To Eliminate Hepatitis C in People Who Inject Drugs, Stop Ignoring Drug User Health

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Despite the existence of highly effective direct-acting antivirals (DAA), hepatitis C (HCV) remains an underdiagnosed and undertreated disease. At present, only 20% of the 71 million cases of HCV have been diagnosed worldwide, and HCV treatment uptake is less than 10%[1–3]. Further, there is ongoing incidence of HCV in people who inject drugs (PWID)[4], particularly in regions hard-hit by the opioid use disorder (OUD) epidemic, reflected by a tripling of acute HCV diagnoses in the United States from 2009 to 2018[5]. Globally, modeling data have demonstrated that transmission among PWID is a primary driver of the HCV epidemic, with a population attributable fraction on average of 43%, with larger proportions in high-income countries[6]. Additional modeling data have demonstrated that scale-up of HCV testing and treatment within PWID is critical to achieving World Health Organization (WHO) elimination targets by 2030[7,8]. Yet strategies specifically targeting PWID, such as integration of HCV and OUD care, have not been widely implemented[9]. In particular, opioid agonist therapy (OAT), an evidence-based intervention for the treatment of OUD, has been shown to reduce the transmission of HCV in PWID[10–13]. However, the role of OAT in HCV testing and treatment has not been well-described.

In this issue of *Clinical Infectious Diseases,* Grebely and colleagues report findings from a comprehensive systematic review and metanalysis, "Effect of opioid agonist therapy on testing, treatment uptake, and treatment outcomes for hepatitis C infection among people who inject drugs". The purpose of this evaluation was to review existing literature to understand the association between OAT and HCV testing and treatment outcomes, and the impact of the timing of OAT relative to these outcomes. Their meta-analysis seeks to extend our understanding of the role of OAT in curtailing the HCV epidemic in PWID, by not only aiding prevention, but by facilitating HCV testing and treatment.

Following the PRISMA format for systematic reviews, the authors included 22 studies with a time restriction of publication from January 2013, corresponding with DAA availability, through September 2018. Eligible studies included subjects with recent injection drug use (IDU), defined as injection within the last year; reported on at least one HCV outcome variable; and reported these outcomes separately among individuals with and without OAT. The narrow focus on individuals with recent IDU is critical, as much of the literature on PWID blends historical and present injection behavior, despite disproportionate risk in those with current injection.

The OAT exposure variable was defined as treatment with either methadone or buprenorphine, further categorized as "ever", if within the subject's lifetime, or "recent", if within the last six months. HCV outcome variables included HCV antibody testing, confirmatory RNA testing, DAA treatment initiation, and sustained virologic response (SVR), and were further categorized as "ever", if within the subject's lifetime, or "recent", if within the last year. The studies included were primarily observational cohort and cross-sectional studies conducted across Australia, Europe, North America, and Thailand. The majority of studies were Australian, and indeed, many from the authors

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of this review, a limitation of the analysis and emblematic of the large gaps in data on PWID from low and middle-income countries. The authors included rigorous methods to appraise the data, including estimates of bias and heterogeneity, which are reported extensively in the supplemental material.

Utilizing random-effect meta-analysis estimates to evaluate the likelihood of outcome variables corresponding with OAT exposure, the authors found, broadly, that OAT was associated with an increased likelihood of HCV antibody testing, confirmatory RNA testing, and DAA treatment initiation. Given that many of the included studies were retrospective or cross-sectional, a significant limitation of these findings is the lack of clear temporality in the association between the exposure of OAT, and HCV outcomes. However, generally across HCV outcomes, the analysis of "recent" OAT exposure demonstrated increased likelihood and lower heterogeneity scores compared to "ever" OAT, suggesting that when temporality was more evident, the association was supported.

These data highlight the importance of HCV testing and treatment strategies that integrate HCV and OUD care, and are supported by the existing literature. Previous studies have demonstrated that OAT decreases the likelihood of HCV acquisition[10–13]; that HCV treatment can successfully be administered in OAT settings[14–18]; that HCV treatment can be used to engage individuals in OAT[19]; and with this systematic review, that OAT is associated with an increased likelihood of HCV testing and treatment uptake.

Importantly, OAT is not a pre-requisite for HCV testing, treatment, or SVR[15,18,19]; nor is HCV care necessary for initiation of OAT. Indeed, this analysis found that OAT was not associated with DAA treatment completion or SVR, which the authors reason is secondary to the high rates of treatment completion and SVR across all patient cohorts. Further, there was insufficient data to assess the impact of OAT on adherence, though increasing evidence has supported that overall treatment completion rather than specific adherence may be a primary predictor of high rates of SVR[20,21].

While these data indicate that OAT may serve as a bridge to HCV testing and treatment, another important conclusion is that PWID not engaged in OAT have insufficient access to HCV services. This may be an indication of provider stigma, systems barriers such as insurance restrictions, or a lack of engagement within the healthcare system. As access to OAT remains limited worldwide[22,23], strategies relying on integration of OAT and HCV treatment alone will exclude the majority of people who use drugs. Qualitative and quantitative investigations[19,24–26] have demonstrated that, like most marginalized populations, the care of PWID can be improved by a culturally competent, low-barrier setting, with a strong and trusted relationship to the drug using community. To improve HCV prevention, testing, and treatment in PWID, it is critical to integrate HCV care not only with OAT, but into a larger framework of drug user health, across all settings accessed by people who use drugs, including syringe service programs, overdose prevention sites, jails and prisons, infectious disease and primary care clinics.

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The lessons learned from the HCV epidemic and identified in this investigation highlight the dangers of separating the healthcare system from drug user health, and can be applied to the current global COVID-19 epidemic. People who use drugs, especially those who inject, face a unique constellation of potential challenges, including increased susceptibility to and severity of COVID-19 due to higher rates of pulmonary and immunologic comorbidities, increased likelihood of transmission due to crowded living facilities or drug consumption spaces, and higher rates of overdose death in re-prioritized emergency medical systems. Further, PWID may face decreased access to sterile drug equipment and OAT, two critical factors in the prevention of HCV and other OUD-related morbidities. Increased incidence of HCV in PWID may be part of the collateral damage driven by COVID-19. Only a complete integration of medical care and harm reduction globally will mitigate the damage of these past and current threats to the health of PWID.

As COVID-19 restructures our daily lives and medical systems, we have the opportunity to stop ignoring drug user health, and build something better- a network of integrated care that relies on common sense and evidence, leaving the stigma of drug use behind.

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Potential Conflicts of Interest

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