



## Commentary

## Prevention, treatment and care of hepatitis C virus infection among people who inject drugs

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## ABSTRACT

People who inject drugs (PWID) represent the core of the hepatitis C virus (HCV) epidemic in many countries. HCV transmission continues among PWID, despite evidence demonstrating that high coverage of combined harm reduction strategies, such as needle syringe programs (NSP) and opioid substitution treatment (OST), can be effective in reducing the risk of HCV transmission. Among infected individuals, HCV-related morbidity and mortality continues to grow and is accompanied by major public health, social and economic burdens. Despite the high prevalence of HCV infection, the proportion of PWID who have been tested, assessed and treated for HCV infection remains unacceptably low, related to systems-, provider- and patient-related barriers to care. This is despite compelling data demonstrating that with the appropriate programs, HCV treatment is safe and successful among PWID. The approaching era of interferon-free directly acting antiviral therapy has the potential to provide one of the great advances in clinical medicine. Simple, tolerable and highly effective therapy will likely address many of these barriers, thereby enhancing the numbers of PWID cured of HCV infection. However, the high cost of new HCV therapies will be a barrier to implementation in many settings. This paper highlights that restrictive national drug policy and law enforcement are key drivers of the HCV epidemic among PWID. This paper also calls for enhanced HCV treatment settings built on a foundation of both prevention (e.g. NSP and OST) and improved access to health care for PWID.

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## Introduction

The hepatitis C virus (HCV) epidemic has been coined a “viral time bomb” by the World Health Organization. HCV is a prevalent chronic infection with potentially deadly consequences. Recent estimates suggest that globally, the HCV viremic (RNA positive) prevalence is forecasted at 1.1% (0.9–1.4%) corresponding to 80 (64–103) million viremic infections (Gower, Estes, Hindman, Razavi-Shaerer, & Razavi, 2014). Despite the looming public health threat that HCV imposes, it receives little public attention. This silent disease often progresses with few symptoms, even during advanced stages of disease. As a blood borne virus, the major route of transmission in most countries is injecting drug use. People who inject drugs (PWID) are heavily affected by this infectious disease. However, despite the high prevalence, ongoing transmission and increasing HCV-related disease burden among PWID, HCV

testing, prevention, assessment and treatment remain suboptimal in this group, and the time-bomb still ticks on. Over recent years, the development of simple, tolerable and highly effective interferon-free directly acting antiviral (DAA)-based therapies for HCV infection has brought great optimism to the sector. However, in order for the roll-out of these new IFN-free regimens to eliminate HCV among PWID, drastic changes and the breaking of some taboos will be required.

## Transmission of HCV infection

Although risk factors commonly associated with transmission of HCV infection include blood transfusion from unscreened donors, unsafe therapeutic injections, and other health-care related procedures, the majority of new and existing infections in most countries have occurred as a result of injection drug use (Hajarizadeh, Grebely, & Dore, 2013). Among PWID, the major route of transmission is through the sharing of drug preparation and injection equipment (e.g. syringes, needles, filters, water and cookers) (Pouget, Hagan, & Des Jarlais, 2012). The hepatitis C virus is resilient and is capable of surviving on drug preparation equipment

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(e.g. needles, syringes, filters and water) for several days to weeks (Doerrbecker et al., 2013; Painsil, He, Peters, Lindenbach, & Heimer, 2010). Also, the risk of HCV transmission is greater than for HIV infection, consistent with greater per contaminated injecting exposure transmission (2.5–5.0% for HCV vs. 0.5%–2.0% for HIV), and higher prevalence of HCV than HIV among PWID (and thus, risk of exposure) (Grebely & Dore, 2011a).

### Epidemiology of HCV among PWID

Given an estimated global HCV prevalence of 67% among PWID (Nelson et al., 2011), around 10 million PWID have been infected with HCV, with an additional large reservoir of infection among former PWID. In some countries, the HCV prevalence is as high as 90% (Hagan, Pouget, Des Jarlais, & Lelutiu-Weinberger, 2008). In absolute numbers, the countries with the greatest number of HCV infected PWID include China (1.6 million), the United States (1.4 million) and the Russian Federation (1.3 million) (Nelson et al., 2011).

The estimated incidence of HCV infection among PWID ranges from 5% to 45% per annum (Grebely & Dore, 2011a; Hagan et al., 2008; Page, Morris, Hahn, Maher, & Prins, 2013). The risk of HCV infection is highest among younger individuals and recent initiates into injecting drug use (Grebely & Dore, 2011a; Page et al., 2013) (2, 3) (1, 2). However, many PWID remain unaware of their infection status. The absence of accurate national surveillance and notification systems also contributes to underreporting of HCV.

