Sexual Activity as a Risk Factor for Hepatitis C

Norah A. Terrault

The accumulated evidence indicates that hepatitis C virus (HCV) can be transmitted by sexual contact but much less efficiently than other sexually transmitted viruses, including hepatitis B virus and human immunodeficiency virus (HIV). However, because sex is such a common behavior and the reservoir of HCV-infected individuals is sizable, sexual transmission of HCV likely contributes to the total burden of infection in the United States. Risk of HCV transmission by sexual contact differs by the type of sexual relationship. Persons in long-term monogamous partnerships are at lower risk of HCV acquisition (0% to 0.6% per year) than persons with multiple partners or those at risk for sexually transmitted diseases (0.4% to 1.8% per year). This difference may reflect differences in sexual risk behaviors or differences in rates of exposure to nonsexual sources of HCV, such as injection drug use or shared razors and toothbrushes. In seroprevalence studies in monogamous, heterosexual partners of HCV-infected, HIV-negative persons, the frequency of antibody-positive and genotype-concordant couples is 2.8% to 11% in Southeast Asia, 0% to 6.3% in Northern Europe, and 2.7% in the United States. Among individuals at risk for sexually transmitted diseases (STDs), the median seroprevalence of antibody to HCV (anti-HCV) is 4% (range, 1.6% to 25.5%). HIV coinfection appears to increase the rate of HCV transmission by sexual contact. Current recommendations about sexual practices are different for persons with chronic HCV infection who are in steady monogamous partnerships versus those with multiple partners or who are in short-term sexual relationships. (HEPATOLOGY **2002;36:S99-S105.**)

Percutaneous exposures, such as blood transfusion and injection drug use, are well-established risk factors for hepatitis C virus (HCV) infection. The risk of HCV transmission by sexual contact, however, is less well defined. The accumulated epidemiologic evidence indicates that HCV can be transmitted by sexual contact but much less efficiently than other sexually-transmitted viruses, including hepatitis B virus and human immunodeficiency virus (HIV).

There are several case reports of acute hepatitis C occurring in persons whose only risk factor appeared to be a HCV-infected sexual partner.[1,2] The strength of these reports lay in their ability to document seroconversion in an individual at risk in temporal relationship to sexual activity with an HCV-infected partner. The mode of transmission was ascertained by carefully questioning the infected individual to exclude nonsexual sources of HCV. A high degree of sequence homology between the viral strains in the sexual partners provided virological confirmation that a transmission event had occurred.

While there is sufficient evidence to support the conclusion that sexual transmission of HCV occurs, quantifying the magnitude of an individual's risk of HCV acquisition by sexual contact is more difficult. Epidemiologic studies have had several methodological shortcomings that tend to overestimate the proportion of HCV infections attributed to sexual contact. Early studies used first-generation antibody to HCV (anti-HCV) assays which have a higher false positive rate than second- and third-generation assays. Studies varied in the completeness of risk ascertainment in partners, and many failed to carefully exclude HCV acquisition from nonsexual sources (Fig. 1). Nondisclosure of injection drug use is particularly important because assessing the independent contribution of sexual activity in HCV transmission is difficult in the presence of injection drug use. Finally, only a limited number of studies performed virological analyses to confirm that anti-HCV concordant sexual partners were infected with the same virus.

Abbreviations: HCV, hepatitis C virus; anti-HCV, antibody to HCV; HIV, human immunodeficiency virus; STD, sexually transmitted disease.

From the Gastroenterology Division, Department of Medicine, University of California, San Francisco, CA.

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Address reprint requests to Norah A. Terrault, M.D., M.P.H., University of California San Francisco, 513 Parnassus Ave., Room S357, San Francisco, CA 94143-0538. E-mail: noraht@itsa.ucsf.edu; fax: 415-502-6714.

