

Redefining the Paradigm: The Role of Sexual Networks and Sexualized Drug Use in the Transmission of Hepatitis C Virus Among Men Who Have Sex With Men

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(See the Major Article by Artenie et al on pages 662–73.)

Keywords. condomless receptive anal intercourse (CRAI); HIV infection; methamphetamine; people who inject drugs (PWID); semen.

The most common route of hepatitis C virus (HCV) transmission in the United States is the sharing of blood-contaminated injection equipment among people addicted to heroin or other narcotics. This group of people is generally described in the literature as “people who inject drugs,” or PWID, and became the focus of the HCV field. Subsequently, however, HCV infection emerged in a new group of people, whose behaviors did not neatly fit this paradigm. In 2004, reports emerged from Western Europe suggesting sexual transmission of HCV among men who have sex with men (MSM) with human immunodeficiency virus (HIV), and over the next decade, case series of transmission of HCV among MSM with HIV were published from large cities around the globe [1]. The incidence rates for primary (ie, the initial) infection were ~0.5 per 100 person years (PY), much lower than incidence rates among PWID, leading to an assumption that sexual transmission among MSM is inefficient [2]. However,

it was subsequently observed that reinfections among MSM occurred at rates over an order of magnitude higher than primary infection, up to 15 per 100 PY [3]. These rates, which approximate those of primary infection rates among PWID, called into question the assumption that sexual transmission among MSM is inefficient, and, in parallel with behavioral and molecular studies, suggested important insights into the epidemiology of HCV among MSM.

Soon after the recognition of primary HCV infection among MSM, case-control studies to determine behavioral risk factors were performed in multiple large cities, including from our 2 groups in the Netherlands and New York City (NYC). The individual findings differed among the multiple studies, but, generally, most studies, including ours, found associations with several sexual behaviors and with drug use behaviors (summarized in [4]). Drug use among MSM is quite different than among PWID, however, in that it is sexualized rather than addictive behavior, that is, becoming “high” for the purposes of/in conjunction with sex, even with injection use (summarized in [4]). With the emergence of reinfection as a significant problem among MSM, our 2 groups then performed studies of risk factors for reinfection, and both found the same striking difference from the results of our studies of primary infection. Although we had

found that primary infection was associated with sexualized drug use in both locales [5, 6], we found that reinfection was not associated with sexualized drug use in either locale [3, 7], although the secondary analysis of the route of drug use in NYC found that sexualized methamphetamine use by injection was associated with reinfection [8], which we will return to. However, our findings about sexual behaviors were the same for reinfection as they had been for primary infection, in particular a strong association with condomless receptive anal intercourse (CRAI), and in NYC, specifically receiving semen into the rectum.

This is the context in which Artenie et al [9] present their mathematical modeling analysis estimating the success of the “End Hep C SF” public health initiative in reducing HCV prevalence and incidence among MSM in San Francisco, published in this issue of the *Journal of Infectious Diseases*. One of the main goals for this modeling was to account for the effect of injection drug use among MSM, rather than the more generic category of “high-risk” groups. They used data from studies that reported relative risks of HCV acquisition attributed to injection drug use among MSM compared to sexual practices. They conclude that injection drug use accounted for 43% of incident HCV infections, although injection use itself was reported by just 13% of

Received 07 July 2023; editorial decision 07 July 2023; accepted 12 July 2023; published online 24 July 2023

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The Journal of Infectious Diseases® 2023;228:657–61

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<https://doi.org/10.1093/infdis/jiad265>

