly between these two groups. Even though HBsAg did not differ significantly

Table 1 Basic characteristics of the participants included in this study.

Item	Value
Total, *n* (%)	566 (100.0)
Age (y)	36.2 ± 7.5
Born before 1985, *n* (%)	541 (95.6)
Born after 1985, *n* (%)	25 (4.4)
Sex	
Male, *n* (%)	406 (71.7)
Female, *n* (%)	160 (28.3)
AST (ratio for UNL)	0.95 ± 0.68
ALT (ratio for UNL)	1.18 ± 1.19
Anti-HIV	
Negative, *n* (%)	265 (48.6)
Positive, *n* (%)	301 (53.2)
HIV RNA [log(IU/ml)][b]	3.16 ± 0.88
HBsAg	
Negative, *n* (%)	479 (84.6)
Positive, *n* (%)	87 (15.4)
Anti-HCV	
Negative, *n* (%)	49 (8.7)
Positive, *n* (%)	517 (91.3)
HCV RNA[a]	
Undetectable, *n* (%)	100 (19.5)
Detectable, *n* (%)	412 (80.5)
CD4 cell count[b]	443.4 ± 180.4
> 500 cells/μL	95 (31.6)
< 500 cells/μL	206 (68.4)

Among hepatitis B surface antigen seropositive participants, the prevalence of hepatitis B virus DNA detectable was 56.3%.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; UNL = upper normal limit.
[a] For 512 hepatitis C virus RNA detectable individuals.
[b] For 301 injecting drug users with human immunodeficiency virus infection.

Table 2 Characteristics of injecting drug users (IDUs) born before and after 1985.

	Univariate analysis		
	Born before 1985	Born after 1985	*p*
Total, *n* (%)	541 (95.6)	25 (4.4)	
Age (y)	36.7 ± 7.1	23.9 ± 1.6	< 0.001
Sex			
Male, *n* (%)	395 (73.0)	11 (44.0)	0.002
Female, *n* (%)	146 (27.0)	14 (56.0)	
AST (ratio for UNL)	0.94 ± 0.67	0.97 ± 0.82	0.88
ALT (ratio for UNL)	1.17 ± 1.31	1.16 ± 1.77	0.38[a]
Anti-HIV			
Negative, *n* (%)	249 (46.0)	16 (64.0)	0.08
Positive, *n* (%)	292 (54.0)	9 (36.0)	
HIV RNA [log(IU/ml)]	4.48 ± 1.77	3.40 ± 1.92	0.005
HBsAg			
Negative, *n* (%)	455 (84.1)	24 (96.0)	0.11
Positive, *n* (%)	86 (15.9)	1 (4.0)	
Anti-HCV			
Negative, *n* (%)	44 (8.1)	5 (20.0)	0.04
Positive, *n* (%)	497 (91.9)	20 (80.0)	
HCV RNA			
Undetectable, *n* (%)	91 (18.6)	9 (40.9)	0.01
Detectable, *n* (%)	399 (81.4)	13 (59.1)	
CD4 cell count[b]	441.1 ± 178.5	519.1 ± 233.7	0.20
> 500 cells/μL	91 (31.2)	4 (44.4)	0.40
< 500 cells/μL	201 (68.8)	5 (55.6)	

ALT = alanine aminotransferase; AST = aspartate aminotransferase; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; UNL = upper normal limit.
[a] Mann–Whitney U test.
[b] For 301 IDUs with human immunodeficiency virus infection.

between the two groups, the prevalence of HBsAg was higher among individuals born before 1985 (15.9% vs. 4.0%, $p = 0.11$).

Table 3 shows the associations of HBsAg seropositivity among IDUs who were born before 1985. Univariate analysis showed that anti-HIV antibody and HCV RNA were related to HBsAg ($p < 0.05$). According to multivariate analysis, anti-HIV seropositivity was related to HBsAg seropositivity (OR = 2.47, 95% confidence interval = 1.26–4.82, $p = 0.008$), and anti-HCV seronegativity was related to HBsAg seropositivity (OR = 0.22, 95% confidence interval = 0.11–0.45, $p < 0.001$). The prevalence of anti-HIV seropositivity was higher among the HBsAg seropositive participants than the HBsAg seronegative participants (65.1% *vs.* 5019%, $p = 0.02$).

