

# Epidemiology, Modes of Transmission, & Risk Factors for Hepatitis C Virus (HCV) Infection

by Michael Marco

*My opinion is that we just can't tell for sure about some of this because we are bad at measuring human behavior.*

—Davis Thomas, e-mail correspondence

## **Background**

During the 1970s and 1980s, no one knew what was causing hepatitis in certain individuals who had received blood transfusions. Screening tests for hepatitis A (HAV) and hepatitis B (HBV) in the mid-1970s revealed that about 25% of these cases of transfusion-associated hepatitis (TAH) were linked to hepatitis B but no hepatitis A. The remaining 75% of TAH cases, by default, were termed non-A-non-B hepatitis (NANBH) (H. Alter 1999). Ten to twenty percent of individuals who had received multiple blood transfusions (or used plasma products) developed NANBH, with a relative risk of 0.45% per unit transfused (Donahue 1992).

Because primary infection was usually asymptomatic or, at worst, mild, clinicians did not initially consider NANBH to be a very serious disease. It was soon recognized, however, that the seemingly benign NANBH could develop into a chronic hepatitis with markedly elevated liver enzymes. Sometimes the hepatitis resulted in cirrhosis.

According to the National Institutes of Health's (NIH) Harvey Alter, attitudes to NANBH changed in the late 1980s:

The NANBH agent remained a virologic enigma....until researchers at the Chiron Corporation used an ambitious molecular approach on large volumes of high-titer infectious chimpanzee plasma from the Centers for Disease Control and Prevention (CDC). They extracted RNA, cloned it into an expression vector, and screened the expressed product with presumed immune sera. A single positive clone was found in the millions screened, and, within a year, the entire genome was sequenced and the agent was identified as a novel flavivirus the hepatitis C virus (HCV). (HJ Alter 1999).

In 1988 Choo and colleagues characterized the hepatitis C virus (HCV), and shortly thereafter, an antibody test was developed to detect infection (Choo 1989; Kuo 1989). When NIH researchers performed HCV assays on archived blood samples, it was determined that 70% to 90% of NANBH cases were actually HCV infections.

## **Prevalence of HCV Infection in the United States (U.S.)**

HCV is considered the most common blood-borne infection and is one of the leading causes for liver transplantation among adults in the U.S. After the HCV antibody test became available, epidemiology studies were performed to ascertain the incidence of the infection. The original studies, however, were considered flawed because they were conducted with first-time blood donors, individuals who had already been screened for risk factors such as infectious diseases.

A recently published study by Miriam Alter and colleagues from the Centers for Disease Control and Prevention (CDC) reported that an estimated four million persons nationwide are HCV- antibody-positive (ab+), indicating exposure to the virus. Roughly three-quarters of these have detectable HCV RNA, indicating chronic infection (MJ Alter, 1999b). These data hail from the CDC's third National Health and Nutrition Examination Study (NHANES III), conducted between 1988 and 1994, and involving a sample of almost 40,000 persons between the ages of 2 and 89 years.

Out of this group, 21,241 individuals agreed to be both interviewed and tested for antibodies to HCV; of these, 1.8% were found to be HCV-antibody-positive. For the entire U.S., this corresponds to approximately 3.9 million residents infected with HCV. Below is a breakdown of the prevalence of HCV-antibody-positivity classified by race or ethnic group and gender.

## **Prevalence of Antibody to HCV (Anti-HCV)**

### **According to Race or Ethnic Group & Gender in NHANES III**

Characteristic	No. Tested	Prevalence (%) of Anti-HCV+ (95% CI)	Estimated No. Infected Nationwide (95% CI)
All Subjects	21,241	1.8 (1.5-2.3)	3,875,000 (3,102,000-4,840,000)
<b>Race/Ethnic Group</b>			
Non-Hispanic White	7,965	1.5 (1.1-2.0)	2,359,000 (1,774,000-3,137,000)
Non-Hispanic Black	6,119	3.2 (2.6--4.0)*	762,000 (609,000-953,000)
Mexican Americans	6,268	2.1 (1.7-2.6)	261,000 (210,000-323,000)
Other	889	2.9 (1.4-5.8)	493,000 (245,000-993,000)
<b>Gender</b>			
Male	10,076	2.5 (2.0-3.2)**	2,586,000 (2,012,000-3,323,000)
Female	11,165	1.2 (0.9--1.6)	1,289,000 (967,000-1,717,000)

\* P<0.05 for comparison with non-Hispanic whites (MJ Alter 1999b)

\*\* P<0.05

### HCV Prevalence in Blood Donors in Southern Europe

Several large HCV epidemiology studies have been published in Italy, France, and Spain. Below is a breakdown of anti-HCV prevalence in selected studies that have been conducted since the early 1990s.

### HCV Incidence Rates in Six Large Southern European Cohorts

N =	Anti-HCV +	Country (Study)
173,038	0.63%	France (Anuelles 1992)
60,960	0.69%	France (Aymard 1993)
30,231	1.2%	Spain (Esteban 1991)
46,741	1.12%	Spain (Salmeron 1996)
55,587	0.93%	Spain (Munoz-Gomez 1996)
6,917	3.2%	Italy (Bellentani 1994)

### HCV Prevalence in Egypt

With an estimated HCV infection rate of 25%, Egypt has a higher incidence of HCV infection than any other country in the world (Arthur 1997). The Nile Valley area has higher rates of infection compared to cities and desert areas. The Egyptian HCV epidemic is a result of a widespread treatment campaign against schistosomiasis, an ancient parasitic disease. From the 1920s to the 1980s, the government administered parenteral antischistosomal therapy (usually 6-12 injections) with reusable syringes (Frank 2000). With course of injections taking two to four weeks, an individual infected early in treatment could then spread HCV on a subsequent injection to others who used the same syringe.

### Modes of Transmission and Risk Groups

Numerous epidemiology studies have documented that individuals from high-risk groups, including

recipients of blood transfusions before 1991, hemophiliacs, intravenous drug users (IDUs), homosexuals, and alcohol abusers, have an exceedingly high prevalence of HCV antibodies.

