Elimination of Hepatitis C Virus Infection Among People Who Inject Drugs Through Treatment as Prevention: Feasibility and Future Requirements

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The demonstration that antiretroviral treatment is effective for the prevention of human immunodeficiency virus (HIV) transmission has important implications for HCV prevention. HCV therapeutic development is advancing rapidly, with effective, simplified regimens available in the near future. In contrast to HIV, HCV treatment is both curative and circumscribed in duration—2 features that hold great promise for the potential effectiveness of HCV treatment as prevention, particularly among PWID. Mathematical modeling studies have suggested that modest increases in HCV treatment uptake could lead to substantial reductions in HCV prevalence. This Viewpoint focuses on issues that are important to consider when discussing the feasibility and future requirements of HCV treatment as prevention among PWID. This includes a need to address low rates of HCV screening and treatment, a limited HCV treatment infrastructure, the cost of therapy, and the balance of health priorities at the population and individual levels.

Keywords. HCV; drug users; injection; HIV; modeling.

The burden of hepatitis C virus (HCV) infection continues to rise. People who inject drugs (PWID) represent the core of the HCV epidemic in developed countries, accounting for the majority of new (80%) and existing (60%) cases [1, 2]. Although harm-reduction strategies such as needle syringe programs (NSP) and opioid substitution treatment (OST) have been successful for human immunodeficiency virus (HIV) [3], these strategies have had more limited impact for HCV prevention [4–6], and an effective HCV vaccine remains remote. In many countries, low coverage of NSP and OST programs further hinders HCV prevention efforts [7].

HCV-related morbidity and mortality continues to rise [8]. The natural history of chronic HCV [9] and

ageing cohorts of PWID (former and current) means that a large burden of advanced liver disease is anticipated in the next decade [10]. Although HCV treatment for PWID with HCV has been demonstrated to be safe and effective [11], treatment uptake remains low [12–15]. However, in the next 2–5 years, simple (oral, once-daily), tolerable, short-duration (12–24 weeks) directly acting antiviral (DAA) regimens with extremely high efficacy (cure rates >90%) are likely to be available for HCV treatment [16].

In the field of HIV, a finding that has generated considerable excitement is the demonstration that antiretroviral therapy (ART) is an effective strategy for the prevention of HIV transmission [17]. This has important implications for HCV and the potential role of HCV treatment as prevention among PWID [18–25]. In contrast to HIV, HCV treatment is both curative and circumscribed in duration—2 key features that hold great promise for the elimination of HCV infection through treatment as prevention. From a public health perspective, elimination refers to the reduction of the incidence of infection caused by a specific agent to zero in

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a defined geographical area as a result of deliberate efforts; however, this requires the presence of continued measures to prevent reestablishment of transmission (eg, measles, poliomyelitis).

The concept of HCV treatment as prevention among PWID presents multiple issues for consideration, including low diagnosis and treatment rates, limited treatment infrastructure, cost of therapy, and the balance of health priorities at the population and individual levels. We discuss these issues in this viewpoint.

HIV TREATMENT AS PREVENTION

The demonstration that ART is an effective strategy for the prevention of HIV transmission has provided considerable optimism to the field [17]. These findings have potential benefits at the individual level for those provided with these medications and at the population level by limiting transmission and reducing the overall burden of infection [26].

Mathematical modeling provides a framework for estimating the potential impact of treatment as prevention at the population level [26]. Two factors influence the impact of a treatment program on the prevention of infection. First, there are transmission events occurring *prior* to treatment that are dependent on the biology of infection, the prevalence of infection, risk behaviors between partners, the effectiveness of other established prevention programs, the rates of testing, and access to care. Second, there are transmission events occurring *after* treatment initiation that are dependent on treatment efficacy, adherence, and retention in care.

In contrast to HIV, antiviral therapy for HCV is both finite in duration and frequently curative. Thus, a reduction in the prevalence of active infection can potentially be achieved in a substantial proportion of cases, in addition to the prevention of secondary transmission events.

