Correspondence

Sexual Transmission of Hepatitis C in MSM May Not Be Confined to Those with HIV Infection

To the Editor—We concur with van de Laar et al. [1] that sexual transmission of hepatitis C virus (HCV) among human immunodeficiency virus (HIV)–infected men who have sex with men (MSM) appears to be increasing. Similar outbreaks have been reported in other parts of the world [2–4]. These reports have demonstrated an association with other sexually transmitted infections. However, it is unclear whether this increasing incidence is occurring exclusively among HIV-infected MSM or whether this apparent exclusivity simply reflects a lack of data from HIV-uninfected MSM. Regular HCV screening is not currently recommended for MSM without HIV infection, and unlike HIV-infected MSM, these individuals are unlikely to have had the opportunity for HCV infection to be suspected on the basis of results of routine liver function tests [5]. The aim of our analysis was to describe the incidence of HCV infection among MSM who attended the only public sexual health clinic in Brighton, United Kingdom, between 2000 and 2006.

We have been performing HCV screening regularly since 2000 among all MSM attending our clinic, regardless of their HIV status. In this analysis, we included all MSM with ⩾2 clinic visits during the study period who had a negative result of their first HCV antibody test. The follow-up interval began on the date of their first HCV antibody test and ended on the date of their first positive HCV test result, 6 months after their most recent clinic visit, or on 31 December 2006, whichever occurred first. Poisson regression analysis was used to assess the impacts of HIV status at the time of the initial HCV test and calendar year on the rate of new HCV infections. We excluded MSM with a history of injection drug use (IDU).

A total of 6124 MSM were seen at least twice in our clinic over the study period, of whom 3536 met the eligibility criteria. Forty-four patients were excluded because the result of their first HCV antibody test was positive, and 2544 were excluded because they had not been tested for HCV. Over the study period, 25 MSM had incident HCV infection, for an incidence rate of 3.7 cases per 1000 person-years (95% confidence interval [CI], 2.3–5.2). Nine diagnoses of incident HCV infection occurred among individuals without HIV infection (rate, 5 cases per 3335 person-years, or 1.5 cases per 1000 person-years [95% CI, 0.5–3.5]) or with an unknown HIV status (rate, 4 cases per 1971 person-years, or 2.0 cases per 1000 person-years [95% CI, 0.6–5.2]) at the time of their first HCV test, whereas 16 diagnoses of incident HCV infection per 1361 person-years (11.8 cases per 1000 person-years [95% CI, 6.7–19.1]) occurred among individuals known to have HIV infection. The number of new HCV diagnoses increased annually during 2003–2006, with incidence rates of 1.6 cases per 1000 person-years (95% CI, 0.2–5.7) in 2003, 2.4 cases per 1000 person-years (95% CI, 0.7–6.1) in 2004, 3.5 cases per 1000 person-years (95% CI, 1.3–7.6) in 2005, and 9.0 cases per 1000 person-years (95% CI, 4.8–15.4) in 2006. During the study period, incidence rates increased annually among MSM known to have HIV infection at the time of their first HCV test (5.9, 11.1, 11.4, and 17.5 cases per 1000 person-years, respectively, during 2000–2003, 2004, 2005, and 2006) and among those whose HIV status was unknown or negative (0, 0.7, 1.5, and 5.8 cases per 1000 person-years, respectively, during 2000–2003, 2004, 2005, and 2006). Multivariable Poisson regression analysis confirmed that HIV status at the time of the first HCV test and calendar year were independently associated with incident HCV infection. Rate ratios were 7.01 (95% CI, 2.55–19.26) for MSM with known HIV infection and 1.49 (95% CI, 0.40–5.58) for MSM with an unknown HIV status, compared with MSM without HIV infection (global $P = .0001$). Rate ratios were 2.37 (95% CI, 0.43–12.97) for 2004, 3.12 (95% CI, 0.63–15.49) for 2005, and 6.79 (95% CI, 1.52–30.24) for 2006, compared with 2000–2003 (global $P = .02$).

