Prevention of Hepatitis C Virus in Injecting Drug Users: A Narrow Window of Opportunity

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(See the article by Mehta et al., on pages 587–94.)

Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infections remain major public health problems among injecting drug users (IDUs). In 2007, it was estimated that there were 15.9 million IDUs worldwide, with 3 million living with HIV [1]. While similar data are not available for HCV, given an HCV prevalence of 65% [2], it is estimated that 10 million active IDUs have been exposed to HCV and 8 million have chronic infection. The global burden of HCV is even greater in former IDUs.

Implementation of harm reduction strategies since the early 1990s among many IDU populations led to decreases in HIV incidence or sustained low-level HIV prevalence and incidence [3]. In contrast, the impact on HCV transmission within the same populations has been much less pronounced [4]. This is likely related to the higher HCV prevalence among IDUs and higher risk of HCV infection following injection with a contaminated syringe (2.5%–5.0% for HCV [5–8] vs .5%–2.0% for HIV [8–11]).

High HCV incidence and rapidly increasing HCV prevalence are observed among young IDUs in different settings [12]. Factors associated with HCV acquisition include recent initiation to injecting [13, 14], unstable housing [15], female gender [16], ethnicity [17, 18], survival sex work [13, 19], frequent injecting cocaine use [13, 16, 20, 21], imprisonment [21], having a partner who injects [20], injecting networks [22], requiring help injecting [20], and borrowing injecting equipment [13]. The high risk of HCV among younger and recent IDUs indicates a narrow window of opportunity for prevention, with estimates of the median time to HCV infection of ~3 years [14, 23]. Among long-term IDUs (injecting for >6 years), HCV prevalence (64%–94%) remains high [12].

It is clear that microenvironmental and macroenvironmental physical, social, economic, and political factors are important in shaping risk behaviors for HIV and HCV acquisition among IDUs [24]. Social network characteristics may be important and are associated with drug injection risk behaviors [25]. Network correlates of drug equipment sharing are multifactorial and include structural factors (network size, density, position, and turnover), compositional factors (network member characteristics and role and quality of relationships with members), and behavioral factors (injecting norms, patterns of drug use, and severity of drug dependency) [25]. In Seattle, Washington, a drug injecting network was highly connected, dense, and cyclic [26], and similar risk behaviors between injectors with and without recent HCV acquisition indicated that infection was associated with network position; that is, injecting with more individuals who happened to be HCV infected [26]. This is consistent with injecting network data from Melbourne, Australia, demonstrating that HCV infection is independently associated with the HCV status of network members [22].

Environmental social changes may also act as drivers of infection. In Australia, the estimated number of current IDUs between 1990 and 2000 doubled from 60,000 to 120,000, accompanied by a near doubling in the number of new HCV infections from 8,000 to 14,000 per year, despite widespread introduction and availability of harm reduction programs (eg, needle syringe programs [NSP] and opiate substitution treatment [OST]) from the early 1990s [27]. Subsequently, a dramatic reduction in the availability of heroin in Australia from 2001 onward resulted in a decline in the estimated number of IDUs and a decline in the estimated number of new HCV

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infections to 10,000 in 2005, although reductions in risk behavior related to drug injecting may have also been a contributing factor [27].

In this issue of the *Journal*, Mehta et al [28] characterized trends of HIV and HCV incidence (and age-specific HCV prevalence) in a long-term, well-defined cohort of IDUs in Baltimore, Maryland, over 4 recruitment periods spanning 20 years. Between 1988 and 1989, participants injecting drugs in the previous 11 years were enrolled (n = 2,946). In an effort to replenish the cohort with active injectors, subsequent recruitment occurred in 1994–1995 (n = 391), 1998 (n = 244), and 2005–2008 (n = 875).

The authors demonstrated that while HIV and HCV incidence declined over the study period, the incidence of HIV declined to zero (5.5/100 per y in 1988–1989 compared with 0/100 per y in 1998 and 2003-2005), while HCV transmission was still observed (22.0/100 per y in 1988–1989 compared with 7.8/100 per y in 2005–2008). Reductions in age-specific HCV prevalence were also observed, but mainly among younger (<39 years) IDUs. The similar prevalence of HCV over time among those who were injecting longer (>15 years) and were older (≥39 years old) suggests that HCV infection was delayed, rather than prevented, at the population level.

This important study by Mehta and colleagues demonstrates a dramatic decline in HIV transmission but ongoing relatively high levels of HCV transmission among IDUs in Baltimore. As the authors propose in this article, these data may support intensifying harm reduction strategies that have markedly reduced HIV transmission [3, 24] to reduce HCV transmission. However, data are sparse on the effectiveness of strategies for HCV prevention and the question remains as to what intensification of HCV prevention really means as we move forward.

