Evidence for Probable Sexual Transmission of the Hepatitis G Virus

Sharon E. Frey,1 Sharon M. Homan,2 Marcia Sokol-Anderson,1 Margarita Torralba Cayco,1∗ Prospero Cortorreal,1∗ Cora E. Musial,1∗ and Adrian Di Bisceglie1

1Saint Louis University School of Medicine, Department of Internal Medicine, and 2Saint Louis University School of Public Health, St. Louis, Missouri

A cross-sectional epidemiology study evaluated the role of sexual activity and sexually transmitted diseases (STDs) in the transmission of hepatitis G virus (HGV/GBV-C) and other hepatitis virus infections in 944 subjects. There was a statistically significant higher prevalence of HGV/GBV-C, hepatitis B virus, and hepatitis C virus exposure in the STD clinic group (i.e., subjects who were currently seeking treatment for an STD) compared with the group who never had received treatment for an STD. In a comparison of the subjects with an STD versus those without an STD, the prevalence of HGV/GBV-C was 11.3% versus 4.9%, on the basis of polymerase chain reaction (PCR) results alone, and 36.6% versus 8.8%, when results of PCR and enzyme-linked immunosorbent assay were combined. Sexual activity and, possibly, the presence of an STD increases the risk of HGB/GBV-C transmission.

The sequence and characterization of hepatitis G virus (HGV/GBV-C) was first reported in the mid-1990s by investigators at Abbott Laboratories [1] and Genelabs [2]. Since that time, multiple epidemiological studies have explored the modes of transmission, prevalence, possible clinical disease process, and pathology of this newly discovered virus, as well as whether it is a cause of non-ABCDE hepatitis virus–induced liver disease. The current consensus is that HGV/GBV-C is not a virulent organism; it does not cause significant liver disease or worsen current liver disease [3–8], nor is the liver the primary site of replication [9, 10]. Little evidence exists about disease due to HGV/GBV-C in patients who have undergone liver transplantation [9]. The presence of HGV/GBV-C has no effect on the course of infection with hepatitis C virus (HCV) [4, 5, 11] or hepatitis B virus (HBV) [12] in coinfected individuals. Some evidence suggests that HIV-infected patients coinfected with HGV/GBV-C may experience a slower progression of HIV disease [13, 14].

Although it is well established that HGV/GBV-C is transmitted as a result of exposure to blood, as evidenced by the association of infection with hemodialysis [15], injection drug use [12, 16], and vertical transmission [17–19], only partial evidence exists for transmission through sexual activity or exposure to mucosal surfaces. Nonetheless, HGV/GBV-C RNA has been isolated from specimens of saliva [20] and semen [21], and several studies have lent support for theories regarding sexual transmission as a probable mode of contracting HGV/GBV-C infection. A relatively high prevalence of HGV/GBV-C RNA was found among non–injection drug–using homosexual and bisexual men [22, 23] and heterosexual persons [23, 24]. The risk of acquiring HGV/GBV-C infection increased with prolonged duration of work as a prostitute [25], frequency of paid sex per month [26], and having sex with a prostitute [27]. Close sequence and phylogenetic sim-
ilarities provided evidence for heterosexual transmission between 2 persons in a stable monogamous relationship [28]. In another study, HGV/GBV-C viremia was determined by PCR and antibody to E2 protein was determined by ELISA with use of samples obtained from individuals attending a genitourinary clinic [29]. Viremia was detected in 27 (31%) of 87 male homosexuals and 9 (18%) of 50 female prostitutes, compared with 2 (3%) of 3 control subjects [29]. Antibody to E2 protein was detected in 14 (23%) of 60 male homosexuals, 11 (27%) of 41 prostitutes, and 1 (21%) of 61 control subjects [29].

The purpose of the present study was to evaluate the role of sexual transmission of HGV/GBV-C by comparing groups of volunteers who were at high risk (the exposed group) with persons at low risk (the unexposed group) of acquiring a sexually transmitted infection. It is assumed that persons who acquire 1 sexually transmitted infection are at risk of acquiring other sexually transmitted infections (in this case, HGV/GBV-C). The primary objective of the present study was to estimate and compare the prevalence of HGV/GBV-C infection in a group of volunteers seeking treatment for a sexually transmitted disease (STD) and a group of volunteers who had never been treated for an STD. The secondary objective of the study was to estimate and compare the prevalence of exposure to HGV/GBV-C, HBV, and HCV between the exposed and unexposed groups.

