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# *Hepatitis C & Sexual behaviors*

The Debate Continues

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## *Individual and Couple-Level Risk Factors for Hepatitis C Infection among Heterosexual Drug Users: A Multilevel Dyadic Analysis* The Journal of Infectious Diseases 2007;195:1572-1581

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0022-1899/2007/

"Our results are consistent with prior research indicating that sexual contact plays little role in HCV transmission. [Read Study](#)

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## *No Evidence of Sexual Transmission of Hepatitis C among Monogamous Couples: Results of a 10-Year Prospective Study*

The risk of sexual transmission of hepatitis C virus (HCV) infection was evaluated among 895 monogamous heterosexual partners of HCV chronically infected individuals in a long-term prospective study, which provided a follow-up period of 8,060 person-years. Seven hundred and seventy-six (86.7%) spouses were followed for 10 yr, corresponding to 7,760 person-years of observation.

One hundred and nineteen (13.3%) spouses (69 whose infected partners cleared the virus following treatment and 50 who ended their relationship or were lost at follow-up) contributed an additional 300 person-years.

All couples denied practicing anal intercourse or sex during menstruation, as well as condom use. The average weekly rate of sexual intercourse was 1.8.

Three HCV infections were observed during follow-up corresponding to an incidence rate of 0.37 per 1,000 person-years. However, the infecting HCV genotype in one spouse (2a) was different from that of the partner (1b), clearly excluding sexual transmission.

The remaining two couples had concordant genotypes, but sequence analysis of the NS5b region of the HCV genome, coupled with phylogenetic analysis showed that the corresponding partners carried different viral isolates, again excluding the possibility of intra-spousal transmission of HCV.

The authors conclude, "Our data indicate that the risk of sexual transmission of HCV within heterosexual monogamous couples is extremely low or even null. No general recommendations for condom use seem required for individuals in monogamous partnerships with HCV-infected partners."

### Reference

Carmen Vandelli and others. Lack of Evidence of Sexual Transmission of Hepatitis C among Monogamous Couples: Results of a 10-Year Prospective Follow-Up Study. *American Journal of Gastroenterology* 99(6): 855-859. May 2004.

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Conclusion: HCV antibody positivity was not associated with sexual risk behaviors.

# *Low incidence and prevalence of hepatitis C virus infection among sexually active non IV drug using adults in San Francisco*

1: Sex Transm Dis. 2003 Dec;30(12):919-24.

Low incidence and prevalence of hepatitis C virus infection among sexually active non-intravenous drug-using adults, San Francisco, 1997-2000.

Hammer GP, Kellogg TA, McFarland WC, Wong E, Louie B, Williams I, Dilley J, Page-Shafer K, Klausner JD.

San Francisco Department of Public Health, San Francisco, California.  
ghammer@epi-center.ucsf.edu

**BACKGROUND:** The rate of sexual transmission of hepatitis C virus (HCV) is debated.

**GOAL:** The goal was to **measure the risk of sexual transmission of hepatitis C virus (HCV)** in a sexually active population.

**STUDY DESIGN:** Sexual behaviors and HCV antibody status were measured in persons seeking repeat HIV testing in San Francisco from October 1997 through March 2000.

**RESULTS:** Among 981 repeat testers, the prevalence of HCV antibody was 2.5%. Among men who have sex with men who denied intravenous drug use (n=746), factors associated with HCV antibody positivity include age greater than 50 years (odds ratio [OR], 8.5; 95% confidence interval [CI], 2.6-27.7), HIV infection (OR, 5.7; 95% CI, 1.6-20.6), and being nonwhite (OR, 3.3; 95% CI, 1.1-10.0). HCV antibody positivity was not associated with sexual risk behaviors.

In 576.6 person-years of observation, no new HCV seroconversions occurred (incidence=0 per 100 person-year; 95% CI, 0-.6), whereas 6 new herpes simplex virus-2 infections (2.8 per 100 person-years) and 10 new HIV infections (1.8 per 100 person-years) occurred.

**CONCLUSION:** The absence of new HCV infections in this sample supports the hypothesis that the risk of sexual transmission of HCV is low.

PMID: 14646642 [PubMed - indexed for MEDLINE]

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## *Sexual transmission of (HCV) is rare in monogamous heterosexual couples*

Sexual transmission of hepatitis C virus (HCV) is rare in monogamous heterosexual couples, according to the results of a 10-year prospective study published in the May issue of the American Journal of Gastroenterology.

"The rate of HCV infection in sexual partners of anti-HCV-positive individuals has been shown to range between very low and as high as 30%," write Carmen Vandelli, MD, from the Università di Modena e Reggio Emilia in Italy, and colleagues. "These discordant findings may partly be explained by the confounding effect of nonsexual transmission routes."

In a long-term study, 895 monogamous heterosexual partners of individuals chronically infected with HCV were followed for a total of 8,060 person-years. Of these 895 partners, 776 spouses (86.7%) were followed for 10 years, corresponding to 7,760 person-years. An additional 300 person-years were contributed by spouses whose infected partners cleared the virus during treatment, who ended the relationship, or who were lost to follow-up. All of these couples denied practicing anal intercourse, vaginal intercourse during menstruation, or condom use. Average frequency of sexual intercourse was 1.8 times per week.

During follow-up, there were three HCV infections, corresponding to an incidence rate of 0.37 per 1,000 person-years. HCV genotyping, sequence analysis, and phylogenetic analysis suggested that the corresponding partners carried different viral isolates, which would rule out spousal transmission of HCV.

However, the authors note that in 33 (3.4%) of 967 couples initially investigated, both partners were anti-HCV positive, suggesting the possibility that HCV could have been transmitted earlier in their relationship.

"Our data indicate that the risk of sexual transmission of HCV is extremely low or even null," the authors write. "No general recommendations for condom use seem required for individuals in monogamous relationships with HCV-infected partners."

Based on other studies, however, the authors strongly advised these couples to avoid sharing personal hygiene items such as toothbrushes, razors and nail clippers.

The Association for the Study of Infectious and Metabolic Diseases of the Liver supported this study.

Am J Gastroenterol. 2004;99:855-859

### Clinical Context

Approximately 2.3% of U.S. adults are positive for anti-HCV antibody, according to a review of screening for HCV, which appeared in the March 16, 2004, issue of the Annals of Internal Medicine. The U.S. Preventive Services Task Force report also noted that most of those infected acquire HCV by large or repeated percutaneous exposures to infected blood, and up to 84% of patients with a positive antibody test will develop chronic infection.

Given the large number of people with chronic HCV infection and the need to control the spread of the disease, accurate data regarding risky behavior for transmission is essential. A common question from patients involves the risk of sexual transmission and the means they might take to prevent their partner from becoming infected. However, according to the authors of the current study, rates of HCV infection from sexual transmission have been estimated to be from less than 1% to 30%.

The authors of the current study performed a prospective trial to determine the risk of sexually acquired HCV infection.

### Study Highlights

a.. Subjects included patients from an internal medicine practice with positive anti-HCV antibody and HCV RNA tests. Participants were involved in heterosexual relationships with a partner who had tested negative for HCV.

b.. Partners of HCV-infected patients were tested annually for liver function tests and anti-HCV antibody over a 10-year period. Those who had one of these tests return positive underwent further HCV RNA testing. Sexual practices and possible parenteral HCV exposure were monitored via questionnaires.

c.. Subjects having extramarital affairs were excluded from participation. Participants were advised not to share personal products such as razors, toothbrushes, and nail scissors. Regular use of condoms was not recommended.

d.. 967 sexual partners of patients with HCV infection were identified, and 3.4% of these partners were anti-HCV positive at baseline and thus excluded from participation. 84.5% of these infected partners had a history of a significant risk factor other than sexual intercourse that could have served as a source of infection. Only 2 infected partners displayed a concordant HCV genotype compared with their partner at baseline.

e.. Mean age of subjects at enrollment was 44.2 years, and the average length of marriage was 23.7 years. The mean HCV RNA level in index cases was 6.7 mEq/L. 90% of index subjects had either moderate or severe hepatitis on analysis of liver biopsy.

f.. 230 index patients had undergone interferon-alpha treatment, and 30% had achieved long-term responses. Spouses of these patients were excluded from the analysis.

g.. 93.9% of couples completed the 10-year follow-up period, accounting for 7,760 person-years of observation. Including patients who subsequently cleared the infection and couples who separated during the study period, the total follow-up was 8,060 person-years.

h.. No patients reported condom use, anal intercourse, or sex during menstruation. The average weekly rate of intercourse was 1.8.

i.. Three spouses, 2 women and 1 man, acquired HCV infection during the follow-up period, an incidence rate of 0.37 per 1,000 person-years. They became infected 7, 8, and 9 years into the monitoring period, respectively.

j.. One of the spouses infected with HCV reported receiving a dental implant 3 months before her positive test, and her HCV genotype was discordant with that of her husband. Another spouse who converted had suffered a needle stick injury involving a patient positive for HCV and HIV. Her HCV genotype was also discordant from that of her spouse. The third spouse who became infected reported no other HCV risk factors and displayed a concordant HCV genotype when compared with his spouse. However, phylogenetic testing revealed that this couple's HCV strains were not linked.