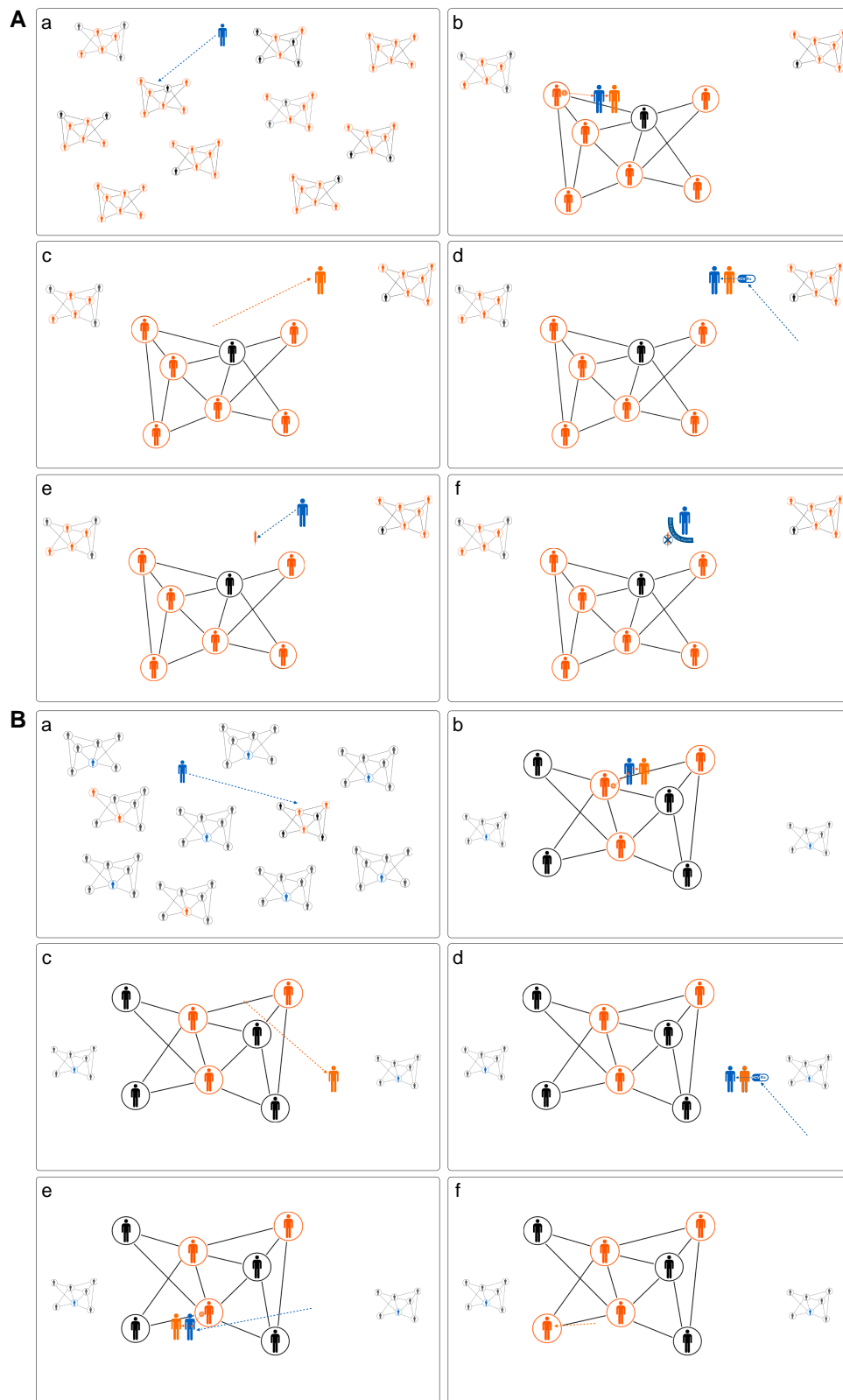


Figure 1. (A and B) Graphical depiction of the effect of hepatitis C virus (HCV) prevalence and prevention methods on primary HCV infection and HCV reinfection in (A) injection networks of people who inject drugs and (B) sexual networks of men who have sex with men (MSM). A, panel a, All injection networks are composed of multiple orange/lighter shade (HCV infected) figures, denoting the uniformly high prevalence of HCV both among and within injection networks. Person without HCV (blue/intermediate shade figure), who is initiating inject drug use, moves to newly join an injection network. A, panel b, Close-up of injection network joined by person without HCV (blue/intermediate shade figure). The newly joined person shares injection equipment with HCV-infected individual (orange, lighter shade figure).

