Association of Hepatitis C Virus Infection with Sexual Exposure in Southern India

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To determine the association between sexual exposure and hepatitis C virus (HCV) infection in urban Chennai, India, a random sample of adults who live in a slum community completed interviews and provided samples to test for HCV, herpes simplex virus type 2 (HSV-2), and other sexually transmitted infections (STIs). All analyses excluded recent and current injection drug users. HCV infection was not associated with the reported number of sex partners for men or women. Women were more likely to be HCV infected if they reported previous genital ulcer disease (adjusted odds ratio [AOR], 3.88; 95% confidence interval [95% CI], 0.94–16.0; marginally statistically significant). Men were more likely to be HCV infected if they were HSV-2 infected (AOR, 3.85; 95% CI, 1.18–12.6) or reported having had sex with men (AOR, 3.61; 95% CI, 1.00–13.1). Sexual transmission of HCV infection may be facilitated by ulcerative STIs and male-male sexual practices, but it appears to occur infrequently in this population.

Hepatitis C virus (HCV) infection persists in ≥50% of infected individuals [1, 2]. It is the leading cause of chronic liver disease in the United States and is associated with substantial morbidity and mortality worldwide [2]. HCV infection is associated with parenteral exposure, particularly injection drug use. The extent to which HCV infection is associated with sexual exposure, however, has been debated extensively [3–25]. Heterosexual partners of HCV-infected individuals have slightly higher rates of HCV infection than the general population [13, 17, 26]. Furthermore, HCV infection is more common in individuals who have sexually transmitted infections (STIs) [13, 20–22]. However, other studies cast doubt on the association between sexual and STI exposure and HCV infection [14, 17, 23–25]. In the absence of other common risk factors, transmission of HCV from an infected person to an uninfected partner appears to be inefficient [15, 16, 18].

High prevalences of HCV infection have been documented among men who have sex with men (MSM) [14, 27–31]. However, male homosexual sex has not been found to be a risk for HCV infection in most studies that have controlled for injection drug use [14, 27, 28, 30, 32].

The prevalence of and risk factors for HCV infection are not well characterized in most developing countries. The World Health Organization estimates that there are 10–24 million HCV-infected persons living in India. Estimates of the prevalence of HCV infection in India vary from <1% among voluntary blood donors to >90% among injection drug users (IDUs) [33–37]. The present study was conducted in Chennai, a city of 6 million people and the capital of Tamil Nadu state in southern India.
Data describing the prevalence of genital ulcer disease (GUD) and nonulcerative STIs in the region are sparse. Available data suggest that genital infections were common in STI clinic patients in Pune, India, where 851 (50%) of STI clinic patients had recurrent GUD in 1993–1995 [38].

We hypothesized that HCV infection would be associated with ulcerative STIs and male-male sex in adults in poor Chennai communities. To our knowledge, this is one of the first studies to address the association of sexual exposure and GUD with HCV infection in Indian populations.

METHODS

The study was conducted in 30 of 965 urban residential communities designated by the Tamil Nadu Slum Clearance Board as “slum communities.” Communities selected housed 100–300 families and were separated from each other by major barriers. Residents were enumerated in a census conducted for an ongoing STI-HIV prevention trial. In each slum, 65 households with someone aged 18–40 years were selected by systematic random sampling. From each household selected, one eligible participant was selected by simple random sampling, invited to participate in the study, and scheduled to attend a health camp. Participants and their families underwent physical examinations and laboratory testing and were given appropriate pharmaceuticals at health camps in slum communities. All services were free, and no monetary incentive was offered for participation.

Data for the study were collected from March through June 2001 at community health camps, where, after providing voluntary informed consent, participants answered questions about health status, history of blood exposures, history of STIs, sexual behavior, and other topics. Same-sex, study-trained interviewers administered questionnaires in the Tamil language in private areas by means of computer-assisted personal interviewing technology; responses were keyed directly into the computer.