The high rate of HCV transmission among HIV-infected MSM who were non-IDUs concurs with the findings reported by van de Laar et al. [1] and others. However, to our knowledge, this is the first report of significant sexual transmission of HCV to MSM whose HIV status was either negative or unknown at the time of their first HCV test. Although some of these MSM subsequently received a diagnosis of HIV infection at the time of their first positive HCV test result, HIV infection had not been diagnosed when they were screened for HCV.

It remains unclear why HIV-infected MSM appear to have a greater risk than HIV-uninfected men for acquiring HCV. MSM with HIV infection have higher seminal HCV loads than HIV-uninfected MSM and are more likely to transmit HCV [6]. Furthermore, studies have demonstrated that many MSM "serosort" (i.e., they have unprotected anal sex only with partners whose HIV-infection status is the same as their own), which may contribute to the imbalanced incidence rate

of HCV infection between HIV-infected and HIV-uninfected MSM [7].

Given the available evidence, we propose that all HIV-infected MSM should be screened for HCV on an annual basis but that all MSM, regardless of HIV status, should be screened for HCV in settings where outbreaks of HCV infection are known to have occurred and where MSM are known to participate in high-risk behaviors [2]. It is also clear that incident HCV infection reflects ongoing HIV risk and that all individuals, particularly those with incident HCV infection, should be targeted by behavioral interventions to reduce ongoing transmission.

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Reply to Richardson et al.

To the editor—We share the concern of Richardson et al. [1] that hepatitis C virus (HCV) might emerge among human immunodeficiency virus (HIV)–negative men who have sex with men (MSM). HCV tests or routine liver function tests are not regularly performed among HIV-negative MSM. Because acute HCV infection is usually asymptomatic, the HCV epidemic among HIV-negative MSM might have remained unnoticed. Although longitudinal screening of 1311 HIV-negative MSM participating in the Amsterdam Cohort Studies did not detect even 1 HCV seroconversion in this population from 1985 through 2002 [2], the possibility of a delayed epidemic among HIV-infected individuals that started after 2002 cannot be excluded. In a semiannual survey of persons who attended a sexually transmitted infection (STI) clinic in Amsterdam in March or November 2007, we anonymously tested 2062 attendees for both HIV and HCV infection and interviewed them about risk factors for blood-borne infections and/or STIs. Preliminary results showed that 423 (19.5%) were MSM, of whom 88 (20.8%) tested positive for HIV, and 335 (79.2%) tested negative for HIV. The prevalence of HCV among HIV-negative MSM was 0.60% (2 of 335), compared with 13.6% (12 of 88) among HIV-positive MSM. Excluding MSM with a history of injection drug use, the HCV prevalence was 0.30% (1 of 328) among HIV-negative MSM and 10.8% (9 of 83) among HIV-positive MSM.

It is apparent that sexual transmission of HCV to HIV-negative MSM is rare in Amsterdam, despite the high prevalence of HCV and the ongoing HCV transmission among HIV-positive MSM in the city. This does not mean, however, that sexual transmission of HCV to HIV-negative MSM never occurs. A single case of sexually acquired HCV in a MSM without HIV infection was described in our study (patient S28) [2] and in a study performed in Rotterdam, the Netherlands (patient L) [3]. Phylogenetic analysis proved that both men were infected with the same HCV genotype 4 strain that circulates among HIV-positive MSM in the Netherlands. Danta et al. [4] published 93 sequences of HCV E1/E2 strains recovered from HIV-positive MSM with acute HCV infection from London and Brighton, United Kingdom. Unfortunately, Richardson and colleagues did not compare HCV strains from MSM without HIV infection or with an unknown HIV status with HCV strains circulating among HIV-positive MSM. Phylogenetic typing of HCV strains isolated from HIV-negative MSM could have strengthened their hypothesis of an expanding epidemic.

The question remains why HIV-positive MSM are at higher risk than HIV-negative MSM for acquiring HCV. HIV infection might facilitate HCV transmission through greater than average HCV seminal loads [5] and/or its detrimental effects on the gastrointestinal immune system [6]. It must be kept in mind, however, that sexual transmission of HIV is more efficient than sexual transmission of HCV and that background HIV loads exceed those of HCV in MSM. In the vast majority of MSM who engage in high-risk sexual behavior, acquisition of HIV will therefore probably precede HCV infection.

