

**Eradication of hepatitis C infection: the importance of targeting people who inject drugs.**

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Hepatitis C virus (HCV) affects approximately 170 million people worldwide and causes significant morbidity and mortality (1). In high-income countries, people who inject drugs (PWID) are at greatest risk of HCV infection (2). Until recently HCV eradication seemed unlikely, but recent advances in HCV treatment and improved understanding of the effectiveness of harm reduction intervention effectiveness give reason for optimism. Current HCV treatments can cure ~75% of patients and new drugs will further improve effectiveness (over 90% cure) and improve tolerability (3). If HCV treatment can be delivered effectively to those at highest risk of onward transmission significant reductions in future HCV cases are possible. The feasibility of disease eradication must be assessed on both scientific criteria (e.g. epidemiological susceptibility, effective and practical intervention available and demonstrated feasibility of elimination) and political criteria (e.g. burden of disease, cost of intervention) (4). With effective, curative treatment now available, HCV meets these criteria.

### **The importance of targeting PWID**

To achieve eradication, public health efforts must focus on PWID, the key drivers of HCV transmission. A sustained, multipronged approach could substantially reduce HCV infection in PWID over the next 10–20 years through a focus on HCV treatment as prevention, meaning improved access to more effective and well-tolerated HCV treatment. Other major elements include increasing coverage of opiate substitution therapy (OST), needle and syringe programs (NSPs), and regular HCV screening and counseling.

PWID are highly marginalised, so effective engagement and inclusion in strategy development are critical to HCV eradication. To date, health services have been unsuccessful in channelling PWID into HCV treatment, despite evidence of willingness to be treated (5) and treatment success (6).

### HCV treatment as prevention

For the past decade HCV treatment has mostly involved pegylated interferon and ribavirin (PEG/RBV); however, trials of direct-acting antivirals (DAAs) show increased rates of cure, improved tolerability, and reduced duration of treatment (3, 7, 8). The first NS3 protease inhibitors, boceprevir and telaprevir, used in combination with PEG/RBV, have already improved outcomes, with up to 75% of patients chronically infected with HCV genotype-1 being cured (3). Emerging therapies that include next-generation NS3 protease inhibitors, NS5A inhibitors and NS5B polymerase inhibitors show great promise (7, 8). An interferon-free 12-week DAA regimen with single daily dosing and over 90% cure is a real possibility (3).

Highly effective and tolerable HCV therapies will make treatment as prevention feasible.

This strategy will require targeting PWID, few of whom undergo HCV treatment despite increasing evidence of success (6). The rarity of PWID undergoing treatment relates to concerns about interferon toxicity and RBV teratogenicity, and unsubstantiated concerns about PWID compliance and high re-infection rates. Apart from managing adverse side effects, we know little about interventions that improve HCV treatment compliance (9).

However, increasing evidence shows that PWID are compliant when treated with PEG/RBV (10), and compliance can only rise with improved treatment tolerability. Similarly, most evidence suggests HCV reinfection following remains low (11).

Models developed by Martin and colleagues suggest that treating a relatively small proportion of PWID could significantly reduce HCV prevalence over 15 years, with the impact varying depending on the number treated, the background HCV prevalence, treatment efficacy and the speed of treatment scale-up (12) (Figure 1). Estimated HCV prevalence halved when treatment was scaled-up to 15, 40, or 76 per 1000 PWID annually in Edinburgh (Scotland), Melbourne (Australia), and Vancouver (Canada) respectively using DAAs.

Current estimated HCV prevalence in PWID in those three jurisdictions is 25%, 50% and 65% respectively. Recent modeling of PWID in Vietnam also revealed treatment's impact on HCV prevalence (13).

[Suggested location of Figure 1]

### **Harm reduction to reduce HCV transmission**

Prevention of HCV transmission is critically important for HCV eradication. Harm reduction strategies for PWID, notably OST and NSPs, have been partially effective in reducing HCV transmission in PWID (14) although poor coverage has limited their impact (15). A recent study estimated that NSPs directly averted 97,000 ( $\approx 50\%$ ) new HCV infections in Australia during 2000–2009 (14). Modeling by Vickerman and colleagues suggests that, in a setting where HCV prevalence is 40%, scaling OST/NSP coverage up from 0% to 20%, 40% and 60% can reduce HCV prevalence over 10 years by 13%, 24% and 33% respectively (16).

However, further increments in coverage produce only marginal improvements (16), suggesting that complementary strategies are required to substantially reduce HCV prevalence.