Table 4 analyzes the factors associated with HBV DNA being detectable and undetectable among HBsAg-positive IDUs. From Table 4, only the CD4 cell count was related to HBV DNA in univariate analysis, but the CD4 cell count was higher among HBV DNA- undetectable individuals. No item was related to HBV DNA according to multivariate analysis. In addition, for 31 HBsAg-positive IDUs with hepatitis B e antigen (HBeAg) data available, HBeAg was not significantly different between HBV DNA-undetectable and -detectable individuals (0.0% *vs.* 10.0%, $p = 0.14$, not shown in table). Unlike HBsAg, the prevalence of anti-HIV seropositivity was higher among HBV DNA-undetectable than HBV DNA-detectable individuals (68.4% *vs.* 63.3%, $p = 0.62$).

This study showed that ALT was associated with anti-HCV and anti-HIV levels. According to the results of univariate analysis, anti-HCV and anti-HIV were significantly different between patients with ALT within the upper normal limit (UNL) and those with ALT greater than UNL, and multivariate analysis showed that anti-HCV and anti-HIV were risk factors for abnormal ALT (OR = 2.11, 95% confidence interval = 1.005–4.42, $p = 0.048$ and OR = 1.47, 95% confidence interval = 1.02–2.10, $p = 0.04$, respectively; Table 5).

Discussion

Previous studies have reported that Taiwan is an area of high prevalence of HBV and HCV infection, the prevalence of HBsAg seropositivity being 15.1% and that of anti-HCV seropositivity being 8.6% [21]. One study from Luxembourg reported that the prevalences of HBV and HCV seropositivity among IDUs are 24.7% (59/239) and 81.3% (218/268), respectively [22], and another study from Dali, China, reported that the prevalences of HBV and HCV seropositivity among IDUs are 72.0% (296/411) and 90.8% (452/498), respectively [23]. In this study, the prevalence of HBsAg

Table 3 Factors associated with hepatitis B surface antigen seropositivity among injecting drug users (IDUs) born before 1985.

	Univariate analysis			Multivariate analysis[a]			
	HBsAg negative	HBsAg positive	*p*	Comparison	Odds ratio	95% CI	*p*
Total, *n* (%)	455 (84.1)	86 (15.9)					
Age (y)	36.9 ± 7.2	35.6 ± 6.7	0.11				
Sex							
Male, *n* (%)	328 (72.1)	67 (77.9)	0.27				
Female, *n* (%)	127 (27.9)	19 (22.1)					
AST (ratio for UNL)	0.94 ± 0.70	0.94 ± 0.52	0.97				
ALT (ratio for UNL)	1.17 ± 1.20	1.17 ± 0.89	0.17[b]				
Anti-HIV							
Negative, *n* (%)	219 (48.1)	30 (34.9)	0.02	Negative = 0, positive = 1	2.47	1.26–4.82	0.008
Positive, *n* (%)	236 (51.9)	55 (65.1)					
HIV RNA [log(IU/ml)][b,c]	4.57 ± 1.70	3.95 ± 2.03	0.08				
Anti-HCV							
Negative, *n* (%)	36 (7.9)	8 (9.3)	0.66				
Positive, *n* (%)	419 (92.1)	78 (90.7)					
HCV RNA							
Undetectable, *n* (%)	68 (16.1)	23 (34.3)	< 0.001	Undetectable = 0, detectable = 1	0.22	0.11–0.45	< 0.001
Detectable, *n* (%)	355 (83.9)	44 (65.7)					
CD4 cell count[d]	439.9 ± 183.6	446.2 ± 156.5	0.81				
> 500 cells/μL	70 (29.7)	21 (37.5)	0.26				
< 500 cells/μL	166 (70.3)	35 (62.5)					

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; UNL = upper normal limit.

[a] Factors used for logistic analysis included sex, aspartate aminotransferase ratio, alanine aminotransferase ratio, hepatitis C virus RNA detectable or undetectable, and anti-human immunodeficiency virus (HIV) status.

[b] Mann–Whitney U test.

[c] Mean ± standard deviation.