Prevention of HIV and HCV infections could occur through reductions in injecting risk behaviors, entry into injecting, or the duration of time spent injecting. There is clear evidence supporting that NSP and OST can lead to reductions in injecting risk behavior [3, 24, 29]. Mathematical modeling of the impact of NSP on HIV and HCV transmission among IDUs in Australia has demonstrated that the number of times each syringe is used before disposal is the most sensitive behavioral factor in determining the incidence of both HIV and HCV infection, followed by the percentage of injections that are shared [29]. Furthermore, modeling suggests that critical levels of needle sharing would need to be fewer than 17 injecting partners per year and fewer than 3, for HIV and HCV, respectively, to control these epidemics [30]. Given estimates of 6 injecting partners per year among Australian IDUs, HIV prevalence is 1% but HCV prevalence has remained elevated [30]. These data suggest that major reductions in HCV transmission among IDU populations with large reservoirs of infection require harm reduction strategies that enable minimal sharing. Data on the impact of OST alone on HCV incidence are sparse and there is limited evidence that NSP interventions alone are effective in preventing HCV infection [4].

Expansion of existing interventions for IDUs, utilization of multiple interventions, and greater emphasis on HCV-specific strategies may all be required for broadly effective HCV prevention. Current coverage of harm reduction strategies for IDUs is inadequate in most settings, with ongoing high rates of sharing of injecting equipment, and access to OST and other drug treatment programs is often limited [3].

Irrespective of the strategy used, intensification of harm reduction programs must consider the generally narrow time window from initiating injecting to HCV infection [14, 23]. As such, NSP coverage and policies that enable greater outreach to high-risk recent injecting initiates are required [3, 24]. Peer-based education programs for IDUs have been shown to reduce injecting risk behavior but not HIV [3, 24] or HCV incidence [31]. Further research is required to evaluate such programs targeting injecting initiates. Strategies to enhance NSP coverage, including expanded mobility and hours of operation, also need to be evaluated.

HCV prevention can also be achieved by reducing entry into injecting. As demonstrated in Australia, decreases in the numbers of people initiating injecting due to the heroin shortage had a major impact on decreasing the number of new HCV infections [27]. In the Netherlands, the transition from injecting to noninjecting drug use over the past several decades may have also had an impact on the reductions in HIV and HCV incidence [32]. To date, behavioral interventions to deter initiation of injection or strategies to encourage a shift to noninjecting routes of administration have not been successful [3].

Decreasing the time spent injecting may have an impact on HCV incidence. Mathematical modeling suggests that the threshold duration of injecting following HIV and HCV acquisition required to sustain an epidemic is 11.6 years for HIV and 2.3 years for HCV [29], with the latter considerably shorter than the estimated average duration of post-HCV injecting of ~10 years [29]. Accelerated access to drug rehabilitation and drug treatment programs for those individuals seeking to reduce or cease injecting drug use is, therefore, required.

Mathematical modeling has led to the proposal that HCV treatment among IDUs may impact HCV transmission [33–35]. However, the harsh clinical reality is that despite comparable response rates to treatment among IDUs and non-IDUs [36], barriers to HCV diagnosis, assessment, and treatment [37] as well as considerable treatment-related toxicity result in extremely low treatment uptake among active IDUs, with <1% treated annually [38–40]. As such, HCV treatment is unlikely to impact

transmission in the short to medium term.

An effective vaccine could impact HCV incidence. Modeling studies suggest that HCV vaccine strategies targeting IDUs can be cost effective and would be the most efficient approach to controlling the epidemic [41]. While candidates are in development, no highly efficacious HCV vaccine has been discovered, and there are challenges of vaccine trials among IDUs including vaccine trial design issues (eg, trial literacy, standard of care, trial size and duration, protocol adherence, and cohort retention), and ethical issues given the social marginalization and vulnerability of IDUs [41]. Efforts to discover an HCV vaccine are crucial.

Although the HCV prevention window may have a narrow opening, improvements in HCV prevention are feasible. Continued surveillance to monitor trends in drug use, HCV incidence, and risk behaviors is required. The development and implementation of national harm-reduction strategies including broader coverage, enhanced early access, and intensification and combination of interventions are probably all needed. However, randomized controlled trials evaluating HCV interventions, including combined strategies, are required. Furthermore, peer-based education, support, and community participation will be essential for the successful delivery and uptake of intervention strategies.

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