HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

EDITORIAL

Eradication of Hepatitis C Infection: The Importance of Targeting People Who Inject Drugs

Hepatitis C virus (HCV) affects ~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.

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 marginalized, so effective engagement and inclusion in strategy development are critical to HCV eradication. To date, health services have been unsuccessful in channeling 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 reinfection 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 treatment remains low.[11]

Models developed by Martin et al.[12] suggest that treating a relatively small proportion of PWID could significantly reduce HCV prevalence over 15 years,

Abbreviations: DAA, direct-acting antiviral; HCV, hepatitis C virus; NSPs, needle and syringe programs; OST, opiate substitution therapy; PEG/RBV, pegylated interferon and ribavirin; PWID, people who inject drugs.

Address reprint requests to: Prof. Margaret Hellard, Centre for Population Health, Burnet Institute, 85 Commercial Road, Melbourne VIC 3004, Australia. E-mail: hellard@burnet.edu.au; fax: +61 3 9282 2138.

M.H., J.D., R.S.D., A.T., and E.M. are supported by the National Health and Medical Research Council. J.D. and R.S.D. are supported by the NHMRC-funded Centre for Research Excellence into Injecting Drug Use. The authors acknowledge the contribution to this work of the Victorian Operational Infrastructure Support Program (Department of Health, Victoria, Australia) to the Burnet Institute.

View this article online at wileyonlinelibrary.com.

DOI 10.1002/hep.26623

Potential conflict of interest: M.H., J.D., R.S.D., E.M.: no conflicts of interest to declare. A.T.: Research / grant support, Merck, Roche, Gilead; Consulting/advisory capacity, Merck, Roche, Janssen-Cilag (Johnson and Johnson), Gilead, Novartis; Speaker's fee, Merck, Roche, Bristol-Myers Squibb, Bayer, Janssen, Gilead. Coinventor of a patent related to the IL28B-*HCV discovery.*

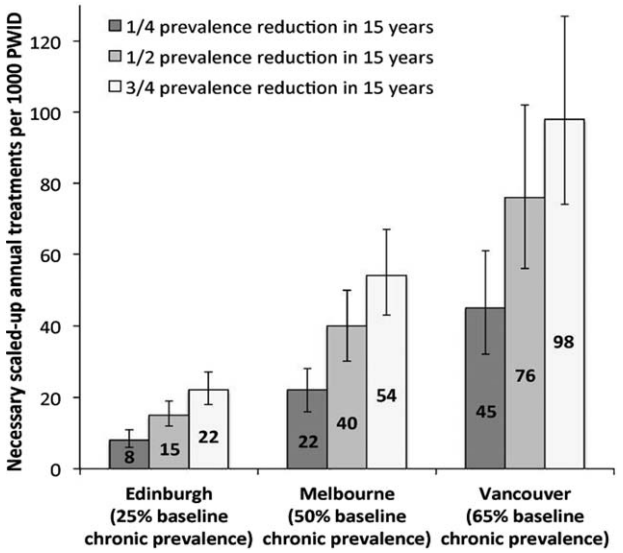

Fig. 1. Annual scaled-up treatment rate required to reduce prevalence by 1/4, 1/2, or 3/4 in Edinburgh, Melbourne, and Vancouver within 15 years (by 2027). Bars (and numbers) indicate the mean value, with whiskers representing the 95% credibility interval.

with the impact varying depending on the number treated, the background HCV prevalence, treatment efficacy, and the speed of treatment scale-up (Fig. 1). Estimated HCV prevalence halved when treatment was scaled up to 15, 40, or 76 per 1,000 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 impact on HCV prevalence.[13]

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 (~50%) new HCV infections in Australia during 2000-2009.[14] Modeling by Vickerman et al.[16] 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. 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 marginalized 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[19] modeling found that treating both current and former PWID for HCV using standard PEG/RBV was cost-effective. Martin et al.'s[20] model included the broader public health benefit of reducing HCV prevalence, and showed antiviral treatment for PWID saved £521 and £2,539 per quality-adjusted life year (QALY) when baseline HCV prevalence was 20% and 40%, respectively, compared with no treatment, well below generally accepted thresholds for cost-effective interventions. 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 homogeneous mixing of PWID with all other PWID 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 sustained virological response (SVR) in chronic infection are in phase 2 and 3 trials.[22] However, experience with the highly effective hepatitis B vaccine

Table 1. Assessing HCV Eradicability

Criteria for Assessing Eradicability	Application of the Criteria to HCV	
Scientific Feasibility (4)	Facilitators	Challenges
Epidemiologic susceptibility (e.g., no nonhuman reservoir, ease of spread, naturally induced immunity, ease of diagnosis)	No nonhuman reservoir Transmission limited to specific risk groups and preventable through behavior 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 modeling demonstrating a reduction in prevalence and incidence	No actual demonstrated feasibility of elimination
Political will and popular support (4)		
Perceived burden of the disease (e.g., extent, deaths, other effects; relevance to rich and poor countries)	Globally it is recognized that HCV morbidity and mortality are increasing as are the associated costs of managing chronic infection Growing political will to address HCV burden in developed countries (e.g., birth-cohort screening programs in USA)	There is significant stigma against people who inject drugs, the group most affected by HCV
Expected cost of eradication	Modeling suggesting reducing HCV prevalence and incidence through treatment is cost effective	Modeling 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 long-term savings. If eradicated the costs associated with HCV screening, vaccination, treatment, and management of disease progression would be reduced	

suggests uptake among PWID may be low.[23] Hence, an HCV vaccine will be just one component of an HCV eradication strategy.

