

# Association of Hepatitis B Virus Infection With Other Sexually Transmitted Infections in Homosexual Men

## ABSTRACT

**Objectives.** This study determined the prevalence and factors associated with hepatitis B virus (HBV) infection among men who have sex with men.

**Methods.** At the baseline visit of an HIV study among men who have sex with men, we asked about HBV vaccination status and tested for HBV markers.

**Results.** Of 625 subjects, 48% had received at least 1 dose of HBV vaccine. Of 328 unvaccinated men, 41% had 1 or more HBV markers. HBV prevalence increased markedly with age and was associated with many sexual and drug-related behaviors. In a multivariate model, 7 variables were independently associated with HBV infection: ulcerative sexually transmitted diseases (odds ratio [OR]=10.1; 95% confidence interval [CI]=2.6, 54); injection drug use (OR=5.2; 95% CI=1.2, 26); gonorrhea or chlamydia (OR=4.0; 95% CI=1.9, 8.9); sexual partner with HIV/AIDS (OR=3.6; 95% CI=1.8, 7.1); 50 or more casual partners (OR=3.4; 95% CI=1.6, 7.1); received money for sex (OR=3.0; 95% CI=1.2, 7.8); and 20 or more regular partners (OR=2.5; 95% CI=1.1, 6.1).

**Conclusions.** In Montreal, men who have sex with men are at risk for HBV infection, but a substantial proportion remain unvaccinated; new strategies are required to improve coverage. Men who have sex with men and who have a sexually transmitted infection, especially a genito-ulcerative infection, appear to be at particularly high risk for HBV infection. (*Am J Public Health*. 2000;90:1570–1574)

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Homosexual men in Montreal, Quebec, have been seriously affected by the HIV epidemic. Of the 4204 AIDS cases in Montreal reported up to June 1999, 2924 (70%) were among men who have sex with men (MSM).<sup>1</sup> In 1996, we began the Omega cohort to estimate HIV incidence among Montreal MSM, to identify risk factors associated with HIV seroconversion, and to characterize sexual behavior and its evolution.<sup>2</sup>

MSM are also at risk for hepatitis B virus (HBV) infection, which is largely related to the same sexual behaviors as is HIV infection.<sup>3–6</sup> Hepatitis B infection is serious; 5% to 10% of infected adults remain chronic carriers, usually for life, and a significant minority progress to chronic active hepatitis, cirrhosis, hepatic insufficiency, and hepatocellular carcinoma.<sup>7</sup> Although an effective and safe vaccine was licensed in 1982, not all homosexual men have been vaccinated, owing to limited knowledge about HBV infection and vaccine, low perceived susceptibility, high cost, and myths about its adverse effects.<sup>8,9</sup>

Given the opportunity afforded by the Omega study, we chose to study the epidemiologic characteristics of HBV infection among MSM in Montreal. Therefore, we included questions concerning history of symptoms possibly related to viral hepatitis, vaccination status, and previous diagnostic testing for HBV infection, in addition to the many questions related to demography and sexual behavior included in the HIV study.

## Methods

### Subject Recruitment

The Omega study recruits HIV-seronegative homosexual men at clinical and community settings; we promoted the study at the offices of physicians with large gay practices, at

gay bars and bathhouses, at Gay Pride Day, through community organizations, and via advertisements and articles in the Montreal gay press. Subjects were men who had had sex with another man in the previous year. (We use the terms *MSM* and *homosexual men* interchangeably in the present report to reflect this behavioral definition.) Enrollment began in October 1996. We oversampled younger men to obtain at least 50% of subjects younger than 30 years. Participants were followed up every 6 months. At each visit, a questionnaire was administered; the questionnaire included interviewer-administered and self-administered questions. The latter focused on sexual practices and constituted about 40% of the questionnaire (the questionnaire is available on request). At each visit, we tested for HIV and syphilis serologic markers; participants who tested positive for HIV on their first visit were excluded from further study.

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To learn about HBV infection among MSM in Montreal, we tested participants for HBV markers at their first visit. Unvaccinated participants without serologic evidence of previous HBV infection were offered vaccination at no charge, and persons who tested positive for hepatitis B surface antigen (HBsAg) were referred for medical evaluation. The questionnaire included questions related to hepatitis B, including vaccination, a history of jaundice, and knowledge of past hepatitis B infection. It also included questions that elicited detailed information about sexual behaviors, which were examined for possible correlation with HBV markers. In our study, we defined types of sexual partners for subjects as follows: "a *regular partner* is someone with whom you had sex at least twice, whom you intended to see and did see again, someone with whom you had a certain relationship (emotional, sexual, or otherwise)," and "a *casual partner* is someone with whom you had sex only once (a 'one-night stand'), someone you did not intend to see again."

