REVIEW

Is Sexual Contact a Major Mode of Hepatitis C Virus Transmission?

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Medical opinion varies considerably regarding the transmission of hepatitis C virus (HCV) through sexual contact. Based on the study design, representativeness of the study population, and the methods used for case ascertainment, we analyzed 80 qualifying reports regarding the evidence for or against sexual transmission. Regarding heterosexual transmission, the weight of evidence is that there is no increased risk of sexual transmission of HCV among heterosexual couples in regular relationships. This risk increases among persons with multiple sexual partners (adjusted odds ratio [aOR] 2.2-2.9), but this association may be confounded by increased likelihood of injection drug use with increased number of partners. There appears to be a real increased risk for women coinfected with human immunodeficiency virus (HIV) or other sexually transmitted infections (aOR 3.3-3.9) and especially for HIV-infected gay men who are having sex with one another compared with HIV-uninfected men (aOR 4.1-5.7). HIV-infected gay men increase their risk of such transmission in association with practices that lead to mucosal trauma (multiple sexual partners, fisting, use of sex toys) and the presence of genital ulcerative disease. *Conclusion:* This review should inform, and not distract from, recommendations to reduce the risk of HCV transmission. Health care providers need to pay special attention to sexual transmission of HCV among HIV-infected individuals. (HEPATOLOGY 2010;00:000-000)

Hepatitis C virus (HCV) infection is a bloodborne infection transmitted mainly through injection drug use (IDU), blood transfusions, organ transplantations, accidental needle sticks,[1,2] and other parenteral exposures, including inappropriate use or reuse of needles and syringes in health care settings.[3,4] Sexual transmission is a controversial mode of HCV transmission that has received considerable attention among health care providers and the lay public. For example, in 2009, the Centers for Disease Control and Prevention's Division of Viral Hepatitis received over 2,600 telephone and email inquiries about hepatitis C. When looking at available data that capture responses to inquiries, transmission modes of hepatitis C and the sexual transmission of hepatitis C infection were among the top used responses (Centers for Disease Control and Prevention, unpublished reports).

The possibility of sexual transmission of HCV infection is supported by the isolation of HCV RNA from semen and cervical smears in some studies[5-7] but not others.[8,9] Furthermore, although the sexual transmission of the same hepatitis C virus strain, as determined by molecular analysis, has been documented in some case reports and case series,[10-20] the magnitude of the risk varies depending on the quality of the study design, the likelihood of unmeasured parenteral routes of transmission, and the level of risk behavior of the study participants.

Given the conflicting evidence and the ongoing inquiries, we conducted a review of the literature to summarize the best available data on the risk of HCV transmission through sexual activity.

Subjects and Methods

Study Identification. Studies addressing the sexual transmission of hepatitis C were identified through a

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injection drug use; MSM, men who have sex with men; STI, sexually transmitted infection.

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comprehensive literature search on PubMed of English-language articles published between 1995 and 2009. We excluded studies published prior to 1995 because hepatitis C case ascertainment depended on laboratory tests that were not as accurate as currently available ones. Search terms such as *hepatitis C*, *HCV*, *sexual transmission*, and *men who have sex with men* were used to identify potentially relevant papers. Cited references in relevant articles were also carefully assessed for inclusion.

Study Rating. Each article was evaluated based on the strength of the study design, representativeness of the study population, adjustment or control of potentially confounding HCV risk factors (such as IDU), and mode of ascertaining hepatitis C infection. The literature search yielded 535 published reports, 444 of which were excluded because they did not address the risk of sexual transmission of HCV. Of the remaining 91 reports, 11 were excluded because they were review papers (n = 8) or editorials and author responses (n = 3). Hence, a total of 80 articles were eligible for inclusion. The magnitude of the risk of sexual transmission of HCV was assessed by presenting the adjusted odds ratios (aORs) obtained from the studies that controlled for the most common routes of HCV transmission.

Results

Heterosexual Transmission. Studies addressing heterosexual transmission of HCV distinguished among three types of sexual contacts: sexual contacts within regular partnerships; sexual contacts with multiple partners; and sexual contacts among persons with preexisting sexually transmitted infections (STIs) and/or human immunodeficiency virus (HIV). Table 1 summarizes major studies that assessed the risk of heterosexual transmission of HCV infection among these different groups.

Several large prospective cohort studies did not show an increased risk for HCV transmission among heterosexual discordant couples (married or steady partners), even after 10 or more years of observation.[21-24] In these studies combined, there was no increased risk of sexual transmission of HCV, even after an estimated 750,000 vaginal and anal contacts between couples; accordingly, the probability of such transmission was less than 1 in 10 million sex contacts. Cross-sectional studies reported HCV prevalence rates among regular partners of infected persons varying between 2% and 10%.[21,25,26] However, no association was found between HCV infection and sexual transmission between partners in regular relationships after controlling for other risk factors.[25-32] Three studies documented the presence of the same virus in very few couples by molecular analysis and attributed this to sexual transmission of HCV,[33-35] but could not definitely exclude other common exposures.