PATIENTS, MATERIALS, AND METHODS

Study design. In this cross-sectional epidemiological study design, the prevalence of exposure to and current infection with HGV/GBV-C, HBV, and HCV among persons exposed to STD who were currently seeking treatment for an STD (the STD group) was compared with the prevalence among persons who had never received treatment for an STD (the non-STD group). Informed consent was obtained prior to obtaining information and blood samples from the subjects. Each subject provided the following information: age, sex, ethnic group, and whether he or she had used injection drugs, exchanged money or drugs for sex, or received blood products. To protect confidentiality, the staff of the Saint Louis University Vaccine Evaluation Unit provided test results only at the direct request of the STD clinic study enrollees. Letters were mailed to volunteers in the non-STD group to notify them of the test results. Results were available within 3 months of enrollment. The study was restricted to persons who were 18–40 years of age at the time of enrollment.

Study sample. From 1 December 1995 through 28 February 1999, a total of 1005 study volunteers were recruited from the greater St. Louis area. Of these 1005 volunteers, 944 were included in the STD (n = 453) and non-STD (n = 491) study groups. For the STD group, 503 volunteers were consecutively recruited at the time they sought STD treatment from a publicly funded health clinic in St. Louis County. Volunteers were excluded from the STD group if they did not meet the age requirement (39 subjects), if they were enrolled on 2 different occasions (6 subjects), or if there were insufficient data (5 subjects).

The 502 volunteers in the non-STD group were persons recruited from the Saint Louis University Health Sciences Center or volunteers attending the Center for Vaccine Development. Of the 502 volunteers, 1 did not meet the age requirement, 7 were enrolled on 2 different occasions, and 3 had history of an STD and/or sought STD treatment; thus, 491 subjects were included in the non-STD group.

Laboratory assays. Clinical staff attempted to obtain a 10-mL blood sample from each volunteer at the time of enrollment; however, not all volunteers had sufficient blood available for all assays. We tested for the following serologic markers: hepatitis B surface antigen (HBsAg), by use of the AUSZYME EIA (Abbott); hepatitis B surface antibody (anti-HBs), by use of the AUSAB EIA (Abbott); hepatitis B core antibody (anti-HBc), by use of the Corzyme EIA (Abbott); antibody to hepatitis C virus (anti-HCV), by use of the HCV EIA 2.0 (Abbott) and HCV PCR that used RNA from QIAGEN Viral RNA mini kit (QIAGEN) HCV RNA extraction, external primers (NAF-1 and NAR-1), and internal primers (NAF-3 and NAR-3) [30]; and HGV/GBV-C PCR that used RNA from QIAGEN Viral RNA mini kit (QIAGEN), external primers (GF1 and GR1), and internal primers (GF2 and GR2) [31]. Testing for anti-
Hepatitis G and STD

Statistical analysis. We planned to study 475–500 volunteers in each group to ensure, with 90% power, that we would detect a 2-fold (or larger) difference between the prevalence of HGV/GBV-C in the STD group and the prevalence in the non-STD group, at a .05 significance level, under the assumption that baseline prevalence of HGV/GBV-C was low (~5%). Thus, enrollment in the study of 453 patients in the STD group and 491 patients in the non-STD group provided an adequate sample to demonstrate statistical significance with 90% power.

Proportions and mean values for the study variables were reported and compared between the STD and non-STD groups by use of the χ² and Fisher’s exact tests, for the categorical variables, and Student’s t test, for continuous variables (table 1). The study variables included personal (i.e., age, sex, and ethnicity), behavioral (i.e., injection drug use or history of exchanging money or drugs for sex), and medical (i.e., receipt of blood products) risk factors for acquiring bloodborne viral infections.

Logistic regression was used to estimate the OR for a positive HGV/GBV-C test result associated with STD exposure, after adjustment for confounding variables. Confounding variables were variables that were (1) related to the likelihood of being in the STD group and (2) considered potential risk variables for HGV/GBV-C infection. The following 6 confounding variables (coded as dichotomous variables, with the higher risk category coded as 1) were included in the logistic regression models: sex (coded 1 for male and 0 for female), race (1 for nonwhite and 0 for white), age (continuous variable), receipt of blood products (1 for yes and 0 for no), injection drug use (1 for yes and 0 for no), and history of exchanging sex for drugs or money (1 for yes and 0 for no). A risk variable was also created to indicate whether a person had any of the latter 3 risk factors. The variables were entered into the logistic regression models by use of a stepwise selection process. Final models included those variables that were significant at the .05 level of statistical significance, controlling for the variables already in the model. The adjusted, or partial, ORs for the STD group variables and the significant confounding variables are reported.