Participants then underwent HIV pretest counseling and provided blood, urine, and cervical specimens to test for HCV, HIV, herpes simplex virus type 2 (HSV-2), syphilis, trichomoniasis, gonorrhea, and chlamydia. Specimens were tested in the Chennai study laboratory. Twenty percent of specimens were sent to Johns Hopkins University School of Medicine (Baltimore, MD) for quality control. Serum samples were tested for HCV infection by HCV 4.0 ELISA (Abbott Murex Biotech), and tests were repeated for confirmation. HIV testing was performed with HIV ELISA 1.2.0 (Abbott Murex Biotech); tests were repeated with Genscreen HIV 1/2 Version 2 ELISA (BioRad), and the results were confirmed by Western blot test (BioRad). HSV-2 testing was performed by Herpesselect 2 EIA (MRL; Focus Technologies); syphilis testing was performed with the Treponema pallidium passive particle agglutination test (Serodia TP-PA Fujirebio). Vaginal swabs were cultured for Trichomonas vaginalis with the InPouch TV 20 test kit (Biomed). Urine and vaginal swabs were tested for chlamydia and gonorrhea DNA by Amplicor CT/NG PCR (Roche).

Data were analyzed using SAS software (SAS Institute) and STATA software (Stata). Unadjusted ORs and adjusted ORs (AORs) were estimated with logistic regression by means of generalized estimating equations to account for the correlation between individuals within the same slum community. All possible effect modification was explored. Associations were deemed statistically significant if 95% CIs did not include unity.

The study methods, procedures, and informed consent forms were approved by Johns Hopkins University Bloomberg School of Public Health (Baltimore, MD) and the Y. R. Gaitonde Centre for AIDS Research and Education (YRG-CARE; Chennai, Tamil Nadu, India) institutional review boards in compliance with US Department of Health and Human Services Office for Human Research Protections guidelines. Informed consent was obtained before collection of all data.

RESULTS

Participation. Of >14,000 adults in the 30 study slum communities, 1947 (13%; 969 men and 978 women) were selected to participate in the study. Of those eligible, 1656 (85%) completed the survey, and of those, 1631 (98%) provided biological samples. More of those selected who did not complete the survey were male, married, and slightly older (table 1). Those who completed the survey but declined to give biological samples were female, married, and slightly older than were those who provided biological samples, although they did not differ from the study population in education, health status, and number of lifetime sex partners (data not shown).

IDUs. Study participants reporting injection of illicit drugs in the previous 3 months (6 men and 1 woman) had a markedly elevated risk of HCV infection, compared with those who denied injection drug use in the previous 3 months (OR, 27.8; 95% CI, 7.25–106.4). To focus on sex-related exposures, these participants were excluded from further analysis.

Characteristics of the study population. A majority of study participants were women (53%), most of the participants were married (71%), one-third had completed high school (34%), and the average (±SD) age was 28 ± 6.6 years. More than one-half (60%) of study participants rated their health status as “moderate” to “very bad.” Almost all acts of sexual intercourse were unprotected (95%), and the number of lifetime sexual partners reported was low but variable (median ± SD, 1.0 ± 6.2). Of the 1620 individuals not reporting currently injecting drugs who had specimens sufficient for testing, 2% of men and 3% of women had evidence of HCV infection.
(table 2). Less than 10% of participants had an STI, including HIV (<1%), trichomons (7%), chlamydia (<1%), gonorrhea (<1%), and syphilis (1%). No HCV-infected participant had antibodies to HIV, trichomons, gonorrhea, or chlamydia. Approximately 5% of women and 16% of men reported ever having had a genital ulcer, and 16% of women and 9% of men had antibodies to HSV-2. Effect modification was noted between sex and several exposure variables; subsequent analyses were stratified by sex.

**Women.** HCV-infected women (n = 24) were somewhat less likely to have gone to a hospital for medical care in the previous 6 months than were HCV-uninfected women (n = 830; OR, 0.50; 95% CI, 0.19–1.30; table 2). The odds of HCV infection did not differ in women by number of lifetime sexual partners (OR, 1.09; 95% CI, 0.73–1.62) or proportion of unprotected sex acts in the previous month (∼100% in each group; OR not calculable).

The prevalence of HSV-2 infection was similar in HCV-infected and -uninfected women (OR, 1.09; 95% CI, 0.33–3.59). However, HCV-infected women were 3 times as likely as HCV-uninfected women to report a genital ulcer (OR, 3.18; 95% CI, 0.88–11.53). There was no association between number of sex partners and HCV infection after controlling for age, hospital use, presence of and genital ulcers (AOR, 1.08; 95% CI, 0.72–1.62; table 3). Although the association was marginally statistically significant, after controlling for age, hospital use, and number of sex partners, women who reported genital ulcers were almost 4 times more likely to be HCV infected than were women who did not report genital ulcers (AOR, 3.88; 95% CI, 0.94–16.0, table 3).

