

Optimizing cure following treatment for hepatitis C among people who inject drugs: Where to next?

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The World Health Organization indicates that, despite some progress, many countries will fail to reach the 2030 target of eliminating hepatitis C virus (HCV) as a public health threat.¹ People who inject drugs (PWID) bear a disproportionate burden of HCV infection² and account for the majority of new infections globally,³ but HCV testing and treatment in this group remain low.⁴

Treatment for HCV infection is safe and effective among PWID,^{4–6} with high adherence^{4–6} and low reinfection rates.⁷ Data from countries with widespread needle and syringe programs (NSP) and opioid agonist treatment (OAT) confirm the efficacy of treatment, albeit slightly reduced compared with that seen in clinical trials.^{4,6,7} Importantly, therapy provides additional societal benefits by reducing the risk of onward transmission.⁸ Interventions to enhance HCV testing and treatment initiation among PWID are well-established.^{9,10} However, there have been fewer trials to improve response to therapy and studies in countries with less developed support programs have not been conducted, leading to a lack of evidence-based interventions in the settings where they are most needed.

In this issue of the *Journal*, Solomon and colleagues used a precision trial design to compare three levels of treatment adherence support with sofosbuvir/velpatasvir therapy on sustained virologic response (SVR) among people with a history of injecting drug use from seven cities in India. Groups were randomized to interventions that included treatment adherence support of low (28-day dispensation at a community clinic with standard adherence counseling), medium (28-day dispensation with flexible weekly patient navigation medication support [in person or remote] and refill pick-up [or home/field delivery]), or high (weekly medication dispensation and directly observed therapy with flexibility in the frequency of pick-up and site of pick-up [clinic, home-based, field-based]) intensity. Failure risk was determined based on variables known to be

associated with HIV therapy adherence. People at elevated risk were randomized 3:2:1 to high, medium, and low adherence support and those at minimal risk were randomized 1:2:3 to high, medium, and low adherence support. The primary outcome was SVR, defined as HCV RNA less than the limit of quantification at 24 weeks post-randomization (visit window 22–72 weeks) or 12 weeks following the anticipated end of treatment. Secondary outcomes included self-reported treatment adherence and self-reported treatment completion.

Overall, 3,000 people were randomized; the median age was 29 years, 99% were male, 66% were unemployed or daily wage earners, 24% were living with HIV infection, and 3.5% had evidence of compensated cirrhosis. None reported prior HCV treatment. Despite 57% reporting recent injecting drug use in the previous three months, only 22% had accessed a NSP and 44% were receiving OAT.

Overall, 63% and 49% achieved SVR in the minimal and elevated risk strata, respectively. There was only modest evidence that the highest intensity intervention of patient navigation and weekly directly observed therapy improved outcomes in those at lower risk for treatment failure and in the overall population after re-weighting. No intervention improved outcomes in those at highest risk for treatment failure. The lower proportion of people with SVR compared to previous studies among PWID^{4,5} is likely explained by sub-optimal adherence and HCV reinfection following successful treatment, although formal virological studies to distinguish between the two possibilities could not be performed.

The great strength of the study was the setting. This is the first study of its kind in India, where support for PWID is less established than in countries where such studies are usually conducted. Combined with the novel study design and large number of participants, this makes one of the largest studies evaluating an intervention to

