

# Hepatitis C Virus Reinfection Rate Among Persons Who Use Drugs and Are Maintained on Medication Treatment for Opioid Use Disorder

Sandra A. Springer

Yale University AIDS Program, New Haven, Connecticut

(See the Major Article by Akiyama et al on pages 2695–72.)

In their extension follow-up study of the previously published 3-arm PREVAIL randomized controlled trial of 3 models of care for treatment of hepatitis C virus (HCV) infection [1, 2], published in this issue of *Clinical Infectious Diseases* [3], Akiyama et al found an extremely low HCV reinfection incidence rate among persons receiving medication treatment for opioid use disorder (OUD) (MOUD) who had been treated with direct-acting antivirals and achieved HCV cure (sustained viral response at 12 weeks and 24 weeks).

The parent PREVAIL trial, from which participants in the current study were recruited, included 150 persons with OUD enrolled in opioid agonist treatment program (methadone/buprenorphine) in the Bronx, New York. Within the PREVAIL study, 94% achieved sustained viral response and thus achieved HCV cure. This is consistent with findings in other studies of persons who use drugs (PWUD) receiving MOUD who were treated for HCV [4–6]. Such similarities to HCV cure have been seen in the treatment of persons living with human immunodeficiency virus (HIV) and OUD who received coadministered MOUD

with antiretroviral therapy that improved HIV suppression rates, the ultimate goal of chronic HIV treatment [7–9]. This particular extension study enrolled participants who completed PREVAIL and achieved sustained viral response, and it then followed them up for an additional 24 months to assess HCV reinfection incidence rates, time to reinfection, and risk factors for reinfection. Eighty-one percent of the primary PREVAIL study participants enrolled in this extension study, and all had OUD, with 75% of them reporting injection as the mode of opioid use. All were receiving MOUD, with 98% receiving methadone and the other 2% receiving buprenorphine treatment.

The first important outcome from this study was that only 3 persons met the study's definition of reinfection over a follow-up period 246 person-years, with the reinfection incidence rate calculated as 1.22/100 person-years. In addition, only 2 of the 3 actually met "clinical" criteria for HCV reinfection based on the persistence of HCV viremia, and 1 had only transient detectable viremia that cleared spontaneously without retreatment for HCV. This low rate of HCV reinfection is similar to that in other studies such as C-EDGE CO-STAR [4, 10], which also included PWID receiving MOUD, and the SIMPLIFY trial [11], which included PWUD with ongoing drug use not receiving MOUD. Overall, MOUD has been shown to reduce an individual's risk of acquiring HCV by about half [12–14].

Second, 19% of the participants in this extension study reported ongoing drug use, and the incidence of reinfection was greater (7.4 per 100 person-years) than among those who did not have ongoing drug use. Ongoing injection drug use also was found to be an independent predictor for HCV reinfection in this study, similar to findings in other published studies [10, 15]. Importantly however, this study identified that injecting opioids plus stimulants or stimulants alone predicted the risk of reinfection, but injecting opioids alone did not. This is an extremely critical point and is often overlooked in studies of reinfection after treatment for HCV among PWUD.

Akiyama et al [3], in the current study, obtained more nuanced results by identifying the form of drug injected when evaluating predictors of reinfection, compared with other published studies that evaluated reinfection risks without considering the form of drug injected. This is important, because it demonstrates that MOUD was not a failure in treating OUD or preventing risk of reinfection, but rather that ongoing stimulant use (cocaine or methamphetamine), alone or in combination with opioids, predicted reinfection. Furthermore, this highlights polysubstance use, in particular methamphetamine combined with heroin and fentanyl, as increasingly associated with new HIV and HCV outbreaks nationally [16–18] as well as increased overdose deaths [19]. Stimulant use can derail benefit of MOUD for OUD treatment, and there is still no identified effective medication

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Correspondence: S. A. Springer, Yale University AIDS Program, 135 College St, Suite 323, New Haven, CT 06437 (Sandra.springer@yale.edu).

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treatment for stimulant use disorders, so more research is needed to develop effective treatments for cocaine and methamphetamine use disorders.

The next important point identified in the current study is that sharing syringes and drug paraphernalia also predicted reinfection, thus identifying the critical need to integrate additional harm reduction services that include needle syringe exchange programs (NSEPs) combined with MOUD during and after HCV treatment to reduce reinfection risk. Systematic reviews and meta-analyses have indicated that NSEPs combined with MOUD are associated with a reduction in an individual's risk of acquiring HCV by as much as 76% and in HIV incidence by 34% [20].

Furthermore, epidemic mathematical models have been used successfully to look at the effects of various coverage levels for interventions to counter the HCV epidemic among PWUD [21–24], and these models have shown that modest increases in levels of HCV treatment among PWUD could substantially reduce HCV prevalence and incidence. The HCV epidemic is slowly expanding among PWUD in the United States, and modeling predicts that scaling up to full harm reduction that includes combining direct-acting antivirals, MOUD, and NSEPs would substantially reduce incidence and prevalence by  $\geq 50\%$  by 2030 [25]. Scott County, Indiana, had a relatively high prevalence of HCV identified among PWUD, coupled with an expanding HCV epidemic related to a surge in the opioid epidemic there [16]. Mathematical modeling indicates a continued increase in HCV prevalence in Scott County that could rise to roughly 83% by year 2030 in the absence of MOUD and NSEPs to prevent new infection and reduce both chronic prevalence and incidence [25, 26].

The final important point of the study by Akiyama et al [3] is that all 3 persons in the study who were reinfected with HCV after sustained viral response were homeless Latino men. Homelessness was another factor that independently predicted HCV reinfection in this study; it makes entering

treatment for substance use disorders or infectious diseases such HIV and HCV more difficult and presents nearly impossible odds of retention in treatment [27, 28]. Expanding access to HCV treatment must be accompanied by addressing housing needs.

Unfortunately, despite the strong evidence to support that PWUD can adhere to and complete direct-acting antiviral therapy and achieve HCV cure with MOUD, few PWUD are receiving treatment. In most states, HCV treatments are restricted by reimbursements to healthcare providers. For example, 2017 Medicaid restrictions for HCV therapy in many states imposed restrictions based on drug and alcohol use, including abstinence-based restrictions, despite clinical recommendations that recent drug use should not be a contraindication to HCV treatment. Some states also imposed restrictions based on liver damage, with HCV treatment prioritized for individuals with more advanced fibrosis. Having restrictions based on both liver damage and abstinence in place excludes most PWUD from eligibility for HCV therapy. Furthermore, the lack of Medicaid expansion and funding sources to care for persons with OUD and other substance use disorders and HCV also markedly reduces the likelihood of eliminating HCV in this country [26].

To address the intersection of these epidemics, it is essential to mandate federal and state resources to fund programs that integrate OUD and other substance use disorders and infectious disease treatment and prevention evidence-based interventions. This study and other published studies show that combined MOUD for treatment of OUD and HCV treatment leads to HCV cure, and integrated harm reduction services, including continued treatment for substance use disorders and NSEPs, lead to low reinfection rates [26, 29].

## Notes

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