MSM. However, the data from which relative risk was calculated were from locales outside of, and during time periods before, significant sexual transmission among MSM, so they were more likely evaluating the consequences of addictive drug use by men who happened to have sex with men (ie, PWID), rather than sexualized drug use by the injection route in sexually active MSM. These important distinctions, which were alluded to recently in other work by Artenie et al [10], are commonly conflated in the HCV field and need to be disentangled. Nonetheless, we agree that the association between sexualized injection use of drugs among MSM with HIV and incident HCV infection is overall correct. However, the reasons for the association are different from those traditionally assumed.

To explain these associations, we propose a model derived from 2 lines of epidemiological evidence that we outlined above: first, that reinfection rates among MSM are much higher than primary infection rates; and second, that among MSM, although sexualized drug use was associated with primary infection in many studies, it was not overall associated with reinfection. The model that best fits these data is that participating in sexualized drug use, whether by injection or not, is an indication of being part of a

sexual network in which the HCV prevalence is high; and conversely, that those who do not participate in sexualized drug use are part of sexual networks in which the HCV prevalence is low enough to result in few, if any, onward transmissions.

This model is most clearly illustrated by comparing the characteristics of injection networks of PWID with sexual networks of MSM. Because injection networks of PWID uniformly have very high HCV prevalence rates [11], a person newly entering an injection network without access to fresh injection equipment is highly likely to use equipment containing blood from a person with HCV, resulting in very high incidence rates of primary HCV. The PWID who enter care to cure this HCV infection are also often offered multimodal harm reduction, which reduces drug use through medication-assisted recovery and reduces contact with blood from others through provision of clean injection supplies, resulting in reinfection rates among PWID that are an order of magnitude lower than primary infection rates, despite returning to the high HCV prevalence injection network (Figure 1A).

In contrast, among MSM, the reinfection rates are an order of magnitude higher than primary infection rates, which infers that HCV prevalence is

both heterogeneously and sparsely distributed among sexual networks [2], very different from HCV in injection networks of PWID, but consistent with the heterogeneous distribution of other infectious agents among sexual networks of MSM [12]. Thus, MSM newly entering a sexual network have a relatively low chance of acquiring HCV overall. The subset of MSM who participate in sexualized drug use, because they are most likely to be part of a sexual network in which HCV is prevalent, with receiving semen into the rectum, are the ones who acquire (primary) HCV. However, after cure of primary infection, MSM have no effective harm reduction programs to decrease re-exposures to HCV. Condom use, the only reliable method to prevent HCV in semen from entering the rectum with CRAI, has not been an accepted practice among MSM who have multiple partners, even in the context of a primary HCV infection [13], nor are there effective interventions for sexualized drug use, which is a trigger for sex/CRAI. Therefore, when returning to the high-prevalence sexual networks, the reinfection rates for MSM are high (Figure 1B).

There are caveats. Sharing of injection equipment does occur among MSM, of course, both accidentally, and purposefully, through sexualized exchanges. We have demonstrated this occurrence using