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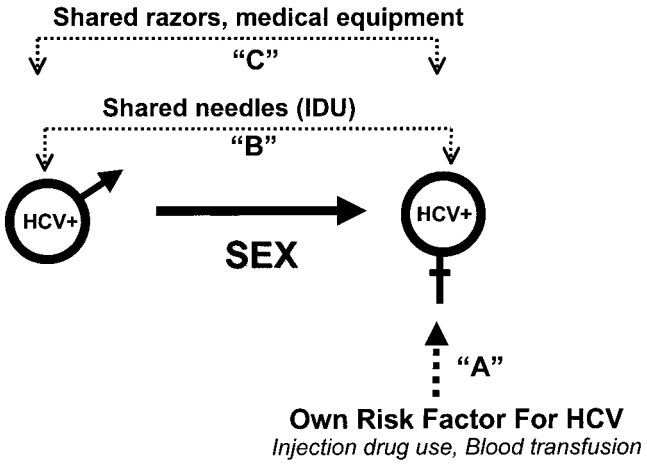

Fig. 1. When evaluating a partner for possible acquisition of HCV through sexual contact, it is essential to exclude other sources of HCV. As shown in this cartoon, the female partner may have her own risk factor for HCV infection, such as a prior history of injection drug use or blood transfusion (A). Alternatively, she may have been infected by her partner, but the mode of transmission may have been nonsexual, such as sharing of needles (B), razors, or other contaminated personal items (C).

Sexual transmission has been evaluated in different populations of HCV-infected individuals. Two main risk groups are discernable: (1) those who are more sexually promiscuous and likely to have multiple sexual partners, including female sex workers, men having sex with men, those in HIV surveillance studies, and attendees of sexually-transmitted diseases (STDs) clinics; and (2) those in steady monogamous sexual relationships. Rates of anti-HCV positivity vary by risk group, with higher rates of HCV reported in persons at risk for STDs and lower rates in heterosexual partners in long-term relationships. This difference in rate of HCV infection may reflect differences in sexual risk behaviors (frequency or type of sexual activities). Alternatively, differences between risk groups may reflect differing rates of exposure to nonsexual sources of HCV, such as injection drug use, as well as other potential risk factors such as intranasal cocaine use and tattooing, or sharing of razors and toothbrushes. The findings regarding sexual transmission defined by one risk group may not be generalizable to others.

Detection of HCV RNA in Body Fluids

Sexual transmission of virus occurs when infected body secretions or infected blood are exchanged across mucosal surfaces. The presence of virus in body secretions is necessary but may not be sufficient for transmission to occur. Other factors that may influence transmission include the titer of virus in body secretions, the integrity of the mucosal surfaces, and the presence of other genital infections (viral or bacterial).

Studies to detect HCV RNA in semen (seminal fluid and cells), vaginal secretions, cervical smears, and saliva have yielded mixed results.[3,4] Failure to detect HCV RNA in body secretions may be caused by technical factors, including specimen collection and storage, and the ability to exclude cellular components and to overcome the presence of polymerase chain reaction inhibitors.[4,5] Even in studies using optimal methods to isolate HCV RNA, the minority of samples were positive for HCV RNA and all positive samples were of low titer (equal to 10^2 copies/mL).[4,6] A low titer of virus in genital secretions may be one reason that HCV is transmitted less efficiently than hepatitis B virus or HIV. Additionally, there may be an absence of suitable target cells in the genital tract to allow infection to occur or infection may require the presence of abnormal mucosa. Finally, while the presence of HCV RNA in semen and vaginal or cervical secretions supports the contention that HCV is sexually transmissible, a cell culture system or animal model is needed to prove that the HCV RNA detected in genital secretions represents infectious virus.

How Prevalent Is the Risk Factor of Sexual Activity in Acute Hepatitis C?

The Centers for Disease Control and Prevention collects detailed risk factor data on cases of acute hepatitis C identified through the Acute Hepatitis Sentinel County Surveillance program. Between 1995 and 2000, 18% of individuals with acute community-acquired HCV infection reported sexual contact with an anti-HCV–positive person in the preceding 6-month period (two thirds of cases) or multiple sexual partners (one third of cases) as their only risk factor for HCV acquisition. Currently, sexual activity ranks as the second most common risk factor for HCV reported by individuals with acute hepatitis. This suggests that sexual transmission may contribute significantly to the total burden of HCV infection in the U.S. population.