#### Laboratory Analysis

We tested subjects for HIV and for syphilis (by rapid plasma reagin) (NCS Diagnostics, Mississauga, Ontario) at each visit. Specimens positive by rapid plasma reagin were confirmed at the Laboratoire de santé publique du Québec by the micro-hemagglutination assay for antibodies to *Treponema pallidum* (MHA-TP; Fujirebio, Tokyo, Japan). We also tested sera of the first 500 subjects by enzyme immunoassay for antibody to hepatitis B core antigen (anti-HBc), antibody to hepatitis B surface antigen (anti-HBs), and HBsAg (Cobas Core System, Roche Diagnostics, Mississauga, Ontario). Subsequently, we tested subjects for anti-HBc and, if the results were positive, for anti-HBs and HBsAg.

We were concerned that self-reported histories of sexually transmitted disease (STD) might not be accurate, especially if infections occurred remotely (syphilis has not been frequent in this population for over 15 years). Therefore, to independently validate syphilis histories, we performed serologic testing for syphilis with the toluidine red unheated serum test (TRUST)<sup>10</sup> and MHA-TP sera from men who reported having had syphilis and from a 1-in-5 random sample of unvaccinated men who did not. If one of the tests was positive or equivocal, sera were tested by fluorescent treponemal antibody absorption test (FTA-ABS-DS; Zeus Scientific, Inc, Raritan, NJ). MHA-TP and FTA-ABS-DS were performed at the Laboratoire de santé publique du Québec.

#### Statistical Analysis

We first carried out descriptive analyses of hepatitis B vaccination coverage and hepatitis B markers among subjects at their first visit. Next, we examined only those men who reported not having been vaccinated against hepatitis B and analyzed the demographic and sexual behavioral variables for possible correlations with HBV infection, including the number of sexual partners, sexual practices, and history of STDs. We considered the presence of any HBV marker as indicative of past or present HBV infection. For the univariate analysis, we tested for significance with the Fisher exact test and the  $\chi^2$  test, using a threshold *P* value of .05. We examined variables associated with HBV in the univariate analysis and those identified in published studies in a multivariate logistic regression model with SAS, version 6.11 (SAS Institute, Cary, NC). We also retained in the model possible confounders if their inclusion changed the odds ratio of other variables by 10% or more.

#### Results

From October 17, 1996, to July 31, 1997, 653 HIV-seronegative men were recruited. Age ranged from 18 to 73 years, with a mean of 34.5 years and a median of 33 years; 39% were younger than 30 years (the age distribution of subjects reflects in part the oversampling of younger MSM). Subjects were predominantly francophone (71%), born in Canada (78%), and resident in Montreal (90%). Although most (74%) had college or higher education, annual income was relatively low (47% below Can \$20000).

Of the 625 men indicating hepatitis B vaccination status, 297 (48%) reported having received at least 1 dose. Overall, 175 study subjects (28%) completed the 3-dose course, 78 (13%) had 2 doses, and 41 (6.6%) received 1 dose. Forty-three percent of subjects had been previously tested for HBV markers, although the date of testing was not known.

Of the 328 men with known HBV marker status who reported not having been vaccinated, 14 (4.3%) were HBsAg positive, 101 (30.8%) had anti-HBc and anti-HBs, 7 (2.1%) had anti-HBs alone, and 12 (3.7%) had anti-HBc alone. Thus, 134 (41%) had an HBV marker and 127 (39%) had either HBsAg or anti-HBc. Of the 297 men who reported having been vaccinated, 1 (0.3%) was HBsAg positive and 40 (14%) had either HBsAg or anti-HBc; it is not known whether the HBV infection occurred before or after vaccination.

With respect to syphilis serology, 11 (41%) of the 27 men who reported having had syphilis tested positive by the FTA-ABS-DS or MHA-TP, compared with none of the 56

randomly selected unvaccinated men who had not reported such history (*P* = .00001, Fisher exact test).

The rest of the results focus on HBV markers among the 328 participants who reported not having been vaccinated. A subject was considered to have had past or to have present HBV infection if we detected anti-HBc, anti-HBs, or HBsAg. As noted above, among unvaccinated men, 41% had at least 1 HBV marker.