#### Pearls for Practice

a.. HCV is a common infection in the U.S., and it frequently becomes chronic.

b.. Vaginal sexual intercourse appears to present a very low risk of HCV transmission

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14 January 2004

Michael Carter

## *No sexual transmission of HCV seen in repeat HIV testers in San Francisco*

No cases of sexual transmission of hepatitis C virus were found in a three year San Francisco study published in the January 2004 edition of *Sexually Transmitted Diseases*. The study, conducted amongst repeat HIV testers, the overwhelming majority of whom were gay men, also failed to find any association between unprotected anal sex and new hepatitis C infections. These findings stand in contrast to a recent study conducted in the UK that found that unprotected anal sex was the sole common risk factor for hepatitis C transmission amongst gay men (see link to this and other recent news stories on the sexual transmission of hepatitis C below).

Investigators from San Francisco conducted a retrospective study involving 981 repeat HIV testers between 1997 and 2000. The investigators aimed to establish the prevalence of hepatitis C infection amongst this population and the incidence of new hepatitis C infections.

The overwhelming majority of individuals included in the analysis were gay men (754 people, 77%), 135 (1%) were women and 92 (15%) were heterosexual men.

A total of 576.6 person years of observation were contributed by the 703 individuals who had blood samples for both HIV tests. There were no new cases of hepatitis C detected giving a hepatitis C incidence of zero. However, six new cases of herpes simplex virus-2 (HSV-2) and ten new HIV infections occurred (incidence rates 2.8 per 100 person years and 1.8 per 100 person years respectively).

The hepatitis C prevalence was 2.5%, and was highest in heterosexual men (4.3%), followed by heterosexual women (3.7%). The prevalence in gay men was 2.1%. Univariate analysis showed that individuals with a history of injecting drug use were over 33 times more likely to be infected with hepatitis C than individuals with no history of injecting drugs.

Gay men over 50 years of age were more likely to be infected with hepatitis C than gay men aged under 30 (odds ratio 6.6; 95% CI, 1.2 ?44.0). HIV-positive gay men were also more likely to be hepatitis C-positive than gay men who were not infected with HIV (odds ratio 5.4; 95% CI, 1.2 ?19.1).

No statistically significant association was found between recent sexual risk behaviour, including either insertive or receptive unprotected anal sex and hepatitis C infection. However, an association was found with increasing age ( $p=0.01$ ), but not for the number of lifetime sexual partners ( $p=0.35$ ).

In multivariate analysis, age 50 or above (odds ratio 8.5; 95% CI, 2.6 ?27.7), HIV infection (odds ratio, 5.7; 95% CI, 1.6 ?20.6) remained associated with hepatitis C infection.

"Despite having more than 575 person-years of observation in this sexually active sample and documented new sexually transmitted viral infections like HSV-2 and HIV, no cases of HCV antibody seroconversion were detected? note the investigators. They add, "In addition, no correlation was found between HCV antibody prevalence and recent sexual behaviors such as number of sexual partners in the past year or unprotected insertive or receptive anal sex...HCV is inefficiently spread through sexual contact.? They conclude that hepatitis C prevention efforts should focus on injecting drug users, "as the sexual transmission of hepatitis C continues to appear uncommon.?"

Hammer GP et al. *Low incidence and prevalence of hepatitis C virus infection among sexually active non-intravenous drug-using adults, San Francisco, 1997 ?2000*. *Sexually Transmitted Diseases* 30: 919 - 924, 2004

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# *Lack of Evidence of Sexual Transmission of Hepatitis C Among Monogamous Couples: Results of a Ten-Year Prospective Follow-Up Study*

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## Introduction

We have evaluated the risk of sexual transmission of hepatitis C virus (HCV) infection among 895 monogamous heterosexual partners of HCV chronically infected individuals in a long-term prospective study.

## Methods / Results

The follow up period was 8060 person-years; 776 (86.7%) spouses were followed up for ten years, corresponding to 7760 person-years of observation and 119 (13.3%) spouses (69 whose infected partners cleared the virus following treatment and 50 who ended their relationship or were lost at follow-up) contributed for additional 300 person-years.

During the follow-up three HCV infections were observed corresponding to an incidence rate of 0.37 per 1,000 person-years. However, in one case the infecting HCV genotype in a spouse was different from that of the partner ((2a, 1b), likely excluding a sexual route of transmission. Despite the remaining two couples had concordant genotypes, sequence analysis of the NS5b region of the HCV genome, coupled with a phylogenetic analysis showed that the corresponding partners carried different viral isolates, again excluding the possibility of intraspousal transmission of HCV.

## Conclusion

These findings indicate an extremely low or even null risk of HCV transmission within heterosexual monogamous couples

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## *HCV in Male Semen*

**NATAP - [www.natap.org](http://www.natap.org)**

from Jules Levin, NATAP

all articles are archived on the NATAP website

It is generally considered today that rates of sexual HCV transmission are low, about 5%. There is much controversy about how and if HCV is transmitted sexually. Although HCV has been found in semen, there does not appear to be evidence yet that the exchange of semen transmits HCV. But I think further research is needed to examine if there are circumstances or conditions in which HCV can be transmitted by semen. How can HCV be transmitted sexually? The CDC says risk for sexual transmission increases if a person has multiple sex partners and is active sexually. Remember HCV is transmitted by blood-to-blood contact. Studies show that risk for sexual transmission may be increased when the following circumstances are present during sexual contact: STDs, open sores, anal sex, and sex during menstruation; several studies show increased risk for sexual transmission among men who have sex when risky sexual behaviors which may draw blood are used such as fisting. Here are some selected study abstracts of interest. Two of these abstracts are from recent presentation and publication, but do not necessarily present new information. Studies suggest that a high HCV viral load may promote sexual transmission. Since higher HCV viral load in HIV-infected individuals has been observed at times it raises the question whether HCV sexual transmission is a greater risk for HIV-infected individuals. I don't think this has been adequately studied. Studies do show that among pregnant women HIV increases the risk for HCV transmission several times.



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## *Intermittent detection of hepatitis C virus (HCV) in semen from men with human immunodeficiency virus type 1 (HIV-1) and HCV*

HCV is usually transmitted via the blood, but HCV RNA has been detected recently in seminal fluid. This study was done to study HCV seminal shedding and factors that could influence the presence of HCV in the seminal fluid of men coinfecting with HCV and HIV-1. HCV and HIV-1 genomes were assayed in multiple paired blood and semen samples obtained from 35 men enrolled in an assisted medical procreation protocol. HCV RNA was found intermittently in semen samples from 9 patients (25.7%). Samples from 9 men with HCV RNA in their semen and 26 men without were compared to further analyze these parameters. No correlation was found between HCV RNA in the seminal fluid and age, HCV virus load, the duration of HIV-1 infection, HIV treatment, the CD4+ cell count, HIV-1 virus load or HIV-1 detection in the semen. The intermittent detection of HCV RNA in semen samples support the systematic search for HCV RNA in semen and the use of processed spermatozoa in assisted medical procreation of infertile HCV serodiscordant couples. J. Med. Virol. 69:344-349, 2003.