### **Blood Transfusion Recipients and Hemophiliacs before 1992**

In the mid-1960s, the rate of post-transfusion hepatitis was greater than 20% (HJ Alter 1972). When donor blood in the U.S. began to be screened and excluded for antibodies to HAV, HBV, and HIV between 1985-1990, the rate of new HCV infections declined by more than 50%, lowering the risk of HCV seroconversion to 1.54% per transfusion patient or to 0.19% per unit transfused (Donahue 1992). In May 1990, a first-generation enzyme immunoassay EIA-1 was introduced to screen U.S. blood donors. It was soon replaced by the much more sensitive multiantigen test (EIA-2) in July 1992. The EIA-2 has dramatically reduced the risk of HCV infection, lowering rates to 0.001% per unit transfused (Schreiber 1996). According to Harvey Alter:

The impact of HCV blood donor screening has been enormous. The single-antigen first-generation enzyme immunoassay (EIA-1) prevented 40,000 HCV infections within the first year, and the second-generation assay (EIA-2) has actually reduced new transfusion-related HCV infections to almost zero. (HJ Alter 1999)

Before 1985, the rate of HCV infection in hemophiliacs who received clotting factor concentrates prepared from plasma pools was at least 90% (CDC 1998). Factor VIII and Factor IX, which inactivated blood-borne viruses such as HCV, were introduced in 1985 and 1987, respectively.

### **Injection Drug Users**

The rate of HCV infection among IDUs who share contaminated needles, syringes, or drug preparation equipment continues to remain high. In numerous studies conducted around the world, the incidence of HCV among IDUs ranges from 70% to 92% (Esteban 1989; van den Hoek 1990; Donahue 1991; Zeldis 1992; Garfein 1996; Broers 1998; Hershov 1998; van Beek 1998).

<b>Rates of Anti-HCV+ from IDU Cohorts in Selected Cities</b>		
<b>% Anti-HCV+</b>	<b>City</b>	<b>Source</b>
70%	Barcelona	Esteban 1989
74%	Amsterdam	van den Hoek 1990
85%	Baltimore	Donahue 1991
72%	San Francisco/Davis	Zeldis 1992
76.9%	Baltimore	Garfein 1996
91.6%	Geneva	Broers 1998
90% (women only)	Chicago	Hershov 1998
75.6% (age <20 years)	Sydney	van Beek 1998

The risk of contracting HCV from shared injection equipment is extraordinarily high-and not only for long-term IV drug users. A study by Garfein and colleagues at Johns Hopkins documented that the risk of acquiring HCV infection was as high 65% for new injectors within 6 to 12 months after beginning injection drug use (Garfein 1996). The risk of acquiring HCV is markedly higher than that of acquiring other viral infections such as HIV. The same study documented a rate of HIV infection among IDUs during this brief window of only 14%.

With regard to non-injectable drug use, intranasal cocaine use was reportedly associated with HCV infection in a study conducted by Conry-Cantilena from Harvey Alter's group at the NIH (Conry-Cantilena 1996). Finding a highly significant correlation in a multivariate analysis, the author theorized that if the device shared for snorting cocaine (a straw) was contaminated with blood, it could convey virus to

denuded nasal mucosa, allowing HCV to enter the bloodstream. This possible mode of transmission—referred to by some as the "bloody straw" theory—was highly debated, and in 1998, the CDC listed intranasal cocaine users in the category of "Persons for whom routine hepatitis C (HCV) testing is of uncertain need" (CDC 1998).

It appears that this finding by Conry-Cantilena and colleagues may have been a fluke, or merely that intranasal cocaine use is a surrogate for other behavior which could foster HCV transmission. More recently Murphy and colleagues, of the NHLBI Retrovirus Epidemiology Donor Study (REDS), published a study reporting that, in a multivariate logistic regression model, intranasal cocaine use (or use of any other powdered drug) was not a risk factor for HCV (Murphy 2000).

### **Occupational (Needlestick) Exposure**

The prevalence of HCV infection in health care workers, including orthopedic, general, and oral surgeons averages 1-2% (Thomas 1993, 1996). The seroconversion rate after an unintentional needlestick injury from an HCV-positive source is ~1.8% (MJ Alter 1994; Puro 1995). It appears that the seroconversion rate with solid needles is lower compared to needlesticks with hollow cannula devices (Puro 1995).

### **Percutaneous Exposure in Other Settings**

While apparently rare, HCV transmission has been associated with commercial barbering, tattooing, ear piercing, and religious scarification (Tumminelli 1995; Abildgaard 1991; Thompson 1996; Conry-Cantilena 1996; Murphy 2000). Tumminelli and colleagues found that 38% of Sicilian barbers studied had antibodies to hepatitis C and suggested that shaving was a potential route of transmission. In the REDS study, Murphy and colleagues determined that religious scarification, sharing toothbrush and/or razor, having been tattooed, and having been pierced (body or ear) were all risk factors for HCV seropositivity after controlling for IVDU (OR = 3.8; 1.6; 3.9; and 2.7, respectively).

### **Perinatal Transmission**

Most U.S. and international studies have reported the incidence of anti-HCV positivity in pregnant women to be between 0.7% and 4.4% (Marcellin 1993; Marranconi 1994; Leikin 1994; Hillemanns 1998; Resti 1998; Conte 2000). One recent perinatal transmission study from the metropolitan New York City area documented an ominous 41% anti-HCV incidence rate in a cohort of pregnant women—79% of whom were past or present IDUs (Granovsky 1998). The rate of HCV RNA detectability in several international cohorts of anti-HCV-positive women ranges from 65% to 72% (Resti 1998; Granovsky 1998; Conte 2000).

Reported rates of mother-to-infant HCV transmission have ranged from 0% to 36% in numerous studies, with higher rates occurring when mothers are HIV-positive (Ohto 1994; Zanetti 1995; Sabatino 1996; Tovo 1997; Granovsky 1998; Resti 1998; Thomas 1998b; Conte 2000). When these data are analyzed together, the average rate of vertical HCV transmission appears to be approximately 5%. Studies have demonstrated that rates of vertical transmission are dependent upon five factors: 1) presence or absence of HCV RNA in the mother; 2) high or low HCV viral load; 3) HIV status of the mother; 4) vaginal vs. caesarean delivery; and 5) breast vs. bottle feeding.

The only consistent factor found in studies is that vertical transmission does not occur if the mother is HCV RNA-negative at time of birth. In 20 perinatal HCV transmission studies analyzed by Dore and colleagues, none of the 735 aggregate HCVab+ but HCV RNA-negative women gave birth to an HCV-infected infant (Dore 1997). Some studies have documented a decreased incidence of vertical transmission from mothers with low HCV viral load (HCV RNA levels differ among studies). Other studies, however, have not found this correlation to be significant.