Among the sociodemographic variables examined (Table 1), HBV infection prevalence was associated with age, varying from 9.8% among those younger than 25 years to 61% among those 35 years or older. HBV marker prevalence was almost twice as high among Montreal residents compared with subjects residing outside Montreal. The univariate results for selected behavioral variables are shown in Table 2. We observed a strong correlation between HBV infection and increasing number of sexual partners: HBV prevalence increased from 6.3% among men with fewer than 6 lifetime casual sexual partners to 70% among those with 100 or more such partners. The prevalence of HBV markers among men who had received money for sex was almost twice that of men who had not. The consumption of alcohol before sex and the use of drugs before sex were both associated with HBV marker prevalence.

Of the 328 subjects, 297 (91%) responded to all 6 questions about a lifetime history of specific STDs; 131 subjects reported having at least 1 STD, and 31 subjects reported a genitoulcerative STD. We observed a strong correlation of HBV markers with each of the STDs examined (Table 3); among those with a history of each STD, HBV prevalence was about twice as high as among those without such a history.

In the multivariate logistic regression analysis including variables significant in the univariate analysis (Table 4), the following 7 variables were independently associated with HBV infection: history of ulcerative STD (herpes, syphilis, or genital ulcer unspecified), injection drug use, history of gonorrhea or chlamydia, having had a partner with HIV or AIDS, 50 or more casual sex partners, received money for sex, and 20 or more regular sex partners. For unprotected anal sex with a casual sex partner, the association was borderline significant. For genitoulcerative infections, the odds ratio was 10.1 (95% confidence interval = 2.60, 53.9).

#### Discussion

We found that a substantial proportion of MSM in Montreal appear to have been exposed to HBV infection but that fewer than half have been vaccinated. HBV infection was frequent among unvaccinated men: 41% had been infected and 4.3% were chronic carriers, a con-

**TABLE 1—Association of Sociodemographic Characteristics With Hepatitis B Virus Infection Among Unvaccinated Participants at First Visit (n = 328): Montreal, 1996–1997**

	n	Infected, %	P
Age category, y			
<25	61	9.8	
25–34	126	34	
≥35	140	61	.001 ( $\chi^2$ for trend)
Cultural background			
French Canadian	144	35	
English Canadian	40	45	
Other	34	53	.04 ( $\chi^2$ )
Region of residence			
Montreal Island	280	44	
Other	43	23	.01 ( $\chi^2$ )
Place of birth			
Montreal region	150	38	
Quebec elsewhere	102	39	
Canada elsewhere	30	47	
Other	39	49	NS
Level of education			
High school or less	170	39	
College or more	156	44	NS
Annual income, Can \$			
<\$20 000	158	37	
≥\$20 000	165	46	NS

Note. NS = not significant.

**TABLE 2—Association of Sexual Behavior and Substance Use With Hepatitis B Virus Infection Among Unvaccinated Participants at First Visit (n = 328): Montreal, 1996–1997**

	n	Infected, %	Odds Ratio (95% CI)
No. of lifetime regular sexual partners			
None	8	13	(Referent)
1	25	16	1.3 (0.10, 37)
2–5	138	33	3.4 (0.40, 76)
6–19	93	45	5.8 (0.66, 130)
≥20	57	70	17 (1.8, 380)
No. of lifetime casual sexual partners			
<6	64	6.3	(Referent)
6–19	47	21	4.1 (1.1, 17)
20–49	61	31	6.8 (2.0, 26)
50–99	46	57	20 (5.5, 76)
≥100	107	70	35 (11, 120)
Received money for sex			
Never	270	36	(Referent)
Ever	56	64	3.2 (1.7, 6.1)
Alcohol before sex			
Never	48	27	(Referent)
Rarely	81	35	1.4 (0.61, 3.4)
Sometimes	106	43	2.1 (0.93, 4.7)
Often	44	59	3.9 (1.5, 10)
Very often	30	50	2.7 (0.93, 7.9)
Drugs before sex			
No	158	33	(Referent)
Yes	152	50	2.0 (1.3, 3.3)
Injection drug use			
No	302	39	(Referent)
Yes	22	77	5.3 (1.8, 17)
Partner with HIV or AIDS			
No	198	27	(Referent)
Yes	126	63	4.5 (2.7, 7.4)
Unprotected anal sex with casual partner			
No	187	27	(Referent)
Yes	133	60	4.1 (2.3, 6.9)

Note. CI = confidence interval.

dition with serious long-term consequences. We also observed that in this population, hepatitis B infection was associated with most sexual behavior variables examined and, in particular, was strongly and independently associated with a history of STD, especially genito-ulcerative infections.