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## ***A STUDY OF THE PRESENCE OF HCV RNA IN SEMEN OF PATIENTS WITH CHRONIC HCV INFECTION***

El Guinaidy and researchers at the Ain Shams University in Cairo, Egypt were reporting this study at the 28th Meeting of the European Association for the Study of the Liver. But the Conference was cancelled due to war, and here is the abstract. Introduction: HCV is a worldwide problem. The prevalence in Egypt approximates 12%. The role of sexual route in transmitting HCV remains controversial. The aim of the study was to detect HCV RNA in semen of chronic HCV infected patients. Patients and methods: Seminal plasma was tested for HCV RNA in 40 married patients with chronic HCV infection (all have positive HCV RNA in their sera) using a nested reverse transcription PCR assay with commercial kits for amplification and detection of HCV RNA (Purescript, Gentra Systems, Minneapolis, USA). Semen was tested for the presence of PCR inhibitors to identify patients with false negative results. Results: 10 patients (25%) had HCV RNA in their semen (seminal plasma was +ve while round cells and motile spermatozoa were -ve for HCV RNA). Three out of the 10 wives of these 10 patients had HCV RNA in serum. Duration of marriage was significantly longer in HCV positive wives compared to non-infected wives. Serum HCV RNA levels were significantly higher in patients with +ve semen samples than in patients with -ve semen samples (mean±SD 1,695,539±1,348,002 vs 241,860±338,504 copies/ml,  $P<0.001$ ). Conclusion: HCV RNA can be detected in semen of patients with high blood viral load. They may transmit the infection to their wives and the risk of transmission increases proportionately with duration of marriage.

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## *Sperm washing and virus nucleic acid detection to reduce HIV and hepatitis C virus transmission in serodiscordant couples wishing to have children.*

**BACKGROUND:** Use of a motile spermatozoa isolation process was assessed for reducing the transmission of HIV and hepatitis C virus (HCV) during artificial insemination in HIV-serodiscordant couples in which the man is infected. **PATIENTS:** Thirty-two HIV-1-infected clinically asymptomatic men, having a median CD4 cell count of  $396 \times 10(6)/l$  and a median blood plasma HIV-1 RNA content of 414 copies/ml. Of these, 16 were infected with both HIV and HCV. **METHODS:** Motile spermatozoa were isolated from 51 semen samples by density gradient and 'swim-up'. HIV-1 and HCV genomes were detected and quantified in the blood plasma and seminal plasma, and detected in seminal cell fractions obtained during spermatozoa isolation. **RESULTS:** HIV-1 RNA was detected in 30% of seminal plasma samples. HIV-1 genomes were found in 18% of seminal cell samples, but in none of the motile spermatozoa fractions after 'swim-up'. There was no correlation between the HIV-1 RNA concentrations in the blood and seminal plasma. HIV-1 genome was detected intermittently in patients who gave more than one sample. HCV RNA was detected in 20% of seminal plasma samples from HCV viraemic patients, but in no seminal cells or motile spermatozoa fractions. **CONCLUSIONS:** Purification of motile spermatozoa by density gradient plus 'swim-up' reduced the HIV-1 and HCV genomes in the semen of infected individuals to undetectable levels. This method, associated with a standardized virus assay, could be useful for serodiscordant couples (males infected) who wish to have children. AIDS 2000 Sep 29;14(14):2093-9

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## *Presence and predictors of hepatitis C virus RNA in the semen of homeless men.*

Although the possibility of sexual transmission of the hepatitis C virus (HCV) remains controversial, little is known of the associations of positive semen specimens with potential demographic and behavioral risk factors. Knowledge of these predictors may suggest factors that increase risk of HCV RNA in the semen. Semen and blood from 80 HCV-infected homeless men were evaluated for the presence of HCV RNA by means of branch DNA and transcription-mediated amplification analyses. Associations of selected demographic and behavioral characteristics of the participants with presence or absence of HCV in their semen were also assessed. HCV RNA was detected in the semen of 36% of the sample. Associations were found with HCV RNA in semen and older age, higher viral loads of HCV in blood, current alcohol and lifetime methamphetamine use, and having been vaccinated for the hepatitis B virus. Findings suggest that sexual transmission of HCV is plausible and shed light on the need to conduct more in-depth investigations. Biol Res Nurs 2002 Jul;4(1):22-30

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## *Detection and characterization of hepatitis C virus RNA in seminal plasma and spermatozoon fractions of semen from patients attempting medically assisted conception.*

To investigate the risk of transmission of hepatitis C virus (HCV) via semen in assisted reproduction techniques, semen samples from 32 men chronically infected with HCV attending a center for assisted procreation were tested for HCV RNA by a reverse transcription-PCR protocol by using a modified version of the Cobas AMPLICOR HCV assay (version 2.0; Roche Diagnostics). The sensitivity of the test was 40 copies/ml. Four of 32 seminal plasma samples (12.5%) were found to be positive for the presence of HCV RNA. The median HCV load in blood was significantly higher in patients who were found to be positive for the presence of HCV RNA in semen than in those who tested negative ( $P = 0.02$ ). In one man, seven consecutive seminal plasma samples tested positive for HCV RNA, as did two consecutive motile spermatozoon fractions; the corresponding fractions obtained after migration of the spermatozoa remained negative. Despite the absence of the proven infectivity of virus in semen samples that test positive for HCV RNA, these findings highlight the fact that seminal fluid may exhibit prolonged HCV RNA excretion. The usefulness of HCV RNA detection in both seminal plasma and spermatozoon fractions before the start of a program of medically assisted reproduction in couples in whom the male partner is chronically infected with HCV would need to be evaluated prospectively with a larger population of subjects exhibiting HCV RNA in their semen. J Clin Microbiol 2002 Sep;40(9):3252-5

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## *Pregnancy after safe IVF with hepatitis C virus RNA-positive sperm.*

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In France, assisted reproductive technology (ART) for hepatitis C virus (HCV)-infected patients is now subject to strict control after the publication of recent guidelines. Infertile serodiscordant couples (HCV-viraemic men and their seronegative female partners) require special care to be carried out in designated 'viral risk' laboratories. Twelve sequential semen samples taken from an HCV chronically infected patient were analysed within 22 months. HCV RNA was detected in all the seminal plasma sampled before antiviral treatment with relatively high viral loads, and in two of the corresponding fractions of motile sperm obtained after a gradient selection, suggesting that a contamination risk by HCV through ART cannot be excluded. When the selection of sperm on a discontinuous gradient was followed by an additional swim-up step, HCV RNA was never detected in the motile sperm suspension that was frozen in highly secure straws. IVF was performed using cryopreserved sperm that tested negative for HCV RNA, resulting in a pregnancy. One month after embryo transfer, testing for HCV RNA and antibodies in the woman gave negative results. Hum Reprod 2002 Oct;17(10):2650-3

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## *Hepatitis C virus infection and genotypes among human immunodeficiency virus high-risk groups in Cameroon*

Parenteral transmission (needles, lvs) of HCV is well established but other possible routes such as heterosexual transmission are still questioned. The Central African region is characterised by a high HCV endemicity without any evidence on the route of transmission. The information on HCV genotypes that circulate in this area is also limited and controversial. HIV infection is very frequent in this region and mostly acquired via the heterosexual route. The aim of this work was to investigate the trend of HCV infection and genotypes among HIV high-risk groups from Cameroon. Four hundred eighty-two patients including 229 tuberculosis clinic attendants, 184 sexually transmitted disease clinic attendants, and 69 HIV clinical suspects from another clinic were enrolled. All plasma samples were screened for antibodies to HCV and HCV RNA. Genotypes were assigned by sequencing a 5UTR amplified fragment. The overall prevalence of HCV markers was 11.6% and a significant increasing trend with respect to age was observed. A proportion of 64.1% (34/53) of HCV antibody positive samples was viraemic. HCV RNA was found in 3 samples that were indeterminate in RIBA 3.0. One was negative in the antibody screening test and the two others were weakly positive. The data on HCV genotypes revealed that genotype 1 was involved in 57% of viraemias, genotype 2 in 24%, while genotypes 4 and 5a accounted for 16 and 3%, respectively. In contrary to the predominance of genotype 4 reported in some African countries and even the neighbouring countries, these data demonstrate clearly that HCV infection in Cameroon is dominated by genotypes 1 and 2. No association was found between the HCV markers and the presence of HIV infection. It is concluded, therefore, that the heterosexual route plays a minor role in HCV transmission in this country. J. Med. Virol. 66:179-186, 2002.

