

# Prevalence of hepatitis B virus (HBV) infection in Singapore men with sexually transmitted diseases and HIV infection: role of sexual transmission in a city state with intermediate HBV endemicity

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## Abstract

**Study objectives** - To describe the prevalence of hepatitis B virus (HBV) infection in patients with sexually transmitted diseases (STD) and human immunodeficiency virus (HIV) infection, and to determine the role of sexual transmission of HBV infection in Singapore.

**Design** - A cross sectional study of all consecutive men presenting with a new episode of STD at a government outpatient clinic and all men with HIV infection on routine follow up at a government hospital. The prevalence of various HBV markers was compared with that of healthy males aged 15 years and above (controls).

**Setting** - Singapore, a city state of intermediate HBV endemicity.

**Subjects** - These comprised 497 STD patients, 47 HIV infected patients, and 418 controls.

**Main results** - The overall seroprevalences of HBV infection in STD patients, HIV infected patients, and control subjects were 41.2%, 61.7%, and 33.3%, respectively ( $p < 0.001$ ). The seroprevalences of hepatitis B surface antigen (6.2%, 8.5%, and 4.5%, respectively) were comparable in the three groups. Using stepwise logistic regression analysis, the adjusted seroprevalences of HBV infection in STD and HIV infected patients were respectively 2.4 times (95% confidence interval (CI), 1.7, 3.3) and 3.3 times (95% CI 1.7, 6.3) higher than in controls. HBV infection rates were higher among Chinese (odds ratio (OR), 1.9; 95% CI 1.6, 3.4) than non-Chinese, and among those aged 25-34 years (OR 2.4; 95% CI 1.6, 3.4), 35-44 years (OR 3.9; 95% CI 2.5, 5.9), and 45+ years (OR 6.2; 95% CI 3.8, 10.2) than in those aged 15-24 years. Sex related factors significantly associated with higher infection rates, independent of age and ethnic group, were reactive VDRL test (OR 2.4; 95% CI 1.2, 4.7), participation in anal intercourse (OR 2.3; 95% CI 1.2, 4.3), and having 10 or more lifetime sexual partners (OR 1.5; 95% CI, 1.0, 2.1).

**Conclusion** - The importance of sexual transmission of HBV in an area of intermediate HBV endemicity was con-

firmed. Patients attending STD clinics should be routinely screened for HBV markers and those found to be seronegative should be strongly advised to be immunised against this virus.

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Hepatitis B has been recognised as an important sexually transmitted disease.<sup>1</sup> Extensive epidemiological studies relating to the sexual transmission of hepatitis B virus (HBV) have been conducted in the low HBV endemic countries of North America and western Europe.<sup>2-12</sup> Its role in countries of intermediate and high HBV endemicity, however, is not so clear. This is because in endemic countries, up to 80% of the population may already have been infected before reaching a sexually active age.<sup>13</sup> Evidence on sexual transmission is therefore difficult to obtain. In Sudan, a serosurvey among prostitutes failed to show the significance of sexual transmission of HBV.<sup>14</sup> Based on serological studies of household contacts in Taiwan,<sup>15</sup> China,<sup>16</sup> Hong Kong,<sup>17</sup> and the Middle East,<sup>18</sup> it was concluded that sexual transmission of HBV infection by spouses is of little significance. However, a recent study on acute hepatitis B cases conducted in Taiwan, a country highly endemic for HBV, convincingly showed the importance of heterosexual transmission.<sup>19</sup>

Singapore is a city state of intermediate HBV endemicity with an overall hepatitis B surface antigen (HBsAg) carrier rate of 5% and HBV infection rate of about 25% in the general population.<sup>20</sup> The role that sexual transmission of HBV plays has not been fully evaluated and is probably underestimated. Serological surveys showed a sharp increase in HBV prevalence in adolescents and young adults. Among family members of acute hepatitis B cases, the prevalence of HBV infection in spouses (73%) was significantly higher than that in siblings, offspring, and other blood relatives,<sup>21</sup> and spouses of hepatitis B e antigen (HBeAg) positive women had a higher seroprevalence of HBsAg and antibody to hepatitis B surface antigen (anti-HBs) than those who were HBeAg negative. Among male and female prostitutes, the prevalence of HBV infection was significantly associated with the duration of prostitution.<sup>22</sup>

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We conducted a cross sectional seroprevalence survey of HBV infection among patients with STD and HIV infection, and provide epidemiological evidence on the importance of sexual transmission of HBV infection in Singapore.