**Men.** Compared with HCV-uninfected men (n = 751), HCV-infected men (n = 15) reported that they sought care from untrained allopathic health care providers (excluding providers at health posts/dispensaries, hospitals, pharmacies, and traditional healers) in the previous 6 months >8 times more frequently than did HCV-uninfected men (OR, 8.76; 95% CI, 2.23–34.5). HCV-infected men were >3 times more likely to drink alcohol at least once a week (OR, 3.76; 95% CI, 1.39–10.13), compared with HCV-uninfected men.

MSM (n = 44) were >3 times more likely to be HCV infected than were those who reported never having had sex with a man (OR, 3.66; 95% CI, 0.95–14.0). However, HCV-infected and -uninfected men reported similar numbers of lifetime sex partners (OR, 1.01; 95% CI, 0.98–1.04) and a similar proportion of unprotected sex acts in the previous month (∼100% in each group; OR not calculable). Although not statistically significant, more HCV-infected men than HCV-uninfected men reported having had genital ulcers (OR, 1.92; 95% CI, 0.65–5.69). Similarly, >3 times as many HCV-infected men had antibodies to HSV-2 (OR, 3.31; 95% CI, 1.11–9.90) relative to HCV-uninfected men. After controlling for age, frequent alcohol use, HSV-2 infection, male-male sexual history, and use of untrained allopathic health care providers, there was no association found between number of sexual partners and HCV infection in men (table 4). However, after controlling for these factors, MSM were >3 times as likely to be HCV infected as those who denied having sex with other men (AOR, 3.61; 95% CI, 1.00–13.1). Furthermore, HCV-infected men were >3 times more likely to be HCV infected than were HSV-2–uninfected men (AOR, 3.85; 95% CI, 1.19–12.6; table 4).

**DISCUSSION**

These results suggest that exposure to previous or current GUD—and in men, specifically HSV-2 and male-male sexual exposure—is associated with HCV transmission in this setting. The data suggest that HCV infection is not associated with having multiple sexual partners, corroborating other study findings [13–17].

It is conceivable that, as with STI, blood containing HCV can penetrate the genital epithelium more efficiently in areas where there are microlacerations. In some circumstances, these
minute exposures may be sufficient for infection, because it is thought that percutaneous exposure to even small quantities of infected blood can result in infection [39].

This association may also be attributable to confounding by unacknowledged and previous injection drug use. In some settings, IDUs are more likely to have both STIs and HCV infection; if our population were similar, HCV infection may be attributable to former or intermittent injection drug use rather than to GUD.

Nevertheless, our results corroborate those of Tedder and colleagues [29], who found that the men attending STI clinics who were MSM 5 times the prevalence of HCV infection as men who denied having sex with men. In other studies, associations between male-male sex and HCV infection were not independently significant, and the authors emphasized that sexual exposure likely played only a minor role in HCV infection relative to parenteral exposures, insertive [29] and receptive anal intercourse [13, 30–32], and “fisting” [30]. If the virus passes efficiently through lacerations from tearing of the anal epithelium, it would not be surprising that men engaging in these behaviors would be at high risk of HCV infection. Although this mechanism of transmission appears biologically plausible, there is substantial literature disputing the association [14, 23, 27, 28]. It is interesting to note, however, that substantial proportions of the MSM in intercity populations may also be IDUs (7%–20% in a Baltimore cohort) [14], and that, even if an association exists between MSM and HCV infection, controlling for injection drug use may preclude detecting an association between HCV infection and male-male sex.

Published studies have linked HCV infection to ulcerative and nonulcerative STIs, specifically trichomonas, gonorrhea, and syphilis [12, 13, 40]. In our population, we had low prevalences of these STIs, and we did not find similar associations. However, in our study, HCV infection was associated with HSV-2 infection in men, consistent with the findings of Shev and