**Mother's HCV RNA Level and Its Correlation with Transmission of HCV to Her Newborn: Conflicting Results**

HCV RNA in transmitting mothers (copies/mL)	HCV RNA in non-transmitting mothers (copies/mL)	P	Study
1,000,000	15,000	<0.001	Ohto 1994
>2,000,000	<1,000,000	<0.001	Lin 1994
~1,000,000	~670,000	NS	Zanetti 1995
2,000,000	350,000	<0.001	Thomas 1998b
380,000	240,000	NS	Resti 1998
>1,000,000	<1,000,000	0.02	Mast 1999
2,150,306	2,038,375	NS	Conte 2000

There is considerable controversy as to whether the rate of HCV vertical transmission is higher when the mother is also HIV-positive. Many studies have been conducted solely in coinfecting pregnant women and others in HCV-positive women with and without HIV. One of the most provocative findings comes from Zanetti and colleagues, a 1995 Italian study which included 116 HCV-positive women—22 of whom were coinfecting with HIV. Of the 22 coinfecting women, 18 had detectable HCV RNA. None of the infants born to 92 HIV-negative women acquired HCV, but 8 of the 22 (36%) infants born to coinfecting mothers acquired HCV. While the eight mothers who transmitted HCV had detectable HCV RNA, there was no significant difference in HCV RNA levels between them and the other ten coinfecting HCV RNA-positive women (Zanetti 1995).

Another Italian study of 245 infants found the incidence of HCV vertical transmission higher in coinfecting mothers. Overall, 28 (11.4%) of the 245 infants acquired HCV: 3 of 80 (3.7%) whose mothers had HCV infection alone vs. 25 of 165 (15.1%) whose mothers were coinfecting ( $P<0.01$ ) (Tovo 1997).

In a study of solely coinfecting mothers, Thomas and colleagues found that the risk of HCV infection was 3.2-fold greater if the infant also acquired HIV compared to HIV-uninfected infants (17.1% of 41 vs. 5.4% of 112,  $P=0.04$ ). All HCV transmissions were from mothers with HCV RNA viral loads over 2,000,000 copies/mL (Thomas 1998b).

A mother's co-infection was found not to be a significant risk factor for transmitting HCV in a New York multicenter study conducted by Granovsky and colleagues (Granovsky 1998). Five of 73 (7%) coinfecting mothers transmitted HCV to their infants compared to 2 of 49 HCV+/HIV- mothers ( $P=0.7$ ). There was also no significant difference in HCV viral load levels between transmitting and non-transmitting mothers. Lastly, an interesting finding about HIV and its possible enhancement of HCV transmission comes from the largest HCV vertical transmission study yet conducted. In a cohort of 370 anti-HCV-positive women, 15 (4.0%) were coinfecting with HIV but did not transmit HCV to their infants. All of the coinfecting women

were receiving HIV antiretroviral therapy during their pregnancy, and investigators believe that reducing HIV-related immunosuppression may have affected HCV titers and the consequent likelihood of HCV transmission (Conte 2000).

A handful of studies have documented modest increases in the rate of HCV vertical transmission to infants delivered vaginally rather than by caesarean section (Tovo 1997; Granovsky 1998). However, larger studies with more patients have not observed any differences due to mode of delivery (Resti 1998; Mast 1999; Conte 2000). HCV transmission through breast feeding has not been considered a route likely source of infection for infants (Kumar 1998). In the vast majority of studies that evaluated breast feeding in infants born to HCV-positive women, no difference has been observed between bottle and breast feeding (Resti 1998; Tovo 1997; Mast 1999; Conte 2000). In fact, the CDC and the American Academy of Pediatrics do not feel that there is a risk from either breast feeding or vaginal delivery and have chosen not to recommend caesarean section or bottle feeding to HCV-infected mothers without HIV (CDC 1998).

Finally, no diagnostic screening criteria for perinatal HCV infection currently exist. Many studies have theorized about the optimal time to determine the infection status of an infant because various patterns have been observed in both infected and uninfected infants of HCV-positive mothers. For example, Conte and colleagues documented that the rate of HCV-positivity at birth for 366 newborns was 100%, but decreased to 90%, 63%, 16%, and 9% after 4, 8, 12, and 18 months respectively (Conte 2000). HCV RNA was detectable in 18 (4.9%) infants at birth, but 16 became negative by month four; and 6 infants who tested negative at birth became positive at month four. With similar findings from a recent CDC-sponsored study, Mast and colleagues concluded that "anti-HCV testing may not be a reliable marker of perinatal HCV infection until the infant is 2 years of age" (Mast 1999).

There appear to be as many knowns as unknowns with regard to HCV vertical transmission and the exact prognostic factors which lead to infection. According to Johns Hopkins' David Thomas:

Without a randomized clinical trial, perinatal transmission cofactors will be difficult to evaluate conclusively. Even multiple consistent results from observational studies could be misleading....The most conclusive randomized trial would have to include more than 800 mother-infant pairs to detect a twofold increase in transmission with 80% power. (Thomas 1998a)

### **Sexual Transmission**

Is HCV sexually transmissible? For the past 11 years, this question has been widely studied and heavily debated among researchers from Atlanta to Australia. Miriam Alter and colleagues in a 1989 JAMA paper reported the first study to suggest that heterosexual transmission may play an important role in the spread of NANB hepatitis (Alter 1989). In this study, of 140 patients with HCV, 64 patients (46%) had no commonly recognized percutaneous risk factors; 7 (11%) had had multiple sexual partners and were believed to have contracted HCV through sex. Since then, there have been at least 50 articles published (not to mention scads of letters to the editors) in major hepatology, virology, and HIV-related peer-reviewed medical journals which have looked at HCV sexual transmission among the general population, hemophiliacs, heterosexuals, homosexuals, people with HIV and STDs, and sex workers.

### **Heterosexuals in Long-term Monogamous Relationships**

Sexual transmission of HCV between heterosexual couples in long-term monogamous relationships who have no identifiable percutaneous risk factors (or after stratifying for such factors) appears to be quite infrequent. Gordon and colleagues reported that 2 of 42 (4.8%) heterosexual adults who were in stable sexual relationships with an HCV-infected partner developed HCV (Gordon 1992). Since one of the individuals had a risk factor for HCV, only 1 of 42 individuals (2.4%; 95% CI, 0.6-12.9%) was thought to have been infected through sex. Osmond and colleagues found the incidence of HCV to be high in their cohort of 170 men and 170 women in sexual partnerships: 31 (18%) of the women and 56 (33%) of the 170 men tested anti-HCV-positive (Osmond 1993b). Sexual transmission was not demonstrated because IV drug use, a history of a blood transfusion, or hemophilia treatment were associated with all but 2 of 87 HCV infections. No HCV transmissions were documented in a study of 94 husbands whose spouses all contracted HCV from contaminated anti-D immunoglobulin (Meisel 1995) nor in an Australian study which tested 50 heterosexual partners of HCV viremic individuals (Brester 1993). In Asian countries, however, higher rates of sexual transmission in married heterosexual couples have been reported, ranging from 8.8 to 28% (Chang 1994; Nakashima 1995; Chayama 1995).