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## *Durban World AIDS Conference*

### *July 9-14, 2000 Durban, South Africa*

#### REPORT45

Lancet 2000; 356: 42 - 43, Marianne Leruez-Ville et al

Using a sensitive testing method (PCR), a French research group reported eight seminal plasma samples of 21 (38%) were found to contain HCV-RNA (6/8 were HIV+, 2/8 were HIV-). HCV viral loads detected in semen were low, which suggests that the risk of HCV sexual transmission is probably also low. Further studies using experimental infection in a cell culture system or an animal model are needed to prove that HCV-RNA positivity in semen reflects the presence of infectious virus.



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## *CDC Sexual Activity*

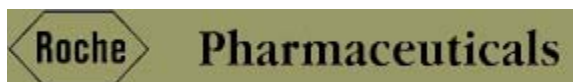
Case-control studies have reported an association between exposure to a sex contact with a history of hepatitis or exposure to multiple sex partners and acquiring hepatitis C. In addition, 15%-20% of patients with acute hepatitis C who have been reported to CDC's sentinel counties surveillance system, have a history of sexual exposure in the absence of other risk factors. Two thirds of these have an anti-HCV-positive sex partner, and one third reported >2 partners in the 6 months before illness.

In contrast, a low prevalence of HCV infection has been reported by studies of long-term spouses of patients with chronic HCV infection who had no other risk factors for infection. Five of these studies have been conducted in the United States, involving 30-85 partners each, in which average prevalence of HCV infection was 1.5% (range: 0% to 4.4%). Among partners of persons with hemophilia co infected with HCV and HIV, two studies have reported an average prevalence of HCV infection of 3%. One additional study evaluated potential transmission of HCV between sexually transmitted disease (STD) clinic patients, who denied percutaneous risk factors, and their steady partners. Prevalence of HCV infection among male patients with an anti-HCV-positive female partner (7%) was no different than that among males with a negative female partner (8%). However, female patients with an anti-HCV-positive partner were almost fourfold more likely to have HCV infection than females with a negative male partner (10% versus 3%, respectively). These data indicate that, similar to other bloodborne viruses, sexual transmission of HCV from males to females might be more efficient than from females to males.

Among persons with evidence of high-risk sexual practices (e.g., patients attending STD clinics and female prostitutes) who denied a history of injecting-drug use, prevalence of anti-HCV has been found to average 6% (range: 1%-10%). Specific factors associated with anti-HCV positivity for both heterosexuals and men who have sex with men (MSM) included greater numbers of sex partners, a history of prior STDs, and failure to use a condom. However, the number of partners associated with infection risk varied among studies, ranging from >1 partner in the previous month to >50 in the previous year. In studies of other populations, the number of partners associated with HCV infection also varied, ranging from >2 partners in the 6 months before illness for persons with acute hepatitis C, to >5 partners/year for HCV-infected volunteer blood donors, to >10 lifetime partners for HCV- infected persons in the general population.

Only one study has documented an association between HCV infection and MSM activity, and at least in STD clinic settings, the prevalence rate of HCV infection among MSM generally has been similar to that of heterosexuals. Because sexual transmission of bloodborne viruses is recognized to be more efficient among MSM compared with heterosexual men and women, why HCV infection rates are not substantially higher among MSM compared with heterosexuals is unclear. This observation and the low prevalence of HCV infection observed among long-term spouses of persons with chronic HCV infection have raised doubts regarding the importance of sexual activity in transmission of HCV. Unacknowledged percutaneous risk factors (i.e., illegal injecting-drug use) might contribute to increased risk for HCV infection among persons with high-risk sexual practices.

Although considerable inconsistencies exist among studies, data indicate overall that sexual transmission of HCV appears to occur, but that the virus is inefficiently spread through this manner. More data are needed to determine the risk for, and factors related to, transmission of HCV between long-term steady partners as well as among persons with high-risk sexual practices, including whether other STDs promote transmission of HCV by influencing viral load or modifying mucosal barriers.



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## Ask-Us About Sex! Column 175

(This week's questions answered by Helen)

*Hi SFSI,*

*I've just started a serious relationship with a man who has Hep C. I have read most of what the CDC has to say about sexual contact and risk of contraction, and I find it confusing and contradictory. They say if you have HCV and have numerous partners, use a condom, and then say if you have a primary partner, there's no need to because chance of sexual transmission is low. This sounds weird because I would assume the repeated contact with one partner would increase risk. I wonder what you know about my risk if I have unprotected sex. Semen doesn't seem to be the risk as much as blood contact. He claims none of his previous partners have contracted it and all have tested negative.*

*I am female, by the way.*

*Risky*

Dear Risky,

To be safe, use protection. Hepatitis C (HCV) is transmitted through contact when contaminated blood enters the body of another person. "Vanilla" sex may be considered safe by some, since there is a low risks of exposure to blood; however, it is not impossible to get Hepatitis C through sex. If, by any chance, blood is introduced into play, you may be at risk. If your boyfriend insists for unprotected sex and you don't want to, consider if you really want to be with a person who tries to convince you to do something that could possibly give you a STD for life. You may find out you'd be better off without someone like that. Really, so what if his ex's didn't test negative. It doesn't mean you will. Figure out what your risk comfort level is in this situation, and discuss it with him. Don't be shy to put yourself first, you're worth it. A STD free life is worth it.

Let's go over information to help you determine your risk comfort level. Again, HCV is caused through direct contact with infected blood. Cuts or sores, caused by such things as STD's or ingrown hairs, serve as an open doorway to the virus if blood comes into contact with them. Also, if you are into BDSM (B&D = Bondage & Discipline and S&M = Sadism and Masochism) sex and a toy breaks your skin, the virus will be on the toy and can infect you again, or the next person where the toy breaks another person's skin. Furthermore, if you're into biting, it's best not to break the skin. If your exposed to the blood, chances are you'll get it. In addition, be very careful sharing household items such as razors and toothbrushes. Since these products are in direct contact with the owner's blood, it's easy for one who uses these products to get it.

<http://www.sfsi.org/ask-us/ask175.html>

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## *Lymphocyte reactivity to hepatitis C virus (HCV) antigens shows evidence for exposure to HCV in HCV-seronegative spouses of HCV-infected patients.*

Author: Bronowicki JP, Vetter D, Uhl G, Hudziak H, Uhlacher A, Vetter JM, Doffoel M, Laboratoire d'Histocompatibilit , and Institut de Pathologie, Hopitaux Universitaires et Facult  de M decine de Strasbourg, France. Source: J Infect Dis 1997 Aug;176(2):518-522

Lymphocyte reactivity against hepatitis C virus (HCV) antigens was studied in 20 couples in which 1 member had chronic hepatitis C. This was done to investigate the possibility of HCV transmission between spouses that was not followed by seroconversion. Twenty healthy subjects without any risk factors for HCV transmission served as negative controls. All the patients' spouses and the healthy controls were negative for HCV RNA and for anti-HCV antibody. Lymphocytes were cultured with recombinant HCV core and nonstructural antigens (c22, c33, c100, c200, and NS5) and with control antigens (sperm whale myoglobin, chicken lysozyme, and superoxide dismutase). Lymphocytes from 10 patients and 4 seronegative spouses proliferated in the presence of at least one HCV antigen. No proliferation was shown with nonspecific antigens or in the control group. *This study gives evidence for possible in vivo priming with HCV antigens that did not lead to seroconversion in spouses of HCV-positive patients.*

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## *Heterosexual transmission of hepatitis C virus among married couples in southwestern Japan.*

Tanaka K, Stuver SO, Ikematsu H, Okayama A, Tachibana N, Hirohata T, Kashiwagi S, Tsubouchi H, Mueller NE Department of Public Health, School of Medicine, Kyushu University, Higashi-ku, Fukuoka, Japan.