There are several limitations to our study. First, subjects were not randomly selected; they volunteered for the study and may not be representative of MSM in Montreal generally. Second, we obtained data on behaviors, sociodemographic status, STD history, and hepatitis B vaccination from a questionnaire. Except in the case of syphilis, we did not independently validate the information obtained, although we have no reason to believe that there was any systematic bias in this regard. We examined lifetime experiences reported at the time of the first visit for possible associations with HBV marker prevalence. In this design, we could not determine whether the reported STD predated the HBV infection. Also, a history of STD may be a correlate of some other high-risk sexual exposure that is responsible for the increased risk of HBV infection, in which case our observed associations of HBV infection with STDs would be spurious. Nevertheless, we adjusted for many variables related to sexual behaviors, and the strong associations remained.

Among unvaccinated subjects, 7 men (2.1%) had anti-HBs but no anti-HBc antibody. These subjects may have been vaccinated but failed to report it, or they may have been infected and lost anti-HBc antibody. In our analysis, we assumed the latter. If some subjects had been vaccinated, this would have introduced misclassification error; however, the impact of such an error would be negligible and, in any case, would have decreased our power to detect differences.

We found an overall prevalence of HBV markers of 48% among men in the Omega cohort. It is difficult to compare HBV marker prevalence among different homosexual populations, since prevalence varies with age, vaccination status, and calendar time, among other variables. The prevalence of anti-HBc or HBsAg (markers of past HBV infection) among unvaccinated men was 39%, compared with 14% among those apparently vaccinated (anti-HBs alone was excluded, since it probably indicates a previous vaccination). The latter figure does not necessarily reflect vaccine failure, since HBV infection may have occurred before vaccination.

To the best of our knowledge, no other data on HBV markers from other studies of MSM in Montreal are available for comparison. A study of 150 homosexual STD clinic patients in Edmonton, Alberta, in 1982 showed an HBV marker prevalence of 39%.<sup>4</sup> One might expect a higher prevalence among STD clinic attendees, but it is difficult to compare Montreal and Edmonton, which is a smaller, more

**TABLE 3—Association of History of Sexually Transmitted Diseases and Hepatitis B Virus Infection Among Unvaccinated Participants at First Visit (n = 328): Montreal, 1996–1997**

History of—	n	Infected, %	Odds Ratio (95% CI)
Gonorrhea			
No	230	29	(Referent)
Yes	81	74	7.1 (3.9, 13)
Chlamydia			
No	287	38	(Referent)
Yes	21	71	4.1 (1.5, 12)
Syphilis			
No	303	38	(Referent)
Yes	14	93	22 (2.9, 450)
Herpes			
No	301	38	(Referent)
Yes	17	88	12 (2.7, 81)
Condylomata			
No	259	36	(Referent)
Yes	57	60	2.6 (1.4, 5.0)
Genital ulcer, unspecified			
No	309	40	(Referent)
Yes	5	80	6.0 (0.62, 140)

Note. CI = confidence interval.

**TABLE 4—Results of Multivariate Logistic Regression Model Examining Associations of Sociodemographic, Sexual Behavioral, and Sexually Transmitted Disease (STD) History Variables With Hepatitis B Virus Markers Among Unvaccinated Study Participants at First Visit (n = 328): Montreal, 1996–1997**

	Odds Ratio	95% CI
History of ulcerative STD (herpes, syphilis, or genital ulcer)	10.1	2.60, 53.9
Injection drug use	5.16	1.20, 26.3
History of gonorrhea or chlamydia	4.04	1.88, 8.92
Sexual partner with HIV or AIDS	3.56	1.81, 7.13
≥50 casual partners during lifetime	3.35	1.60, 7.10
Received money for sex	3.01	1.21, 7.75
≥20 regular partners during lifetime	2.49	1.05, 6.09
Unprotected anal sex with casual partner	1.96	0.980, 3.93
Age (per year)	1.02	0.988, 1.06
Alcohol and drugs before sex	0.562	0.260, 1.17

Note. CI = confidence interval.

isolated city. In a more comparable population of MSM in Vancouver recruited from general medical practices in 1982 through 1984,<sup>5</sup> HBV marker prevalence was 68%. It is likely that, owing to the dramatic decreases in risky sexual behavior among MSM in response to the HIV epidemic, hepatitis B infection among Montreal MSM is less than it was previously.

More recent studies have been carried out elsewhere. Among 306 unvaccinated homosexual men attending a genitourinary clinic in London, England, in 1990, anti-HBc prevalence was 50%.<sup>11</sup> A study of 417 unvaccinated HIV-negative MSM in Seattle in 1995 showed an HBV marker prevalence of 35%.<sup>12</sup> This was somewhat lower than the HBV prevalence of 48% we observed despite very similar study populations with respect to demographic characteristics, STD histories, and HIV status.