A potentially confounding factor in the sexual transmission of HCV in heterosexual couples is the duration of the relationship, an index of the number of sexual exposures to HCV from an infected partner. Whereas a few studies found an increased risk of acquiring HCV infection with a longer relationship,[28,35-37] other larger studies that controlled for age did not find a significant association between the duration of the relationship and HCV infection.[26,27,38,39] The higher prevalence of HCV infection in older couples may represent a cohort effect (in which couples of the same age might be exposed to common sources of infection or common practices, such as the reuse of nondisposable but contaminated medical equipment), as was reported in Spain[40] and Taiwan.[41]

Unlike couples in regular relationships, persons having multiple sexual partners have more than twice the likelihood of acquiring HCV infection (aOR 2.2-2.9).[42-45] Notably, a study conducted among pregnant women in Spain showed that women who had unprotected sexual relations with two to four partners were almost three times (aOR 2.8, 95% confidence interval [CI] 1.1-6.9) more likely to acquire HCV than women with only one steady partner.[42]

Data regarding heterosexual transmission of hepatitis C should be interpreted with caution, however. Three large Italian cross-sectional studies showed that the risk of spousal transmission could also be explained by the common practice of sharing syringes.[25,30,36] Furthermore, a recent analysis of acute HCV infections in the United States has indicated that increased numbers of sexual partners correlates with increased likelihood of injection drug use (Monina Klevens, Centers for Disease Control and Prevention, unpublished data).

The presence of preexisting STIs has also been found to increase the risk of acquiring HCV by heterosexual contact.[46,47] A cross-sectional study in India showed that men infected with herpes simplex virus 2 were almost four times more likely to have HCV than men without herpes simplex virus 2 infection (aOR 3.85, 95% CI 1.18- 12.6).[47] Similarly, individuals with *Trichomonas* infection were much more likely to acquire HCV than individuals without an STI (aOR 3.3, 95% CI 1.7-6.3).[46]

More unequivocal is the risk of heterosexual transmission to those who are infected with HIV. Two cross-sectional studies confirm a substantial increase in

Table 1. Selected Studies Assessing Heterosexual Transmission of Hepatitis C

Study	Country (Years of Study)	Study Sample	Sample Size (% HIV-Positive)	HCV Prevalence	HCV Incidence (Cases per 100 Person-Years)	Phylogenetic Testing*	Sexual Transmission Reported as a Risk Factor (aOR [95% CI])
Cohort studies							
Vandelli et al. (21)	Italy (1991-2001)	Monogamous couples	967 (0%)	3.4%	0.037	Yes	No
Marincovich et al. (22)	Spain (1991-2001)	Couples	171 (0.6%)	–	0.0	No	No
Kao et al. (33)	Taiwan (1990-1997)	Spouses	112	–	0.233	Yes	Yes
Case-control studies							
Salleras et al. (42)	Spain (1992)	Pregnant women	43 cases,172 controls	–	–	No	Yes if unprotected sex with $\geq$2 sexual partners (2.9 [1.1-7.4])
Mele et al. (43)	Italy (1985-1996)	Acute HCV surveillance data	708 cases; 3,746 controls	–	0.001	No	Yes if unprotected sex with multiple sexual partners (2.2 [1.6-3.0])
Cross-sectional studies							
Stroffolini et al. (25)	Italy (1994-1996)	Couples	311	10.3%	–	No	No
Tahan et al. (26)	Turkey (1999-2002)	Spouses	600	2.0%	–	No	No
Atome et al. (27)	Gabon	Household	195	6.7%	–	Yes	No
La Torre et al. (28)	Italy (1995-2000)	Household	259	8.9%	–	No	No
Brusaferro et al. (29)	Italy (1994-1995)	Household	514	10.3%	–	No	No
Caporaso et al. (30)	Italy (1995)	Household	1,379	7.3%	–	No	No
Feldman et al. (44)	United States (1990-1991)	Women engaging in high-risk behavior	502† (2.0%)	1.6%	–	No	Yes (14.2 [1.8-642.5])
Hershow et al. (48)	United States (1994-1995)	Women with HIV or at high risk for HIV infection	296 (82.1%)	42.0%	–	No	Yes (2.7 [1.1-7.0])
Frederick et al. (49)	United States (1994-2002)	Non-IDU women	3,636 (74.3%)	31.5%	–	No	Yes among HIV-positive women (1.9 [1.2-2.9])

*To characterize specimens by molecular means.
†No confirmatory HCV testing was performed.

risk of acquiring HCV infection among heterosexual persons with preexisting HIV, particularly among those engaging in high-risk sexual behaviors and having unprotected sex with multiple sexual partners (Table 1).[48,49] Notably, the large Women's Interagency HIV Study found that, controlling for IDU, HIV-infected women were still almost twice as likely as HIV-negative women to acquire HCV (aOR 1.9, 95% CI 1.2-2.9).[49] Likewise, a cross-sectional study among STD clinic attendees in Baltimore showed a four-fold increase in the risk of HCV infection among HIV-infected patients compared with those who were HIV-seronegative (aOR 4.4, 95% CI 1.9-10.3).[46] In a study of hemophilic men and their partners[23] in which unacknowledged IDU was unlikely to be a confounding variable, 6% of hemophiliac men who were coinfected with HIV compared with only 2% of the men infected with HCV alone transmitted HCV to their spouses. In contrast, a smaller cohort study did not show evidence of sexual transmission of HCV from partners who were both HCV/HIV-coinfected.[22]