HCV EPIDEMIOLOGY, NATURAL HISTORY, AND TREATMENT AMONG PWID

In the developed world, HCV transmission is concentrated among PWID [1]. Globally, HCV antibody prevalence among PWID is 67% [2]. Given that 25% of PWID spontaneously clear HCV [27], approximately 50% will have chronic HCV infection. Estimated HCV incidence among PWID ranges from 5% to 45% per annum [6, 28–39]. The risk of HCV infection is highest among younger individuals and recent initiates into injecting drug use [38, 39]. Harm reduction strategies that have been successful for HIV prevention among PWID populations have been less effective for HCV prevention [4, 6, 40, 41]; this is consistent with greater per contaminated injecting exposure transmission (2.5%–5.0% for HCV [42–45] vs 0.5%–2.0% for HIV [45–48]) and higher prevalence (and thus, risk of exposure).

Following chronic HCV infection, there is a risk of progressive hepatic fibrosis culminating in cirrhosis and liver failure or hepatocellular carcinoma [49]. In those with spontaneous HCV clearance, reinfection in the setting of ongoing HCV exposure is possible [50]. Although many of those with reinfection clear repeatedly, others develop persistent infection [50]. The slowly progressive nature of chronic HCV means that the prevalence of advanced liver disease is low in the initial 10–15 years of infection but progressively increases over several decades [9, 10, 51]. In fact, younger individuals with HCV, particularly PWID, are at greater risk of dying of drug-related causes rather than liver-related causes [52]. Older individuals with multiple cofactors for progression to advanced liver disease are at greatest risk of HCV-related morbidity and mortality [10].

The goal of HCV therapy is sustained virological response (SVR; HCV RNA undetectable in the blood 3–6 months following treatment), equating to cure. HCV treatment with pegylated-interferon (PEG-IFN)/ribavirin can achieve SVR in approximately 50% of individuals. Among PWID, HCV treatment is successful [11, 53], but uptake remains low [12–15]. This poor uptake of, and access to, therapy results from multiple barriers at the levels of the system, provider, and patient. Factors associated with not receiving HCV treatment include older age [54], minority ethnicity [54], ongoing/former drug use [55–58], ongoing alcohol use [54, 55], advanced liver disease [57], comorbid medical disease [54, 58], psychiatric disease [54, 57], and OST [55, 56].

Between 2004 and 2005, community-based studies of PWID in Australia, Canada, and the United States demonstrated HCV treatment uptake rates ranging from 0.5% to 1.0% per year (5 to 10 per 1000 infected) [13, 14, 59]. More recently, data from cohorts of current PWID in Canada and Australia suggest that HCV treatment uptake in PWID settings has increased to 1.5%–2.0% in 2009–2010 (15 to 20 per 1000 infected) [60]. This is consistent with trends in HCV treatment uptake among the general population in Australia [61], Europe [62], and the United States [63].

In PWID, treatment of chronic HCV is safe and effective [11, 64]. International guidelines recommend treatment for PWID following individualized assessment [65, 66]. In a systematic review of studies assessing treatment for active PWID, the overall SVR was 56% [64]. Although there is concern that reinfection may negate the potential benefits of treatment, the reported rates of reinfection following successful HCV treatment among PWID are low (1%–5% per year) [64, 67–71]. Looking forward, the effectiveness of HCV treatment as prevention will be closely linked to a foundation of enhanced HCV treatment uptake, adherence, and retention in care among PWID.

INSIGHTS FROM MATHEMATICAL MODELING STUDIES

The potential preventative utility of HCV treatment for active PWID has been explored in mathematical modeling studies [18–25].

Initial modeling studies utilized IFN-based therapy. In one study, assuming a prevalence of chronic HCV of 45%, treatment efficacy of 50% over 10 years, and treatment uptake rate of 10% per year among HCV-infected PWID was predicted to translate to a 32% reduction in HCV prevalence [24].