## Methods

### STUDY POPULATIONS

All consecutive male patients presenting with a new episode of STD at a government outpatient clinic and all sexually infected HIV positive patients on routine follow up at a government hospital during the period September 1990 to June 1992, were recruited into the study. Those with a history of HBV immunisation were excluded. Blood was taken from each individual after consent had been obtained. Relevant epidemiological information obtained at the time of blood collection included age, sex, ethnic group, highest educational level attained, past medical history, and history of parenteral procedures. Specific details on sexual behaviour such as sexual orientation (homosexual, bisexual, or heterosexual), type of sexual intercourse practised (vaginal, anal, or both), sexual role (insertive, receptive, or both), type of sexual partner(s) in the previous 12 months (spouse/regular partner, casual, or prostitutes), number of lifetime STD episodes, and number of lifetime sexual partners, were also obtained using a structured questionnaire. As every patient attending the STD clinic would have had a routine blood test for syphilis (VDRL test), medical records of all study participants were also checked for serological evidence of syphilis – that is reactive VDRL test.

The seroprevalence of various HBV markers in STD and HIV infected patients was compared with that of an apparently healthy population group (control group). These comprised male students aged 15 years and above and healthy male government employees whose blood was collected for other health surveys in 1990 and 1991. None had a history of immunisation against HBV. Only demographic information was available for the control group, and details of sexual behaviour were not elicited.

### TEST METHOD

Blood was despatched at the end of each day's collection to the Department of Pathology, Singapore General Hospital. The sera were separated, transferred to polypropylene tubes, and stored in the freezer at  $-20^{\circ}\text{C}$  before being tested in batches. Specimens were tested by enzyme immunoassay for HBsAg, total antibody to hepatitis B core antigen (anti-HBc), and anti-HBs using commercial kits (Auszyme Monoclonal, Corzyme, and Ausab EIA, respectively; Abbott Laboratories). Sera positive for HBsAg were also tested for HBeAg and anti-HBc IgM (HBe [rDNA] EIA and IMx Core-M, respectively). The manufacturer's criteria were used to grade the sera as positive or negative.

### DEFINITIONS AND ASSUMPTIONS

A regular partner was defined as a person with whom the respondent had had sexual intercourse three times or more in the previous three months. A person other than the wife or regular partner with whom the respondent had sex was considered a casual partner, while a prostitute was one who offered sex in exchange for money. It was assumed that marriages and regular partnerships were stable relationships, and any act of sexual intercourse outside of marriage/regular partnership carried some risk.

### STATISTICAL ANALYSIS

The microcomputer based *Statistical Analysis Systems* (SAS) software was used for data analysis. Differences in proportions observed were initially compared by  $\chi^2$  tests with Yates's continuity correction and probability values less than 0.05 were considered significant. To determine whether or not the seroprevalence of STD patients and HIV infected patients was significantly higher than that of control population, while adjusting for possible confounders, stepwise multiple logistic regression was performed on the three comparison groups. In the model, seropositivity for any HBV marker was the outcome variable, STD and HIV patients the independent covariates, and the control population the reference category. Other potentially confounding covariates included in the regression model were age, sex, ethnic group, educational level, and history of parenteral procedures in the previous six months. Similarly, to identify risk factors associated with increased seroprevalence, stepwise logistic regression was carried out on STD and HIV infected patients. Additional independent covariates included in the model were sexual orientation (homo/bisexual *v* heterosexual), sexual practices (anal or anal and vaginal *v* vaginal), sexual role (receptive or receptive and insertive *v* insertive), number of lifetime STD episodes (three or more *v* fewer than three), number of lifetime sexual partners (10 or more *v* fewer than 10), and VDRL seroreactivity (reactive *v* non-reactive). Logistic regression analysis with seropositivity for HBsAg as the outcome variable was carried out similarly, using the same covariates in the models. As virtually all patients had had contact with either casual acquaintances or prostitutes, or both, in the previous year, the type of sexual contact as a covariate was not included in the analyses.