Homosexual Transmission. Incidence rates of HCV infection among HIV-uninfected men who have sex with men (MSM) have varied between zero cases per 100 person-years in Amsterdam[50] to 1.5 cases per 1,000 person-years in the United Kindgdom.[51] The Omega Cohort Study, the only study that has included a large sample of MSM and controlled for all other HCV risk factors, did not find an increased risk for HCV infection among HIV-uninfected MSM, even among those engaging in risky sexual behaviors such as having multiple partners or unprotected anal sex[52]; however, the observation time in this study was only 1 year, and few of the subjects engaged in such high-risk behavior. A prospective study from Australia showed lack of sexual transmission of HCV among HIV-negative MSM,[53] whereas another cohort study reported an HCV incidence of 0.11 per 100 person-years (95% CI 0.03-0.26) among HIV-negative MSM.[54] However, IDU was a common practice among these HCV-infected patients. Studies from Canada and Argentina also did not find an association between HCV infection and homosexual contact in HIV-uninfected men.[55,56]

The situation is entirely different for HIV-infected gay men, especially those who engage in high-risk and traumatic sex practices involving anal mucosal damage. Studies addressing the emerging public health problem of HCV in HIV-infected men are limited and are mainly from western Europe (Table 2), but they suggest that the incidence of HCV infection among HIV-positive MSM has been increasing. A cohort study in Amsterdam showed a significant increase in HCV incidence among HIV-infected MSM, from 0.08 cases per 100 person-years between 1984 and 1999 to 0.87 cases per 100 person-years between 2000 and 2003.[50] Similarly, it has been estimated that the incidence of acute HCV infections among HIV-infected MSM in the United Kingdom has increased by 20% every year since 2002.[57,58] The French PRIMO cohort study also showed an increase in the incidence of HCV infection among HIV-infected individuals from 1.2 per 1,000 person-years before 2003 to 8.3 per 1,000 person-years after 2003.[59]

Several longitudinal studies of HIV-infected MSM totaling more than 12,000 person-years of follow up have shown that these men are at much higher risk for sexually acquired HCV than HIV-uninfected MSM (aOR, 4.1 to 5.7).[50,51,60] Likewise, a large cross-sectional study in Amsterdam reported that HIV-infected MSM were almost 43 times (95% CI 8.49-215.1) more likely to acquire HCV infection than HIV-uninfected MSM.[61] HIV-positive men were much more likely to be coinfected with HCV in a few Australian studies,[53,62] but IDU was also known to be widely prevalent among MSM in Australia.[53,54,62] A smaller cross-sectional study from the United States showed that HCV-infected MSM with were more likely to be coinfected with HIV than those who were HCV-negative (70% versus 29%).[63] Similarly, sexual transmission was the sole identified route of HCV infection among HIV-infected MSM in France.[59] Only a few cross-sectional studies have not shown an increased risk of HCV infection among HIV-infected MSM or found an association between HCV and HIV coinfection.[64-67]

The practice of "serosorting" among HIV-infected MSM – unprotected sex between two HIV-infected men who are aware of their own and their partners' HCV infection (but not necessarily HCV infection) – has been commonly reported in recent studies.[15,16,68,69] Many common themes or risks have been observed in the majority of studies that have addressed HCV infection among HIV-infected MSM: engaging in unprotected sex with multiple partners,[14-16,20,53,69-74] anal fisting, use of sex toys, and the presence of genital ulcerative disease.[15-20,50,54,61,63,69,70,74-78] In the only well-designed case control study thus far, participation in group sex was more prevalent among HIV-coinfected HCV cases compared with controls (88% versus 52%).[69] Participation in group sex significantly increased the odds for HCV infection (aOR 9.16, 95% CI 3.51-23.9) if it involved at least two of the following four sexual practices: receptive and insertive anal intercourse and receptive and insertive fisting.[69] Fisting significantly