Two large studies looking at the sexual transmission among female sex partners of HCV-infected

hemophiliac males documented a low transmission rate. Eyster and colleagues and Brettler and colleagues found a sexual transmission rate of 2.6% and 2.7%, respectively (Eyster 1991; Brettler 1992).

In an elegant, high-tech study, Zylberberg and colleagues conducted genotypic, sequence and phylogenetic analyses on 24 anti-HCV-positive couples to ascertain if they harbored the same strain of virus (Zylberberg 1999). The mean duration of the partnership was 12 years (range 1 to 36). Serum HCV RNA was detected in both partners in 18 (75%) of the couples and in only one partner in the other 6 (25%) couples. In the 18 couples who had detectable HCV RNA in both spouses, 11 of 18 (61%) had the same genotype while 7 of 18 (39%) did not. Phylogenetic analysis was conducted in 7 of the 12 genetically concordant couples. In three couples, HCV strains differed by 1 to 3 nucleotides with a sequence similarity of 98% (evolutionary distance 0.065) suggesting that these spouses were infected by a common source. The other four couples differed by 4 to 15 nucleotides (evolutionary distance 0.0129) and thus their strains were considered unrelated. Sexual transmission of HCV was, however, ruled out in the three matched couples because all six spouses had at least one identifiable parental risk factor.

### Sex Workers

A small number of studies, mostly outside the U.S., have been conducted among sex workers to ascertain if they are at higher risk for HCV transmission. Wu and colleagues studied 622 sex workers in Taiwan for anti-HCV antibodies and risk factors of transmission (Wu 1993). Seventy-four (12%) of the women were anti-HCV-positive and 60 (~10%) were HCV RNA-positive. In a multivariate analysis, history of paid sex for longer than six months and blood transfusion were positively associated with anti-HCV ( $P < 0.001$ ). Less than 20% of the HCV-infected sex workers had undergone a blood transfusion. Lissen and colleagues tested 310 Spanish female sex workers and 88 of their clients for anti-HCV (Lissen 1993). All denied prior transfusion or intravenous drug use. The prevalence of anti-HCV by ELISA, confirmed by a RIBA-2, was 6.4% among the sex workers and 6.8% among the clients. In contrast to these two studies, a very low rate of HCV positivity was reported in a study of Peruvian sex workers (Hymans 1993). Of 966 sex workers tested, only 7 (0.7%) had antibodies to HCV.

### Homosexuals, People with HIV and STDs, and Sex Partners of IDUs

The prevalence of HCV appears to be substantially higher in homosexuals (men who have sex with men [MSM]), and people with HIV and STDs than in the general population. Below is an analysis of 16 studies, most in high-risk populations, which document either sexual transmission or an infectious disease as a risk factor for HCV.

Sexual Transmission or an Infectious Disease as a Risk Factor for HCV					
MSM	US	926	15 (1.6%)	HAV	Donahue 1991
STD Clinic (MSM & HET)	UK	MSM 275 HET 771	19 (6.9%) 8 (1.0%)	HIV+, HBV+, and lifetime number of STDs (MSM only)	Tedder 1991
Female (F) sex partners of male (M) hemophiliacs	US	F 234 M 231	5 (2.6%)	Sex with an HCV+/HIV+ M: 3% HCV+ for sex with HIV+/HCV+ M vs. 0% with HIV-/HCV+ M	Eyster 1991 <sup>^</sup>
MSM	US	735	34 (4.6%)	≥ 50 sex partners/year ≥ 25 oral receptive partners per year	Osmond 1993
MSM, prostitutes, & HET partners of an HCV+ person	Spain	MSM 168 HET 147	7 (4.2%) 11 (7.4%)	Sex with HCV+/HIV+ (9.2% vs. 4.1% for HET sex with HCV+/HIV+ vs. HCV+ only)	Lissen 1993 <sup>^</sup>
Prostitutes	Taiwan	622	74 (12%)	History of paid sex ≥ 6 months	Wu 1993

STD Clinic (MSM & HET)	US	1,257	122 (9.7%)	M = $\geq 29$ years & lack of condom use F = $\geq 29$ years & $\geq 1$ sex partner prior month	Thomas 1994
STD Clinic (MSM & HET)	US	1,039: M 555 F 484	M 37 (7%) F 19 (4%)	Age $\geq 28$ ; $\geq 24$ lifetime sex partners; HIV+; Trichomonas infection; cigarette smoking. Omitting HIV+ showed MSM significant risk (p = 0.012)	Thomas 1995
MSM	Australia	1,038	79 (7.6%)	HIV+	Bodsworth 1996
Women with or at risk for HIV	US	296	123 (42%)	HIV+, sex with male IDU, history of gonorrhea, $\geq 35$ years, not graduating high school	Hershow 1996
Volunteer blood donors	US (REDS)	862,398	3,126 (0.36%)	HTLV I or II, HBV or HIV (OR, 10.4)	Murphy 1996
HCV+ blood donors & HCV- controls	Canada	HCV+ 267 HCV- 1,068	N/A	Sex with an IDU (OR, 6.9)	Delage 1999
HCV+ blood donors & HCV- controls	US (REDS)	HCV+ 2,316 HCV- 2,316	N/A	Sex with an IDU (OR, 6.3)	Murphy 2000
MSM	Canada	120 HIV+ 112 HIV-	20 (8.6%): HIV+ 14% HIV- 2.7%	For the HIV+ men: Fisting (OR, 4.06) Rimming (trend)	Craib 2000
^ = subset analysis; BT; blood transfusion; MSM = men having sex with men; HET = heterosexual; STD = sexual transmitted disease; ID = Infectious disease					

In recent NEJM letters to the editor, CDC's Miriam Alter and Edward Murphy and colleagues from the NHLBI REDS sparred over the plausibility of HCV sexual transmission, citing selected studies to make their cases. Murphy started with, "[a] review of the literature suggests that sexual transmission of HCV is inefficient at best," and Alter countered that "results of both incidence and prevalence studies [show] that high-risk sexual behavior accounts for 15 to 20 percent of HCV infections in the United States." (Murphy 1999; MJ Alter 1999a).

