Sex, Drugs, and Hepatitis C Virus

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(See the article by McMahon et al., on pages 1572–81.)

Nearly 20 years after the identification of the hepatitis C virus (HCV), there is still debate about the extent of sexual transmission of HCV. Because the pool of infected persons is very large (the World Health Organization estimates that 170 million people worldwide are infected with HCV) and sexual intercourse is common, even a low rate of sexual transmission can account for a large number of new cases. This explains why the Centers for Disease Control and Prevention (CDC) does not recommend condom use for long-term serodiscordant heterosexual couples to prevent HCV transmission [1] while attributing 15% of new HCV infections to sexual transmission [2].

The literature about HCV is rife with conflicting data about sexual transmission, to a large degree because of the difficulties in studying this phenomenon. The most important challenge in studying sexual transmission of HCV lies in the fact that the most common route of HCV transmission—injection drug use—can only be measured by self-report. Injection drug use, because of its illicit nature, is likely to be denied, whereas sexual activity, although perhaps uncomfortable to discuss, may be more likely to be reported. Therefore, especially in studies of the general population, it is impossible to rule out the possibility that statistically significant associations of HCV infection with variables that suggest sexual transmission, even in multivariate models that adjust for injecting, do not represent unreported injecting [3–7]. It is possible that many of the 15% of new HCV infections ascribed to sexual transmission by the CDC result from unacknowledged injecting. The study described in this issue of the *Journal* by McMahon et al. [8] is unique in that the study entry criteria included illicit drug use in addition to participation in an active sexual relationship. These entry criteria are a significant strength, because persons reporting illicit drug use at study entry may be less likely to underreport injection drug use; therefore, spurious associations of sexual behavior with HCV will be less likely than in studies of broader population groups.

Previous studies have provided evidence that sexual transmission of HCV within low-risk heterosexual partnerships occurs at most with very low frequency [9]. For example, in studies that conducted genotyping to rule out pairs with discordant viral subtypes, the prevalence of HCV concordance between persons with chronic liver disease and their long-term noninjecting heterosexual partners was 2%–3% in the United States and Europe [10–12]. A prevalence of 3% concordance in relationships with an average duration of 10–15 years of exposure translates to a yearly risk of transmission of 0.2%–0.3%. Several prospective partner studies that used RNA sequencing to corroborate transmission reported incidence rates consistent with this estimate. The incidence rates in studies of monogamous heterosexual partners of persons chronically infected with HCV was 0 in 4 studies [12–15] and 0.23% and 0.8%/year in 2 other studies [16, 17]. Although we cannot conclude that the new infections that occurred in the latter 2 studies were actually due to sexual transmission rather than to unreported injecting or other common exposures [18], these studies provide an upper boundary for the incidence rate of transmission in monogamous HCV-serodiscordant sexual partnerships.

The studies described above demonstrate a very low risk of sexual transmission of HCV in long-term heterosexual monogamous couples. However, these studies were conducted in predominantly low-risk populations, with reports of little (8/171 couples) [14] or no anal intercourse [12, 15] and no sexually transmitted infections (STI) or lesions [12, 15], except for HIV infection in 12 of 30 participants in 1 study [13]. Sexual transmission of HCV may occur more readily in the presence of biological cofactors, such as high-risk sexual contact or STIs that traumatize the anal or genital mucosa