### Morbidity and mortality among PWID

HCV is a major cause of liver failure and liver-related death (Grebely & Dore, 2014; Hajarizadeh et al., 2013). In the United States, HCV-related mortality has now surpassed death related to HIV (Ly et al., 2012). Globally, the burden of HCV infection is expected to substantially increase within the next few decades (Grebely & Dore, 2014; Hajarizadeh et al., 2013).

Given around 25% of people infected with HCV spontaneously clear virus (4), ~50% of PWID will have chronic HCV infection (represents 8 million PWID globally). In those with spontaneous HCV clearance, re-infection in the setting of ongoing HCV exposure is possible (Grebely et al., 2012). Although many of those with re-infection clear repeatedly, others develop persistent infection.

Development of chronic HCV infection may lead to progressive hepatic fibrosis, cirrhosis, and complications of liver failure or hepatocellular carcinoma (Grebely & Dore, 2011b). Progression to advanced liver disease is uncommon in the initial 10–20 years of infection, particularly among PWID who generally acquire infection at a younger age, but becomes more common with each subsequent decade of infection (Grebely & Dore, 2011b). Among PWID, factors contributing to fibrosis progression such as age, continued moderate-heavy alcohol use, and HIV are often compounded. Although younger individuals with HCV infection are at lower risk of HCV-related morbidity and mortality, and drug-related mortality is significant among PWID, the ageing cohort nature of PWID populations means that liver disease-related mortality is increasing (Grebely & Dore, 2011b, 2014). There is also increasing evidence that HCV infection is associated with an increase in both hepatic and extra-hepatic disease, including circulatory diseases, renal diseases, and neuropsychiatric disorders (Grebely & Dore, 2011b, 2014). However, HCV treatment can attenuate hepatitis C-related disease consequences, and prevent death associated with HCV (van der Meer et al., 2012).

### Prevention of HCV infection among PWID

There is currently no HCV vaccine. But, HCV infection is a preventable disease, especially among PWID. Basic requirements for successful HCV prevention according to the WHO guidance are access to health care and justice, health literacy and need adapted services for PWID (World Health Organisation, 2012). Key measurements for effective HCV prevention are needle syringe programs (NSPs, including provision of sterile injection equipment) and opioid substitution treatment (OST) (Turner et al., 2011). With the combination of these two preventive steps at high coverage, those in need and at right scale the individual risk can be minimized (Hagan, Pouget, & Des Jarlais, 2011; Martin, Hickman, Hutchinson, Goldberg, & Vickerman, 2013; Turner et al., 2011). In many countries, the coverage of OST and sterile injection equipment provision is insufficient (Mathers et al., 2010). As Page and colleagues have highlighted, even in a country like the United States, “public health and political efforts to increase clean syringe/needle availability have been met with ideological, social, and political barriers, effectively thwarting the delivery of one of the most efficacious biomedical technologies for preventing injection-related infections” (Page et al., 2013).

Most prevention programs, if available at all, are driven by insights from the field of HIV prevention, where a lower coverage of needle and syringes is sufficient to stem HIV transmission compared to HCV (Grebely & Dore, 2011a). However, the higher infectivity of HCV compared to HIV and greater prevalence demands broader injecting equipment provision (cooker, filter, water), higher coverage and greater scale-up. The requirements for injecting equipment may vary by the type of drug used and the type of users (e.g. a heroin user needs up to 6 sets of injection equipment per day, while a “krokodil (desmorphine)” user may require 12 sets).

In an attempt to address the HCV epidemic and reduce prevalence of infection in the community, prevention measures such as NSP and OST may be coupled with HCV treatment (Martin, Vickerman, et al., 2013). It has been suggested that with even modest rates of HCV treatment uptake it will be possible to substantially reduce the viral reservoir in the community and decrease the number of potential sources for transmission, particularly in the era of IFN-free HCV therapy (Martin, Vickerman, et al., 2013). However, HCV treatment as prevention will require a strong foundation of harm reduction programs, such as NSP and OST programs to reduce ongoing transmission. As such, countries with low coverage of OST and sterile injection equipment provision should first concentrate on the scale-up these two important prevention strategies, given their importance in preventing HCV transmission (Hagan et al., 2011; Martin, Vickerman, et al., 2013; Turner et al., 2011; Vickerman, Martin, Turner, & Hickman, 2012). Successful HCV prevention strategies among PWID can also prevent HIV infection, given the similar routes of transmission, higher coverage and increased scale that are required. However, further research is needed to better understand the optimal combination of HCV prevention strategies for reducing HCV transmission.