[d] For 301 IDUs with HIV infection.

Table 4 Factors associated with hepatitis B virus DNA-detectable and -undetectable among hepatitis B surface antigen (HBsAg)-positive injecting drug users (IDUs).

	HBV DNA-undetectable	HBV DNA-detectable	*p*
Total, *n* (%)	38 (43.7)	49 (56.3)	
Age (y)	36.0 ± 6.0	35.1 ± 7.4	0.53
Sex			
Male, *n* (%)	32 (84.2)	36 (73.5)	0.23
Female, *n* (%)	6 (15.8)	13 (26.5)	
AST (ratio for UNL)	0.98 ± 0.54	0.90 ± 0.49	0.47
ALT (ratio for UNL)	1.22 ± 0.87	1.13 ± 0.91	0.66
Anti-HIV			
Negative, *n* (%)	12 (31.6)	18 (36.7)	0.62
Positive, *n* (%)	26 (68.4)	31 (63.3)	
Anti-HCV			
Negative, *n* (%)	4 (10.5)	4 (2.2)	0.71
Positive, *n* (%)	34 (89.5)	45 (91.8)	
HCV RNA[a]			
Undetectable, *n* (%)	9 (28.1)	15 (47.1)	0.24
Detectable, *n* (%)	23 (71.9)	21 (58.3)	
HIV RNA [log(IU/ml)][b]	3.07 ± 0.88	3.28 ± 0.56	0.28
CD4 cell count[b]	497.2.4 ± 161.2	406.2 ± 139.9	0.03
>500 cells/μL	12 (46.2)	10 (32.3)	0.28
<500 cells/μL	14 (53.8)	21 (67.7)	

ALT = alanine aminotransferase; AST = aspartate aminotransferase; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; UNL = upper normal limit.

[a] For 68 HBsAg-positive IDUs with hepatitis C virus RNA data available.

[b] For 57 HBsAg-positive IDUs with human immunodeficiency virus infection.

seropositivity was 15.4% among IDUs, but for HCV, the prevalence of anti-HCV seropositivity among IDUs was significantly higher than that in the general population [24]. These results reflect that in Taiwan, Dali (China) and Luxembourg, the prevalence of HBV infection among IDUs is higher than that in the general population in Taiwan, and HCV is significantly dominant among IDUs in Taiwan, Dali (China), and Luxembourg [22,24]. So, for IDUs, HBV and HCV infections are important public health issues. In addition, the prevalence of HCV infection was greater than 90% in this study, whether HBV seropositive or seronegative, and there was no relationship between HBC and HCV infection in this study. These results reflected that the lack of neutralizing antibodies for HCV and the transmission routes and modes of HCV were similar to HBV and HIV. HCV may be transmitted more easily than HBV and HIV among IDUs, and we believe that for IDUs, the influence of HCV for HBV infection is not as dominant.

In populations of the United States and Europe, HBV is most often transmitted by sexual intercourse, followed by injecting drug use [25,26]. In Asia and sub-Saharan Africa, HBV is principally transmitted from mother to infant or during early childhood [27]. In one global system survey, the prevalence of HBsAg seropositivity was reported to be 16.7% in 2005 [7], which was higher than our result (15.3%), though the two results were similar. In addition, approximately 10% of the HIV-infected population has concurrent chronic hepatitis B, and HBV-HIV coinfection is more common in areas of high prevalences of both viruses. In countries in which the viruses are highly endemic [28], the rate can be as high as 25% [29], and in areas where HBV is less endemic (North America, Europe, and Australia), HBV and HIV are most often acquired during adolescence or adulthood through sexual transmission or injecting drug use. The prevalence of HIV–HBV coinfection in these regions is generally lower than 10% of the HIV-infected population [30]. Besides, in Taiwan, for IDUs with HIV infection, the prevalence of HBsAg is 19.8% [31], and in this study, the prevalence of HBV coinfection among IDUs with HIV infection was 18.9% (57/301). These results are higher than those reported in a previous study (5–15%) [13]. In this study, the prevalence of anti-HIV seropositivity was higher among the HBsAg seropositive individuals than the HBsAg seronegative individuals, and anti-HIV seropositivity was related to HBsAg seropositivity. Therefore, we propose that in Taiwan, for IDUs, especially HIV-infected individuals, screening for HBsAg is necessary.