What Is the Prevalence of HCV in Persons at Risk for STDs?

In U.S. seroprevalence studies conducted among those at risk for STDs, 1.6% to 25.5% of individuals were anti-HCV positive (Table 1). Median rates of anti-HCV positivity were 6% among female sex workers, 4% among men having sex with men, and 4% among attendees of STD clinics and individuals participating in HIV surveillance studies (Table 1). The HCV seroprevalence rates were lower than other viral infections such as hepatitis B virus and HIV.[7] In those studies including persons with a history of injection drug use, anti-HCV positivity was

Table 1. Seroprevalence of Anti-HCV Among Individuals at Risk for STDs

Risk Group	% Anti-HCV Positive Range (Average)	Factors Associated With Anti-HCV Positivity
Female sex workers	1%-19% (6%)	Number of partners, other STDs, non-use of condoms, sex with trauma
MSM	2.9%-13% (4%)	With IDU included: risk for IDU > sexual factors; if IDU excluded: anti-HIV positivity, number of partners
STD clinic attendees	1.6%-26% (4%)	With IDU included: risk for IDU > sexual factors
	1.6%-7% (if no IDU history)	If IDU excluded: number of recent and lifetime sexual partners, high-risk sexual contacts, anti-HIV positivity

Abbreviations: STDs, sexually transmitted disease(s); MSM, men who have sex with men; IDU, injection drug use; HIV, human immunodeficiency virus.

more strongly associated with drug use than with factors related to sexual practices. In those studies limited to individuals without a history of injection drug use, factors predictive of anti-HCV positivity included the number of recent and lifetime partners, high risk sexual practices (variably defined), other STDs, and anti-HIV positivity.[7-12] These factors are consistent with a sexual route of transmission.

In persons engaged in higher-risk sexual behaviors, those with HIV infection were more likely to be anti-HCV positive (odds ratio, 2.5 to 4.4) than those who were HIV negative, even after controlling for other sexual factors that might enhance risk of transmission such as number of partners, non-use of condoms, and other STDs.[9,13] The precise mechanism by which HIV increases the risk of sexual transmission of HCV is unknown.

What Is the Prevalence of HCV Infection in Monogamous Heterosexual Partners?

Seroprevalence studies in monogamous, heterosexual partners of HCV-infected, HIV-negative persons have reported prevalence rates ranging from 0% to 24% in studies from Southeast Asia and Southern Europe but lower rates in studies from the United States and Northern Europe (Fig. 2). The factors most consistently associated with HCV positivity among heterosexual partners were the presence of percutaneous risk factors for HCV (injection drug use, blood transfusion, sharing glass syringes).[11,14-16] Early studies found the rate of HCV positivity in partners increased with the longer duration of marriage, suggesting risk of sexual transmission correlated with frequency of contact.[17] However, subsequent studies adjusting for age did not find a consistent relationship between the duration of the sexual relationship and HCV positivity in partners.[16]

The majority of published studies did not evaluate antibody-concordant couples with additional virological testing to confirm that partners were infected with the same virus. In the more informative studies, genotyping was used to evaluate antibody-concordant couples. In all cases, use of genotyping led to a reduction in the estimated rate of transmission by sexual contact (Table 2).[14-18] Genotyping, however, is suboptimal for determining whether partners are infected with the same virus because HCV genotypes that are prevalent in the population may be present in both partners but represent HCV infection from different sources. The importance of nucleotide sequencing was highlighted in a detailed study of 24 anti-HCV concordant heterosexual couples from France.[19] The investigators found 12 of the 24 couples (50%) had concordant genotypes, 7 had discordant genotypes, and 5 were untypable. Seven of the 12 genotype-concordant couples were further analyzed by sequence analysis of the hypervariable region of E2 (envelope region of the HCV genome) and only 3 couples had highly homologous viral strains that were consistent with a transmission event. Interestingly, in each of the 3 concordant couples, an alternative, nonsexual mode of HCV transmission was present. Thus, overestimation of the rate of sexual transmission of HCV occurs if antibody testing alone is used to assess sexual pairs. Based on only those seroprevalence studies using genotyping or sequence analysis to evaluate antibody concordant couples, the estimated prevalence of HCV among heterosexual couples in monogamous relationships is 2.8% to 11% in Southeast Asia, 0% to 6.3% in Northern Europe, and 2.7% in the United States (Table 2).