The heterosexual transmission of hepatitis C virus (HCV) remains controversial, and data from general populations are scanty. In this cross-sectional study, we assessed the seroprevalence of antibodies to hepatitis C virus (anti-HCV) and the presence and genotype of HCV-RNA among 109 married couples within an endemic, community-based Japanese population. Overall, 25% of the husbands and 32% of the wives had anti-HCV. Spouses with anti-HCV-positive partners were around 2 times more likely to have anti-HCV than spouses with anti-HCV-negative partners ( $p = 0.01$ ). Of 6 couples in which both spouses had HCV-RNA, however, 3 presented discordant HCV genotypes (type 1b vs. 2b). The couples' anti-HCV concordance status was not significantly influenced by the presence or absence of HCV-RNA among anti-HCV-positive partners (odds ratio [OR]: 0.8 for wives, 0.6 for husbands), nor by the length of marriage, the number of pregnancies or the use of contraceptives. No significant associations with anti-HCV were observed for serum markers of sexually transmitted agents, including human T-lymphotropic virus (OR = 1.1, 95% confidence interval [CI] 0.5-2.3), *Treponema pallidum* (OR = 0.7; CI 0.1-6.1) and hepatitis B virus (OR = 1.6; CI 0.9-3.0). Our results suggest that the clustering of HCV infection among specific couples within this endemic population may not be attributable to heterosexual transmission. Follow-up studies are necessary to determine the risk of heterosexual transmission of HCV in endemic areas.

PMID: 9212222, MUID: 97355741

*New*  
***Spouses of Hepatitis C Virus Patients At Increased Risk  
For Infection***

Am J Gastroenterol 1996;91:2069-2070,2087-2090.

WESTPORT, Oct 17 (Reuters) - Spouses of patients with chronic hepatitis C virus (HCV) are at increased risk of acquiring the virus, and the risk goes up as time goes by, Taiwanese researchers report.

Dr. Ding-Shinn Chen and colleagues of the National Taiwan University Hospital, Taipei, studied 100 anti-HCV-positive index patients and their spouses. "Chronic HCV infection was defined by a positive reaction for second-generation anti-HCV assay...for at least 6 months," Dr. Chen said.

Seventeen spouses (17%) were anti-HCV positive, and 15 of them were also positive for hepatitis C virus RNA. In addition, 11 couples were infected with the same genotype.

Couples married longer than 20 years had a 22% rate of infection, compared to 6% for couples married less than 20 years. Dr. Chen found that "the infected couples had more frequent sexual contacts and more commonly shared toothbrushes than those with uninfected spouses."

Because risk of transmission increases over time, Dr. Chen's team concludes that spouses of chronic hepatitis C virus patients should be "...followed regularly for HCV markers and...educated about how to prevent contraction of HCV infection."

In a related editorial, Drs. Timothy M. McCashland and Daniel F. Schafer of the University of Nebraska in Omaha, spell out those prevention measures. Sharing of personal hygiene items that could be contaminated with blood should be avoided; sexual activity should be restricted if bleeding (menstruation, hematuria) is present; routine condom use is not recommended, although couples should weigh the consequences of HCV infection "...to decide if the risk is sufficient to consider use of condoms."

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## *Long-Married Couples Share Hepatitis*

SOURCE: The American Journal of Gastroenterology (1996;91(10):2087-2090)

NEW YORK (Reuters) -- Researchers in Taiwan have come up with new support for the old saying that a hand held over a flame long enough is bound to get burned.

According to their report in The American Journal of Gastroenterology this month, a spouse whose partner of 20 years or more is infected with hepatitis C is more likely to also catch the virus than spouses of infected partners in marriages of shorter duration.

Dr. Jia-Horng Kao and his colleagues at Taipei's National Taiwan University Hospital say frequent sexual contact and sharing toothbrushes make infection with the hepatitis C virus (HCV) even more likely.

These findings suggest that spouses of people who test positive for HCV should also be checked periodically for infection and "be educated [as to] how to prevent contraction of HCV infection from their spouses."

The researchers note that prevention techniques may include using condoms, and avoiding shared toothbrushes and other personal hygiene products -- razors, dental products -- that might transfer blood from one spouse to the other.

"I think it's reasonable to say that we've always suspected this about hepatitis C transmission. The information is not that new. It confirms our suspicions," says Dr. Alan I. Leibowitz, department of medicine chief at Good Samaritan Hospital and Medical Center in Phoenix.

Leibowitz points out that HCV is the most common form of post-transfusion hepatitis. "Blood units can be tested for hepatitis C, but the screening test could have false negatives [erroneous negative results], so there still are occasional cases of hepatitis C transmission from blood transfusions," he says, adding that about 35% to 40% of people who have hepatitis C have no known source of exposure to the virus.

The Phoenix hepatitis expert also notes that an estimated 3.9 million people in the U.S. might test positive for hepatitis C, and 90% or more become chronic carriers of the virus.

"But people should not become alarmed about this because it takes a long time for the infection to hurt the liver, that could be 20-plus years," Leibowitz points out. "This is not HIV."

In terms of cure, Leibowitz explains that the use of interferon to clear out the virus is about 12% to 25% successful.

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## *Sexual Transmission of HCV & Transmission from Mother-to-Child*

Durban World AIDS Conference  
July 9-14, 2000 Durban, South Africa

### REPORT45

An Italian study reported recently that HCV was transmitted from mother to newborn 5% when HIV was not present but 17% when the mother had HIV. At the Feb. 2000 HIV Retrovirus Conference, Craib from British Vancouver reported on a study to determine HCV prevalence and identify risk factors in a group of sexually active homosexual men. In a random sample of 232 men, 120 were HIV+ (112 were HIV-). Of the 232 men 20 (8.6%) had HCV and HCV prevalence was significantly higher (6-fold) among HIV+ than HIV- men (17/120 14% vs 3/112 2.7%). They reported the risk factors for the HCV+ men. HCV+ men had more sexual partners in the past year ( $\geq 20$  partners: 80% vs 40%), and in their lifetime ( $\geq 100$  partners: 90% vs 61%). They also had greater incidence of receptive fisting (30% vs 12%;  $p=0.40$ ), insertive fisting (55% vs 25%;  $p=0.004$ ), more often reported receptive oral-anal contact (100% vs 85%;  $p=0.067$ ), more often reported injection drug use (21% vs 2%;  $p<0.001$ ), cocaine use (50% vs 24%;  $p=0.013$ ), MDA use (70% vs 36%;  $p=0.003$ ), and amphetamine use (30% vs 13%;  $p=0.056$ ). Multivariate analysis showed injection drug use ( $p=0.024$ ), being HIV+ ( $p=0.056$ ), low education level ( $p=0.031$ ) and insertive fisting ( $p=0.032$ ) to be independent risk factors for being HCV+.

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## *HIV Could Play A Role In Making Hepatitis C An STD*

HIV infection could play a role in making the hepatitis C virus a sexually transmissible disease. This is just one of the possible interactions that could be taking place between these two viruses, suggest scientists at Johns Hopkins University in a guest commentary in the September 2001 issue of the journal Clinical and Diagnostic Laboratory Immunology.

The commentary is an overview of known research on the interaction between HIV and HCV in individuals infected with both viruses. It is estimated that as many as 1 in 4 HIV patients is co-infected with HCV.

One finding is that while HCV infection appears to have little effect on HIV progression and treatment, HIV infection does affect HCV. Co-infected individuals appear to have higher levels of HCV in their blood, progress to liver damage more quickly and require different treatment regimens than individuals infected with HCV alone.

On the issue of HCV as a sexually transmitted disease, "coinfection with HIV appears to increase the rate of sexual transmission of HCV," say the authors.

In one example, they cite a study in which 3 percent of female partners of coinfecting men were HCV positive, while there was no evidence of transmission in couples where the man was infected only with HCV.

"There are many interactions between HCV and HIV," say the authors. "It is important that research efforts be increased in order to better understand HIV-HCV coinfection and optimal means of treating the large number of coinfecting persons."

(Reference: K. Nelson and D. Thomas. 2001. Reciprocal interaction of human immunodeficiency virus and hepatitis C virus infections. Clinical and Diagnostic Laboratory Immunology, 8: 867-870.)

25-Sep-2001



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## *16% HCV Sexual Exposure Prevalence in Spanish Study*

Durban World AIDS Conference  
July 9-14, Durban, South Africa

### REPORT45

In a study designed to evaluate the prevalence, route of transmission and clinical significance that current co-infection with TT virus (TTV), hepatitis C virus (HCV), and hepatitis G virus (HGV) in HIV-1 infected patients, M Martinez from Barcelona, Spain analyzed the presence of HCV in plasma samples from 160 infected patients with parenteral (38 intravenous drug users 'IVDU's' and 41 patients with hemophilia) or sexual (39 homosexuals and 42 heterosexuals) risk of exposure, and in 168 volunteer blood donors. Alanine aminotransferase (ALT) levels and CD4+ T cell counts were also analyzed. Prevalences of HCV infection was higher among patients with parenteral (needles by drug abuse) (62% and 68%) than in those with sexual (17% and 16%) risk of exposure. But the study authors report 16% risk of sexual transmission. Some of this 16% could be due to unidentified drug use or an unwillingness to admit drug abuse.