The role of other STDs, especially genitoulcerative infections, in HBV infection is of interest. Previous studies have examined possible risk factors for HBV infection in both heterosexual<sup>13–16</sup> and homosexual<sup>3,5,14,17–21</sup> populations. Since associations observed in such studies may be markers for other associations, studies that collected demographic and risk-related data (e.g., on sexual practices and past STDs) and used multivariate analysis to adjust for possible confounding are of particular interest. Both the duration of homosexual activity<sup>17,18</sup> and the number of male sexual partners<sup>5,17,19,21</sup> were independently associated with HBV infection in studies carried out in Canada, the United States, and Europe. Receptive anal intercourse was identified in at least 3 studies<sup>5,17,18</sup> and insertive anal intercourse in 1 study.<sup>20</sup> This is analogous to HIV infection

(these 4 studies examined behaviors that occurred before the HIV epidemic, when condom use among MSM was not frequent).

The independent association of HBV infection with STD has been observed previously in heterosexual<sup>13,15,16</sup> and homosexual populations.<sup>5,17,19,21,22</sup> In a study of 1062 homosexual men in Baltimore in 1984,<sup>17</sup> both a history of gonorrhea and a history of any STD were associated with HBV markers among at least 3 of the 5 subgroup analyses presented, with odds ratios in the range of 2.5 to 4.6 and 1.4 to 1.7, respectively. Willoughby and colleagues, studying 576 MSM recruited from medical practices in Vancouver,<sup>5</sup> found that a self-reported history of syphilis was associated with the presence of HBV markers, with an adjusted odds ratio of 2.9. A study of HBV infection among 317 MSM attending colleges in Boston<sup>19</sup> observed a statistically significant association with a history of STD, with an adjusted odds ratio of 3.1. Finally, Stroffolini and colleagues studied 252 homosexual men attending an STD clinic in Rome, Italy,<sup>21</sup> and, in a multivariate model, found an association with positive syphilis serology (odds ratio = 1.9).

In our study, we were unable to independently validate the self-reported episodes of clinical syphilis; a history of syphilis may be a marker for a sexual practice not captured in our study, and the observed association with HBV infection may be artifactual. This, however, is unlikely. A similar association has been observed in studies in which active syphilis was diagnosed directly at the time of the study. Second, our subjects were well educated and would likely have excellent knowledge of STD. A diagnosis of syphilis is specific, and we asked about this by using the exact term in French. Finally, we observed a strong association between the presence of antibody and a self-reported history of syphilis. Although we detected treponemal antibody in only 41% of the 27 men with a history of syphilis, this is not surprising, since antibodies do not persist indefinitely in all patients.<sup>23</sup>

Only about half of our subjects reported having received hepatitis B vaccine, a vaccine that is safe and effective. MSM are at high risk for hepatitis B, and vaccination for this group was recommended almost 10 years ago.<sup>24</sup> Clearly, new strategies are needed to improve vaccine coverage. For this reason, we have analyzed our data specifically to identify factors associated with failure to initiate and complete HBV vaccination.<sup>25</sup>

Our finding of a strong association of HBV infection with STD reinforces the importance of timely diagnosis and treatment of STDs and, in particular, genitoulcerative infections. This will also help to prevent HIV infection. Persons diagnosed with an STD must also be offered hepatitis B vaccination.<sup>24</sup> □

## Contributors

R. S. Remis was a principal investigator and helped to develop the study protocol and oversee the analyses; he also prepared the manuscript. A. Dufour, a PhD student whose thesis focused on the Omega study, was the data manager and carried out the descriptive and regression analyses. M. Alary, a principal investigator, developed the study protocol, supervised the study implementation, and provided significant input into the data analysis and manuscript revision. J. Vincelette, coinvestigator, helped to develop the study protocol and carried out the serologic tests for hepatitis B and syphilis. J. Otis, a principal investigator, helped to develop the study protocol and designed the questionnaires. B. Mâsse, coinvestigator, helped to develop the study protocol and provided statistical advice. B. Turmel, coinvestigator, helped in the conception and implementation of the study and ensured liaison with the Montreal Public Health Department. R. LeClerc and R. Lavoie, coinvestigators, helped in the conception and implementation and developed the community component of the study. R. Parent, coinvestigator, helped in the conception and implementation of the study. All coauthors reviewed and approved the manuscript.

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