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REVIEW

A framework for approaching hepatitis C reinfection in people who use drugs

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Despite tremendous advances in the management of HCV, including the availability of a curative treatment, an estimated 57 million people worldwide are living with chronic HCV.[1] People who inject drugs (PWIDs) are a key at-risk population for both prevalent and incident HCV, and thus are a critical focus for HCV elimination efforts.[2,3] Direct-acting antiviral (DAA) therapy is both safe and effective in PWID.[4–6] Moreover, in the absence of an effective vaccine for HCV, modeling studies support scaling up DAA access in PWID in a "treatment-as-prevention" strategy.[7] However, HCV reinfection after successful DAA treatment remains a concern and could hinder elimination efforts. This review will summarize HCV reinfection incidence and outcomes among PWIDs and will describe a multi-faceted approach to addressing HCV reinfection among PWIDs.

INCIDENCE OF HCV REINFECTION IN PWIDs

In the pre-DAA era, 2 systematic reviews evaluated the incidence of HCV reinfection among PWID who had achieved sustained virologic response (SVR) after HCV treatment. Although over 50 studies were included, they were relatively small with heterogenous populations.[8,9] Since the development of DAAs, HCV treatment has become more widely available and effective, and over time, DAA uptake among PWID has increased. In this context, a recent large meta-analysis with over 3790 PWIDs found an overall HCV reinfection rate of 6.2/100 person years (PY) (95% CI: 4.3–8.9) among people reporting recent injection drug use (IDU) and 3.8/100 PY (95% CI: 2.5–5.8) among those receiving opioid agonist therapy (OAT).[10] Several additional studies have since been published, with reinfection rates ranging from 1.8/100 PY (95% CI: 0.6–5.6) in a UK cohort treated at an addiction center to 28.7/100 PY (95% CI: 16.3–50.6) among persons in an Australian prison who reported recent IDU and sharing of needles/syringes (Table 1).[11–20] In addition to IDU, factors associated with higher rates of reinfection include younger age, experiencing unstable housing or homelessness, receipt of HCV treatment while in prison, and recent needle or syringe sharing.[11,13,15,19] Notably, much of this research has been conducted outside of the United States. Given the highly regional nature of drug use epidemics, more data on reinfection rates and risk factors in the United States are needed.

OUTCOMES OF HCV REINFECTION IN PWID

Existing studies suggest that SVR rates are high among patients retreated with DAAs for reinfection, although multiple reinfections can occur.[18,20,21] Importantly, high rates of HCV reinfection may be an indicator of high overall mortality. In one study of 94 individuals who underwent HCV treatment at a community needle and syringe program in the United Kingdom, HCV reinfection rate among those who achieved SVR was 21.5/100 PY (95% CI: 13.0–35.7).[21] The mortality rate

Abbreviations: DAA, direct-acting antiviral; IDU, injection drug use; OAT, opioid agonist therapy; PWID, people who inject drugs; PY, person years; SVR, sustained virologic response.

TABLE 1 Incidence of HCV reinfection after sustained virologic response among persons who use drugs

References	Location	Population	Study design	No. subjects	No. reinfections	Reinfection rate, per 100 PY (95% CI)
Hajarizadeh et al[10]	International	Recent drug use or receiving OAT	Meta-analysis	3790 (36 studies)	NR[a]	Recent drug use: 5.9 (4.1, 8.5) Recent IDU: 6.2 (4.3, 8.9) Receiving OAT: 3.8 (2.5, 5.8)
Cunningham et al[11]	International	People with recent IDU and receiving OAT	Clinical Trial	177	8	Overall: 3.1 (1.6–6.3) Sharing needles/syringes: 17.9 (5.8–55.6)
Lens et al[20]	Spain	Harm Reduction Center	Prospective	168	42	Overall: 31/100
Hosseini-Hooshyar et al[12]	International	HIV/HCV	Meta-analysis	9024 (41 studies)	435	Overall: 3.8 (2.8–5.1) MSM: 6.1 (4.5–8.0) IDU: 3.3 (2.0–5.4)
Carson et al[13]	Australia	Prison	Prospective	161	18	Overall: 12.5 (7.9–19.8) Sharing needle/syringe: 28.7 (16.3–50.6)
Beiser et al[19]	United States	Homeless	Retrospective	535	74	Overall: 12.0 (9.5–15.1)
Young et al[14]	Canada	HIV/HCV	Prospective	814	62	Interferon era overall: 2.6 (1.2–4.1) Interferon era IDU: 4.7 (1.4–.79) DAA era overall: 3.4 (2.5–4.4) DAA era IDU: 7.6 (5.3–10)
Lindqvist et al[15]	Sweden	Needle and Syringe Program	Prospective	339	43	Overall: 9.3 (7.0–12.3)
O'Sullivan et al[16]	UK	Addiction Center	Prospective	146	19	2013–2017: 1.7 (0.9–3.4) 2017–2021: 1.8 (0.6–5.6)
Martinello et al[17]	International	Recently acquired HCV	Clinical Trial	196	28	Overall: 14.2 (9.8–20.5)
Sacks-Davis et al[18]	International	HIV/HCV	Pooled data from 6 contributing cohorts	6144	643[b]	Interferon era: 4.6 (4.1–5.1) Early DAA era: 3.4 (2.9–3.9) Broad DAA era: 3.1 (2.6–3.6)

