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EDITORIAL COMMENTARY

A Call to Action: HCV Treatment of People Who Inject Drugs in the United States

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(See the Major Article by Graf et al on pages 2355–65.)

As the United States experiences an unprecedented opioid epidemic, the number of people who inject drugs (PWID) continues to rise, paralleled by increasing rates of hepatitis C virus (HCV) [1, 2]. Mortality from HCV has now surpassed the combined death rates from the 60 other reportable infectious diseases, including human immunodeficiency virus (HIV) [3, 4]. Direct acting antiviral medications (DAA) have changed the paradigm of HCV treatment, providing highly effective (over 95% cure rates), all oral medications with few side effects and short treatment durations [5]. Given this tremendous opportunity, the World Health Organization (WHO) issued its first global strategy on HCV, with the goal to reach HCV elimination by 2030 [6]. Due to the lack of engagement and treatment of HCV-infected PWID, the United States is not on track to meet these targets [7]. Due to clinician concerns about poor adherence and low cure rates, as well as a fragmented healthcare system, most PWID living in the US have yet to be offered life-saving HCV treatment [8–10].

The systematic review, by Graf et al in this issue of *Clinical Infectious Diseases*, provides further and robust evidence that PWID, both on opioid agonist therapy (OAT) and/or actively injecting drugs, can indeed be successfully treated for HCV with sustained virologic response (SVR) similar to non-PWID. Including data from 2010–2018 of all oral DAA regimens, authors compared HCV outcomes (adherence, discontinuation, SVR) of controls (non-PWID) to over 1700 patients on OAT and over 500 patients actively injecting drugs. The authors also reported pooled reinfection rates. Of the 23 studies included, 12 were from Europe, 7 from Australia, and 3 from North America.

In this meta-analysis, the SVR rates for PWID were high and no different than controls. The overall intention to treat SVR was 90% for PWID on OAT and 88% for those PWID actively using drugs. Importantly, the majority of those who did not achieve SVR were those lost to follow-up (LTFU) rather than true virologic failures, with 43% of those LTFU having completed the full HCV treatment regimen. As such, although these SVR rates appear slightly lower than in registration trials, the per protocol SVR (which the authors do not report) would likely be consistent with expected cure rates. Real-world HCV treatment of PWID does not pose a problem for achieving cure but instead difficulty with obtaining SVR data due to the 12-week time gap after HCV treatment completion [11]. As we continue to collect outcome data among this population it will be important to study interventions designed to keep people engaged in care after treatment completion. Alternatively, checking HCV viral load 4 weeks after treatment completion may be one method at obtaining more accurate SVR data, given its 98% concordance with SVR12 in patients treated with sofosbuvir-based regimens (and likely all new DAAs) [12].

Many of the PWID in these studies received HCV treatment outside of hepatology or infectious disease settings. Most participants on OAT in this meta-analysis received HCV treatment at their opioid treatment center, a few studies taking advantage of directly observed therapy (DOT). This does not undermine the impressive HCV cure rates, but instead provides evidence of a useful intervention—colocated care—that can be taken advantage for the nearly 1500 opioid treatment programs (OTP) in the United States, as well as the increasing number of people in buprenorphine treatment. As more persons seek out treatment for their opioid use disorder (OUD), an efficient "test and treat" approach for HCV needs to be taken [13]. Our current healthcare infrastructure has failed to include PWID, and referrals to specialty care have not provided the answer. In order to meet WHO targets and eliminate HCV, we will need to remove the silos of care and integrate services for HCV and OUD. Task shifting to community-based providers has been highly successful, showing no differences in SVR rates by practitioner type [14]. As such, states should assume policies that allow nonspecialists such as primary

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care physicians, addiction specialists, and nurse practitioners to treat HCV. If the clinical infrastructure does not exist within these OUD treatment programs, telemedicine and telementoring—also shown to be effective—should be used (though not required) to aid in the roll-out of HCV treatment for PWID [15, 16]. Other settings where PWID are already accessing care, such as federally qualified health centers, OTPs, syringe exchange programs, homeless shelters, and jails and prisons, can also be used to expand HCV treatment to this population.

Although many clinicians have concerns over poor adherence among PWID, this meta-analysis shows that adherence rates were found to be similar between PWID and controls. This is true despite a very high adherence cutoff of 90%. These data should be taken with caution given most studies provided self-reported adherence, known to be higher than other adherence measures. Interestingly, there were no differences in SVR rates between those that were defined as adherent, and those that were not. This may indicate that a 90% adherence threshold is too high in the era of DAAs to predict failure. Indeed, the PREVAIL study showed an overall SVR of 94% among 150 PWID, with an overall daily adherence of only 78% [17]. In order to reach HCV elimination, we must expand HCV to a broad population of PWID including those not enrolled in substance use treatment programs, some who may potentially have suboptimal adherence. In the era of potent DAA regimens, high adherence may not be necessary for SVR. Further studies should evaluate the threshold of adherence needed to reach cure in the DAA era.

This meta-analysis also adds to the evidence that concerns of high reinfection rates are not substantiated. Reinfection rates varied from 0 to 12.5 reinfections per 100 person-years, with the majority of studies having no reinfections. The variability is likely due to the heterogeneity of risk behaviors among the study populations, as well as follow-up time. Another recent meta-analysis analysis found 3.81 reinfections per 100 person-years for those on OAT, and 5.86 per 100 person-years for those with recent injection drug use [18]. Ultimately, reinfections among PWID have not been as high as many feared. Nevertheless, results should be interpreted with caution given the short follow-up period, as well as the fact that the majority of these studies have been conducted in Europe where harm reduction services are much more widespread than in the United States.

It has been shown in multiple studies that the combination of HCV treatment, OAT, and syringe exchange is the most robust response to reducing both new infections and reinfections in PWID and thereby the population at large [19]. As such, the WHO has set goals for improving OAT coverage and increasing syringe coverage to 300 syringes per PWID per year in order to reach HCV elimination [6]. Currently in the United States, we have low to moderate OAT coverage and poor syringe exchange coverage—20 syringes per PWID per year [20]. As exemplified by the HCV outbreak in Scott County, Indiana, harm reduction coverage is often worse in rural and suburban areas—regions where we are currently experiencing the highest rise in opioid injection use and incident HCV infections. A study by Fraser et al determined that in places like Scott County, we would need to treat 25% of PWID a year in order to reach the HCV elimination goal by 2030; this number drops by half if we simultaneously scale up OAT and syringe exchange [21]. Now, there are emerging real-world data from Australia that HCV treatment as prevention combined with syringe exchange has reduced the incidence of HCV among PWID [22]. As such, the United States must have the political and social will to increase harm reduction services in all states, particularly in rural and suburban regions, and come up to par with other industrialized nations on track to eliminate HCV. Furthermore, alternative payment models that are being designed to improve the care of the growing number of patients with opioid use disorder should also include treating infectious diseases such as HCV [23].

Finally, US efforts to reach WHO elimination goals will never be reached if payors continue to have policies that specifically exclude people who use drugs. Many states in the United States continue to have sobriety requirements anywhere from 3 to 6 months of documented nondrug use [24]. Given the irrefutable evidence that PWID can be successfully cured, and that rapid treatment scale-up of this key population is the only approach to reduce transmission and incident infection, payor polices must immediately allow for treatment of PWID. This is not only the right approach for public health but the ethical approach for the individual PWID who is at risk of poor health outcomes due to HCV. Eliminating stigma associated with PWID may prove to be the largest hurdle to overcome if we are to truly eliminate HCV in the United States.

Note

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