We concur with Richardson et al. [1] that the growing hepatitis C epidemic requires targeted prevention and routine HCV testing in HIV-positive MSM. Concordant with findings from a large multicenter study performed across HIV/genitourinary medicine clinics in London and Brighton [7], our results indicate that there is currently little evidence that sexual transmission of HCV occurs among HIV-negative MSM. Moreover, we think that the findings of Richardson and col-

leagues do not exclude the possibility that the increased incidence of HCV among MSM whose HIV status was negative or unknown at the time of initial HCV testing was mainly caused by MSM with an unknown HIV status, particularly because some of these MSM eventually received a diagnosis of HIV infection at the time of their first positive HCV test result [1]. Second, the study of Richardson and colleagues might suffer from selection bias, as 2544 (42%) of 6124 MSM were excluded because they had never been tested for HCV.

We think that advice to implement regular HCV screening of HIV-negative MSM is premature at this moment. We agree, however, that the incidence of HCV infection has the potential to increase among HIV-negative MSM, and we therefore believe that trends in the spread of HCV should be closely monitored. If future data provide stronger evidence for an increase in the incidence of HCV infection among HIV-negative MSM, regular HCV screening may become advisable for this population.

Thijs J. W. van de Laar,[1] Anouk T. Urbanus,[1] Sylvia M. Bruisten,[1,2] Henry J. C. de Vries,[1,3] Harold F. J. Thiesbrummel,[1] Roel A. Coutinho,[2,4] and Maria Prins[1,2]

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Congenital Transmission of HHV-6

To the Editor—The article by Caserta et al. [1] and the editorial by Pellett and Goldfarb [2] raise interesting issues about the congenital transmission of human herpesvirus 6 (HHV-6). In the editorial, an analogy is made between HHV-6 infection and congenital cytomegalovirus (CMV) infection, and the authors state that only 1% of infants infected with CMV at birth are symptomatic [2]. However, a higher rate has been observed among infants with congenital CMV infection acquired from mothers with primary CMV infection: 5%–10% of such infants are likely to be symptomatic, and many more will show sequelae.

The data in the article suggest that, because nearly all mothers have previously been infected with HHV-6, viremia during pregnancy may arise from reactivation of latent infection, either episomally or from viral DNA integrated into the chromosomes [1]. This would be partly analogous to the situation in CMV-seropositive women, who will occasionally transmit virus to their infants but whose infants will rarely show symptoms at birth, in contrast to infants born to seronegative mothers. Therefore, I conclude that we do not yet know what the consequences of congenital HHV-6 infection are in the absence of maternal immunity.

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Reply to Plotkin

To the Editor—We appreciate the thoughtful comments of Plotkin [1] about the article in which we described human herpesvirus (HHV)–6 and HHV-7 infections in pregnant women and their newborns [2]. We agree that, because all mothers have had previous HHV-6 infection, congenital infection with HHV-6 is not completely analogous to congenital infection with cytomegalovirus (CMV). We also agree that we do not know and probably will never know the consequences of congenital infection with HHV-6 in the absence of maternal immunity, because the lack of such immunity is exceedingly rare.

However, these assertions do not rule out the possibility that congenital infection with HHV-6 may result not only from maternal reactivation but also from reinfection with a new strain of HHV-6 despite preconceptional immunity, as has been shown for CMV [3]. Symptomatic congenital CMV infection may be more common than previously recognized in

newborns of women with preexisting immunity and, at one center, has been shown to be as frequent a mechanism of transmission as primary maternal infection in children with symptomatic disease [4].

Our study indeed showed that there are multiple mechanisms of transmission of congenital HHV-6 infection, all of which involve women with preexisting immunity. On the basis of our data and the recognized potential of congenital CMV infection to cause severe disease after maternal reinfection, we believe it is critically important to determine the biological, epidemiological, and clinical characteristics of congenital HHV-6 infection.

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