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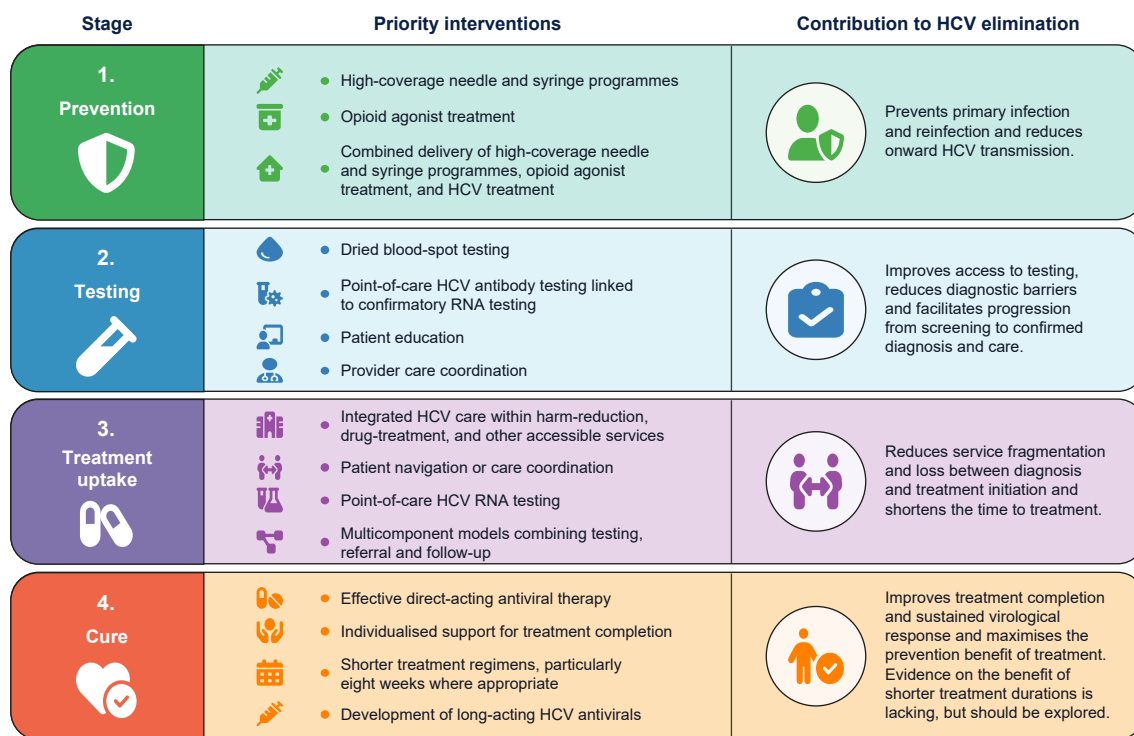
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Abbreviations: HCV, hepatitis C virus; RNA, ribonucleic acid.

Fig. 1. Priority interventions across the HCV care cascade among people who inject drugs.

enhance HCV treatment outcomes in PWID. Study follow-up was impressive, with 94% of participants completing the SVR assessment, but the wide window for the SVR visit (22–72 weeks) and limited virological testing reduced the opportunity to distinguish treatment failure from reinfection. Adherence and treatment completion were assessed via self-report, which substantially overestimates adherence^{11–14} and it is known that people who discontinue therapy within the first or second month and people who miss ≥ 14 consecutive adherent days are less likely to achieve SVR.¹³ However, the study provides good evidence to suggest that the interventions evaluated did not have a major impact on response to therapy, suggesting that novel approaches to support compliance and reduce reinfection need to be considered.

Interventions to enhance prevention, testing, treatment, and cure should now be prioritized (Fig. 1). Longer treatment durations present barriers that can be overcome by shortening treatment duration, presenting a practical and scalable intervention. In acute and chronic infection, different therapy combinations have shown high SVR with 8 weeks of therapy, albeit glecaprevir-pibrentasvir is the only therapy licensed for 8 weeks.^{15,16} In recent HCV infection, pilot studies have demonstrated high SVR with glecaprevir/pibrentasvir treatment durations of 6 (intention-to-treat, 90%; per-protocol, 96%)¹⁷ or 4 weeks (intention-to-treat, 78%; per-protocol, 82%).¹⁸ Cure was achieved in 100% of people receiving 4 weeks of treatment with baseline HCV RNA < 6.5 log₁₀ IU/ml.¹⁸ In a randomised controlled trial in people with recent HCV infection, a shortened course of 6 weeks of sofosbuvir/velpatasvir was less effective than a standard 12-week course.¹⁹ In chronic infection, response to therapy is reduced with shorter duration regimens