### **Treatment access and cost**

PWID are highly marginalised and few receive HCV treatment despite increasing evidence that treatment works (6). Effective engagement with PWID is critical to HCV eradication. Integrated multidisciplinary approaches that include clinicians, nurses and other support services, located in community-based settings or OST clinics, can increase HCV assessment and treatment (17). Infrastructure, workforce capacity and education programs focused on

PWIDs' needs are needed for timely and effective strategy implementation; currently many primary care clinicians and health service staff know little about HCV assessment and care (18).

Current HCV treatment is expensive and the cost of scale-up with more expensive therapies will be considerable. Visconti et al's modeling found that treating both current and former PWID for HCV using standard PEG/RBV was cost effective (19). Martin et al's model included the broader public health benefit of reducing HCV prevalence, and showed antiviral treatment for PWID saved £521 and £2,539 per QALY when baseline HCV prevalence was 20% and 40% respectively compared with no treatment, well below generally accepted thresholds for cost-effective interventions (20). Despite the cost effectiveness of treating PWID, the actual costs of HCV treatment, particularly DAAs, will challenge governments in both developed and resource-limited settings; nonetheless, the models suggest standard HCV therapy still has considerable benefits.

### **Injecting networks**

Most models assume injectors homogenous mixing with all other injectors in the population; few consider the impact of PWIDs' social and injecting networks on HCV transmission or clearance. A recent HCV PWID network model derived from empirical data indicated that injecting networks substantially impact transmission (21). Further modeling suggested that treating PWIDs and their immediate contacts simultaneously (as opposed to ad hoc treatment) reduces the overall number of PWID needing treatment, reducing long-term HCV prevalence and treatment costs.

### **HCV vaccination**

Candidate vaccines designed to prevent initial infection, reduce viral persistence in acute infection, or lead to SVR in chronic infection are in phase 2 and 3 trials (22). However, experience with the highly effective hepatitis B vaccine suggests uptake amongst PWID may be low (23). Hence an HCV vaccine will be just one component of an HCV eradication strategy.

### **Conclusion**

Eradicating HCV in PWID is ambitious but, based on the criteria for assessing disease eradicability (4), achievable (Table 1). Treatment costs will be substantial and recruiting sufficient PWID to treatment programs challenging. However, scale-up of HCV diagnosis and treatment with new highly efficacious and tolerable drugs, plus effective and relatively inexpensive harm reduction and prevention approaches, will considerably reduce HCV prevalence. Eradicating HCV needs a sustained, focused and multipronged approach; the time to start is now.

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### **Authors' experience/expertise, contribution, and sources of information (150 words)**

MH and EM are experienced HCV clinicians, epidemiologists and modellers.

AT is an experienced HCV clinician and scientist.

JD is an infectious diseases clinician, epidemiologist and PhD candidate, and RSD is a PhD candidate studying aspects of HCV treatment and epidemiology respectively and have first-authored and co-authored several articles in their fields.

MH wrote the first draft of the manuscript. All authors reviewed and edited the primary and subsequent revised versions of the manuscript.

### **Disclosure statement**

MH, JD, RSD, EM: no conflicts of interest to declare

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Table 1: Assessing HCV eradicability

<b>Criteria for assessing eradicability</b>	<b>Application of the criteria to HCV</b>	
<b>Scientific feasibility (4)</b>	<b>Facilitators</b>	<b>Challenges</b>
Epidemiologic susceptibility (e.g., no nonhuman reservoir, ease of spread, naturally induced immunity, ease of diagnosis)	No non-human reservoir Transmission limited to specific risk groups and preventable through behaviour change. Simple diagnostic test	Limited naturally induced immunity
Effective, practical intervention available (e.g., vaccine, curative treatment)	Curative treatments with improving efficacy and tolerability.	No current effective vaccine
Demonstrated feasibility of elimination (e.g., documented elimination from island or other geographic unit)	Mathematical modelling demonstrating a reduction in prevalence and incidence	No actual demonstrated feasibility of elimination
<b>Political will and popular support (4)</b>		
Perceived burden of the disease (e.g., extent, deaths, other effects, relevance to rich and	Globally it is recognised that HCV morbidity and mortality are increasing as are the	There is significant stigma against people who inject drugs, the

poor countries)

associated costs of managing chronic infection group most affected by HCV

Growing political will to address HCV burden in developed countries (e.g. birth-cohort screening programs in USA)

Expected cost of eradication

Modelling suggesting reducing HCV prevalence and incidence through treatment is cost effective Modelling suggesting reducing HCV prevalence and incidence through treatment is expensive