[a]Not reported for all studies.
[b]First reinfections.
Abbreviations: DAA, direct-acting antiviral; IDU, injection drug use; MSM, men who have sex with men; NR, xxx; OAT, opioid agonist therapy; PY, person years.

was also high at 5.6/100 PY (95% CI: 2.8–11.1) and was predominantly due to drug overdose or other complications of drug use. In another UK study of 270 PWID who received HCV treatment at an addiction center observed 41 deaths (15%) during the 8-year study period; drug overdose was the most common cause of death among those whose cause of death could be ascertained.[16] In a third Canadian study of people living with HIV in clinical care, mortality was three times higher in individuals who experienced HCV reinfection after initial SVR.[14] These data underscore the importance of addressing non-liver outcomes and the syndemic of opioid use and viral infections in patients at high risk of HCV reinfection.

APPROACH TO HCV REINFECTION IN PWID

A framework for approaching reinfection in PWID can be found in Figure 1. First and foremost, treating clinicians should anticipate reinfection to occur in some patients. As more people with HCV are treated and cured, we can expect HCV infections to be concentrated in those at highest risk for exposure. Thus, rather than viewing reinfection as a failure, it should be seen as a positive sign that the population at greatest risk of HCV is being treated.[22] Indeed, a recent analysis of pooled data from 6 contributing cohorts of people living with HIV demonstrated that while the overall incidence of HCV declined in people living with HIV from 2015 to 2019, reinfection represented an increasing proportion of incident HCV cases.[18] In other words, new HCV infections are occurring in a shrinking population of people at risk, including those with prior successful HCV treatment. Reassuringly, the overall decline in incident cases in the study reinforced the concept of "treatment-as-prevention" and suggested that reinfections did not substantively impact HCV elimination efforts. Thus, providers should not withhold treatment out of fear of reinfection. Instead, providers should be mindful to counsel on reinfection risks early and often and monitor for reinfection with HCV RNA at least annually after SVR. Modeling studies also suggest that simultaneously treating HCV in injecting partners and social networks may reduce reinfection risk.[23]

Patients who experience reinfection report strong negative emotional responses, especially shame.[24] Therefore, it is critical that clinicians are mindful to destigmatize reinfection. Conversations about reinfection should be normalized, and HCV RNA screening after SVR should be standard of practice among individuals with active IDU. Stigmatizing language around HCV "cure," drug use, and sexual practices should be avoided. Lastly, retreatment should be offered when reinfection occurs.

Studies demonstrate a lower risk of reinfection in people receiving OAT; therefore, drug use treatment in addition to DAAs should be offered to all patients with active drug use.[10] However, this should not be a requirement prior to DAA treatment. Studies show that