Table 2. Selected Studies Assessing Transmission of Hepatitis C Among MSM

Study	Country (Year of Study)	Sample Size	HCV Prevalence	HCV Incidence (Cases per 100 Person-Years)	HIV Prevalence	Phylogenetic Testing*	Sexual Transmission Reported as a Risk Factor
Cohort studies							
Van de Laar et al. (50)	Netherlands (1984-2003)	1,836	1.3%	0.07 (non-HIV, 0; HIV, 0.18)	28%	Yes	Yes
Alary et al. (52)	Canada (1996-2001)	1,085	2.9%	0.038	0%	No	No
Jin et al. (54)	Australia (2001-2007)	1,398 non-HIV; 245 HIV	Non-HIV, 1.1% (range, 0.6-1.8); HIV, 9.4% (range,6.0-13.8)	Non-HIV, 0.11 (range, 0.03-0.3); HIV, 0 (range, 0-1.5)		No	Yes among HIV-coinfected HCV- prevalent cases
Ghosn et al. (59)	France (1996-2005)	327	5.8%	0.35	100%	No	Yes
Hammer et al. (60)	United States (1997-2000)	754	2.1%	0	6.6%	No	No
Rauch et al. (75)	Switzerland (1988-2004)	7,899	33%	0.64	100%	No	Yes
Case-control studies							
Danta et al. (69)	United Kingdom (1999-2005)	60 cases; 130 controls	–	-	100%	Yes	Yes
Fierer et al. (72)	United States (2005-2008)	21 cases; 21 controls	–	21 cases	100%	Yes	Yes
Cross-sectional studies							
Matthews et al. (53)	Australia (2004-2006)	120†	–	120 cases	21.7%	No	Yes among HIV-positive MSM
Myers et al. (55)	Canada	3,304†	1.9%	–	9%	No	No
Urbanus et al. (61)	Netherlands (2007-2008)	689	4.4%	–	22.8%	Yes	Yes
Turner et al. (70)	United Kingdom (1999-2000)	308†	3.6%	–	100%	No	Yes
Morin et al. (71)	France (1999-2007)	126 cases	–	126 cases	12%	No	Yes
Ndimbie et al. (76)	United States (1984-1985)	1,058	2.9%	–	19.6%	No	Yes

*To characterize specimens by molecular means.

†No confirmatory HCV testing was performed.

increased the risk of HCV infection among HIV-infected MSM by more than five-fold (aOR 6.27-12.6),[61,70] as did the use of sex toys (78% versus 43%).[69] Fisting was highly correlated with use of sex toys, group sex, and bleeding in a cross-sectional study from Amsterdam.[61] In addition, the use of psychoactive substances was common among HCV/HIV-coinfected MSM and might have acted as a disinhibitor for risky sexual practices, leading to traumatic sex and mucosal damage.[55,74] Thus, some researchers have concluded that the real risk of sexual transmission in HIV-infected persons results from blood-to-blood contact during sex.[78]

It is worth noting that phylogenetic analyses in cohort studies[50,75] and in an international network of MSM[68] have also indicated concordance of gene sequences in recovered HCV strains. The difficult-to-treat genotypes 1a and 4d were usually recovered.[17,18,50,59,61,68,69,74,79]

Discussion

This review focused on the risk of sexual transmission of hepatitis C infection and distinguished between heterosexual and homosexual contact. The real risk for sexual transmission appeared to be predominantly related to HIV infection: of all the practices considered in this review, the clearest and least equivocal risk behavior was unprotected sex between HIV-infected partners, particularly HIV-positive MSM.

Since the last review of this topic in Hepatology,[80] the most notable trend has been a growing number of reports from European and American cities, indicating an increase in incidence and prevalence of HCV infection among HIV-infected MSM.[14,18,50,54,55,57-59,61,69,74,75] This increase has mostly been reported after the introduction of highly active antiretroviral therapy treatment, which may contribute to risky sexual behavior due to the belief among these men that treatment will eliminate further risk of HIV infection. It has also been postulated that a greater proportion of HIV-infected MSM have been engaging in serosorting,[15,16,18,74,81-83] which is thought to be the source of a specific pan-national cluster of HCV infection in Europe.[68] In addition, the presence of several activities and conditions that disrupt anal mucosal integrity (traumatic sex, sex with visible blood, genital ulcerative diseases, use of sex toys) were frequently noted in these instances of putative sexual transmission.

The use of molecular sequencing in some case reports has led some researchers to conclude that HCV transmission between spouses was caused by sexual contact. However, this finding does not preclude that the virus might have been transmitted through unacknowledged needle (or other sharp object) sharing.[31,84,85] In fact, when the risk of spousal HCV transmission was analyzed in Italy, this resulted from the common practice of sharing syringes.[25,30,36] Although phylogenetic analysis is a useful laboratory technique to demonstrate genetic similarities or variations in recovered viruses, it does not obviate the role of careful epidemiological analysis.

The studies included in our review had several limitations. A major limitation common to all the studies was the unavoidable reliance on self reports for the ascertainment of IDU. Unacknowledged or unascertained IDU among men and women with multiple sex partners undoubtedly confounds all analyses of association of HCV infection with number of sex partners. Another limitation is that the risk from and exposure to other sharp objects as potential vehicles for transmission cannot be excluded.[63,65,66,70] Furthermore, prospective cohort studies of heterosexual couples in a single-partner relationship may have preselected persons who would be unlikely to transmit the virus—that is, if transmission of HCV occurred in one of the first sexual encounters, choosing discordant couples for analysis (those who have not previously transmitted) may represent a selection bias.

Despite these limitations, studies could be categorized and evaluated as to their quality and credibility and conclusions drawn. The use of condoms and refraining from high-risk sexual behavior is definitely indicated among persons who have HIV infection or another STI or who are not in a single-partner relationship. Health care providers need to pay special attention to HIV-infected MSM. Initial testing for HCV is recommended for all individuals in the United States who are entering HIV care,[86] but annual or other regular testing should receive serious consideration. This review should form a basis for appropriate health messages to inform susceptible individuals of the real risks of HCV infection rather than distract them with highly unlikely sources of transmission.