Table 5 Analysis of alanine aminotransferase and hepatitis B surface antigen, anti-hepatitis C virus, and anti-human immunodeficiency virus.

	Univariate analysis			Multivariate analysis		
	ALT within UNL	ALT more than UNL	*p*	Odds ratio	95% CI	*p*
HbsAg						
Negative, *n* (%)	285 (85.1)	170 (82.5)	0.43	1.14	0.71–1.82	0.60
Positive, *n* (%)	50 (14.9)	36 (17.5)				
Anti-HCV						
Negative, *n* (%)	34 (10.1)	10 (4.9)	0.03	2.11	1.005–4.42	0.048
Positive, *n* (%)	301 (89.9)	196 (95.1)				
Anti-HIV						
Negative, *n* (%)	169 (50.4)	80 (38.8)	0.009	1.47	1.02–2.10	0.04
Positive, *n* (%)	166 (49.6)	126 (61.2)				

ALT = alanine aminotransferase; CI = confidence interval; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; UNL = upper normal limit.

There were no significant differences between HBV DNA and anti-HIV antibody in this study, and the prevalence of anti-HIV seropositivity was higher among the HBV DNA-undetectable group. Previous studies have reported that the natural history of HBV infection is modified by HIV infection, which can result in higher rates of HBV and clinically-significant disease [15,32—34]. In addition, one study reported that persons with HIV coinfection have higher levels of hepatitis B viremia than those with HBV infection alone [35]. Highly active antiretroviral therapy (HAART) can suppress HBV DNA to an undetectable level, but in this study, only 11 participants took HAART (3TC), and only one of these 11 participants had HBV infection, so we believe that the number of HBV patients taking HAART therapy was too low and almost without influence on the results of this study. Therefore, the differences between our results and those of a previous study [35] might be due to the different study bases (IDUs vs. the general population), and we suggest that the differences between our results and those reported in a previous study [35] should be examined in the future. In this study, anti-HCV and anti-HIV, not HBsAg (even OR >1, but $p > 0.05$), were identified as risk factors for abnormal ALT. We believe that this might be due to the cases of HBV infection in this study being limited, and this issue should be studied in the future.

A previous study mentioned that in individuals in Taiwan who were born in or after 1986 and who engaged in high-risk sexual behaviors, neonatal HBV vaccination and catch-up vaccination provides long-term protection against HBsAg seroconversion and HBsAg positivity [36]. In this study, the percentage of HBsAg seropositivity was 4.0% (1/25) and 15.9% (86/541) in individuals who were born after 1985 and before 1985, respectively, but no significant difference was noted. However, the prevalence was higher among individuals born before 1985, and we believe that the effect of the mass vaccination program against HBV infection was observed among IDUs; the reason for no significant difference might be due to the number of individuals born after 1985 being too small in this study. Even the risk factors for infection with HIV differed between this study and a previous study [36], and individuals who were born in the era of neonatal HBV vaccination had a lower prevalence of HBsAg seropositivity.

The CD4 cell count was higher in the HBsAg seropositive group but lower in the HBV DNA-detectable group. The HBV DNA level was not related to the CD4 cell count. In addition, the CD4 cell count was also not related to anti-HBV in this study. Therefore, we believe that the CD4 cell count is not related to HBV among IDUs, and further advanced study to support our result is necessary.

A limitation of this study was that the IDU participants in this study were prisoners, so visiting and following-up these individuals was very difficult, meaning that data collection, such as serial changes in the disease course and therapy given, could not be assessed completely.

In conclusion, the prevalence of HBsAg seropositivity was found to be 15.4% among IDUs. Anti-HIV seropositivity was related to HBsAg seropositivity. HBsAg was not found to be a risk factor for abnormal ALT. We believe that even though the prevalence of HBV infection among IDUs is similar to that in the general population, HBV infection among IDUs is still an important public health issue; therefore, from our results, we suggest that for IDUs, HBsAg should be monitored closely, and abstinence from drug abuse is a very important method by which to prevent HBV infection in IDUs.

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