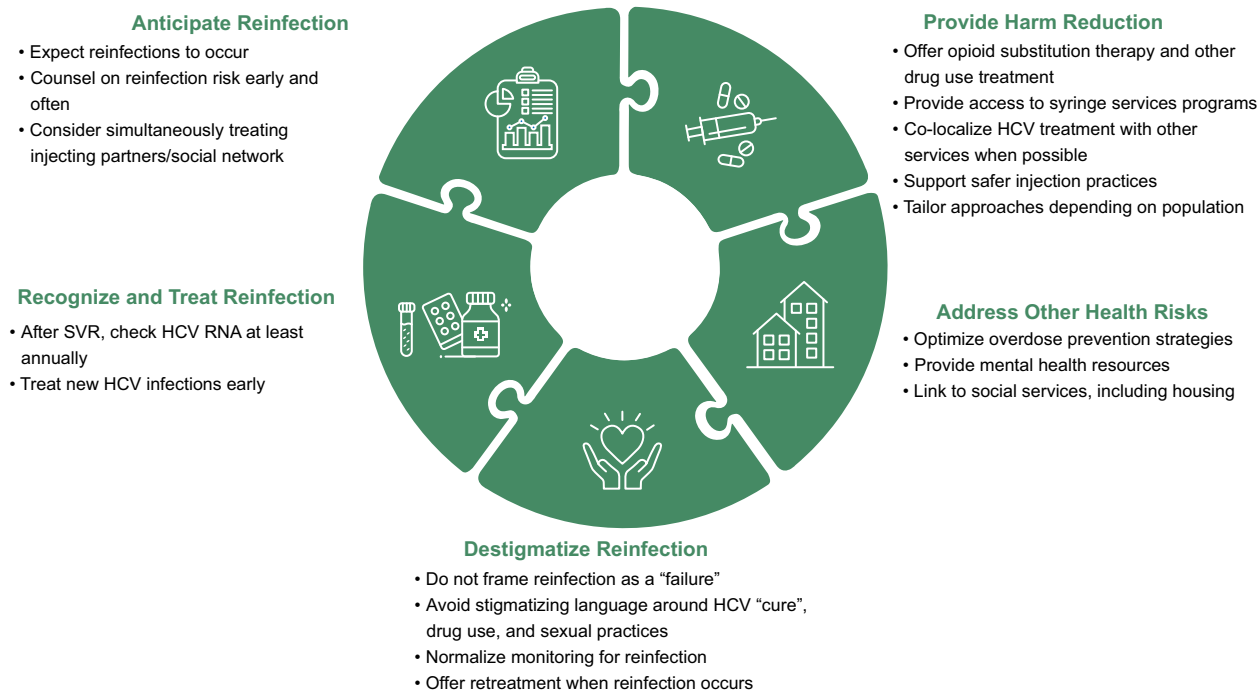

FIGURE 1 Multifaceted approach to addressing HCV reinfection among people who inject drugs. Abbreviation: SVR, sustained virologic response.

reducing payor restrictions (eg, substance use abstinence) leads to increased DAA uptake, particularly among patients with a history of drug use.[25] Access to syringe services and safer injection practices is also critical, as sharing needles and syringes is associated with the highest risk of reinfection.[11,26] Harm reduction is essential not only for preventing reinfection but also for providing comprehensive whole-person care. PWIDs who experience reinfection have a significantly higher risk of overdose-related death than liver-related death. Thus, optimizing overdose prevention strategies and providing mental health resources is necessary. Finally, homelessness is prevalent among PWIDs.[27] People experiencing homelessness have lower rates of SVR with initial treatment and higher rates of reinfection.[6,15,19] This may be attributed to their unique challenges with medication retention, including frequent relocation and high rates of property theft, as well as the association of homelessness and injection risk behaviors.[17,28] Efforts should be made to link people with unstable housing to social services and to design tailored interventions to improve their access to HCV and drug use treatment.

CONCLUSIONS

In summary, HCV reinfection should be anticipated, screened for, and treated, particularly among high-risk populations such as PWIDs. HCV retreatment should not be restricted by payers, and persons at higher risk of reinfection should be counseled on harm reduction strategies while also screened for reinfection. Normalization of this approach and destigmatization of reinfection are critical. Nationally, HCV elimination among PWID is a priority, and the Centers for Disease Control and Prevention has numerous approaches to achieve this. Specifically, the Centers for Disease Control and Prevention commits to increase the utilization of HCV prevention services among PWID, to establish comprehensive national viral hepatitis surveillance for public health action, including additional data collection on reinfection rates in the United States, and to reduce barriers to HCV treatment by eliminating eligibility restrictions and expand treatment sites to include substance use treatment centers and correctional facilities.[29] The Centers for Disease Control and Prevention's 2025 Strategic Plan to address viral hepatitis emphasizes the need to support clean needle exchange programs and local policies like the Harm Reduction Community Linkage Projects in Illinois.[30] At the systems level, health care systems can support the use of telehealth to improve health care access throughout the HCV care continuum, including evidence-based practices like project Extension for Community Healthcare Outcomes and community-based facilitated telemedicine programs.[31,32] Safe medication storage devices to improve medication adherence and achieve SVR with initial treatment and after reinfection should be considered, particularly among people experiencing homelessness.[33] HCV point of care testing, when available, can be used to shorten the time to HCV diagnosis and initiation of treatment and to monitor for reinfection.[34] Lastly, funding for HCV elimination efforts, innovative treatment approaches like shorter-duration treatment options and long-acting injectables, and research into effective HCV vaccines must be prioritized.

CONFLICTS OF INTEREST

Jennifer Price received grants from Gilead, AbbVie, Vir, Zydus, and Genentech. The remaining author has no conflicts to report.

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