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References

1. Alter MJ. Epidemiology of hepatitis C virus infection. World J Gastroenterol 2007;13:2436-2441.

2. Centers for Disease Control and Prevention. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. MMWR Recomm Rep 1998;47:1-39.
3. Thompson ND, Perz JF, Moorman AC, Holmberg SD. Nonhospital health care-associated hepatitis B and C virus transmission: United States, 1998-2008. Ann Intern Med 2009;150:33-39.
4. Hauri AM, Armstrong GL, Hutin YJ. The global burden of disease attributable to contaminated injections given in health care settings. Int J STD AIDS 2004;15:7-16.
5. Leruez-Ville M, Kunstmann JM, De Almeida M, Rouzioux C, Chaix ML. Detection of hepatitis C virus in the semen of infected men. Lancet 2000;356:42-43.
6. Manavi M, Watkins-Riedel T, Kucera E, Czerwenka K, Hofman H. Evidence of hepatitis C virus in cervical smears. J Infect 1999;38: 60-61.
7. Nyamathi A, Robbins WA, Fahey JL, Wiley D, Pekler VA, Longshore D, et al. Prevalence and predictors of hepatitis C virus RNA in the semen of homeless men. Biol Res Nurs 2002;4:22-30.
8. Cavalheiro NP, Santos ACO, Melo CE, Morimitsu SR, Barone AA. Hepatitis C virus detection in the semen of infected patients. Br J Infect Dis 2008;12:358-361.
9. Debono E, Halfon P, Bourliere M, Gerolami-Santandrea V, Gastaldi M, Castellani P, et al. Absence of hepatitis C genome in semen of infected men by polymerase chain reaction, branched DNA and in situ hybridization. Liver 2000;20:257-261.
10. Halfon P, Riflet H, Renou C, Quentin Y, Cacoub P. Molecular evidence of male-to-female sexual transmission of hepatitis C virus after vaginal and anal Intercourse. J Clin Microbiol 2001;39:1204-1206.
11. Quer J, Murillo P, Esteban JI, Martell M, Esteban R, Guardia J. Sexual transmission of hepatitis C virus from a patient with chronic disease to his sex partner after removal of an intrauterine device. Sex Transm Dis 2002;30:470-471.
12. Capelli C, Prati D, Bosoni P, Zanuso F, Pappalettera M, Mozzi F, et al. Sexual transmission of hepatitis C to a repeat blood donor. Transfusion 1997;37:436-440.
13. Healey CJ, Smith DB, Walker JL, Holmes EC, Fleming KA, Chapman RWG, et al. Acute hepatitis C infection after sexual exposure. Gut 1995;36:148-150.
14. Browne R, Asboe D, Gilleece Y, Atkins M, Mandalia S, Gazzard B, et al. Increased numbers of acute hepatitis C infections in HIV infected homosexual men; is sexual transmission feeding the increase? Sex Transm Infect 2004;80;326-327.
15. Ghosn J, Pierre-François S, Thibault V, Duvivier C, Tubiana R, Simon A, et al. Acute hepatitis C in HIV-infected men who have sex with men. HIV Med 2004;5:303-306.
16. Ghosn J, Thibault V, Delaugerre C, Fontaine H, Lortholary O, Rouzioux C, et al. Sexually transmitted hepatitis C virus superinfection in HIV/hepatitis C virus co-infected men who have sex with men. AIDS 2008;22:658-661.
17. Serpaggi J, Chaix ML, Batisse D, Dupont C, Vallet-Pichard A, Fontaine H, et al. Sexually transmitted acute infection with a clustered genotype 4 hepatitis C virus in HIV-1-infected men and inefficacy of early antiviral therapy. AIDS 2006;20:233-240.
18. Götz HM, Van Doornum G, Niesters HGM, den Hollander JG, Bing Thio H, de Zwart O. A cluster of acute hepatitis C virus infection among men who have sex with men—results from contact tracing and public health implications. AIDS 2005;19:969-974.
19. Cotte L, Queyron PC, Schlienger L, Trabaud MA, Brochier C, Andre P, et al. Sexually transmitted HCV infection and re-infection in HIV-infected homosexual men. Gastroenterol Clin Biol 2009;33:977-980.
20. Fierer DS, Uriel AJ, Carriero DC, Klepper A, Dieterich DT, Mullen MP, et al. Liver fibrosis during an outbreak of acute hepatitis C virus infection in HIV-infected men: a prospective cohort study. J Infect Dis 2008;198:683-686.
21. Vandelli C, Renzo F, Romanò L, Tisminetzky S, De Palma M, Stroffolini T, et al.Lack of evidence of sexual transmission of hepatitis C among monogamous couples: results of a 10-year prospective follow-up study. Am J Gastroenterol 2004;99:855-859.