A problem with this initial modeling was somewhat unrealistic HCV treatment uptake rates with PEG-IFN/ribavirin, given the substantial side effects and substantive healthcare infrastructure required for therapy. Using more realistic HCV treatment uptake estimates, further modeling assessed the impact of HCV treatment as prevention in the United Kingdom [20, 21]. Based on a chronic HCV prevalence of 40% and a response to therapy of 63%, treating only 2%, 4%, and 6% of chronic infections per year among PWID suggested a reduction in HCV prevalence of more than 15%, 33%, and 50% over 20 years [21]. A more useful measure may be the absolute number that would need to be treated annually to reduce prevalence. Assuming a baseline prevalence of chronic HCV of 20%, annual treatment of 5, 10, 20, or 40 per 1000 PWID would lead to a 15%, 31%, 62%, and 72% reduction in HCV prevalence over 10 years [20]. At an HCV treatment uptake rate of 10 infections per 1000 PWID and an increasing baseline HCV prevalence (20%, 40%, and 60%), the impact on achieving a relative decrease in HCV prevalence diminished from 31%, 13%, to 7%, respectively, over 10 years [20]. The greater impact of HCV treatment as prevention in lower prevalence settings is driven by the fact that the proportion of those with chronic infection who are treated is greater and the risk of reinfection is lower.

THE AGE OF DAA-BASED HCV THERAPY

Numerous antiviral agents targeting specific HCV viral functions have been developed (direct acting antivirals [DAAs]) [72]. The first 2 DAAs approved for treatment of genotype 1 infection in combination with PEG-IFN/ribavirin are the NS3–4A protease inhibitors, telaprevir and boceprevir. Nucleoside/nucleotide analogues and nonnucleoside inhibitors of the HCV RNA-dependent RNA polymerase (NS5B) and inhibitors of NS5A are in advanced clinical evaluation [72]. The first phase 3 studies of IFN-free therapy began in 2012 [16], and it is anticipated that highly effective IFN-free DAA regimens will be available in the next 2-5 years. These regimens offer increased efficacy (>90%), reduced toxicity, shortened treatment durations (12–24 weeks) and simplified dosing (all oral, possibly once-daily regimens), and monitoring schedules [16]. The availability of such regimens will improve the feasibility of enhanced HCV treatment uptake and responses among PWID, making HCV treatment as prevention a possibility.

To evaluate the potential impact of IFN-free DAA-based therapy on HCV prevalence, a deterministic mathematical model of HCV transmission was applied to 3 settings with varying HCV prevalence (chronic HCV prevalence: Edinburgh, Scotland, 25%; Melbourne, Australia, 50%; and Vancouver, Canada, 65%) [73]. With the introduction of IFN-free DAA-based therapy (cure rate of 90% and 12 weeks therapy), HCV prevalence could be halved within 15 years if treatment is scaled up to 15, 38, and 75 per 1000 PWID in Edinburgh, Melbourne, and Vancouver, respectively. Scaling up HCV treatment to 40 per 1000 PWID annually could achieve a prevalence reduction of 91% in Edinburgh, 54% in Melbourne, and 22% in Vancouver over 15 years. These data suggest that if these treatment uptake and response rates to IFN-free DAA-based therapy can be achieved among PWID, HCV treatment as prevention could achieve substantial reductions in the prevalence of HCV.

KEY COMPONENTS FOR FEASIBILITY

There are 2 key drivers of the impetus toward HCV treatment as prevention. First, there is no HCV vaccine, and prospects remain distant [74]. Second, despite intensive efforts over the past 2 decades, HCV prevention strategies among PWID have had moderate success [4–6]. Alternative prevention strategies have to be considered, including HCV treatment. A number of key components will be required for HCV treatment to have a population-level prevention impact (Table 1).