## Results

### DESCRIPTION OF DATA

A total of 497 STD patients, 47 HIV infected patients, and 418 control subjects were tested for various HBV markers. None of the subjects were intravenous drug users. The prevalence of various HBV markers in the three comparison groups is shown in table 1. The prevalence of HBV infection (any HBV marker positive) in relation to age, ethnicity, and educational level is given in table 2, and the prevalence of HBV infection in the STD and HIV infected patients

Table 1 Prevalence of various markers of hepatitis B virus (HBV) infection in patients with sexually transmitted diseases (STD), human immunodeficiency virus infection (HIV) and healthy individuals (control) in Singapore

Marker	STD (n=497) No (%)	HIV (n=47) No (%)	Control (n=418) No (%)	p value*
HBsAg	31 (6.2)	4 (8.5)	19 (4.5)	NS
HBcAg	8 (1.6)	1 (2.1)	3 (0.7)	NS
Anti-HBc IgM	3 (0.6)	0 (0)	ND	—
Anti-HBc, total	175 (35.2)	22 (46.8)	116 (27.8)	0.006
Anti-HBs	155 (31.2)	19 (40.5)	86 (20.6)	<0.001
Any HBV marker	205 (41.2)	29 (61.7)	139 (33.3)	<0.001

\* By  $\chi^2$  test with Yates's continuity correction.

NS  $p \geq 0.05$ .

ND not done.

in relation to various risk factors is shown in table 3.

Most STD patients (465 or 94%) had had sex with casual partners or prostitutes, or both, in the previous year. Of the 211 who were married or had regular partners, 173 (82%) had had sex concurrently with their spouses or regular partners in the previous year. Of these extramarital/extra-regular partnership sexual encounters, 129 (75%) were with prostitutes.

Eight of 31 (25.8%) STD patients who were HBsAg positive were HBcAg positive. All eight

Table 2 Seroprevalence (%) of hepatitis B virus (HBV) markers in relation to age, ethnicity, and educational level in patients with sexually transmitted diseases (STD), HIV infection (HIV) and healthy individuals (control) in Singapore

	STD			HIV			Control		
	No	HBsAg+ve	HBV+ve	No	HBsAg+ve	HBV+ve	No	HBsAg+ve	HBV+ve
All	497	6.2	41.4	47	8.5	59.6	418	4.5	33.2
Age group (y):									
15-24	211	4.7	28.3	6	0	50.0	54	1.9	11.1
25-34	187	6.4	44.9	21	19.0	61.9	111	5.4	25.2
35-44	67	11.9	64.2	18	0	55.6	137	3.6	35.8
45+	31	3.2	61.3	2	0	100	116	6.0	48.3
Unknown	1	0	0	0	0	0	0	0	0
Ethnic group:									
Chinese	347	8.4	45.2	40	10.0	55.0	234	6.8	39.3
Malay	59	0	30.5	4	0	100	120	2.5	25.8
Indian	80	1.3	32.5	2	0	50.0	60	0	20.0
Others	11	9.1	45.5	1	0	100	4	0	100
Highest educational level attained:									
None or primary school	150	4.0	49.3	12	0	50.0	274	3.3	32.1
Secondary school	291	7.6	38.1	21	9.5	57.1	68	10.3	38.2
Beyond secondary school	56	5.4	37.3	14	14.3	71.4	76	3.9	32.9