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Gut 1999;45:112-116 ( July )

## *Epidemiological and virological analysis of couples infected with hepatitis C virus*

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### Abstract

#### BACKGROUND

If transmission of hepatitis C virus (HCV) infection through parenteral exposure is well documented, sexual transmission of HCV is still debated.

#### AIMS

To perform extensive epidemiological and virological analysis in 24 couples in which each spouse was anti-HCV positive in order to delineate more precisely potential sexual transmission of HCV.

#### PATIENTS

Twenty four couples in which each partner was anti-HCV positive. These 48 spouses were recruited in a liver unit by regular screening of spouses of index patients.

#### METHODS

All 48 spouses completed an epidemiological questionnaire on risk factors for HCV. Qualitative detection of serum HCV RNA and determination of HCV type by genotyping and serotyping were performed. Sequence analysis of HCV strains by phylogenetic analysis was carried out in seven couples with concordant genotypes.

#### RESULTS

The mean (SD) partnership duration was 12 (10) years. Serum HCV RNA was detected in both partners in 18 of the couples (75%) and in only one partner in six of the couples (25%). HCV typing showed concordant genotypes in 12 couples (50%), discordant genotypes in seven (29%), and in the other five couples (21%) only one spouse could be genotyped. Of the 48 spouses, 33 had a major risk factor for HCV transmission such as transfusion (n = 6) and intravenous drug use (n = 27). Eleven of the 12 couples infected with the same HCV genotype had at least one parenteral risk factor for viral transmission in both spouses. Whatever the genotype concordance, in most couples (75%), both spouses showed parenteral risk factors for viral transmission. Sequence analysis of HCV strains was possible in seven of 12 couples

with identical genotype and showed different and identical isolates in four and three couples respectively.

## CONCLUSION

The study emphasises the risk of overestimating the importance of a very low sexual HCV transmission risk as against other, mainly parenteral, risk factors.

## Introduction

The issue of sexual transmission of hepatitis C virus (HCV) is still debated. Conflicting results have indeed been reported, as the rate for such transmission ranges from 0 to 27%,<sup>1-6</sup> and it is still unclear whether or not HCV RNA can be detected in semen.<sup>7,8</sup> These discrepancies can be partly explained by a lack of exhaustive epidemiological analysis, parenteral risk factors representing a potentially major epidemiological bias. Finally, although some studies have included sequence analysis, the number of patients tested was still low.<sup>2</sup> The aim of this work was therefore to delineate more precisely sexual transmission of HCV by performing an extensive epidemiological and virological analysis in 24 couples in which both husband and wife were anti-HCV positive.

## Patients and methods

We studied 24 couples in which each partner was anti-HCV positive. These couples were randomly recruited in our liver unit by regular screening of spouses of index patients followed in our active file of 1640 anti-HCV positive, including 11.1% anti-HIV positive patients. Extraconjugal sexual partners were not included in this screening. As many spouses refused anti-HCV determination for various reasons, the exact prevalence of HCV in spouses of our index subjects was not available. Eight spouses (17%) in seven couples were anti-HIV positive. Thirty eight of 48 (79%) spouses underwent liver biopsy which showed chronic hepatitis and cirrhosis in 32 (84%) and six (16%) respectively. Four additional couples in which both spouses were anti-HCV positive were not included in this study because serum samples were not available for virological analysis in one spouse of the couple.

All 48 subjects responded to a detailed epidemiological questionnaire on risk factors for HCV including history of intravenous drug use, transfusion, acupuncture, tattooing, and suspicion of nosocomial (endoscopy, surgery, mesotherapy) and sporadic transmission (ritual scarring, stay in an endemic geographical area).

## VIROLOGICAL METHODS

Serum antibodies to HCV were detected by the second generation HCV enzyme linked immunosorbent assay (ELISA2) and recombinant immunoblot assay (RIBA2) from Ortho Diagnostic (Raritan, New Jersey, USA), according to the manufacturer's instructions.

### Qualitative detection of serum HCV RNA

Briefly, RNA was extracted from 150 µl serum, reverse transcribed to cDNA and amplified by polymerase chain reaction (PCR) by a modified nested PCR method with primers located in the 5' non-coding region as previously described.<sup>9</sup> Amplified products were stained with ethidium bromide and hybridised with a radiolabelled oligonucleotide probe within the amplified sequence.

### Genotyping

Briefly, cDNAs were subjected to amplification. This analysis was based on a restriction fragment length polymorphism assay. Products were digested by three specific restriction endonucleases, BstNI, BstUI, and Sau3a, under the manufacturer's conditions (Biolabs, Beverly, Massachusetts, USA). The fragments were electrophoresed and detected by ethidium bromide staining in comparison with a standard sized DNA marker (100 bp ladder; Promega, Madison, Wisconsin, USA). Their sizes determined the different genotypes 1, 2, 3, 4, and 5 and the subtypes 1a and 1b.<sup>9</sup>

### Genotyping by serological assay

A serological assay was performed on the serum of HCV RNA negative spouses. The Murex HCV serotyping 1-6 assay<sup>9</sup> was used to determine the HCV serotypes. Briefly this analysis is a rapid enzyme immunoassay using synthetic peptides derived from the variable antigenic regions of NS4 of HCV types 1, 2, 3, 4, 5, and 6.

#### Sequence and phylogenetic analysis

To compare the HCV strains from the 12 couples with concordant genotype, the NS5b region was chosen for analysis. PCR fragments were characterised by direct sequencing of this region and by comparing the sequences with published sequences using a phylogenetic software package (Phylip-Felsenstein, 1991; University of Washington, Seattle, Washington, USA). Distances between pairs of sequences were estimated using the DNADIST program and further analysed in NEIGHBOR using the neighbor-joining setting. The program Drawgram was used to create a graphic output.

#### STATISTICAL ANALYSIS

The  $\chi^2$  and Student's t tests were used for statistical comparisons between couples according to genotype concordance.

#### Results

Mean (SD) age of spouses was 40 (13) years (range 25 to 77). The mean (SD) duration of the partnership was 12 (10) years (range 1 to 36). Among the 24 couples, serum HCV RNA was detected in both partners in 18 cases (75%) and in only one partner in six (25%). In couples in which HCV RNA was detected in both spouses, 11 of 18 (61%) had the same genotype while seven of 18 (39%) had different genotypes. Genotyping by serological assay was used in the four HCV RNA negative spouses and disclosed one infection by type 1, and was not conclusive in three cases; in the other two cases, serum was not available for serotyping analysis and thus HCV genotype could not be determined. One couple in which one spouse was infected by genotype 1b and the other by a serotype 1 were assumed to be infected by a "concordant" genotype. Thus, among the 24 couples, concordant genotypes were observed in 12 (50%), discordant genotypes in seven (29%), and in the remaining five (21%) only one spouse could be genotyped, precluding any conclusion about concordance.

Of seven couples in whom at least one partner was anti-HIV positive, three were infected by concordant and two by discordant genotypes; genotype determination was possible in only one spouse for two couples.

The various potential risk factors were analysed in all 48 spouses. Thirty three (69%) had a major risk factor of HCV transmission such as transfusion ( $n = 6$ ) and intravenous drug use ( $n = 27$ ). In addition, 13 spouses had other potential risk factors such as history of tattooing, acupuncture, mesotherapy, and history of endoscopy with biopsy or major surgery. Seven spouses (15%) had at least two parenteral risk factors while nine (19%) had no risk factors other than sexual. Of the 19 couples in whom genotype concordance analysis was feasible, 11 of the 12 couples infected with the same HCV genotype had at least one parenteral risk factor for viral transmission in both spouses (including 18 intravenous drug users and two who had received blood transfusions); six of the seven couples infected with different HCV types had at least one parenteral risk factor for viral transmission in both spouses (including six intravenous drug users and two patients who had received blood transfusions (table 1)). In all, 18 of 24 couples (75%) had at least one parenteral risk factor for viral transmission in both spouses. In the other six couples, nine spouses had no evidence of parenteral risk factors. Moreover, there was no difference in the distribution of epidemiological risk factors nor in the duration of the relationship according to genotype concordance

(table 1).