Any combination of prevention strategies must take into account that the highest risk of HCV infection is at the beginning of an injecting career. As such, comprehensive prevention measures should ensure targeting to new initiates to injecting and young people who inject drugs (Page et al., 2013).

Access and provision of HCV prevention services is hindered in countries with restrictive drug law enforcement. The criminalization of drug use and the fear of arrest drives people away from HCV prevention services, resulting in increased risk behaviors and increased transmission of HCV infection. Restrictions in OST provision leads to low coverage, thereby limiting the potential effect on HCV prevention. In countries with repressive drug policy, PWID

often end up in prison, where the risk of HCV infection is often higher, given a high prevalence of HCV infection and the absence of effective prevention measures.

### Treatment of HCV infection among PWID

Hepatitis C virus infection is a curable chronic disease. Although new DAA-based HCV therapies are already available in some countries, for most areas, the current standard of care consists of treatment with pegylated-interferon (one injection per week), ribavirin (1–3 tablets twice a day) and telaprevir or boceprevir (6–12 tablets, 2–3 times a day) for those with HCV genotype 1. These treatments are arduous (6–12 months), poorly tolerated and cure only 60–70% of individuals.

Initially, HCV treatment guidelines excluded PWID from consideration, citing concerns about adherence, increased susceptibility to side effects (e.g. depression) and re-infection (NIH, 1997). However, there is now compelling evidence that HCV treatment is safe and effective among PWID (Aspinall et al., 2013; Dimova et al., 2012). In two systematic reviews of studies assessing treatment for PWID (one specifically focusing on those with recent injecting at the time of treatment initiation), the overall proportion with viral cure was 56% (Aspinall et al., 2013; Dimova et al., 2012). These response rates are comparable to large randomized controlled trials of HCV treatment (Manns, Wedemeyer, & Cornberg, 2006). International guidelines now recommend treatment for PWID following individualised assessment (Robaeyts et al., 2013).

Although there is concern that HCV re-infection may negate the potential benefits of treatment, the reported rates of reinfection following successful HCV treatment among PWID are low (1–5% per year) (Aspinall et al., 2013). Treatment of HCV infection among current and former PWID has also been demonstrated to be cost-effective (Martin et al., 2012).

### New therapies for the treatment of HCV infection

Numerous antiviral agents targeting specific HCV viral functions have been developed (direct acting antivirals [DAAs]) (5). Over the next 2–3 years several, interferon free combination DAA regimens should be licensed. These regimens offer increased efficacy (>90%), reduced toxicity, shortened treatment durations (8–12 weeks), simplified dosing (all oral, possibly once-daily regimens) and monitoring schedules. The availability of such regimens should markedly improve the feasibility of enhanced HCV treatment uptake and responses among PWID, further enhancing the prevention potential of HCV therapy, making elimination of HCV infection among PWID a possibility (Grebely & Dore, 2014; Martin, Vickerman, et al., 2013).

### Models of care for the treatment of HCV infection among PWID

Traditionally, the provision of HCV care and treatment has been provided at hospital-based specialist services (Bruggmann, 2012). This setting is often not suitable for PWID, given the risk of stigmatization, exclusion due to prejudices and the absence of expertise in addiction treatment (Bruggmann & Litwin, 2013). Furthermore, the limited infrastructure for delivery of HCV therapies and the lack of HCV knowledge in drug and alcohol clinics and primary care centres may limit the ability to provide treatment settings that are suitably adapted for the needs of this vulnerable population (Bruggmann, 2012). A multidisciplinary approach is the foundation of a need-adapted HCV care setting for PWID (Bruggmann & Litwin, 2013). Close collaboration of all involved health professionals is crucial for every model to be successful. To adopt a nonjudgmental attitude

toward PWID is essential for all parties involved. A high level of acceptance of the individual life circumstances of PWID rather than rigid exclusion criteria will determine the level of success of any model of hepatitis C management. Integrating HCV treatment in a primary care-based, multidisciplinary OST clinic has proven to be an efficient way to treat a poly-morbid population of PWID (Bruggmann & Litwin, 2013).

### Barriers to the treatment of HCV infection among PWID

Despite the high prevalence of HCV infection, proven favourable HCV treatment responses, available guidelines recommending treatment among PWID, and high treatment willingness, treatment uptake remain as low as 1–2% per year, even in countries where treatment is available and affordable for everyone (Grebely & Dore, 2014). Further research is needed to better understand the best interventions to enhance HCV screening, assessment and treatment to reduce the burden of HCV infection among PWID.