The feasibility of HCV treatment as prevention will rest heavily on the ability to achieve high HCV screening and diagnosis rates among PWID and subsequently link infected individuals into care. Within clinics with large populations of PWID where systematic programs are established for comprehensive HCV screening and diagnosis, uptake of HCV testing and assessment of >85% can be achieved [75–78]. However, a vast number of HCV-infected PWID remain undiagnosed and unlinked to care. In the primary care setting, interventions based on targeted case finding [79], risk-based assessment [80, 81], and birth cohort screening [81] can be effective in increasing HCV testing. Simplified HCV surveillance and diagnostic testing

Table 1. Key Components That Will be Required for the Feasibility of Hepatitis C Virus Treatment as Prevention

- High rates of screening and diagnosis among people who inject drugs (PWID) and linkage to clinical care
- Infrastructure for provision of clinical services to PWID, including hepatitis C virus (HCV) treatment
- Willingness of PWID to undertake HCV treatment
- Therapeutic regimens that optimize treatment adherence and completion
- Harm reduction strategies to reduce pretreatment prevalence and prevent reinfection
- Cost-effective regimens and public health investment in care for PWID

Abbreviations: HCV, hepatitis C virus; PWID, people who inject drugs.

procedures should be further evaluated, including HCV dried blood spot testing. The challenge will be to ensure that newly diagnosed individuals are effectively linked with services offering HCV care.

There are a number of barriers to HCV care among PWID, and treatment uptake remains low in many settings [13, 14, 59]. Data from Australia suggest that HCV treatment uptake is increasing, with 2% and 10% of PWID reporting currently having or ever having received treatment in 2011 [60]. Programs most successful in treating HCV among PWID have often been built upon existing medical infrastructures for drug-user health (eg, community health centers, OST clinics, prison-based settings, general practitioners). In Australia [78, 82], Canada [83], Europe [75], and the United States [77], when programs are specifically designed to address barriers to care among PWID with an appropriate infrastructure for screening, testing, and assessment, PEG-IFN/ribavirin treatment uptake is 3%–5% per year (30–50 per 1000 infected) [75, 78, 83]. Prison-based settings provide considerable opportunity for HCV treatment as prevention, given high HCV incidence [84, 85], moderate prevalence (25%) [84, 85], availability of effective screening and treatment programs [85, 86], and high rates of transitioning between prisons and communities. Given enhanced response rates and less-demanding health infrastructure associated with IFN-free DAA therapy, the feasibility of HCV treatment as prevention in PWID appears even more promising.

A higher uptake of therapy will require a high willingness among PWID to undertake HCV treatment. Across a number of studies, 53%–86% of PWID report willingness to initiate HCV treatment, even in the era of PEG-IFN/ribavirin [15, 87–91]. The motivation to receive treatment increases as the treatment response increases, with 1 study demonstrating that willingness increased from 63% to 93% if told that there was a 40% and 70% chance of treatment being effective, respectively [87]. In the IFN-free era, treatment willingness would be expected to increase.

Therapeutic regimens that optimize adherence and completion will also be essential. A simplified regimen consisting of combination antiviral agents in 1 tablet taken once daily would be ideal. As demonstrated in HIV, improved and simplified ART has led to successful treatment outcomes for PWID [92]. Interventions shown to enhance adherence include adherence management strategies (pill boxes, electronic reminders), peer counseling at point of ART delivery, case management and nurse counseling, integrated treatment into existing health services (eg, prisons, OST clinics, primary care), directly observed therapy, and incentives or contributions to food/transport costs [92]. Similar strategies should be explored for HCV treatment among PWID.

Strategies for HCV treatment as prevention will also rely on an existing framework of harm reduction interventions for PWID. Modeling studies in the United Kingdom have suggested that in the absence of OST and NSP programs, the prevalence of HCV could be almost 60% higher [93]. In modeling studies projecting the impact of combining OST, high coverage NSP, and HCV treatment on HCV prevalence and incidence among PWID, large reductions (>45%) in chronic prevalence over 10 years can be achieved with very feasible HCV treatment rates, together with OST and NSP [94]. As such, any HCV treatment as prevention strategy will need to be built upon the foundation of existing HCV prevention strategies, such as OST and NSP programs. The feasibility of HCV treatment as prevention in many countries where coverage of NSP and OST programs is low [7] will depend on enhanced NSP/OST services.