Synergy of eradication efforts with other interventions (e.g., potential for added benefits or savings)

Strategies are available to reduce the cost of eradication e.g. using a contact tracing (network) approach for HCV treatment

Harm reduction strategies are inexpensive and contribute to reductions in HCV burden – needle and syringe programs, OST

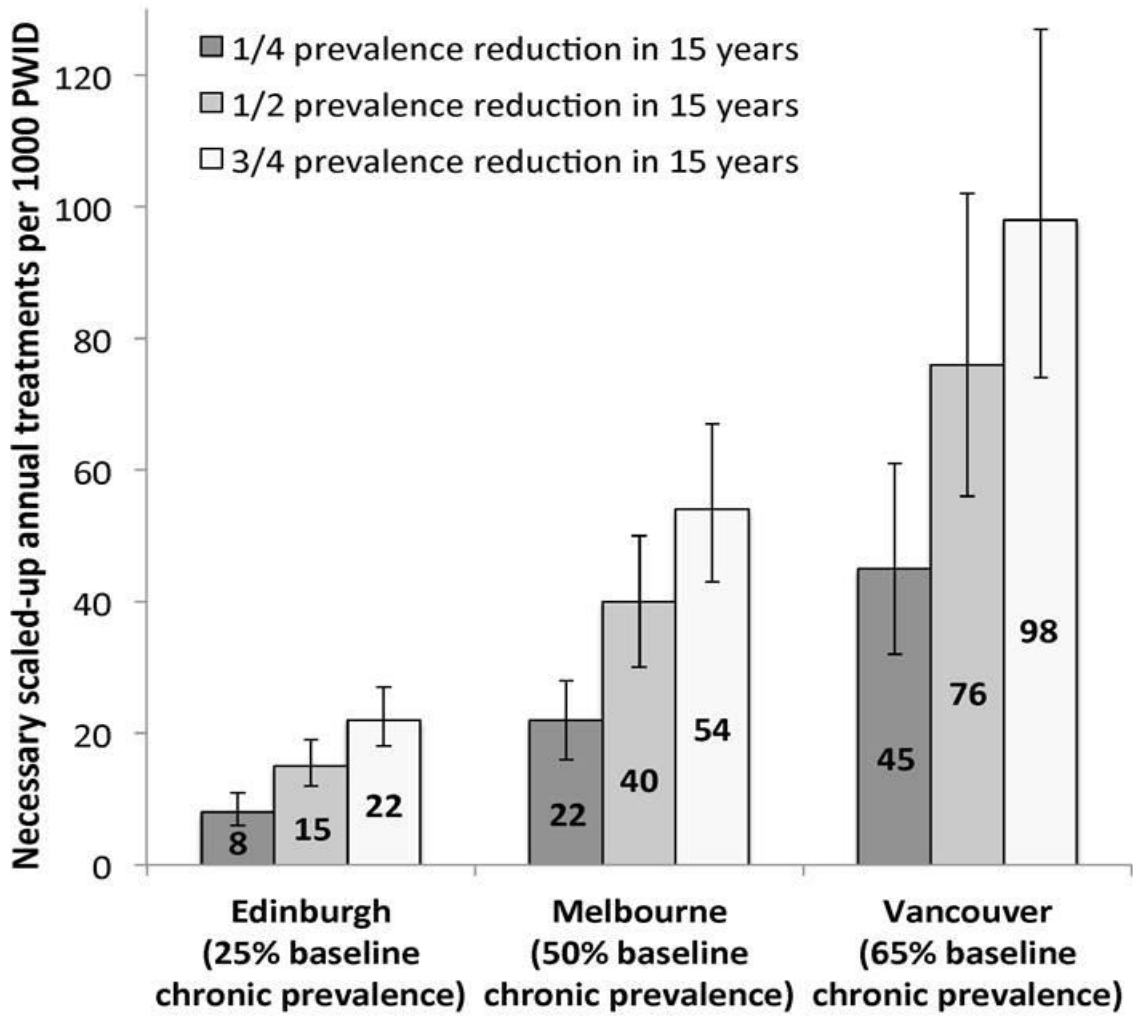
Need for eradication rather than control

Despite the short term expense of eradication it would lead to

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long-term savings. If eradicated the costs associated with HCV screening, vaccination, treatment, and management of disease progression would be reduced.

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**Figure 1. Annual scaled-up treatment rate required to reduce prevalence by , , or in Edinburgh, Melbourne, and Vancouver within 15 years (by 2027). Bars (and numbers) indicate the mean value, with whiskers representing the 95% credibility interval**