Statistical analyses were also performed to explore the relationships among the laboratory assays. Specifically, the χ² test was used to compare the distributions of the various combinations of other positive test results that co-occurred with HGV/GBV-C PCR–positive results in the STD and non-STD groups.

RESULTS

Characteristics of study samples. Table 1 summarizes the characteristics and risk factor prevalences of the STD and non-STD study groups. The STD group was composed predominantly

| Table 2. Prevalence estimates of hepatitis viruses G (HGV), C (HCV), and B (HBV) among subjects who were currently seeking treatment for a sexually transmitted disease (the STD group) and subjects who never received treatment for an STD (the non-STD group). |
|-----------------|-----------------|-----------------|-----------------|
|                  | n/N (%)         |                  |                  |
|                  | STD group       | Non-STD group    |                 |
|                  | (n = 453)       | (n = 491)        |                 |
| HGV              |                 |                  |                 |
| HGV nested PCR   | 50/444 (11.3)   | 24/490 (4.9)     | <.001           |
| Anti-HGV antibody| 118/442 (26.7)  | 21/487 (4.3)     | <.001           |
| HGV PCR or anti-HGV antibody | 162/441 (36.6) | 43/487 (8.8)     | <.001           |
| HCV              |                 |                  |                 |
| HCV PCR          | 4/7 (57)        | 0/0 (—)          | —               |
| Anti-HCV antibody| 7/452 (1.5)     | 0/491 (0)        | <.01            |
| HCV PCR or anti-HCV antibody | 7/7 (100)² | 0/0 (—)          | —               |
| HBV              |                 |                  |                 |
| HB-surface antigen | 5/453 (1.1)    | 1/491 (0.2)      | .11             |
| Anti-HB antibody |                 |                  |                 |
| Core             | 44/453 (9.7)    | 23/491 (4.7)     | <.001           |
| Surface          | 51/450 (11.3)   | 231/491 (47.0)   | <.005           |
| HB or anti-HB antibody | 80/453 (17.7) | 241/491 (49.1)   | <.001           |

ª Not all subjects had sufficient blood samples obtained for performance of all tests.

b Determined by means of Fisher’s exact test.

c Antibody to E2 protein, determined by ELISA.

d Only 7 subjects in the STD group had both HCV-PCR and anti-HCV tests performed.
of black men, whereas the non-STD group was composed predominantly of white subjects; 73% of the subjects in the non-STD group were women, and 2 of the 3 ethnic groups (Asian/Pacific Island, Native American, and Hispanic subjects) had higher percentages in the non-STD group (P<.01). Subjects in the STD group had a lower median age (24 vs. 25 years; P<.01) and more subjects reported injection drug use (P<.05), a history of exchanging money for drugs or sex (P<.05), and receipt of blood products (P<.01) than did patients in the non-STD group. The 2 groups had statistically different distributions of age, sex, race, and the risk variables of injection drug use, receipt of money or drugs for sex, and receipt of blood products. Because the groups differed in the distribution of these confounding variables (i.e., variables that are related both to the prevalence of hepatitis and the risk of having an STD), stratified and multivariate analyses were used to examine the relationship between STDs and HGV/GBV-C, HBV, and HCV infection, adjusting for the influence of these variables.

Prevalence of serologic markers for hepatitis. There were statistically significant differences between the STD group and the non-STD group in the prevalence of exposure to HGV/GBV-C, HBV, and HCV. The prevalence of HGV/GBV-C was estimated for each group on the basis of the results of HGV/GBV-C PCR assays for 453 subjects in the STD group and 491 subjects in the non-STD group. The prevalence was 11.3% (50 of 444 patients) in the STD group and 4.9% (24 of 490) in the non-STD group (P<.001). When data from subjects with positive HGV/GBV-C PCR results and patients with anti-HGV/GBV-C antibody were combined, the prevalence was 36.6% (162 of 441 patients) in the STD group, compared with 8.8% (43 of 487) in the non-STD group (P<.001). When laboratory assay results for the STD group were compared with those for the non-STD group, there were significant differences in the prevalences of the following antibodies: anti-HCV (7 [1.5%] of 452 patients vs. 0 [0%] of 491 patients; P<.01), anti-HBc (44 [9.7%] of 453 vs. 23 [4.7%] of 491; P<.001), anti-HBs (51 [11.3%] of 450 vs. 231 [47%] of 491; P<.005), and anti-HB (80 [17.7%] of 453 vs. 241 [49%] of 491; P<.001); hepatitis B vaccination status is not known), respectively (table 2). The prevalence of HBsAg did not statistically differ between the groups.