Both make statements that are far too general and more importantly do not acknowledge that sex is not a defined act; it means different things to different people, and sexual practices can and do differ widely from household to household. These limitations (i.e., lack of detailing sexual acts or high-risk behavior) are common in a majority of studies reviewed. While some studies document that sleeping with an HIV-positive or HBV-positive individual is a risk factor for transmission, we don't know what was done in bed (if it was in a bed) that created the extra risk. Too often, "high-risk sexual behavior" and "sexual promiscuity" are not defined, nor are we privy to whether condoms were used. Thus, it is the particular sexual act (e.g., insertive vaginal or anal intercourse, oral sex, anal fisting, etc.) that needs to be explored for its risk of HCV transmission. Murphy's belief that sexual transmission is "inefficient at best" is surprising since it contradicts his 1996 JAMA and 2000 Hepatology papers on risk factors for HCV transmission in the REDS cohort, which document that HIV and HBV, and sex with an IDU, respectively, are risk factors in multivariate analyses (Murphy 1996, 2000).

Murphy's argument against sexual transmission-even in homosexuals-is weakly supported by a single review article, which fails to note that most studies rejecting the risk of sexual transmission were too small and underpowered to detect such risks (MacDonald 1996). According to Donahue and colleagues, who documented a 1.6% incidence rate of HCV in a cohort of 926 homosexuals, "the small number of HCV-seropositive subjects may have limited the power to identify risk factors for infection" (Donahue 1991).

Likewise, Buchbinder acknowledged that the small sample size of her 1994 study (Buchbinder 1994) may have limited its power to find sexual transmission as a risk factor in the multivariate analysis, even though numerous sex acts were identified in the univariate analysis (Susan Buchbinder, personal communication, 2000).

It is not surprising that the risk of HCV sexual transmission appears greater for homosexuals than for heterosexuals. From HIV studies, we have excellent data documenting that the risk of transmitting HIV is greater for homosexuals than heterosexuals, for women from men than for men from women, and for anal than vaginal intercourse (Padian 1991; Kingsley 1990). Moreover, specific sex acts as well as the physical condition of an individual play major roles in establishing risk. For example, Moss and colleagues in 1987 documented that douching before anal sex (vs. not douching) was independently associated with HIV seropositivity (OR, 2.2-2.8) (Moss 1987). Chmiel and colleagues from the Multicenter AIDS Cohort Study (MACS) examined numerous types of sexual behavior between homosexual men and found that, aside from unprotected receptive anal intercourse, "the factor most strongly associated with prevalent HIV infection according to a multiple logistic regression model was rectal trauma, a composite variable which included receptive anal fisting, enemas before sex, reporting of blood around the rectum, and the observation of scarring, fissures or fistulas on rectal examination (OR, 7.7)." (Chmiel 1987)

While such behaviors are physical symptoms are not universal among all homosexual men, if one partner with HCV has penile sores or ulcers and the other partner has blood around the rectum, fistulas or fissures, it is plausible that there will be blood-to-blood contact and possible HCV transmission. Documentation of specific risk factors like these is necessary in order to 1) elucidate various ways the virus might enter the body; and 2) define specific "high-risk behavior" so that individuals can be counseled about which sexual practices to lower the risk-no matter how small it might be-of contracting HCV.

The CDC states that "data indicate overall that sexual transmission of HCV appears to occur, but that the virus is inefficiently spread through this manner." They do, however, call for further research into this controversial area:

More data are needed to determine the risk for, and factors related to, transmission of HCV between long-term steady partners as well among persons with high-risk sexual practices, including whether other STDs promote transmission of HCV by influencing viral load or modifying mucosal barriers. (CDC 1998)

After this call for more data, it is interesting to see that the CDC in its Recommendations for Prevention and Control of Hepatitis C Virus (HCV) Infection places both "long-term steady partners of HIV-positive persons" and "persons with a history of multiple sex partners or sexually transmitted diseases" in the same category of "persons for whom routine HCV testing is of uncertain need [emphasis added]" (CDC1998).

The CDC and the Infectious Disease Society of America took a more proactive stance in 1999 calling for HIV-infected individuals to be screened for HCV in its revised USPHS/IDSA Guidelines for the Prevention of Opportunistic Infections in People with Human Immunodeficiency Virus (CDC 1999). Acknowledging that many HIV-infected individuals are coinfecting with HCV, the guidelines give a nod to the safer-sex practice of condom use:

Although the efficiency of sexual transmission of HCV remains controversial, safer-sexual practices should be encouraged, and barrier precautions (e.g., latex condoms) are recommended to reduce the exposure of sexually transmitted diseases. (CDC 1999)

Why did it take until 1999 for the CDC to issue such a recommendation? In 1993, University of California-San Francisco (UCSF) epidemiologist Dennis Osmond sounded a calm but serious warning, which appeared to fall on deaf ears:

Despite the infrequency of HCV sexual transmission, sexual behavior may still be an important mode of spread if the pool of asymptomatic but infectious carriers is large. Because HCV infection becomes chronic in a high proportion of cases and subclinical hepatitis may be common, there is reason to believe that this carrier pool could be large, and even a low level of sexual transmission may result in a substantial attributable risk. (Osmond 1993a)

### **A Warning for Veterans**

A fascinating study was recently presented which infers that the rate of HCV infection in U.S. veterans is 10 times higher than in the general population, and that combat blood exposure is a highly significant risk factor for HCV transmission. Briggs and colleagues from Teresa Wright's group at the San Francisco

Veterans Affairs Medical Center (SFVAMC) conducted a study with 791 veterans undergoing routine outpatient phlebotomy at the SFVAMC (Briggs 1999). Participants had their blood screened for anti-HCV positivity by EIA II, which was confirmed by Chiron bDNA. All were asked to answer a detailed questionnaire regarding sociodemographic characteristics and potential HCV risk factors. Of the 791 participants (95% male), 150 (19%) and 110 (13.9%) were anti-HCV-positive and HCV RNA-positive, respectively. The multivariate analysis below documents four significant risk factors, including the surprising finding that those exposed to blood during combat were 2.5 times more likely to develop HCV.