HBV+ve any HBV marker positive

Table 3 Seroprevalence of HBV infection in patients with sexually transmitted diseases (STD) and HIV infection (HIV) in relation to various risk factors

Risk factors	STD		HIV		Total	Odds ratio (95% CI)	p value*
	No	HBV+ve	No	HBV+ve			
All	497	41.4	47	59.6	544	44.9	
Parenteral procedure in previous 6 months:							
Yes	189	41.3	22	63.6	211	43.6	1.0 (0.7, 1.5)
No	308	41.6	25	56.0	333	42.6	1
Sexual orientation:							
Homo-bisexual	23	6.5	22	72.7	45	64.4	2.6 (1.3, 5.1)
Heterosexual	473	40.8	25	48.0	498	41.2	1
Unknown	1	0	0	0	0	0	
Type of intercourse:							
Vaginal only	462	41.1	25	48.0	487	41.5	1
Anal/anal and vaginal	27	55.6	22	72.7	49	63.3	2.4 (1.3, 4.7)
Oral only	2	0	0	0	2	0	
Unknown	6	16.7	0	0	6	16.7	
Type of sexual role:							
Insertive only	486	54.1	28	50.0	514	42.2	1
Receptive/receptive and insertive	5	40.0	19	73.7	24	66.7	2.7 (1.1, 7.1)
Unknown	6	16.7	0	0	6	16.7	
Total no of lifetime STD episodes:							
<3	422	38.4	45	62.2	467	40.7	1
3+	75	58.7	2	0	77	57.1	1.9 (1.2, 3.3)
Total no of lifetime sexual partners:							
<10	257	35.0	15	46.7	272	35.7	1
10+	240	48.3	32	65.6	272	50.4	1.8 (1.3, 2.6)
VDRL serology:							
Reactive	38	63.2	7	85.7	45	66.7	2.9 (1.5, 5.9)
Non-reactive	442	39.6	25	56.0	467	40.5	1
Not done	17	41.1	15	53.3	32	46.9	

\* By  $\chi^2$  test with Yates's continuity correction.

HBV+ve any HBV marker positive.

NS  $p \geq 0.05$ .

Table 4 Variables significantly associated\* with hepatitis B virus infection† among patients with sexually transmitted diseases and HIV infection and healthy individuals (controls) in Singapore

Variable	Regression coefficient	Odds ratio	(95% CI)	p value
<i>Whole sample (n = 962)</i>				
Age group (y):				
25-34	0.85	2.4	(1.6, 3.4)	<0.0001
35-44	1.35	3.9	(2.5, 5.9)	<0.0001
45+ [15-24]	1.83	6.2	(3.8, 10.2)	<0.0001
Ethnic group:				
Chinese [Non-Chinese]	0.64	1.9	(1.4, 2.6)	<0.0001
Risk group:				
STD patients	0.86	2.4	(1.7, 3.3)	<0.0001
HIV infected patients [Control]	1.18	3.3	(1.7, 6.3)	0.0004
<i>STD and HIV infected patients (n = 544)</i>				
Age group (y):				
25-34	0.70	2.0	(1.3, 3.1)	0.001
35-44	1.32	3.8	(2.2, 6.5)	<0.0001
45+ [15-24]	1.47	4.3	(2.0, 9.6)	0.0003
Ethnic group:				
Chinese [non-Chinese]	0.57	1.8	(1.2, 2.7)	0.007
Sexual practice:				
Anal/anal and vaginal [vaginal only]	0.83	2.3	(1.2, 4.3)	0.01
Total no of lifetime sexual partners:				
10+ [<10]	0.39	1.5	(1.0, 2.1)	0.04
VDRL test:				
Reactive [Non-reactive]	0.86	2.4	(1.2, 4.7)	0.01

\*  $p < 0.05$  by stepwise logistic regression analysis.

† any HBV marker positive.