### Table 2. Differences in demographic characteristics and sexual risk factors in hepatitis C virus (HCV)-infected and HCV-uninfected residents of Chennai, India, in a study assessing the link between sexual exposure and HCV infection.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Women</th>
<th>HCV infection</th>
<th>OR (95% CI)</th>
<th>Men</th>
<th>HCV infection</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td></td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Sex-based blood exposurea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Had a genital ulcer</td>
<td>13</td>
<td>5</td>
<td>3.18 (0.88–11.5)</td>
<td>29</td>
<td>17</td>
<td>1.92 (0.65–5.69)</td>
</tr>
<tr>
<td>Tested HSV-2 EIA positive</td>
<td>17</td>
<td>16</td>
<td>1.09 (0.33–3.59)</td>
<td>27</td>
<td>10</td>
<td>3.31 (1.11–9.91)</td>
</tr>
<tr>
<td>Men who have sex with men</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>20</td>
<td>5</td>
<td>3.67 (0.95–14.1)</td>
</tr>
<tr>
<td>Other sexual risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of lifetime sex partners</td>
<td>1.1</td>
<td>0.9</td>
<td>1.09 (0.73–1.62)</td>
<td>2.4</td>
<td>3.0</td>
<td>1.01 (0.98–1.04)</td>
</tr>
<tr>
<td>Demographic characteristics/general risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>79</td>
<td>78</td>
<td>0.90 (0.26–3.11)</td>
<td>67</td>
<td>63</td>
<td>1.13 (0.50–2.59)</td>
</tr>
<tr>
<td>Age, mean years</td>
<td>27.6</td>
<td>28.3</td>
<td>1.01 (0.96–1.07)</td>
<td>29.1</td>
<td>28.6</td>
<td>0.99 (0.92–1.07)</td>
</tr>
<tr>
<td>Reported bad health statusb</td>
<td>60</td>
<td>58</td>
<td>0.99 (0.39–2.53)</td>
<td>59</td>
<td>86</td>
<td>4.10 (1.17–14.4)</td>
</tr>
<tr>
<td>Frequent alcohol usec</td>
<td>0</td>
<td>0</td>
<td>NC</td>
<td>73</td>
<td>41</td>
<td>3.76 (1.39–10.1)</td>
</tr>
<tr>
<td>Health care usedd</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital</td>
<td>46</td>
<td>63</td>
<td>0.50 (0.19–1.31)</td>
<td>53</td>
<td>51</td>
<td>1.15 (0.37–3.62)</td>
</tr>
<tr>
<td>Informal providera</td>
<td>0</td>
<td>1</td>
<td>NC</td>
<td>13</td>
<td>2</td>
<td>8.77 (2.23–34.5)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are percentage of subjects, unless otherwise indicated. The OR is the unadjusted OR from logistic regression modeling using generalized estimating equations. HSV-2, herpes simplex virus type 2; NC, could not be calculated.

a Behavior reported ever.

b Self-reported health status of “moderate” and “very bad,” compared with “good” and “very good.”

c “Frequent” indicates more than once a week.

d Behavior report in 6 months before interview.

e Excludes providers at health post/dispensaries, hospitals, pharmacies, and traditional healing centers.

Table 3. Association of sexual risk factors and hepatitis C virus infection in 854 women in Chennai, India, estimated from multiple logistic regression by generalized estimating equations.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-reported genital ulcer</td>
<td>3.88 (0.94–16.0)</td>
</tr>
<tr>
<td>No. of lifetime sex partners</td>
<td>1.08 (0.72–1.62)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are controlled for age and hospital use.
These women had a 34% prevalence of HSV-2 infection, and a lower prevalence of HCV infection than did HSV-2 seronegative women. Thus, our results are supported by a recent study indicating that HCV infection may also be due to increased exposure to injections. Our results are consistent with colleagues [21, 22], in which a similar association in HCV status–discordant couples and blood donors was reported. Likewise, our results are supported by a recent study indicating that HSV-2–seropositive, low-income women had 3 times the prevalence of HCV infection than did HSV-2 seronegative women. These women had a 34% prevalence of HSV-2 infection, and authors attributed >50% of their risk of HCV infection to HSV-2 infection [41].

In our study, HCV infection was not associated with HSV-2 infection in women, although HCV-infected women reported genital ulcers more often than did uninfected women. After investigating the etiology of self-reported genital ulcers, despite differences in the association with HCV infection, men and women who had evidence of HSV-2 infection were twice as likely to report genital ulcers (OR, 2.10; 95% CI, 1.36–7.30) than were those without evidence of HSV-2 infection. Conversely, we found no association between genital ulcers and previous infection with syphilis (OR, 1.25; 95% CI, 0.23–6.85). Although isolated episodes of a GUD due to curable STIs such as syphilis may confer some risk of blood exposure and thus HCV infection, the risk from cumulative exposure of recurrent, incurable HSV-2 infection may be stronger.