In 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.

Author Roles: M.H. wrote the first draft of the article. All authors reviewed and edited the primary and subsequent revised versions of the article.

Margaret Hellard[1-3]
Joseph S. Doyle[1-4]
Rachel Sacks-Davis[1,3]
Alexander J. Thompson[4,5]
Emma McBryde[1,4]
[1]Centre for Population Health, Burnet Institute, Melbourne, Victoria, Australia
[2]Infectious Diseases Unit, The Alfred Hospital, Melbourne, Victoria, Australia
[3]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Victoria, Australia
[4]Victorian Infectious Disease Service, Royal Melbourne Hospital, Parkville, Victoria, Australia
[5]Department of Gastroenterology, St Vincent's Hospital, Melbourne, Victoria, Australia

References

1. Shepard C, Finelli L, Alter M. Global epidemiology of hepatitis C virus infection. Lancet ID 2005;5:558-567.
2. Nelson P, Mathers B, Cowie B, Hagan H, Des Jarlais D, Horyniak D, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. Lancet 2011;378: 571-583.
3. Doyle JS, Aspinall E, Liew D, Thompson AJ, Hellard ME. Current and emerging antiviral treatments for hepatitis C infection. Br J Clin Pharmacol 2013;75:931-943.
4. Hopkins D. Disease eradication. N Engl J Med 2013;368:54-63.
5. Doab A, Treloar C, Dore GJ. Knowledge and attitudes about treatment for hepatitis C virus infection and barriers to treatment among current injection drug users in Australia. CID 2005;40(Suppl 5):S313-S320.
6. Aspinall E, Corson S, Doyle J, Grebely J, Hutchinson S, Dore G, et al. Treatment of HCV infection among people who are actively injecting drugs: a systematic review and meta-analysis. CID 2013 [Epub ahead of print].
7. Gane EJ, Stedman C, Hyland RH, Ding X, Svarovskaia E, Symonds W, et al. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. N Engl J Med 2013;368:34-44.
8. Poordad F, Lawitz E, Kowdley KV, Cohen D, Podsadecki T, Siggelkow S, et al. Exploratory study of oral combination antiviral therapy for hepatitis C. N Engl J Med 2013;368:45-53.
9. Redulla R, Dudley-Brown S. Adherence and completion in hepatitis C management. Gastro Nurs 2013;36:53-58.
10. Grebely J, Matthews G, Hellard M, Shaw D, van Beek I, Petoumenos K, et al. Adherence to treatment for recently acquired hepatitis C virus (HCV) infection among injecting drug users. J Hepatol 2011;55: 76-85.
11. Grady BPX, Vanhommerig JW, Schinkel J, Weegink CJ, Bruisten SM, Lindenburg CEA, et al. Low incidence of reinfection with the hepatitis C virus following treatment in active drug users in Amsterdam. Eur J Gastroenterol Hepatol 2012;24:1302-1307.
12. Martin N, Vickerman P, Grebely J, Hellard M, Hutchinson S, Lima V, et al. HCV treatment for prevention among people who inject drugs: modeling treatment scale-up in the age of direct-acting antivirals. HEPATOLOGY 2013 [Epub ahead of print].
13. Durier N, Nguyen C, White L. Treatment of hepatitis C as prevention: a modeling case study in Vietnam. PLoS ONE 2012;7:e34548.
14. Kwon J, Anderson J, Kerr C, Thien H, Zhang L, Iversen J, et al. Estimating the cost-effectiveness of needle-syringe programs in Australia. AIDS 2012;26:2201-2010.
15. Mathers B, Degenhardt L, Ali H, Wiessing L, Hickman M, Mattick R, et al. HIV prevention, treatment, and care services for people who inject drugs: a systematic review of global, regional, and national coverage. Lancet 2010;375:1014-1028.
16. Vickerman P, Martin N, Turner K, Hickman M. Can needle and syringe programmes and opiate substitution therapy achieve substantial reductions in hepatitis C virus prevalence? Model projections for different epidemic settings. Addiction 2012;107:1984-1995.
17. Bruggmann P, Litwin A. Models of care for the management of HCV among people who use drugs: one size does not fit all. CID 2013;57: S56–S61.
18. Hellard M, Wang Y. The role of general practitioners in managing and treating hepatitis C. MJA 2009;191:523-524.
19. Visconti A, Doyle J, Weir A, Shiell A, Hellard M. Assessing the cost-effectivenss of treating chronic hepatitis C virus in people who inject drugs in Australia. J Gastroenterol Hepatol 2013;28:707-716.
20. Martin N, Vickerman P, Miners A, Foster G, Hutchinson S, Goldberg D, et al. Cost-effectiveness of hepatitis C virus antiviral treatment for injection drug user populations. HEPATOLOGY 2012;55:49-57.
21. Rolls D, Daraganova G, Sacks-Davis R, Hellard M, Jenkinson R, McBryde E, et al. Modelling hepatitis C transmission over a social network of injecting drug users. J Theor Biol 2012;297:73-87.
22. Houghton M. Prospects for prophylactic and therapeutic vaccines against the hepatitis C viruses. Immun Rev 2011;239:99-108.
23. Maher L. Hepatitis B vaccination and injecting drug use: narrowing the efficacy-effectiveness gap. Int J Drug Policy 2008;19:425-428.