The feasibility of HCV treatment as prevention will also depend on issues related to cost effectiveness and government approval of IFN-free DAA regimens, particularly in low- and middle-income countries where access to new therapies will be delayed. HCV treatment for both active and former PWID is cost effective (driven by the prevention benefit among active PWID) [22, 95]. However, it is uncertain whether HCV treatment as prevention for PWID will be cost effective in the era of DAA-based therapy. Newer, more effective regimens will undoubtedly come at an increased cost. Price reform and enhanced access to therapy for those with HCV will require considerable public health advocacy from all sectors in the HCV community, including community organizations representing PWID.

OPTIMAL HCV TREATMENT DELIVERY AMONG PWID

At the population level (Figure 1), HCV treatment as prevention may have the greatest impact on reducing the prevalence and incidence of HCV infection in the long term if therapy is targeted to groups and settings associated with the highest risk of transmission (prisons, younger injectors, and newer initiates to injecting). Modeling studies have demonstrated that if the primary goal is the prevention of new HCV infections and a reduction in the overall prevalence of HCV infection, the majority of therapy should be allocated to active PWID as compared to those receiving OST [25] or noninjecting drug users [20]. At the population level, this approach will clearly limit the prevalence of HCV and reduce the overall burden of infection.

However, at the individual level (Figure 1), in the short term, HCV treatment may have the greatest impact on disease morbidity and mortality if targeted to those PWID who have already been infected with HCV for many years and have the greatest risk of disease progression and death. This population may include those receiving OST (some of whom will also be actively injecting) and PWID who have ceased injecting (although active and former PWID populations are dynamic, given initiation and cessation of injecting). Targeting therapy to these groups might not achieve a large prevention benefit given the lower risk of transmitting infection. However, given higher levels of HCV
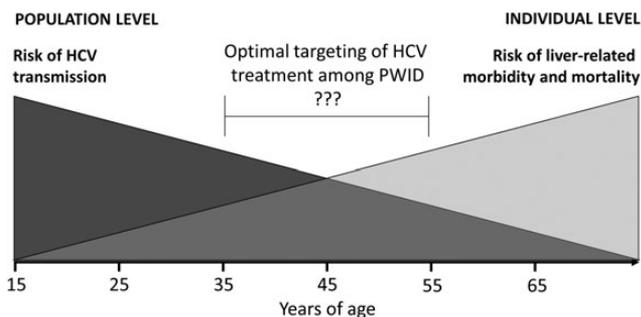
Figure 1. Optimal targeting of hepatitis C virus (HCV) treatment among people who inject drugs. At the population level, HCV treatment as prevention may have the greatest impact on reducing the prevalence and incidence of HCV infection if therapy is targeted to those at greatest risk of transmitting infection (younger injectors or newer initiates to injecting). However, at the individual level, HCV treatment may have the greatest impact on disease morbidity and mortality if targeted to individuals with the greatest risk of disease progression and death (former people who inject drugs (PWID) who are older and have more advanced disease but may be at lower risk of transmitting infection). Abbreviations: HCV, hepatitis C virus; PWID, people who inject drugs.

treatment uptake among former PWID [55–58] and greater healthcare engagement among those receiving OST, HCV assessment and treatment may be more easily targeted toward these groups initially. At the individual level, this approach will clearly limit HCV-related morbidity and mortality but will have less impact on the overall prevalence and incidence of HCV at the population level. Given this balance of individual-level and population-level health and the uncertainties related to the cost of future IFN-free DAA-based regimens, further research (including mathematical modeling of cost effectiveness) is needed to understand the optimal delivery of HCV treatment among PWID in the short and long term.

CONCLUSIONS

This is an exciting era for the field of HCV. As newer IFN-free DAA regimens become available, HCV treatment as prevention may be an attractive option for reducing the future burden of HCV-related disease. Any strategy will need to build upon the existing foundation of prevention and care for PWID. HCV treatment as prevention is part of a larger challenge to expand access to HCV testing and care. Both individual-level and population-based strategies will be required for a comprehensive approach for the control and eventual elimination of HCV transmission and disease. Cost-effectiveness evaluations are needed to determine how services can be optimally allocated. Future research in this area will increase our understanding of the role of HCV treatment as prevention in the hope of eliminating HCV infection.

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