Any attempt to avert the public health care threat posed by the looming burden of HCV among PWID will urgently require groundbreaking changes to alter the currently inefficient system for the care of HCV infection among this vulnerable population. A relevant scale-up of treatment among PWID is impossible without massively reducing the barriers to care. Low awareness (among patients, health care providers, policy makers, political leadership and general public), as well as low HCV literacy (among healthcare professionals and patients) and discrimination and stigmatization of drug use are all major barriers for PWID to access HCV care (Bruggmann, 2012; Paterson, Hirsch, & Andres, 2013). Many of those barriers are a result of the criminalization of drug use (The Global Commission on Drug Policy, 2013). Repressive drug policy is hindering effective public health measures for PWID and therefore fuelling the HCV and HIV epidemic in this population. De-penalization of drug use would therefore be an important step toward eliminating hepatitis C (Bruggmann, 2013).

Another major barrier to treatment for PWID is the price of medication. HCV treatment for both active and former PWID is cost-effective (driven by the prevention benefit among active PWID) (Martin et al., 2012; Martin, Vickerman, Miners, & Hickman, 2013). However, the cost of today's standard-of care HCV treatment is prohibitively expensive for middle- and low-income countries. Even in Western European countries, access to current therapies is restricted because of the exorbitant cost of the medication. High tolerability of those regimens will bring the potential of high applicability. But, their extortionate cost will exceed even the healthcare budgets of rich countries. Offering HCV treatment at affordable prices is crucial in the fight of the global HCV crisis (Bruggmann, 2013).

It is uncertain whether HCV treatment for PWID will be cost-effective, particularly in the initial 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 infection will require considerable public health advocacy from all sectors in the HCV community, including community organizations representing PWID. The involvement of several pharmaceutical companies in development of DAA-based therapy may enable more competitive drug pricing in high-income countries. In low- and middle-income countries, production of generic DAA regimens will be required, similar to antiretroviral therapy for HIV.

Ultimately, markedly enhanced global public health advocacy and investment along the lines of the Global Fund for HIV, tuberculosis and malaria, will be required to enable broadened access to highly effective HCV therapy, including for PWID.

HCV infection is widely ignored politically, resulting in low attention, resources and commitment. Political efforts to improve prevention and access to care and to secure affordable treatment lag far behind those of HIV. With the availability of novel, highly efficacious HCV therapies, the elimination of HCV among PWID is now feasible. At this moment, evidence-based harm reduction measures and specific care elements need to be optimized and expanded in order to efficiently prevent the further spread and secondary liver disease burden of HCV and to halt the growing individual, social and economic harm of the epidemic.

## Conclusion

HCV infection is highly prevalent among PWID. Globally, 67% of PWID are HCV positive.

Awareness is low among policy makers, political leadership and general public, particularly in the regions most affected by the HCV epidemic among PWID. Despite this, the public health threat is considerable and will manifest itself in the next five years.

Overall, only 10–50% of all PWID worldwide receive HCV testing, less than 10% have access to assessment and treatment of the disease, despite the evidence that treatment is effective. Restrictive drug policy and law enforcement are key drivers of the HCV epidemic among PWID, in even greater magnitude than of HIV, as HCV is more contagious and 3.5 times more prevalent. Successful HCV prevention strategies combine high coverage of harm reduction measures with HCV treatment provision at the right scale. The integration of needs-adapted HCV treatment services into harm reductions services like opioid substitution treatment has the potential to enhance therapy uptake and cure rates. Novel, well-tolerated, and efficacious interferon-free HCV treatment regimens administered once daily as a pill over 8–12 weeks bring along the potential to cure the majority of infected people who inject drugs. With these new medicines, the elimination of HCV among PWID becomes achievable. The contents and conclusions of the paper reflect a broad consensus among social and clinical scientists participating in a UNODC Scientific Consultation on HIV/AIDS (UNODC, 2014).

### Conclusion Statements:

- HCV prevalence is high among PWID. Globally, 67% of PWID are HCV positive.
- The public health threat by the HCV epidemic is considerable and will continuously increase in the next years. Still, Hepatitis C awareness is generally low, even among health care providers and health ministries, particularly in the regions most affected by the HCV epidemic among PWID.
- Access to testing, assessment and treatment for PWID is poor, despite the evidence that treatment is effective.
- The HCV epidemic among PWID is relevantly driven by restrictive drug policy and law enforcement.
- HCV can be prevented by a combination of high coverage of harm reduction measures with HCV treatment provision at the right scale.
- Treatment uptake and cure rates can be enhanced by the provision of HCV care integrated into harm reductions services like opioid substitution treatment.
- New interferon-free HCV treatment regimens have the potential to cure the majority of infected people who inject drugs. With these well tolerated and easy to administer medicines, the elimination of HCV among PWID becomes achievable.

## Conflict of interest statement

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