22. Marincovich B, Castilla J, del Romero J, Garcia S, Hernando V, Raposo M, et al. Absence of hepatitis C virus transmission in a prospective cohort of heterosexual serodiscordant couples. Sex Transm Infect 2003;79:160-162.
23. Hisada M, O'Brien TR, Rosenberg PS, Goedert JJ. Virus load and risk of heterosexual transmission of human immunodeficiency virus and hepatitis C virus by men with hemophilia. J Infect Dis 2000;181: 1475-1478.
24. Riestra S, Fernandez E, Rodriguez M, Rodrigo L. Hepatitis C virus infection in heterosexual partners of HCV carriers. J Hepatol 1995;22:509-510.
25. Stroffolini T, Lorenzoni U, Menniti-Ippolito F, Infantolino D, Chiaramonte M. Hepatitis C virus infection in spouses: sexual transmission or common exposure to the same risk factors? Am J Gastroenterol 2001;96:3138-3141.
26. Tahan V, Karaca C, Yildirim B, Bozbas A, Ozaras R, Demir K, et al. Sexual transmission of HCV between spouses. Am J Gastroenterol 2005;100:821-824.
27. Atome GRN, Njouom R, Padilla C, Bisvigoua U, Makuwa M, Mirdad Kazanji M. Absence of intrafamilial transmission of hepatitis C virus and low risk for sexual transmission in rural central Africa indicate a cohort effect. J Clin Virol 2009;45:349-353.
28. La Torre G, Miele L, Mannocci A, Chiaradia G, Berloco F, Gabrieli ML, et al. Correlates of HCV seropositivity among familial contacts of HCV infected patients. BMC Public Health 2006;6:237.
29. Brusaferro S, Barbone F, Andrian P, Brianti G, Ciccone L, Furlan A, et al. A study on the role of the family and other risk factors in HCV transmission. Eur J Epidemiol 1999;15:125-132.
30. Caporaso N, Ascione A, Stroffolini T. Spread of hepatitis C virus infection within families. Investigators of an Italian Multicenter Group. J Viral Hepat 1998;5:67-72.
31. Cavalheiro NP, De La Rosa A, Elagin S, Tengan FM, de Araújo ESA, Barone AA. Hepatitis C: sexual or intrafamilial transmission? Epidemiological and phylogenetic analysis of hepatitis C virus in 24 infected couples. Rev Soc Bras Med Trop 2009;42:239-244.
32. McMahon JM, Pouget ER, Tortu S. Individual and couple-level risk factors for hepatitis C infection among heterosexual drug users: a multilevel dyadic analysis. J Infect Dis 2007;195:1572-1581.
33. Kao JH, Liu CJ, Chen PJ, Chen W, Lai MY, Chen IS. Low incidence of hepatitis C virus transmission between spouses: a prospective study. J Gastroenterol Hepatol 2000;15:391-395.
34. Chayama K, Kobayashi M, Tsubota A, Koida I, Arase Y, Saitoh S, et al. Molecular analysis of intraspousal transmission of hepatitis C virus. J Hepatol 1995;22:431-439.
35. Piazza M, Sagliocca L, Tosone G, Guadagnino V, Stazi MA, Orlando R, et al. Sexual transmission of the hepatitis C virus and efficacy of prophylaxis with intramuscular immune serum globulin. Arch Int Med 1997;157:1537-1544.
36. Guadagnino V, Stroffolini T, Focà A, Caroleo B, Loiacono L, Giancotti A, et al. Hepatitis C virus infection in family setting. Eur J Epidemiol 1998;14:229-232.
37. Kao JH, Hwang YT, Chen PJ, Yang PM, Lai MY, Wang TH, et al. Transmission of hepatitis C virus between spouses: the important role of exposure duration. Am J Gastroenterol 1996;91:2087-2090.
38. Neumayr G, Propst H, Schwaighofer H, Judmaier G, Vogel W. Lack of evidence for the heterosexual transmission of hepatitis C. Q J Med 1999;92:505-508.
39. Saltoğlu N, Taşova Y, Burgut R, Dündar IH. Sexual and non-sexual intrafamilial spread of hepatitis C virus: intrafamilial transmission of HCV. Eur J Epidemiol 1998;14:225-228.
40. Diago M, Zapater R, Tuset C, Carbonell P, Gonzalez C, Cors R, et al. Intrafamilial transmission of hepatitis C virus: sexual and non-sexual contacts. J Hepatol 1996;25:125-128.
41. Sun CA, Chen HC, Lu CF, You SL, Mau YC, Ho MS, et al. Transmission of hepatitis C virus in Taiwan: prevalence and risk factors based on a nationwide survey. J Med Virol 1999;59:290-296.