Figure 1. continued. HCV, denoted by orange, lighter shade figural virus, is transmitted to blue, intermediate shade figure, with the transition of the figure to orange/lighter shade. A, panel c, Newly HCV-infected person (orange/lighter shade figure) is diagnosed with HCV and seeks treatment. A, panel d, Treatment with direct-acting antiviral (DAA) is provided, denoted by figural medication tablet labeled "HCV Rx," resulting in cure, denoted by return of figure to blue/intermediate shade. A, panel e, Newly cured person (blue/intermediate shade figure) contemplates returning to injection network and resuming injection drug use with potentially blood-contaminated equipment, denoted by figural syringe. A, panel f, Newly cured person (blue/intermediate shade figure) engages in programmatic treatment of addiction, which prevents exposure to blood-contaminated equipment, denoted by figural barrier labeled "medication assisted recovery" and figural "X," and the person remains free from reinfection. B, panel a, Sexual networks are composed of a range in proportions of orange/lighter shade (HCV infected) figures from none (indicated by a single blue/intermediate shade figure among all black figures) to relatively high (multiple orange/lighter shade figures), denoting the heterogeneity of HCV both among and within sexual networks. MSM, who is initiating sexual activity, moves to newly join a sexual network that has a relatively high HCV prevalence. B, panel b, Close-up of sexual network joined by MSM without HCV (blue/intermediate shade figure). The newly joined man has sex with HCV-infected man (orange/lighter shade figure). HCV, denoted by figural virus, is transmitted to blue/intermediate shade figure, with the transition of the figure to orange/lighter shade. B, panel c, Newly HCV-infected man (orange/lighter shade figure) is diagnosed with HCV and seeks treatment. B, panel d, Treatment with DAA is provided, denoted by figural tablet labeled "HCV Rx," resulting in cure, denoted by return of figure to blue/intermediate shade. B, panel e, Newly cured man (blue/intermediate shade figure) returns to sexual network, does not start using condoms to prevent HCV-containing semen from entering his rectum, encounters a different man with HCV infection, and is reinfected, denoted by orange/lighter shade figural virus. B, panel f, Newly reinfected man (orange/lighter shade figure now within circle) further increases the HCV prevalence within this high-prevalence sexual network. Legend: Groupings of figures within circles represent individual sexual or injection networks. Networks with prevalent HCV are represented by figure(s) in orange/lighter shade, along with the other member of the network, who are without HCV, represented in black. Networks without HCV are represented by one figure in blue/intermediate shade among other figures in black, none of whom have HCV. The higher the ratio of orange/lighter shade to black figures in a grouping, the higher the HCV prevalence within that network. Segmented orange/lighter shade and blue/intermediate shade lines with arrow head represent directionality of movement of the person or object at the origin; orange/lighter shade represents events of HCV infection; blue/intermediate shade represents events without encountering HCV.

single-genome sequencing in the case of a known sharing exposure [4]. However, in this same study, we found that most acquisition was likely through receiving semen in the rectum, including in those with injection use of methamphetamine when no sharing of injection equipment occurred [4]. Injection use of methamphetamine by MSM may also lead to more, or more intense, exposures to HCV-containing fluids. In addition, in our experience in NYC, a subset of those who inject methamphetamine have had poorer engagement in healthcare, some whom we were not able to cure for years after the incident infection. The sexual networks of these MSM who use methamphetamine by injection would therefore have the highest HCV prevalence, which we think is the likely explanation of our finding of an association between injection use of methamphetamine (but not use overall) and reinfection in NYC. How HCV entered sexual networks of MSM is not known, but we speculate that HCV may have been introduced by distant heroin injection among MSM, with a subsequent shift to sexualized methamphetamine use (ie, we have found no current heroin use among these sexual networks in NYC). Phylogenetic studies are underway to evaluate this hypothesis. Fomite/fomite-like transmission may also occur during group sex via fists, toys, and penises mediated by HCV in rectal fluid [14, 15], or by rectal blood in Germany, where frequent rectal trauma was reported [16]. However, with the findings from our NYC studies that semen ejaculated into the rectum was the primary risk for both primary infection and reinfection, and with the finding that HCV is detectable in semen of a significant proportion of MSM with HCV [17, 18], and with almost all other risk factor studies from other locales also showing associations with CRAI, we suggest that most HCV infections among MSM are mediated by intrarectal deposition of seminal HCV. Finally, regardless of route of infection, HCV transmission among MSM necessarily

requires being part of one of the sparsely distributed sexual networks in which HCV is prevalent.

The paradigm of blood as the medium of HCV transmission through drug use that has been so well studied in PWID was transferred to the newer risk group of MSM. This paradigm has continued to be applied to MSM despite the predominance of evidence accumulated over the last approximately 2 decades that drug use itself does not explain transmission among MSM who are not actually “PWID.” We call for a paradigmatic shift to recognize the more complex problems presented by the multiple routes of transmission and the unevenly distributed risk of exposure due to the heterogeneity of HCV prevalence among sexual networks of MSM. This shift in understanding is essential for effecting elimination of HCV as an important pathogen among MSM, which, despite early progress through treatment, has not been successful overall [19], notwithstanding this welcome note of optimism from San Francisco described by Artenie et al [9].