<b>Table 1 Epidemiological and virological analysis according to genotype concordance in couples</b>			
	<b>Genotype discordance (n=7)</b>	<b>Genotype concordance (n=12)</b>	
<b>Genotype (n)</b>	<b>1a/3a (2)</b>	<b>1b (4)*</b>	
	<b>1b/1a (1)</b>	<b>3a (5)</b>	
	<b>3a/2a (1)</b>	<b>1a (2)</b>	
	<b>1b/3a (1)</b>	<b>4 (1)</b>	
	<b>3a/4 (1)</b>		
	<b>1/3a (1)</b>		
<b>Parenteral risk factor in both spouses; n (%)</b>	<b>6 (85)</b>	<b>11 (91)</b>	<b>NS</b>
<b>Mean (SD) duration of relationship (years)</b>	<b>7.6 (5.8)</b>	<b>13.2 (11.3)</b>	<b>NS</b>
<b>* Including one couple in which one spouse was only determined by serotyping as type 1.</b>			

Owing to the HCV genetic variability, identification of the same HCV genotype in some couples obviously does not imply infection by identical strains. To go further in this issue we analyzed the genomic sequence of HCV strains of 12 couples with concordant genotype.

Phylogenetic trees were calculated from the region encompassing nucleotides 7947-8259 of the NS5b region (fig 1). Of the 12 couples infected with concordant genotypes, only seven could be investigated (for some partners the NS5b fragment could not be amplified). The HCV strains from couples 2, 7, and 11 differed by 1 to 3 nucleotides with sequence similarity of 98% or more (evolutionary distance 0.065). These results were further reinforced by >75% bootstrap support confirming that these isolates were closely related and suggesting that these spouses were infected by a common source. In contrast, the strains from couples 4, 5, 6, and 12 showed less similarity to each other. They differed by 4 to 15 nucleotides with evolutionary distance 0.0129. These strains were therefore judged to be unrelated.

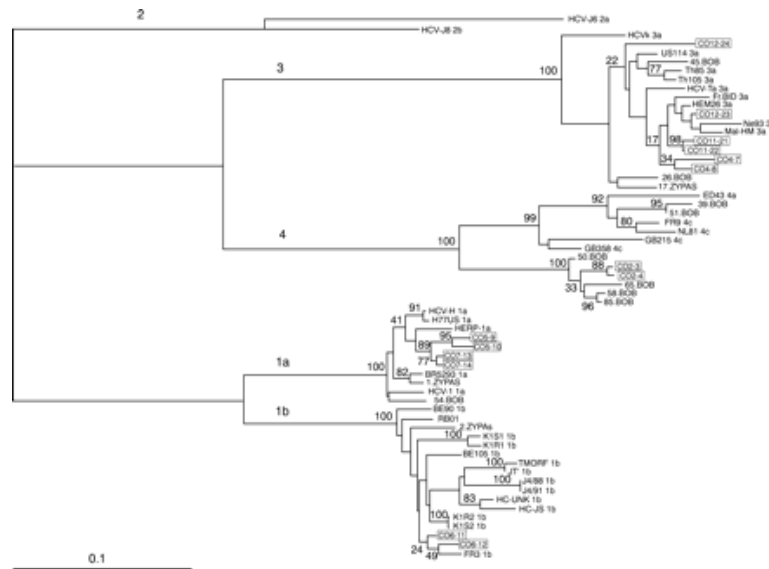


Figure 1 Phylogenetic analysis in seven couples with concordant genotype showing different and identical isolates in four and three couples respectively. The phylogenetic tree is shown of the NS5b region (312 bp fragment; nucleotides 7947-8259) from study cases and previously reported reference sequences. Boxed strains are those recovered in the couples and are identified by the number of the couples from whom they originate—that is, Co12-1 and Co12-2 from couple 12. Accession numbers for the reference isolates used to create this tree have been detailed previously<sup>17</sup> and identified by the isolate's name. Furthermore sequences originating from our geographical area were introduced into the phylogenetic analysis (X.BOB). Bootstrap values obtained from 100 replicas are given as percentages at the branching forks.

To rule out the possibility of PCR contamination, unrelated sera (1.ZYPAS, 2.ZYPAS, 17.ZYPAS belonging to subtypes 1a, 1b, and 3a respectively) were included and processed together with the samples of interest. These three samples were found on separate branches when compared with the isolates observed in the spouses.

In summary, sequence analysis coupled with phylogenetic analysis showed different isolates in four and identical isolates in three couples (fig 1). Among the couples with identical isolates, risk factors other than sexual were identified in each couple and in three of the four with different isolates.

## Discussion

Our study provides a detailed epidemiological and virological analysis of 24 couples in which both partners were anti-HCV positive and offers evidence, at least in our selected population, that sexual transmission may be mistaken for others factors and thus a careful search for parenteral transmission is needed.

Some 37% of the couples (in whom concordance genotype analysis was available) did not have the same genotype, which is definitive evidence against sexual transmission. This suggests that the usual major parenteral risk factors (intravenous drug use and blood transfusion) identified in 57% of these spouses are the cause of the transmission of HCV. In the 12 couples with an identical genotype, sexual transmission of HCV may be hypothesised. However, concordance of genotype within a couple does not provide definitive evidence for sexual transmission. Indeed sequence analysis showed that about 60% of couples analysed with identical genotypes had different isolates. Moreover, identical isolates found in both partners of a couple could be due to parenteral or sporadic transmission and does not systematically prove sexual transmission. Indeed, among the three couples with identical isolates, risk factors other than sexual were identified in each couple, and some subjects reported near exclusive sharing of needles with their partners. Moreover, most if not all of the patients with the same genotype had multiple parenteral risk factors for transmission of HCV, including 19 intravenous drug users and two patients who had received transfusions. It is noteworthy that an absence of well characterised parenteral risk factor for HCV does not necessarily imply sexual transmission, as inapparent parenteral transmission could be involved in HCV transmission. In addition, there was no difference in the distribution of epidemiological risk factors nor in

the length of the relationship according to genotype concordance (table 1), and for 16 of the 48 spouses (33%), the parenteral risk factor of viral transmission preceded the partnership. Along the same lines, it is interesting to note that in 20 stable couples of our cohort in which only one partner was anti-HCV positive, no major parenteral risk factor such as intravenous drug use or history of transfusion was recognised in the anti-HCV negative spouses (data not shown).

A correlation between anti-HCV positivity in spouses of index patients and history of parenteral risk factor has been previously suggested.<sup>10</sup> Interestingly, the authors failed to demonstrate any link between anti-HCV positivity in spouses of index patients and sexual behaviour (number of sexual partners, anal intercourse, sexually transmitted disease in couples), suggesting that transmission of HCV did not involve a sexual route. Moreover, in the spouses of HCV infected haemophiliacs, the rate of anti-HCV positivity in wives of index patients has been reported not to exceed the 1% prevalence observed in the general population.<sup>11</sup> Finally it is important to note that, despite conflicting results on HCV RNA in semen, no HCV RNA was found in any of the seminal fractions in a large recent study involving 90 subjects.<sup>8</sup> In contrast, a higher rate of anti-HCV positivity in spouses has been reported in Japan<sup>2 5</sup>: 27% and 21% of HCV infection markers were reported for spouses of 154 and 48 index patients respectively. Concordance in genotypes and homology of nucleotides in HCV sequences in some couples, on the one hand, and correlation between HCV infection in both spouses and duration of marriage (30% of couples with more than 30 years of marriage were infected as compared with 0% of those with less than 10 years) on the other hand, were taken as evidence for sexual transmission.<sup>2</sup> It is noteworthy that a higher prevalence of anti-HCV was observed after more than 30 years of marriage, although sexual activity usually decreases with time. One may therefore hypothesise that a community-acquired or another route of transmission is more likely. This is reinforced by the reported association between HCV infection and traditional practices (acupuncture, "vacuuming") in Asia.<sup>12</sup> From the same viewpoint, age related factors (either longer period of exposure to potential risk factors or exposure to risk factors that have considerably diminished or disappeared such as the use of non-disposable medical material) may explain the high anti-HCV prevalence in 60 year old sexual partners rather than the sexual route.<sup>13</sup> Finally the level of HCV viraemia may also partly account for different results among the studies. However, it is noteworthy that no major HCV infection prevalence was found in spouses of patients who had received liver transplantation for HCV related cirrhosis, in whom the level of viraemia is usually high.<sup>14</sup>

The relatively high frequency of HIV co-infection (18%) reflects the high rate of intravenous drug use in our population (six of eight HIV co-infected spouses). However, it is noteworthy that intravenous drug using patients are likely to have intravenous drug using partners, and this underlines the conclusions of our study that sexual transmission may be mistaken for other factors in the absence of extensive epidemiological analysis of risk factors for HCV transmission.