of 6 weeks (81%; 95% CI 75%, 87%) and 4 weeks (63%; 95% CI 40%, 84%), although high SVR has been observed with some regimens of ≤ 4 weeks duration.¹⁵ In one study of sofosbuvir/ledipasvir with ribavirin and/or interferon in young, treatment-naïve PWID with no cirrhosis (F0–2) and a low baseline HCV RNA level (< 2 million IU/ml), intention-to-treat SVR was 94% (interferon + ribavirin; 100% per protocol) and 75% (ribavirin alone; 93% per protocol).²⁰ In another study, a protease inhibitor (asunaprevir or simeprevir) combined with 3 weeks of sofosbuvir/daclatasvir or sofosbuvir/ledipasvir in people with genotype 1b, no cirrhosis, and baseline HCV RNA < 10 million IU/ml who achieved an ultra-rapid virologic response (HCV RNA < 500 IU/ml on day 2), SVR was 100% ($n = 18$).²¹ It may be that three potent antivirals used in combination may be required for short duration HCV therapy. An ongoing pilot study (STRIVE4, NCT03855917) evaluating sofosbuvir/glecaprevir/pibrentasvir for 4 weeks may provide insight into this approach. A short duration regimen with good efficacy could address issues of non-adherence and treatment completion and improve cost-effectiveness, which would be important in low- and middle-income countries.

Long-acting HCV antiviral therapy could also enhance adherence and treatment completion and such approaches have been key additions to the HIV prevention and treatment toolkit. Although short-duration and long-acting injectable therapies would represent significant innovations for the field, these options are not currently available, and the community should advocate for funding and support for their development. Alternative approaches to pharmacological interventions include financial incentives^{9,22,23} and the use of peer navigators.^{9,24} These approaches have been assessed in a range of

study settings, designs, and populations and have not shown unequivocal benefits.^{9,22–24} It is to be hoped that others will follow Solomon's lead and conduct well-designed randomized trials of novel interventions in the settings where interventions are likely to have most impact.

In addition to concerns regarding compliance, the study highlights the risk of reinfection in those who may be continually exposed to infection. In countries with well-developed OAT and high-coverage NSP programs there is abundant evidence of efficacy in preventing transmission.^{25,26} OAT alone is associated with a 50% reduction in HCV transmission and in combination with high-coverage NSP is associated with an 80% reduction in HCV transmission.²⁶ In India, coverage of OAT and NSP is low, with 4 per 100 people primarily injecting opioids accessing OAT and 34 needles and syringes distributed per person who injects drugs per year. The STOP-C study highlights the inadequacy of current programs – despite 57% of participants reporting recent injecting drug use, only 22% had accessed NSP and only 44% were receiving OAT. Given that the combination of HCV treatment with OAT and NSP is synergistic for prevention of HCV at a population level,²⁷ further efforts to improve provision of harm-reduction strategies alongside enhanced access to antiviral treatment should be prioritized. In countries such as Australia and the United Kingdom, where HCV care models are embedded within

harm reduction services, there is strong political commitment to HCV elimination and good coverage of harm reduction services, and progress towards HCV elimination among PWID has been encouraging.^{25,28}

New HCV therapies have been available for over a decade, but treatment numbers are declining globally.²⁹ Although we have made great strides in the identification of interventions to enhance HCV testing and initiation of treatment for PWID,^{9,30} we are not that much closer to having universally defined interventions to improve SVR or reduce reinfection risk in high-risk populations. Perhaps we should look to the field of implementation science to consider a more systematic approach to identify and develop strategies to improve outcomes.³¹ This would include more clearly articulating patient and provider behaviors related to adherence and treatment completion, identifying enablers and barriers associated with identified behaviors, and developing strategies to address barriers and amplify enablers. Such studies should also evaluate the added value of addressing other health issues among PWID beyond viral infections. The unequal progress in HCV elimination globally highlights the critical need for continued efforts to understand how best to deliver and implement highly curative HCV therapies, prevent reinfection, and reduce associated co-morbidities among PWID to support global elimination efforts.

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Conflict of interest

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Authors' contributions

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Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT Edu (OpenAI; GPT-5.6 Sol) to assist in transforming content developed by the authors for this editorial into a figure. The authors reviewed and edited the AI-assisted outputs to ensure that they accurately represented the underlying content and take full responsibility for the final figure and manuscript.

Supplementary data

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