The U.S.-specific published data are sparse, with 1 small study (N = 42) conducted in heterosexual partners

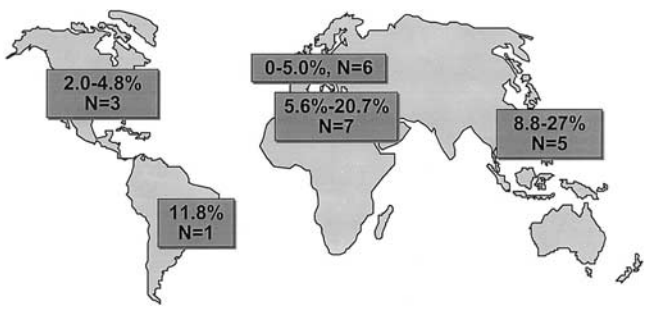

Fig. 2. The reported rates of anti-HCV positivity differ geographically. High rates have been reported in Southern Europe, Brazil, Turkey, and Southeast Asia. Each box depicts the range of seroprevalence rates reported in each country (**upper numbers**) and the number of studies available to provide these estimates (**lower number**).

Table 2. Seroprevalence Studies in Longer-Term Heterosexual Couples*

Study	Study Population	N	Prevalence Based on Presence of Anti-HCV in Partner	Prevalence Based on Concordant Genotypes in Couple
Akahane, 1994[17]	Japanese couples, liver clinics	154	27%	24% (all genotype 1b)
Chayama, 1995[36]	Japanese couples	295	8.8%	4.7%
Kao, 1996[18]	Taiwanese couples, monogamous attending liver clinic	100	17%	11% (all genotype 1b)
Neumayr, 1999[16]	Austrian clinic patients	80	5%	2.5%
Sun, 1999[15]	Taiwanese men identified in a national survey; spouses of anti-HCV positive men tested	214	24%	2.8%
Stroffolini, 2001[14]	Italian chronic liver disease patients	311	10.3%	6.3%†
Terrault, 2002‡	U.S. Community and Liver Clinic Sources	401	4.2%	2.7%

*Higher quality studies only included. Quality based on 2 criteria: (1) assessment of non-sexual risk factors in partners; (2) use of genotyping to assess antibody concordant couples.

†In those studies performing genotyping on subset of total anti-HCV concordant couples only, the proportion of genotype-concordant was applied to the total anti-HCV positive group to calculate the percent genotype-concordant for total population.

‡Unpublished data.

of patients attending a liver clinic and 2 studies conducted in hemophiliacs (variable proportion HIV coinfected). Seroprevalence rates varied from 2.0% to 4.8%.[20-22] Preliminary data from the HCV Partners Study, a cross-sectional study of heterosexual monogamous couples, provides the best available estimate of risk among U.S. couples. In this study, which excludes couples in which injection drug use is present in both partners, the prevalence of anti-HCV among 401 partners was 4.2%, with genotype concordance present in 2.7% of couples (Terrault N, unpublished data).

What Is the Incidence of HCV Infection in "At Risk" Individuals?

A prospective cohort study of discordant couples followed closely for newly acquired infection is the ideal method to characterize the risk of transmitting HCV through sexual contact. However, even this method may not be perfect because the exclusion of couples in which the partner is already infected may leave a more selected and less representative population of sexual partnerships for follow-up.