[ ] reference category.

were heterosexuals with multiple partners (three had had 100 or more lifetime partners). Of the four HIV infected patients who were HBsAg positive, one, a bisexual who had engaged in anal (insertive and receptive) and vaginal intercourse with more than a 100 lifetime partners, was HBeAg positive. All these nine with HBeAg were Chinese aged 23-40 years. Three of the STD patients but none of the HIV infected patients were anti-HBc IgM positive.

#### UNIVARIATE ANALYSIS

The prevalence of anti-HBc, anti-HBs, and any positive HBV marker was significantly higher among patients with STD and HIV infection than in the control population (table 1). As expected, the prevalence of HBV infection increased progressively with age, and it was higher in the Chinese than in the non-Chinese. There was no correlation with educational level (table 2). Risk factors which were significantly associated with higher HBV seroprevalence rates were homo-bisexuality, history of anal intercourse, receptive sexual role, three or more lifetime episodes of STD, 10 or more lifetime sexual partners, and a reactive VDRL test (table 3).

#### STEPWISE LOGISTIC REGRESSION ANALYSIS

The adjusted seroprevalences of STD patients and HIV infected patients were 2.4 times (95%

CI 1.7, 3.3) and 3.3 times (95% CI 1.7, 6.3), respectively, higher than that of the control population (table 4). Two variables – that is, increasing age and Chinese ethnic group – were associated with a high seroprevalence. Among patients with STD and HIV infection, seroprevalence was also significantly associated with the following risk factors: practice of anal intercourse, having 10 or more lifetime sexual partners, and a reactive VDRL test. This association was independent of age and ethnic group. Although the adjusted HBV seroprevalence of HIV infected patients was higher than that of STD patients, the difference was not statistically significant.

The difference in the adjusted seroprevalence of HBsAg among STD patients, HIV infected patients, and controls was not significant. However, the Chinese had a significantly higher adjusted rate compared with the non-Chinese (OR 7.2; 95% CI 1.7, 30.5). This association was independent of age. The adjusted prevalence of HBsAg was not associated with any of the variables related to sexual behaviour.

#### Discussion

Our study showed that patients with STD and HIV infection in an intermediate HBV endemic area have a significantly higher prevalence of HBV infection, independent of age and ethnic group, than healthy individuals (controls). Although immunocompromised people have a higher risk of developing the carrier state when

infected with HBV,<sup>23</sup> the prevalence of HBsAg in HIV infected patients (8.5%) was not significantly different from that in patients with STD (6.2%) and healthy individuals (4.5%).<sup>24-26</sup> This is because the number of HIV infected patients was small, and no deduction can be made from the hepatitis B profiles of the few HIV infected patients who were HBsAg positive. It is also not possible from such a cross sectional serological survey to determine whether HBV infection was acquired before or after HIV infection. We also confirmed the risk factors found to be significantly associated with HBV transmission in areas of low endemicity – that is, multiple sexual partners,<sup>5 11-12 27-28</sup> anal intercourse,<sup>7 10</sup> and positive serology for syphilis.<sup>9 11</sup>

In Singapore, with the successful implementation of the national childhood immunisation programme against HBV infection,<sup>29</sup> perinatal transmission has been reduced by 80%, while horizontal transmission has declined through other public health measures.<sup>20</sup> Sexual transmission will inevitably emerge as the leading cause of HBV infection among healthy susceptible adolescents and adults as in the west.<sup>2-12</sup> Routine epidemiological investigations into reported cases of acute hepatitis B showed that more than 98% occurred in persons aged 15 years and above, with the highest morbidity among those aged 15–34 years. More than 80% of those with acute hepatitis B had no history of known exposure to percutaneous procedures before the onset of illness. Discreet enquiries also showed that up to 50% of the cases had had heterosexual contacts, other than with their spouses, especially when they travelled overseas, compared with only 16% in the general male population.<sup>30</sup>

Based on the findings of the study, we recommend that patients attending STD clinics should be routinely screened for HBV markers and those found to be seronegative should be strongly advised to be immunised against HBV.

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