As sexual transmission of HCV may be favoured in a sexual partner of HCV-HIV co-infected subjects, such a transmission cannot be ruled out in couples in which one of the spouses is HIV infected.<sup>15</sup> Finally, our findings are in accordance with a recent study in which transmission of HCV was not observed in couples at risk through sexual contact alone, in contrast with couples in which partners were additionally exposed through intravenous drug use.<sup>16</sup>

We did not test all the sexual partners of our HCV infected subjects in our series and thus we cannot establish the exact prevalence of HCV positivity among the partners of index cases. The results of our study, however, are in accordance with low sexual transmission of HCV and underlines the fact that sexual transmission may be mistaken for other factors and therefore a careful search for parenteral transmission is needed. The over-representation of intravenous drug use in our own experience of HCV infected spouses reinforces the hypothesis of parenteral transmission of HCV even if we cannot exclude the possibility that this over-representation could indeed hide other routes of HCV transmission, and therefore extrapolation of our results to the general population should be made carefully.

Abbreviations used in this paper

Abbreviations used in this paper: HCV, hepatitis C virus; PCR, polymerase chain reaction.

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## *Transmission (HCV) "Safer Sex Practice for Chronic HCV Carriers: Is It Necessary?"*

Blood Weekly, September 29, 1997, Research from Conferences, p. 19. A.R. Davis and A.M. Kowalik

According to an abstract submitted by the authors to the First Australasian Conference on Hepatitis C, held March 16-18, 1997, in Sydney, Australia, "The efficiency of sexual transmission of Hepatitis C virus (HCV) is an important issue for individuals with HCV infection and the role of sexual transmission in the epidemiology of HCV infection continues to be debated. In particular, whether HCV-discordant couples in established monogamous relationships should be advised to use condoms is controversial. We have routinely offered testing of the current heterosexual partner to Sydney donors identified anti-HCV positive attending for follow-up since January 1994. As at September 1996, the partners of 40 such donors had been tested. Only one of the 40 partners tested anti-HCV positive. This partner had an independent established parenteral risk factor for HCV infection. The median duration of the couples sexual relationships was five years (range four months to 42 years). Thirty-eight couples reported rarely or never using condoms in their sexual relationships; two couples reported using condoms for the majority but not all of their sexual relationships. Our findings support larger epidemiological studies in blood donors, multiply transfused patients and recipients of contaminated Rh anti-D immunoglobulin which suggest that heterosexual transmission of HCV is extremely uncommon. We counsel couples in established monogamous relationships that it is probably unnecessary to modify their sexual practice, other than to consider using condoms during menstruation, anal intercourse or when genital ulceration is present."

# Intrafamilial transmission of hepatitis C virus: a systematic review

Ackerman Z, Ackerman E, Paltiel OJ *Viral Hepat* (2000 ) Mar;7(2): 93-103 Abstract

To examine the risk of hepatitis C virus (HCV) transmission between patients infected with HCV and their household members (siblings, offspring and parents), as well as their stable heterosexual partners, a systematic search of the MEDLINE database was undertaken for all relevant articles published up to June 1997. English language publications or those supplemented with an English abstract that reported studies concerning hepatitis C, and household, intrafamilial, sexual and intraspousal transmission of HCV, were reviewed. Data from uncontrolled and controlled studies were collected and analyzed separately. Studies reporting the exclusive use of first-generation anti-HCV antibodies without supplemental tests were excluded. Pre- or postnatal mother-to-child transmission of HCV and homosexual and heterosexual transmission of HCV among non-permanent couples were not included. Unweighted data from individual studies were pooled for each category of family member. Data were also analyzed separately for Japanese and non-Japanese studies because there is evidence that intrafamilial transmission may differ, based on endemicity of the viral infection. Comparisons were drawn only from controlled studies that reported the prevalence of HCV in family members of both HCV-positive and HCV-negative controls. Pooled odds ratios (OR) and 95% confidence intervals (CI) were calculated for each family category. In uncontrolled studies, the pooled prevalence of anti-HCV among 4250 stable sexual contacts of patients with HCV-related chronic liver disease (CLD) was 13.48%, while the pooled prevalence of anti-HCV among 580 stable sexual contacts of patients who contracted HCV as a result of multiple transfusions was 2.41%. In controlled studies, the pooled prevalence of anti-HCV among 175 siblings and household contacts of patients with CLD was 4.0% compared with 0% among 109 contacts of anti-HCV-negative controls (OR 9.75, 95% CI 0.91- $\infty$ ). The pooled prevalence of anti-HCV among offspring of Japanese HCV-infected CLD patients was 17% compared with 10.4% among offspring of HCV-negative Japanese controls (OR 1.77, 95% CI 1.21-2.58,  $P=0.002$ ). The pooled prevalence of anti-HCV among spouses of non-Japanese HCV-infected CLD patients was 15.2% compared with 0.9% in the spouses of non-Japanese HCV-negative controls (OR 20.57, 95% CI 6.05-84.08,  $P=0.0001$ ). The prevalence of anti-HCV among non-Japanese offspring and Japanese spouses of HCV-infected patients was not increased compared with controls. HCV genotype homology and mutant analysis studies in pairs of HCV-infected patients and their HCV-infected contacts showed that concordant genotype homology was found in 66% of non-sexual contacts and in 74% of sexual contacts. Sequence homology of greater than 92% was found in 19 out of 35 pairs. Hence, evidence exists that familial, non-sexual and sexual transmission of HCV does occur. In Japanese patients, transmission probably occurs in younger family members while, in non-Japanese patients, transmission probably occurs at an older age, after contact with an HCV-infected spouse.

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## *Risk of Sexual Transmission of Hepatitis C*

Piazza M, Sagliocca L, Tosone G, Guadagnino V, Stazi MA, Orlando R, Borgia G, Rosa D, Abrignani S, Palumbo F, Manzin A, Clementi M

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**OBJECTIVE:** To estimate the risk of sexual transmission of hepatitis C and to assess the value of prophylaxis with periodic intramuscular immune serum globulin administration. **METHODS:** Of 1102 steady heterosexual partners of patients with antibodies to the hepatitis C virus (HCV), 899 were enrolled in a single-blind, randomized, controlled trial. All the partners tested negative for antibodies to HCV and had normal baseline serum aminotransferase concentrations. The partners were assigned to receive 4 mL of 16% polyvalent immune serum globulin prepared from unscreened donors every 2 months (n = 450) or a placebo (n = 449). Tests for HCV infection were performed every 4 months.

**RESULTS:** Eight hundred eighty-four partners completed the study. Seven partners became infected with HCV: 6 in the control group (incidence density, 12.00 per 1000 person-years; 95% confidence interval, 3.0-21.61) and 1 in the immune serum globulin group (incidence density, 1.98 per 1000 person-years; 95% confidence interval, 0-5.86). The risk of infection was significantly higher for partners in the control group (P = .03): for each year approximately 1% of the partners became infected. Sequence homology studies strongly suggest the sexual transmission of HCV. All immune serum globulin lots used had high enzyme-linked immunosorbent assay titers of neutralizing antibodies to HCV envelope glycoproteins and high neutralization titers in the neutralization of binding assay.

**CONCLUSIONS:** Hepatitis C can be sexually transmitted. Immune serum globulin prepared from unscreened donors significantly reduced the risk. The treatment was safe and well tolerated. Because only immune serum globulin from unscreened donors (and not from those screened for HCV) contain anti-HCV neutralizing antibodies, hyperimmune anti-HCV immune serum globulin should be prepared from blood testing positive for antibodies to HCV, which is currently discarded.

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Review

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