**Risk Factors for HCV Infection in San Francisco Veterans: Multivariate Analysis**

Risk Factor	Relative Risk	95% CI	P
IV drug use	24.74	8.17-74.86	<0.0001
Incarceration >48 hours	3.37	1.36-8.31	<0.0080
Blood transfusion <1992	2.23	0.90-5.53	<0.0820
Combat blood exposure	2.47	1.06-5.73	<0.0350
(Briggs 1999)			

**Conclusion**

The discovery of the HCV virus by molecular techniques and the development of an antibody assay in 1989 were the first steps in understanding and identifying the cause of liver disease in blood transfusion recipients. Since then, the sensitivity and specificity of the EIA has markedly improved, and the screening of blood donors has made the blood supply significantly safer (risk of 0.001% per unit transfused). In the U.S., approximately 2% of the population (four million people) are infected with HCV, and HCV appears to be more common in Blacks and Hispanics. Internationally, the prevalence ranges from 0.1% to 5%, but in Egypt, it is estimated to be 25%. It is almost certain that blood-to-blood contact is the only way to transmit HCV. Intravenous drug use (IVDU) remains the main mode of transmission, with rates of infection ranging from 75% to 92% in various cohorts. Those engaging in IVDU should be tested for HCV and refrain from sharing syringes, cotton, and cooking equipment. The rate of perinatal transmission of HCV is approximately 5%, and the CDC does not feel that there is a risk from either breast feeding or vaginal delivery. The risk of transmitting HCV sexually is a controversial subject. In monogamous heterosexual couples, there appears to be little if no risk, yet in certain populations, including homosexuals and people with HIV or STDs, the risk appears to be 5–15%. Larger studies are needed to determine which sexual practices place individuals at increased risk of contracting HCV. Until then, individuals with “multiple sexual partners” engaging in “high-risk” sexual behavior should always use condoms.

## References

- Abildgaard N, Peterslund NA. Hepatitis C virus transmitted by tattooing needle [letter]. *Lancet* 338:460, 1991.
- Aguelles O, Janot C: Epidemiology of anti-HCV antibodies in France. Viral Hepatitis Study Group of the French Blood Transfusion Society. *Arch Virol Suppl* 4:249-52, 1992.
- Alter MJ, Coleman PJ, Alexander WJ, et al. Importance of heterosexual activity in the transmission of hepatitis B and non-A, non-B hepatitis. *JAMA* 262:1201-5, 1989.
- Alter MJ, Moyer LA: The importance of preventing hepatitis C virus infection among injection drug users in the United States. *J Acquir Immune Defic Syndr Hum Retrovirol* 18 Suppl 1:S6-10, 1998.
- Alter MJ, Kruszon-Moran D, McQuillan GM: Prevalence of Hepatitis C Virus Infection in the United States [letter]. *N Engl J Med* 341:2095, 1999.
- Alter MJ, Kruszon-Moran D, Nainan OV, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. *N Engl J Med* 341:556-62, 1999.
- Alter HJ, Holland PV, Purcell RH, et al. Posttransfusion hepatitis after exclusion of commercial and hepatitis-B antigen-positive donors. *Ann Intern Med* 77:691-9, 1972.
- Alter HJ, Hadler SC, Judson FN, et al. Risk factors for acute non-A, non-B in the United States and association with hepatitis C virus infection. *JAMA* 264:2231-35, 1990.
- Alter HJ: Discovery of non-A, non-B hepatitis and identification of its etiology. *Am J Med* 107(6B):16S- 20S, 1999.
- Arthur RR, Hassan NF, Abdallah MY, et al. Hepatitis C antibody prevalence in blood donors in different governorates in Egypt. *Trans R Soc Trop Med Hyg* 91:271-4, 1997.
- Aymard JP, Botte C, Contal P, et al. Seroprevalence of hepatitis C antibodies among blood donors. Study of second generation ELISA and RIBA tests and surrogate markers. *Pathol Biol Paris* 41:149-53, 1993.
- Bellentani S, Tiribelli C, Saccoccio G, et al. Prevalence of chronic liver disease in the general population of northern Italy: the Dionysus Study. *Hepatology* 20(6):1442-9, 1994.
- Bellentani S, Pozzato G, Saccoccio G, et al. Clinical course and risk factors of hepatitis C virus related liver disease in the general population: report from the Dionysus study. *Gut* 44:874-80, 1999.
- Bodsworth NJ, Cunningham P, Kaldor J, et al. Hepatitis C virus infection in a large cohort of homosexually active men: independent associations with HIV-1 infection and injecting drug use but not sexual behavior. *Genitourin Med* 72:118-22, 1996.
- Bresters D, Mauser-Bunschoten EP, Reesink HW, et al. Sexual transmission of hepatitis C virus. *Lancet* 342:210-1, 1993.
- Brettler DB, Mannucci PM, Gringeri A, et al. The low risk of hepatitis C virus transmission among sexual partners of hepatitis C-infected hemophilic males: an international, multicenter study. *Blood* 80:540-3, 1992.
- Briggs ME, Bzowej N, Baker C, et al. The prevalence and risk factors for hepatitis C virus (HCV) infection in U.S. Veterans [abstract]. *Hepatology* 30:504A, 1999.
- Broers B, Junet C, Bourquin M, et al. Prevalence and incidence rate of HIV, hepatitis B and C among drug users on methadone maintenance treatment in Geneva between 1988 and 1995. *AIDS* 12:2059-66, 1998.
- Buchbinder SP, Katz MH, Hessel NA, et al. Hepatitis C virus infection in sexually active homosexual men. *J Infect* 29:263-9, 1994.
- Centers for Disease Control and Prevention. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. *MMWR* 47(No. RR-19):1-39, 1998.
- Centers for Disease Control and Prevention. 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus: U.S. Public Health Service (USPHS) and Infectious Disease Society of America (IDSA). *MMWR* 48(RR-10), 1999.
- Chang TT, Liou TC, Young KC, et al. Intrafamilial transmission of hepatitis C virus: the important role of inapparent transmission. *J Med Virol* 42:91-6, 1994.
- Chayama K, Kobayashi M, Tsubota A, et al. Molecular analysis of intraspousal transmission of hepatitis C virus. *J Hepatol* 22:431-9, 1995
- Chmiel JS, Detels R, Kaslow RA, et al. Factors associated with prevalent human immunodeficiency virus (HIV) infection in the Multicenter AIDS Cohort Study. *Am J Epidemiol* 126:568-77, 1987.
- Choo QL, Kuo G, Weiner AJ, et al. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science* 244:359-62, 1989.
- Conte D, Fraquella M, Prati D, et al. Prevalence and clinical course of chronic hepatitis C virus (HCV) infection and rate of HCV vertical transmission in a cohort of 15,250 pregnant women. *Hepatology* 31:751-755, 2000.
- Conry-Cantilena C, VanRadden M, Gible J, et al. Routes on infection, viremia, and liver disease in blood donors found to have hepatitis C virus infection. *N Engl J Med* 334:1691-6, 1996.
- Craib KJP, Sherlock CH, Hogg RS, et al. Risk factors for hepatitis C virus (HCV) infection in a well- characterized long-term cohort of homosexual men [abstract]. 7th Conference on Retroviruses and Opportunistic Infections, San Francisco, 2000.
- Delage G, Infante-Rivard C, Chiavetta JA, et al. Risk factors for acquisition of hepatitis C virus infection in blood donors: results of a case-control study. *Gastroenterology* 116:893-9, 1999.
- Donahue JG, Nelson KE, Munoz A, et al. Antibody to hepatitis C virus among cardiac surgery patients, homosexual men, and intravenous drug users in Baltimore, Maryland. *Am J Epidemiol* 134:1206-11, 1991.
- Donahue JG, Munoz A, Ness PM, et al. The declining risk of post-transfusion hepatitis C virus infection. *N Engl J Med* 327:369-373, 1992.
- Dore GJ, Kaldor JM, McCaughan GW. Systematic review of role of polymerase chain reaction in defining infectiousness among people infected with hepatitis C virus. *BMJ* 315: 333-337, 1997.