In our study, HSV-2 was more strongly associated with HCV infection than genital ulcers in men, but not for women. Perhaps women had genital ulcers due to infections with STIs we did not test for, such as donovanosis or chancroid. Chancroid, for instance, is thought to be an important etiologic agent in GUD in southern India [42]. However, we have no data suggesting that women had more undetected STIs than did men. To ascertain whether recurring genital infections facilitate transmission of HCV infection and curable infections, studies should use laboratory testing for a complete battery of bacterial STIs, comprehensive clinical evaluation of GUD symptoms, and serial assessments of infection status.

Regardless of the etiology, the association of GUD and HSV infection may also be due to increased exposure to injections because men may notice genital ulcers more frequently and request antibiotic injections to treat ulcers more often than do women. According to anecdotal reports, men in this region often request antibiotic injections after risky sexual encounters to treat possible STI infection. In this study, more HCV-infected men had recently sought care from an untrained allopathic health care provider, compared with HCV-uninfected men. These providers often administer therapies parenterally, often with unsterilized syringes, conferring a high risk of HCV infection to patrons. These men could have been exposed to HCV in blood from contaminated injection equipment.

We did not have the statistical power to model sexual and genital ulcer risk of HCV infection while controlling for other factors among current IDUs because only 7 individuals reported currently or recently injecting drugs. Nevertheless, we did detect a strong association between HCV infection and current or recent injection drug use, corroborating results of numerous other studies [40, 43–45]. Separate studies targeting IDUs are needed to explore routes of HCV and STI transmission and approaches to prevention of HCV infection in this subpopulation.

We defined IDUs as participants reporting injection drug use in the previous 3 months. Use of this restrictive definition may have led to misclassification, and it is an important limitation of the study. As was previously mentioned, it is possible that injection drug use confounded the relationship between STIs and HCV. However, because of the small sample size, we could not ascertain whether current and recent IDUs in south India were more likely to have STIs than those denying current or recent injection drug use. Thus, it is unclear whether this potential misclassification qualitatively affected results.

Behavioral data were based on self-reports to interviewers. The low levels of risky behavior reported by study participants may be due to reluctance to report high-risk behavior, thereby diluting associations. Participants may have given socially desirable responses, particularly to questions about sensitive behaviors. Socially desirable responding may have been more pronounced in women than in men, because women’s behavior is more closely monitored and scrutinized in Indian culture. Although socially desirable responding may explain, in part, why we were unable to detect substantial high-risk behavior in women, reluctance to report high-risk behavior was probably not more pronounced among HCV-infected than among HCV-uninfected participants and thus should not have affected the evaluation of associations. Furthermore, behavioral data were coupled with laboratory testing to enhance the overall quality of the data.

These data were all collected cross-sectionally, so there is no way to know whether exposures preceded HCV infection.

In addition, most studies confirm HCV test results with the recombinant immunoblot assay, but, in this study, we used a repeated positive result via ELISA to confirm results, as recommended by Pawlotsky et al. [46]. Although some misclas-

**Table 4. Association of sexual risk factors and hepatitis C virus infection in 765 men in Chennai, India, estimated from multiple logistic regression by generalized estimating equations.**

<table>
<thead>
<tr>
<th>Risk factor or group</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herpes simplex virus type 2 infection</td>
<td>3.85 (1.19–12.6)</td>
</tr>
<tr>
<td>Men who have ever had sex with men</td>
<td>3.61 (1.00–13.1)</td>
</tr>
<tr>
<td>No. of lifetime sex partners</td>
<td>1.05 (0.96–1.14)</td>
</tr>
</tbody>
</table>

**NOTE.** One man from the study sample is not included in this model because he declined to give his age. Data are controlled for age, frequent alcohol use, and use of untrained allopathic health care providers.
sification of HCV infection may have resulted from adopting this protocol and we may have overestimated the prevalence of HCV infection overall, we expect that this bias would also occur without regard to exposure categories and thus would not affect measurement of associations.

Finally, the results of this study may have limited generalizability to other cities. Nevertheless, because the population of this study was randomly selected from defined populations, it may be generalizable to other slum communities in Chennai or in other similar Asian cities.

In this study, we found that GUD and male-male sex were associated with HCV infection in an urban slum population. These data suggest that HCV infection is not easily sexually transmitted, although genital ulcers and anal trauma may increase the risk. It is important to educate public health officials on how to recognize GUD lesions and when to seek appropriate treatment. In addition, health care providers should remind at-risk patients about the importance of using condoms to provide barrier protection and lubricants to reduce the incidence of bleeding during sex. These and other strategies may reduce the transmission of HCV infection, as well as other blood-borne infections and STIs.

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