Logistic regression. Multiple logistic regression analyses were used to estimate the ORs for probable sexual transmission (as measured by STD exposure/treatment) and other risk factors for HGV/GBV-C, HBV, and HCV infection. These adjusted ORs are shown in table 3. On the basis of the findings of this model, patients in the STD group were 12.4 times more likely to have a positive anti-HGV/GBV-C response than were those in the non-STD group, controlling for other risk factors (OR, 12.4; 95% CI, 6.9–22.6). Sex (not shown) was not a statistically significant variable in any of the models, nor was exchanging money for drugs or sex. Subjects of a race other than white were 2.9 times more likely to test positive for HGV/GBV-C by PCR (OR, 2.9; 95% CI, 1.7–4.9) and 4.0 times more likely to test positive for anti-HBc (OR, 4.0; 95% CI, 2.1–7.6) than were

### Table 3. Adjusted odds ratios (ORs) for probable sexual transmission of hepatitis viruses G (HGV), B (HBV), and C (HCV) and other risk factors: multiple logistic regression results.

<table>
<thead>
<tr>
<th>Virus, assay</th>
<th>Age, years</th>
<th>Race other than white</th>
<th>Exposure to STD</th>
<th>Injection drug use</th>
<th>Exchange of money for drugs or sex</th>
<th>Receipt of blood products</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGV nested PCR</td>
<td>NS</td>
<td>2.9 (1.7–4.9)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Anti-HGV antibody</td>
<td>1.1 (1.0–1.2)</td>
<td>NS</td>
<td>12.4 (6.9–22.6)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>HBV surface antigen</td>
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<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Anti-HBV antibody Core</td>
<td>1.1 (1.0–1.1)</td>
<td>4.0 (2.1–7.6)</td>
<td>4.2 (1.2–14.2)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>HCV PCR</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Anti-HCV antibody</td>
<td>300 (39–2307)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

**NOTE.** Only statistically significant risk factors are included in the final models. Estimated ORs, adjusted for variables included in the final model, are reported. STD, sexually transmitted disease.

* a Multiple logistic regression models were fitted to the dichotomous outcomes (i.e., presence vs. absence) of each of the laboratory assays used in this study.

* b Antibody to E2 protein, determined by ELISA.

* c The total number of test results (n = 7) was too small to fit a logistic regression model.

* d The number of positive test results was too small to fit multiple predictors. The unadjusted OR for injection drug use is reported. Injection drug use is a statistically significant predictor; however, the 95% CI is wide because of the small number of persons who reported injection drug use.
white subjects. Injection drug users were 300 times more likely to test positive for anti-HCV (OR, 300; 95% CI, 39–2307) than were non–injection drug users, and subjects who had received blood products were 4.2 times more likely to test positive for anti-HBc (OR, 4.2; 95% CI, 1.2–14.2) than were subjects who had not received blood products.

DISCUSSION

This large epidemiological study evaluated the point prevalence of HGV/GBV-C RNA and HGV/GBV-C antibody as evidence for sexual transmission of HGV/GBV-C. Potential confounding variables in this study included race and sex, which were controlled in the multivariate analyses. Reporting bias is probably present and may have resulted in biased estimates of the relationship between hepatitis transmission and exchange of sex for drugs or money, the use of injection drugs, and history of STD. Recall bias may play a role in the underreporting of receipt of blood products in both groups.

In the present study, persons seeking treatment for an STD were found to be at higher risk of being infected with HGV/GBV-C than were those who had never been treated for an STD. If it is assumed that persons who contract an STD are more sexually active or have more sexual partners than are persons who are not seeking treatment for an STD, then this study provides strong evidence for the role of sexual activity as a predominant mode of transmission of HGV/GBV-C. The results of the present study strongly support the findings of other studies regarding the role of sexual transmission of HGV/GBV-C [22–29] and the presence of HGV/GBV-C in specimens of saliva [20] and semen [21]. As is the case for transmission of other STDs, such as HIV, the simultaneous presence of another STD may indeed facilitate the transmission of HGV/GBV-C. The importance of the findings of this study is not clear, in light of the limited pathology or disease [33] caused by this organism, and no recommendations are made for the prevention of acquisition of the organism. However, it is important to note the occurrence of another sexually transmitted and bloodborne pathogen in the current era of emerging infections.

Acknowledgments

We acknowledge the volunteers who made the study possible, the staff of the Vaccine Treatment and Evaluation Unit at Saint Louis University, and the staff of the John C. Murphy Health Center. In addition, we thank Robin Gutierrez and Robert Kyrk of the Viral Discovery Group at Abbott Laboratories and Patricia Osmack, Division of Gastroenterology and Hepatology, Saint Louis University, for their technical assistance.

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