Esteban JI, Esteban R, Viladomiu L, et al. Hepatitis C virus antibodies among risk groups in Spain. *Lancet* 2:294-7, 1989.

Esteban JI, Lopez-Talavera JC, Genesca J, et al. High rate of infectivity and liver disease in blood donors with antibodies to hepatitis C virus. *Ann Intern Med* 115:443-9, 1991.

Eyster ME, Alter HJ, Aledort LM, et al. Heterosexual co-transmission of hepatitis C virus (HCV) and human immunodeficiency virus (HIV). *Ann Intern Med* 115:764-8, 1991.

Frank C, Mohamed MK, Strickland GT, et al. The role of parenteral antischistosomal therapy in the spread of hepatitis C virus in Egypt. *Lancet* 355:887-91, 2000.

Garfein RS, Vlahov D, Galai N, et al. Viral infections in short-term injection drug users: the prevalence of the hepatitis C, hepatitis B, human immunodeficiency, and human T-lymphotropic viruses. *Am J Public Health* 86:655-61, 1996.

Garfein RS, Doherty MC, Monterroso ER, et al. Prevalence and incidence of hepatitis C virus infection among young adult injection drug users. *J Acquir Immune Defic Syndr Hum Retrovirol* 18 Suppl 1:S11- 9, 1998.

Gordon SC, Patel AH, Kulesza GW, et al. Lack of evidence for the heterosexual transmission. *Am J Gastroenterol* 87:1849-51, 1992.

Granovsky MO, Minkoff HL, Tess BH, et al. Hepatitis C virus infection in the mothers and infants cohort study. *Pediatrics* 102:355-359, 1998.

Hershow RC, Kalish LA, Sha B, et al. Hepatitis C virus infection in Chicago women with or at risk for HIV infection: evidence for sexual transmission. *Sex Transm Dis* 25:527-32, 1998.

Hillemanns P, Langenegger P, Langer BC, et al. Prevalence and follow-up of hepatitis C virus infection in pregnancy. *Z Geburtsh Neonatol* 202:127-130, 1998.

Hyams KC, Phillips IA, Tejada A, et al. Three-year incidence study of retroviral and viral hepatitis transmission in a Peruvian prostitute population. *J Acquir Immune Defic Syndr* 6:1353-7, 1993.

Kingsley LA, Rinaldo CR Jr., Lyter DW, et al. Sexual transmission efficacy of hepatitis B virus and human immunodeficiency virus among homosexual men. *JAMA* 264:230-4, 1990.

Kumar RM, Shahul S. Role of breast-feeding in transmission of hepatitis C virus to infants of HCV-infected mothers. *J Hepatol* 29:191-7, 1998.

Kuo G, Choo QL, Alter HJ, et al. An assay for circulating antibodies to a major etiologic virus of human non-A, non-B hepatitis. *Science* 1989;244:362-4.

Leikin EL, Reinius JF, Schmell E, et al. Epidemiologic predictors of hepatitis C virus infection in pregnant women. *Obstet Gynecol* 84:529-534, 1994.

Lin HH, Kao JH, Hsu HY, et al. Possible role of high-titer maternal viremia in perinatal transmission of hepatitis C virus. *J Infect Dis* 169:638-41, 1994.

Lissen E, Alter HJ, Abad MA, et al. Hepatitis C virus infection among sexually promiscuous groups and the heterosexual partners of hepatitis C virus infected index cases. *Eur J Clin Microbiol Infect Dis* 12:827-31, 1993.

MacDonald M, Crofts N, Kaldor J. Transmission of hepatitis C virus: rates, routes, and cofactors. *Epidemiol Rev* 18:137-48, 1996.

Malbaie M, Biggar RJ, Want in P, et al. Sexual transmission of hepatitis C virus: cohort study (1981-9) among European homosexual men. *BMJ* 301:210-2, 1990.

Marcellin P, Bernuau J, Martinot-Peignoux M, et al. Prevalence of hepatitis C virus infection in asymptomatic anti-HIV1 negative pregnant women and their children. *Dig Dis Sci* 38:2151-2155, 1993.

Marranconi F, Fabris P, Stecca C, et al. Prevalence of anti-HCV and risk factors for hepatitis C virus infection in healthy pregnant women. *Infection* 22:333-337, 1994.

Mast EE, Hwang L-Y, Seto, D, et al. Perinatal hepatitis C virus transmission: maternal risk factors and optimal timing of diagnosis [abstract:]. *Hepatology* 30:499A, 1999.

Meisel H, Reap A, Flatus B, et al. Transmission of hepatitis C virus to children and husbands by women infected with contaminated anti-D immunoglobulin. *Lancet* 345:1209-11, 1995.

Morales MA, Pineau JA, Leal M, et al. Prevalence of antibodies against hepatitis C virus in a sample of homosexual males. (Prevalence de anticuerpos frente al virus de la hepatitis C en un colectivo de varones homosexuales.) *Med Clin (Barcelona)* 100:50-2, 1993.

Moss AR, Osmond D, Bacchetti P, et al. Risk factors for AIDS and HIV seropositivity in homosexual men. *Am J Epidemiol* 125:1035-47, 1987.