or behaviors that lead to blood-blood contact. Many studies of persons at risk for STIs and/or high-risk sex—such as those presenting for STI treatment [6, 19], men who have sex with men (MSM) [20, 21], and female sex workers [22, 23]—have reported independent associations of HCV with STIs and numbers of sex partners, although such associations have not been seen in all studies [24–29]. HIV status has also been frequently reported as an independent risk factor for HCV transmission after adjustment for STIs and sexual behavior [19, 30–32]. In addition, recent case studies have suggested an increased risk of sexually transmitted HCV among HIV-positive MSM in association with sexual behaviors (such as unprotected anal sex, fisting, and the use of sex toys), STIs, and noninjection drug use [33–38]. Risk-factor analyses have supported these reports [39, 40]. Several studies have also cited trends in the incidence of sexually acquired HCV infection in HIV-positive persons [41] and in HIV-positive MSM over time [42]. However, the absolute risk of infection appears to be low; the incidence of HCV in HIV-positive noninjecting MSM who reported unprotected sex in the Swiss HIV Cohort Study from 1998 to 2004 was 0.7%/year, compared with 0.2%/year in those denying unprotected sex [40], and the incidence rate in the French Prédiction du Risque Musculaire en Observationnel study of HIV-positive persons was 0.8%/year from 2003 to 2005 [41].

Although there is increasing evidence that some behaviors and infections increase susceptibility to HCV infection, factors that increase the transmissibility of HCV have not been well examined. For one, a high HCV load may increase the risk of sexual HCV transmission. The HCV load is higher in blood [43, 44] and semen of HIV-positive persons [45] than in those of HIV-negative persons. An increased HCV load is associated with an increased risk of vertical transmission of HCV in association with HIV coinfection [46–48] and occupational transmission of HCV to health care workers [49]. How-

ever, there were no new infections observed in the partners of HIV/HCV-co-infected index participants in 2 studies described above [13, 14], and there was little association of HCV load with HCV transmission in another prospective partners study in which the majority of indexes were HIV/HCV coinfected [43]. HIV is very infectious during acute infection [50], and the acute period of HCV infection is associated with high viral replication in the absence of antibody [51–53] and may similarly be highly infectious. The study by McMahon et al. [8] in this issue examined several risk factors for HCV infection in long-term heterosexual drug-using couples. They examined risk behaviors and biological and psychosocial cofactors for infection on the individual, partner, and couple level. This approach allowed for the simultaneous examination of cofactors of susceptibility and infectivity and should serve as a model for the further study of HCV transmission.

The study by McMahon et al. emphasizes that active injection drug use is the single most important factor for HCV transmission, even in a population with high sexual risk. The association of HCV with recent injecting within the couples is consistent with previous findings that injecting risk commonly occurs within the context of intimate relationships [54, 55]. After adjustment for actor- and couple-level injection drug use, there was no additional risk of HCV due to sexual behaviors or infections. It is not surprising that these variables were not associated with HCV, because injection drug use is a highly efficient means of transmitting HCV, and, as we noted above, sexual transmission of HCV is uncommon, even in high-risk groups. Therefore, studies of HCV that include injection drug users (IDUs), while minimizing bias due to underreporting of injecting by including IDUs in the study, have low statistical power to detect other independent associations with HCV. After stratification by injecting, there are very few non-IDUs that are infected with HCV and very few IDUs

who are not infected with HCV. Studies in high-risk but noninjecting populations are needed to quantify increases in risk due to various biological factors and to high-risk sexual practices. However, given the low level of absolute risk for sexually transmitted HCV, the required sample sizes will be quite large [10]. Regardless of the results of such studies, those at high risk for sexual acquisition or transmission of HCV are advised to use condoms to avoid the acquisition and/or transmission of other infections.

The best way to reduce the sexual transmission of HCV in the long term is to reduce the pool of infectious persons. Aggressive pursuit of interventions to prevent HCV transmission in IDUs, including the reduction of injecting in general, will be the most effective way to combat the HCV epidemic. Current estimates of HCV incidence in young IDUs in the United States are 9%–35%/year [55–58]. Although there is some optimism that a therapeutic vaccine can be developed [59], such a vaccine is unlikely to be completely efficacious; therefore, other strategies, which themselves may only be moderately efficacious, must also be developed for use in combination with vaccine. Such strategies may include biomedical approaches, such as targeted HCV treatment to reduce the level of infectivity among those at highest risk of transmitting HCV. Behavioral interventions for IDUs to reduce the risk of acquiring and transmitting HCV also need to be developed. Such interventions will need to address the injecting risk that occurs within the context of close injecting partnerships [60].

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