42. Salleras L, Bruguera M, Vidal J, Plans P, Dominguez A, Salleras M, et al. Importance of sexual transmission of hepatitis C virus in seropositive pregnant women: a case-control study. J Med Virol 1997;52: 164-167.
43. Mele A, Tosti ME, Marzolini A, Moiraghi A, Ragni P, Gallo G, et al. Prevention of hepatitis C in Italy: lessons from surveillance of type-specific acute viral hepatitis. J Viral Hepat 2000;7:30-35.
44. Feldman JG, Minkoff H, Landesman S, Dehovitz J. Heterosexual transmission of hepatitis C, hepatitis B, and HIV-1 in a sample of inner-city women. Sex Transm Dis 2000;27:338-342.
45. Wang CC, Krantz E, Klarquist J, Krows M, McBride L, Scott EP, et al. Acute hepatitis C in a contemporary US cohort: modes of acquisition and factors influencing viral clearance. J Infect Dis 2007;196: 1474-1482.
46. Thomas DL, Zenilman JM, Alter HJ, Shih JW, Galai N, Carella AV, 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 1995;171:768-775.
47. Marx MA, Murugavel KG, Tarwater PM, SriKrishnan AK, Thomas DL, Solomon S, et al. Association of hepatitis C virus infection with sexual exposure in Southern India. Clin Infect Dis 2003;37:514-520.
48. Hershow RC, Kalish LA, Sha B, Till M, Cohen M. Hepatitis C virus infection in Chicago women with or at risk for HIV infection: evidence for sexual transmission. Sex Transm Dis 1998;25:527-532.
49. Frederick T, Burian P, Terrault N, Cohen M, Augenbraun M, Young M, et al. Factors associated with prevalent hepatitis C infection among HIV-infected women with no reported history of injection drug use: the Women's Interagency HIV Study (WIHS). AIDS Patient Care STD 2009;23:915-923.
50. Van de Laar TJ, Van der Bij AK, Prins M, Bruisten S, Brinkman K, Ruys TA, et al. Increase in HCV incidence among men who have sex with men in Amsterdam most likely caused by sexual transmission. J Infect Dis 2007;196:230-238.
51. Richardson D, Fisher M, Sabin CA. Sexual transmission of hepatitis C in MSM may not be confined to those with HIV infection. J Infect Dis 2008;197:1213-1214.
52. Alary M, Joly JR, Vincelette J, Lavoie R, Turmel B, Robert S, et al. Lack of evidence of sexual transmission of hepatitis C virus in a prospective cohort study of men who have sex with men. Am J Public Health 2005;95:502-505.
53. Matthews GV, Hellard M, Kaldor J, Lloyd A, Dore GJ. Further evidence of HCV sexual transmission among HIV-positive men who have sex with men: response to Danta et al. AIDS 2007;21:2112-2113.
54. Jin F, Prestage GP, Matthews GV, Zablotska I, Rawstorne P, Kippax SC, et al. Prevalence, incidence and risk factors for hepatitis C in homosexual men: data from two cohorts of HIV negative and HIV positive men in Sydney, Australia. Sex Transm Infect 2010;86:25-28.
55. Myers T, Allman D, Xu K, Remis RS, Aguinaldo J, Burchell A, et al. The prevalence and correlates of hepatitis C virus (HCV) infection and HCV—HIV co-infection in a community sample of gay and bisexual men. Int J Infect Dis 2009;13:730-739.
56. Osella AR, Massa M, Joekes S, Blanch N, Yacci MR, Centonze S, et al. Hepatitis B and C virus sexual transmission among homosexual men. Am J Gastroenterol 1998;93:49-52.
57. Giraudon I, Ruf M, Maguire H, Charlett A, Ncube F, Turner J, et al. Increase in diagnosed newly acquired hepatitis C in HIV-positive men who have sex with men across London and Brighton, 2002-2006: is this an outbreak? Sex Transm Infect 2008;84:111-116.
58. Ruf M, Cohuet S, Maguire H, Brant LJ, Ramsay M, Lattimore S, et al. Setting up an enhanced surveillance of newly acquired hepatitis C infection in men who have sex with men: a pilot in London and south east region of England. Euro Surveill 2008;13:pii=19042. http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19042.
59. Ghosn J, Deveau C, Goujard C, Garrigue I, Saichi N, Galimand J, et al. Increase in hepatitis C virus incidence in HIV-1 infected patients followed up since primary infection. Sex Transm Infect 2006;82: 458-460.
60. Hammer GP, Kellogg TA, McFarland WC, Wong E, Louie B, Williams I, et al. Low incidence and prevalence of hepatitis C virus infection among sexually active non-intravenous drug-using adults, San Francisco, 1997-2000. Sex Transm Dis 2003;30:919-924.
61. Urbanus A, Van de Laar TJ, Stolte IG, Schinkel J, Heijman T, Coutinho RA, et al. Hepatitis C virus infections among HIV-infected men who have sex with men: an expanding epidemic. AIDS 2009;23:F1-F7.
62. Bodsworth NJ, Cunningham P, Kaldor J, Donovan B. 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 1996;72:118-122.
63. Cohen DE, Russell CJ, Golub SA, Mayer KH. Prevalence of hepatitis C virus infection among men who have sex with men at a Boston community health center and its association with markers of high-risk behavior. AIDS Patient Care STD 2006;20:557-564.
64. Buffington J, Murray PJ, Schlanger K, Shih L, Badsgard T, Hennessy RR, et al. Low prevalence of hepatitis C virus antibody in men who have sex with men who do not inject drugs. Public Health Rep 2007;122:63-67.
65. D'Oliveira A Jr, Voirin N, Allard R, Peyramond D, Chidiac C, Touraine JL, et al. Prevalence and sexual risk of hepatitis C virus infection when human immunodeficiency virus was acquired through sexual intercourse among patients of the Lyon University Hospitals, France, 1992-2002. J Viral Hepat 2005;12:330-332.
66. Lama JR, Lucchetti A, Cabezas C, Ognio LS, Sanchez J. Lack of evidence of hepatitis C and HIV co-infection among men who have sex with men in Peru. Am J Trop Med Hyg 2009;81:184-186.
67. Kim JH, Psevdos G Jr, Suh J, Sharp VL. Co-infection of hepatitis B and hepatitis C virus in human immunodeficiency virus-infected patients in New York City, United States. World J Gastroenterol 2008;14:6689-6693.
68. Van de Laar T, Pybus O, Bruisten S, Brown D, Nelson M, Bhagani S, et al. Evidence of a large, international network of HCV transmission in HIV-positive men who have sex with men. Gastroenterology 2009; 136:1609-1617.
69. Danta M, Brown D, Bhagani S, Pybus OG, Sabin CA, Nelson M, et al. for the HIV and acute HCV (HAAC) group. Recent epidemic of acute hepatitis C virus in HIV-positive men who have sex with men linked to high-risk sexual behaviors. AIDS 2007;21:983-991.
70. Turner JM, Rider AT, Imrie J, Copas AJ, Edwards SG, Dodds JP, et al. Behavioral predictors of subsequent hepatitis C diagnosis in a UK clinic sample of HIV positive men who have sex with men. Sex Transm Infect 2006;82:298-300.
71. Morin T, Pariente A, Lahmek P, Rabaud C, Silvain C, Cadranel JF. Acute hepatitis C: analysis of a 126-case prospective, multicenter cohort. Eur J Gastroenterol Hepatol 2010;22:157-166.
72. Fierer DS, Uriel AJ, Carriero DC, et al. Characterization of an epidemic of sexually-transmitted acute hepatitis C infection in HIV-infected men in New York City [Abstract]. Hepatol 2009;50(4 Suppl.):342A-343A.
73. Filippini P, Coppola N, Scolastico C, Rossi G, Onofrio M, Sagnelli E, et al. Does HIV infection favor the sexual transmission of hepatitis C? Sex Transm Dis 2001;28:725-729.
74. Gambotti L and the Acute Hepatitis C Collaborating Group. Acute hepatitis C infection in HIV positive men who have sex with men in Paris, France, 2001-2004. Euro Surveill 2005;10:pii=535. http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=535.
75. Rauch A, Rickenbach M, Weber R, Hirschel B, Tarr PE, Bucher HC, et al. Unsafe sex and increased incidence of hepatitis C virus infection among HIV-infected men who have sex with men: the Swiss HIV cohort study. Clin Infect Dis 2005;41:395-402.
76. Ndimbie OK, Kingsley LA, Nedjar S, Rinaldo CR. Hepatitis C virus infection in a male homosexual cohort: risk factor analysis. Genitourin Med 1996;72:213-216.
77. Russel M, Chen MJ, Nochajski TH, Testa M, Zimmerman SJ, Hughes PS. Risky sexual behavior, bleeding caused by intimate partner violence, and hepatitis C virus infection in patients of a sexually transmitted disease clinic. Am J Public Health 2009;99:S173-S179.
78. Schmidt AJ, Vogel M, Krznaric I, and the Study Group on Sexual Risk Factors for Hepatitis C. The trouble with bleeding: why do HIV-