Munoz-Gomez R, Garcia-Monzon C, Garcia-Buey L, et al. Hepatitis C virus infection in Spanish volunteer blood donors: HCV RNA analysis and liver disease. *Eur J Gastroenterol Hepatol* 8:273-7, 1996.

Murphy EL, Bryzman S, Williams AE, et al. Demographic determinants of hepatitis C virus seroprevalence among blood donors. *JAMA* 275:995-1000, 1996.

Murphy EL, Bryzman S, Williams AE: Prevalence of Hepatitis C Virus Infection in the United States [letter]. *N Engl J Med* 341:2093, 1999.

Murphy EL, Bryzman SM, Glynn SA, et al. Risk factors for hepatitis C virus infection in United States blood donors. *Hepatology* 31:756-62, 2000.

Nakashima K, Ikematsu H, Hayashi J, et al. Intrafamilial transmission of hepatitis-C virus among the population of an endemic area of Japan. *JAMA* 274:1459-61, 1995.

Ohto H, Terazawa S, Nobuhiko S, et al. Transmission of hepatitis C virus from mothers to infants. *N Engl J Med* 330:744-50, 1994.

Osmond DH, Charlebois E, Sheppard HW, et al. Comparison of risk factors for hepatitis C and hepatitis B virus infection in homosexual men. *J Infect Dis* 67:66-71, 1993.

Osmond DH, Padian NS, Sheppard HW, et al. Risk factors for hepatitis C virus seropositivity in heterosexual couples. *JAMA* 269:361-5, 1993.

Padian NS, Shiboski SC, Jewell NP. Female-to-male transmission of human immunodeficiency virus. *JAMA*

266:1664-7, 1991

Pallas JR, Farinas-Alvarez C, Prieto D, et al. Coinfections by HIV, hepatitis B and hepatitis C in imprisoned injecting drug users. *Eur J Epidemiol* 15:699-704, 1999.

Puro V, Petrosillo N, Ippolito G. Risk of hepatitis C seroconversion after occupational exposures in healthcare workers. *Am J Infect Control* 23:273-7, 1995.

Resti M, Azzari C, Mannelli F, et al. Mother to child transmission of hepatitis C virus: prospective study of risk factors and timing of infection in children born to women seronegative for HIV-1. Tuscany Study Group on Hepatitis C Virus Infection. *BMJ* 317:437-41, 1998. Sabatino G, Ramenghi LA, di Marzio M, et al. Vertical transmission of hepatitis C virus: an epidemiologic study on 2980 pregnant women in Italy. *Eur J Epidemiol* 12:443-47, 1996. Salmeron FJ, Palacios A, Perez-Ruiz M, et al. Epidemiology, serological markers, and hepatic disease of anti-HCV ELISA-2-positive blood donors. *Dig Dis Sci* 41:1933-8, 1996.

Sreiber GB, Busch MP, Kleinman SH, et al. The risk of transfusion-transmitted viral infections. *N Engl J Med* 334:1685-90, 1996.

Soto B, Rodrigo L, Garcia-Bengoechea M, et al. Heterosexual transmission of hepatitis C virus and the possible role of coexistent human immunodeficiency virus infection in the index case. A multicentre study of 423 pairings. *J Intern Med* 236:515-9, 1994.

Tedder RS, Gilson RJ, Briggs M, et al. Hepatitis C virus: evidence for sexual transmission. *BMJ* 302:1299-302, 1991. Thomas DL, Factor SH, Kelen GD, et al. Viral hepatitis in health care personnel at the Johns Hopkins Hospital. *Arch Intern Med* 153:1705-12, 1993.

Thomas DL, Cannon RO, Shapiro CN, et al. Hepatitis C, hepatitis B, and human immunodeficiency virus infections among non-intravenous drug-using patients attending clinics for sexually transmitted diseases. *J Infect Dis* 169:990-5, 1994.

Thomas DL, Zenilman JM, Alter HJ, et al. Sexual transmission of hepatitis C virus among patients attending sexually transmitted diseases clinics in Baltimore--an analysis of 309 sex partnerships. *J Infect Dis* 171:768-75, 1995.

Thomas DL, Gruninger SE, Siew C, et al. Occupational risk of hepatitis C infections among general dentists and oral surgeons in North America. *Am J Med* 100:41-5, 1996.

Thomas DL. Mother-infant hepatitis C transmission: second generation research [editorial]. *Hepatology* 29:992-3, 1998.

Thomas DL, Villano SA, Riester KA, et al. Perinatal transmission of hepatitis C virus from human immunodeficiency virus type 1-infected mothers. *J Infect Dis* 177:1480-88, 1998.

Thompson SC, Hernberger F, Wale E, et al. Hepatitis C transmission through tattooing: a case report. *Aust N Z J Public Health* 20:317-8, 1996.

Tovo P, Paloma E, Ferraris G, et al. Increased risk of maternal infant hepatitis C virus transmission for women coinfecting with human immunodeficiency virus type 1. Italian Study Group for HCV Infection in Children. *Clin Infect Dis* 25:1121-24, 1997.

Tumminelli F, Marcellin P, Rizzo S, et al. Shaving as potential source of hepatitis C virus infection [letter]. *Lancet* 345:658, 1995.

van Beek I, Dwyer R, Dore GJ, et al. Infection with HIV and hepatitis C virus among injecting drug users in a prevention setting: retrospective cohort study. *BMJ* 317:433-7, 1998.

van den Hoek JA, van Haastrecht HJ, Goudsmit J, et al. Prevalence, incidence, and risk factors of hepatitis C virus infection among drug users in Amsterdam. *J Infect Dis* 162:823-6, 1990.

Weinstock HS, Bolan G, Reingold AL, et al. Hepatitis C virus infection among patients attending a clinic for sexually transmitted diseases. *JAMA* 269:392-4, 1993.

Wu JC, Lin HC, Jeng FS, et al. Prevalence, infectivity, and risk factor analysis of hepatitis C virus infection in prostitutes. *J Med Virol* 39:312-7, 1993.

Zanetti AR, Tanzi E, Paccagnini S, et al. Mother-to-infant transmission of hepatitis C virus. *Lancet* 345:289-91, 1995.

Zeldis JB, Jain S, Kuramoto IK, et al. Seroepidemiology of viral infections among intravenous drug users in northern California. *West J Med* 156:30-5, 1992.

Zylberberg H, Thiers V, Lagorce D, et al. Epidemiological and virological analysis of couples infected with hepatitis C virus. *Gut* 45:112-6, 1999.