Notes

Potential conflicts of interest. No financial support was received for this work. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Kaplan-Lewis E, Fierer DS. Acute HCV in HIV-infected MSM: modes of acquisition, liver fibrosis, and treatment. *Curr HIV/AIDS Rep* **2015**; 12:317–25.
2. Hagan H, Jordan AE, Neurer J, Cleland CM. Incidence of sexually transmitted hepatitis C virus infection in HIV-positive MSM: a systematic review and meta-analysis. *AIDS* **2015**; 29:2335–45.
3. Newsum AM, Matser A, Schinkel J, et al. Incidence of HCV reinfection among HIV-positive MSM and its association with sexual risk behavior:

a longitudinal analysis. *Clin Infect Dis* **2021**; 73:460–7.

4. Li H, Marks KM, Talal AH, et al. Assessing routes of hepatitis C transmission in HIV-infected men who have sex with men using single genome sequencing. *PLoS One* **2020**; 15:e0235237.
5. Fierer DS, Factor SH, Uriel AJ, et al. Sexual transmission of hepatitis C virus (HCV) among HIV-infected men who have sex with men (MSM), New York City, 2005–2010. *MMWR Morb Mortal Wkly Rep* **2011**; 60:945–50.
6. Vanhommerig JW, Lambers FA, Schinkel J, et al. Risk factors for sexual transmission of hepatitis C virus among human immunodeficiency virus-infected men who have sex with men: a case-control study. *Open Forum Infect Dis* **2015**; 2:ofv115.
7. Factor SH, Carollo JR, Rodriguez-Caprio G, et al. Sex, not drug use, is driving HCV reinfection among HIV-infected MSM in New York City [abstract 594]. 27th Conference of Retroviruses and Opportunistic Infections (virtual) 8–12 March 2020.
8. Fierer DS, et al. Forthcoming.
9. Artenie A, Stone J, Facente SN, et al. Impact of HCV testing and treatment on HCV transmission among men who have sex with men and who inject drugs in San Francisco: a modelling analysis. *J Infect Dis* **2023**; 228:662–73.
10. Artenie A, Facente SN, Patel S, et al. A cross-sectional study comparing men who have sex with men and inject drugs and people who inject drugs who are men and have sex with men in San Francisco: implications for HIV and hepatitis C virus prevention. *Health Sci Rep* **2022**; 5:e704.
11. Nelson PK, Mathers BM, Cowie B, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. *Lancet* **2011**; 378:571–83.
12. Sullivan PS, Satcher Johnson A, Pembleton ES, et al. Epidemiology of HIV in the USA: epidemic burden,

- inequities, contexts, and responses. *Lancet* **2021**; 397:1095–106.
13. Künzler-Heule P, Fierz K, Schmidt AJ, et al. Response to a sexual risk reduction intervention provided in combination with hepatitis C treatment by HIV/HCV co-infected men who have sex with men: a reflexive thematic analysis. *BMC Infect Dis* **2021**; 21:319.
 14. Foster AL, Gaisa MM, Hijdra RM, et al. Shedding of hepatitis C virus into the rectum of HIV-infected men who have sex with men. *Clin Infect Dis* **2017**; 64:284–8.
 15. Chromy D, Schmidt R, Mandorfer M, et al. HCV-RNA is commonly detectable in rectal and nasal fluids of patients with high viremia. *Clin Infect Dis* **2020**; 71:1292–9.
 16. Schmidt AJ, Rockstroh JK, Vogel M, et al. Trouble with bleeding: risk factors for acute hepatitis C among HIV-positive gay men from Germany—a case-control study. *PLoS One* **2011**; 6:e17781.
 17. Bradshaw D, Lamoury F, Catlett B, et al. A comparison of seminal hepatitis C virus (HCV) RNA levels during recent and chronic HCV infection in HIV-infected and HIV-uninfected individuals. *J Infect Dis* **2015**; 211: 736–43.
 18. Turner SS, Gianella S, Yip MJ, et al. Shedding of hepatitis C virus in semen of HIV-infected men. *Open Forum Infect Dis* **2016**; 3: ofw057.
 19. Factor SH, Fierer DS. Can treatment, without prevention, eliminate hepatitis C among men who have sex with men? *J Viral Hepat* **2022**; 29: 1048–9.