positive gay men get hepatitis C? Presented at: 12th European AIDS Conference; November 11-14, 2009; Cologne, Germany.
79. Palacios R, Mata R, Aguilar I, Muñoz L, Ríos MJ, Vergara S, et al. High seroprevalence but low incidence of HCV infection in a cohort of patients with sexually transmitted HIV in Andalusia, Spain. J Int Assoc Physicians AIDS Care 2009;8:100-105.
80. Terrault NA. Sexual activity as a risk factor for hepatitis C. HEPATOLOGY 2002;36(Suppl. 1):S99-S105.
81. Truong HHM, Kellogg T, Klausner JD, Katz MH, Dilley J, Knapper K, et al. Increases in sexually transmitted infections and sexual risk behavior without a concurrent increase in HIV incidence among men who have sex with men in San Francisco: a suggestion for HIV serosorting? Sex Transm Infect 2006;82:461-466.
82. Ma X, Zhang Q, He X, Sun W, Yue H, Chen S, et al. Trends in prevalence of HIV, syphilis, hepatitis C, hepatitis B, and sexual risk behavior among men who have sex with men. Results of 3 consecutive respondent-driven sampling surveys in Beijing, 2004 through 2006. J Acquir Immune Defic Syndr 2007;45:581-587.
83. Pelgrom JM, Vogelaers D, Colle I. Hepatitis C-seroconversion within three to six months after having contracted clinical syphilis and/or lymphogranuloma venereum rectitis in five homosexually active, HIV seropositive men. Acta Clin Belg 2008;63:335-338.
84. Zylberberg H, Thiers V, Lagorce D, Squadrito G, Leone F, Berthelot P, et al. Epidemiological and virological analysis of couples infected with hepatitis C virus. Gut 1999;45:112-116.
85. Orlando R, Lirussi F. Hepatitis C virus infection: sexual or non-sexual transmission between spouses? A case report and review of the literature. Infection 2007;35:465-468.
86. Kaplan JE, Benson C, Holmes KH, Brooks JT, Pau A, Masur H; Centers for Disease Control and Prevention; National Institutes of Health; HIV Medicine Association of the Infectious Diseases Society of America. Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR Recomm Rep 2009;58:1-207.