In retrospective cohorts of female partners of hemophiliacs, the incidence of HCV infection, defined by presence of anti-HCV, was 1 to 1.87 per 1,000 person-years[23,24]; among male partners of women infected by contaminated anti-D immunoglobulin, it was 0.28 per 1,000 person-years[25,26]; and among liver clinic patients and their sexual partners it was 1 to 3.86 per 1,000 person-years[16,27,28] (Table 3). In a prospective cohort study of 499 Italian heterosexual monogamous couples followed for a mean of 12.4 months, the incidence of new infection in sexual partners was 12 per 1,000 person-years. Sequence analysis of the anti-HCV positive couples showed a high degree of sequence homology in only 50% of couples, suggesting a true incidence of 6 per 1,000 person-years (Table 3).[29] In another prospective cohort of 112 Taiwanese couples followed for an average of 46 months, the incidence was 2.3 per 1,000 person-years (Table 3).[18] The variability in risk of HCV infection reported in studies of long-term partners may reflect differences in the frequency or types of sexual activity in the different populations, but more likely represents differences in the rates of nonsexual HCV transmission.

The incidence of new HCV infections among individuals who are at risk for sexually transmitted diseases is higher than in monogamous heterosexual couples. In prospective studies conducted in sex workers and attendees of STD clinics who were not injection drug users, the incidence of HCV was 0.4 to 1.8 per 100 person-years with follow-up periods of 1 to 3.7 years (Table 3).[30-32] In retrospective cohorts of hemophiliacs with high rates of HIV and HCV coinfection (more than 50%), the incidence of HCV infection was 0 to 0.19 per 100 person-years in sexual partners (primarily females) with a median follow-up of 12 to 15 years.[22,24,33] In these coinfected cohorts, HIV was transmitted more frequently than HCV, and partners were more likely to be infected with HIV and HCV than HCV alone.[22]

What Factors Increase the Risk of HCV Transmission by Sexual Contact?

HIV coinfection is associated with higher rates of anti-HCV in persons engaged in higher-risk sexual practices.[9,13,34] Additionally, in studies of STD clinic attendees and men having sex with men, other STDs (herpes simplex virus, Trichomonas, gonorrhea) and sexual practices that may traumatize the mucosa (*e.g.*, anal receptive sex) are more frequent in anti-HCV positive than anti-HCV negative individuals, suggesting these factors

Table 3. Incidence of HCV Transmission by Risk Group

Study	Patient Population	N, Duration of Sexual Contact	Incidence
Retrospective and Prospective Cohort Studies, Persons at Risk for Sexually Transmitted Diseases			
Giuliani, 1997[30]	STD clinic in Rome, cohort developed for HIV detection	709 (16% HIV positive, 2.1% IDU, 34% MSM) Follow-up 1 to 3.7 yrs	1.25 per 100 person-yrs
Wu, 1993[32]	Licensed prostitutes at STD clinic in Taiwan	109 Mean follow-up 1 yr	1.8 per 100 person-yrs
Nakashima, 1992[31]	Prostitutes in Japan, HIV negative	152 Mean follow-up 1.6 yrs	0.4 per 100 person-yrs
Prospective Cohort Studies, Monogamous Heterosexual Couples			
Piazza, 1997[29]	Italian discordant couples in placebo group of immunoglobulin trial	499 Mean follow-up 12 mo	6.0 per 1,000 person-yrs
Kao, 2000[37]	Taiwanese discordant couples from infectious disease and liver clinics	112 Mean follow-up 46 mo	2.3 per 1,000 person-yrs
Retrospective Cohort Studies, Monogamous Heterosexual Couples			
Bresters, 1993[23]	German hemophiliacs	50 Average duration of relationship 13 yrs	0 per 1,000 person-yrs
Scotto, 1996[27]	Italian patients in liver clinics or on dialysis	83 Average 15.6 yrs cohabitation	3.86 per 1,000 person-yrs
Neumayr, 1999[16]	Austrian clinic patients	80 Average duration of 21.4 yrs	1 per 1,000 person-yrs
Retrospective Cohort Studies, Monogamous Heterosexual Couples With Higher Risk (=40% HIV Coinfected)			
Wyld, 1997[11]	HIV cohort of heterosexuals in Scotland	30 (40% HIV infected) Median 44 mos unprotected sex	0 per 1,000 person-yrs
Brettler, 1992[33]	U.S., Australian, and Italian hemophiliacs	106 (62% HIV infected) Average duration of contact 12.5 yrs	1.5 per 1,000 person-yrs
Hallam, 1993[24]	English hemophiliacs	104 (56% HIV infected) Median duration of relationship 15 yrs	1.9 per 1,000 person-yrs

Abbreviations: HIV, human immunodeficiency virus; STD, sexually transmitted diseases; MSM, men who have sex with men.

increase the sexual transmission of HCV.[9,13,35] Whether the risk of HCV transmission differs for males versus females is unclear. In one study of heterosexual couples in STD clinics, anti-HCV–positive female clinic attendees were 3.7 times more likely to have an anti-HCV-positive male partner than the anti-HCV-positive male clinic attendees.[9] The titer of HCV RNA and HCV genotype do not appear to influence the risk of HCV transmission, but high-quality studies to assess these virological factors are lacking. The stage or clinical status of liver disease of the HCV-infected individual is also not predictive of transmission risk.[14,17] However, studies to date have focused only on individuals with chronic disease; whether individuals with acute hepatitis represent a subgroup at particular risk for HCV transmission is unknown.

Summary

The available data indicate HCV can be sexually transmitted, but the efficiency of transmission by the sexual route is low. Nonetheless, because sex is a common behavior and the reservoir of HCV-infected individuals is substantial (approximately 2.7 million), sexual contact likely contributes to the total burden of HCV infection in the United States. The contribution of sexual transmission is supported by findings from the Acute Hepatitis Surveillance Study, in which 18% of newly infected individuals reported sexual contact with an HCV-infected person or multiple sexual partners as their only risk factor for HCV acquisition.

For the individual with chronic HCV infection, the estimated risk of sexual transmission of virus is 0% to 0.6% per year for those in monogamous relationships, and 1% per year for those with multiple sexual partners. Because risk varies by type of sexual relationship, the recommendations for preventing transmission of HCV differ for those in monogamous relationships versus those with multiple or short-term sexual partners. The latter group is not only at risk for HCV acquisition, but also for other types of sexually transmitted diseases, including HIV. Current recommendations are as follows:

1. HCV-positive individuals in longer-term monogamous relationships need not change their sexual practices. If couples wish to reduce the already low risk of HCV transmission by sexual contact, barrier precautions may be used. Partners of HCV-positive persons should be considered for anti-HCV testing.

2. For HCV-infected individuals with multiple or short-term sexual partners, barrier methods or abstinence are recommended.

The following are additional "common-sense" recommendations:

3. Use of barrier precautions if other STDs are present, if having sex during menses, or if engaging in sexual practices that might traumatize the genital mucosa.

4. Couples should not share personal items that may be contaminated by blood such as razors, toothbrushes, and nail-grooming equipment.

Future Research Needs

Additional prevalence and incidence studies may help to refine the current estimates of risk but will not be predicted to substantially change the overall findings of a low risk of HCV transmission by sexual contact. To be informative, such studies must include detailed virological analyses of antibody- and genotype-concordant sexual partners and perform complete ascertainment of nonsexual sources of HCV. Because the rate of transmission is low, a large sample size (greater than 1,000 individuals and/or partners) would be required to have sufficient power to determine the specific factors associated with HCV transmission. Given the cost, time, and logistics of executing large prevalence and incidence studies, and the questionable ability of such studies to advance our knowledge about key features of sexual transmission of HCV, alternative research strategies are necessary.

The key research questions relate to identifying the specific factors that promote or prevent sexual transmission of HCV. Issues of critical importance include whether the level of HCV RNA predicts risk of transmission, if other STDs such as herpes simplex virus 2 or Trichomonas increase the risk of HCV acquisition, whether specific sexual practices (*e.g.*, anal versus vaginal sex) affect the risk of HCV, whether transmission is more likely to occur during acute rather than chronic hepatitis C, and whether females are at higher risk of HCV acquisition through sex than males. The insights gained by addressing these specific questions will allow more detailed future recommendations for HCV-infected persons and their sexual partners and ultimately lead to interventions that may reduce the risk of transmission of HCV through sexual contact.

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