Modelling antiviral treatment to prevent hepatitis C infection among people who inject drugs in Victoria, Australia

Margaret E Hellard PhD, FRACP, FAFAHP, Head, and Head of Hepatitis Services
Rebecca Jenkinson BEng(Eng), MEngip, PhD, Research Officer
Peter Higgins BSW, MA, PhD, NHMRC Post Doctoral Fellow
Mark A Stoové BA(Hons)[Arts]), GradDip(Eng), PhD, Head HIV/STI Research Group and Adjunct, Research Fellow
Rachel Sacks-Davis BA BSc(Hons), PhD, Research Assistant, and PhD student
Judy Gold BDiomedSci(Hons), PhD, Research Assistant, Centre for Population Health, Burnet Institute
Matthew Hickman MSc, PhD, FFPH, Professor of Public Health and Epidemiology
Peter Vickerman DPhil, BSc, Senior Lecturer
Natasha K Martin PhD, Economic Modeller, and Honorary Research Fellow

Centre for Population Health, Burnet Institute, Melbourne, VIC.
Infectious Diseases, Alfred Hospital, Melbourne, VIC.
The Kirby Institute, Sydney, NSW.
Department of Epidemiology and Preventive Medicine, School of Public Health, Monash University, Melbourne, VIC.
The School of Public Health and Primary Care, London School of Hygiene and Tropical Medicine, London, UK.

Methods

Mathematical model and assumptions
A previously developed model of HCV transmission among PWID
fully described in the Appendix; online at mja.com.au) was parameterised using data from Victoria, Australia. It consists of differential equations that track change among PWID who are susceptible (never infected, or previously infected and underwent spontaneous or treatment-induced clearance); who have chronic HCV infection; who are currently receiving treatment; and who do not achieve a sustained viral response (SVR) after treatment (and cannot be retreated). Previous modelling indicated that the presence of immunity has a negligible effect on treatment impact, hence this model assumes no immunity. People who begin to inject drugs enter the susceptible pool and leave (by dying or ceasing to inject) at fixed rates. Susceptible PWID become infected at a rate proportional to infection risk and the prevalence of HCV among PWID. PWID enter treatment at a fixed rate (\(\Phi\) PWID with chronic HCV infection per 1000 PWID annually) unless the number infected is driven below \(\Phi\), whereupon all PWID with chronic HCV infection are treated. The model does not explicitly model individual genotypes, but we weighted the average SVR rate and treatment duration to the genotype distribution in Victoria.

Model parameters
We assumed treatment with pegylated interferon alfa and ribavirin leads to a 45% SVR rate for genotype 1 and 80% for genotype 2 or 3. A systematic review estimated that 26% of people with acute HCV infection spontaneously clear the disease.

The baseline model included the Victorian estimates: population of PWID, 25,000 (based on the number of PWID enrolled in opioid substitution treatment in Victoria, and self-reported opioid substitution treatment uptake data from epidemiological studies), average duration of injecting, 14 years; prevalence of chronic HCV infection among PWID (as determined by a positive polymerase

Abstract

Objectives: To develop a mathematical model to project the potential impact of hepatitis C virus (HCV) treatment on HCV infection prevalence among people who inject drugs (PWID).

Design and setting: An existing model of HCV transmission among PWID was parameterised using data from Victoria, Australia, including specific parameter estimates of the number of people who are currently active injecting drug users, average duration of injecting, chronic HCV infection prevalence among PWID, annual mortality, and annual HCV treatment rate. We also explored the impact of prevalence uncertainty, program scale-up, and new treatments.

Main outcome measure: Prevalence of chronic HCV infection among people who are currently active injecting drug users.

Results: With annual treatment rates of 13, 17, or 25 per 1000 PWID, the model predicts relative prevalence reductions of 20%, 30%, and 50%, respectively, within 30 years. If new treatments giving higher sustained viral response rates are available in 5 years, estimated impact is increased by 21%–23% at 15 years, and 17%–38% at 30 years, depending on treatment rates.

Conclusions: This model suggests that modest rates of current HCV treatment among PWID in Victoria, Australia could halve HCV infection prevalence among PWID in 30 years. This finding suggests that interventions aimed at increasing access to HCV treatment in community clinics will benefit individual PWID and reduce HCV infection prevalence.
chain reaction test result), 50%,4,15 genotype 2 or 3, 44%, and genotype 1, 56%,15,16 mortality rate, 0.0083% per year,17 and annual HCV treatment rate, 1/1000 PWID.4 The Appendix (online at mja.com.au) contains a table of parameters.

Baseline scenario
We identified the treatment rates necessary to reduce HCV infection prevalence among PWID by 20%, 30%, and 50% over 30 years, projecting the decrease in chronic infection prevalence at 5, 15, and 30 years. We determined the 15-year and 30-year relative prevalence reductions with annual treatment rates ranging from 5/1000 PWID to 40/1000 PWID.

Alternative scenarios
As estimates for baseline chronic infection prevalence among PWID in Victoria are uncertain, we explored the impact of lower (45%) and higher (55%) prevalences. Additionally, because of uncertainty in the average length of injecting and SVR rates among PWID, we examined scenarios with longer (16 years) and shorter (12 years) injecting durations (Appendix; online at mja.com.au).

As a substantial increase in treatment rates would require a gradual scale-up, we also explored a scenario where treatment increased linearly from baseline to the full treatment rate over 5 years. In this model, we explored the potential impact of new, direct-acting antiviral therapies with improved efficacy and shorter treatment duration. We modelled scenarios with an 80% SVR rate and a 24-week treatment duration for all genotypes after year 5.

Finally, we examined a scenario where uptake increased because of new treatments with higher SVR rates and shorter duration. We compared treating 5/1000 PWID annually with baseline SVR rates to the following scenario: 5/1000 treated for 5 years with baseline SVR and treatment duration rates, followed by 20/1000 treated for the remaining years with an 80% SVR rate and 24 weeks of treatment.

Results
Our model predicted that reducing chronic HCV infection prevalence by 50% among PWID within 30 years (from 50% to 25%) could be achieved with an annual treatment rate of 625 PWID in Victoria (25/1000 PWID), including reductions in prevalence of 14% by 5 years and 32% by 15 years (Box 1). We also estimated the effect of treating 13/1000 and 17/1000 PWID annually (Box 1).

Box 2 shows the estimated relative reductions in prevalence at 15 and 30 years with varying annual treatment rates. Increasing annual treatment rates resulted in greater prevalence reductions at 30 years compared with 15 years, but above a rate of 30/1000 PWID the incremental impact plateaued (maximum relative prevalence reduction, approximately 70%) because many PWID become persistent non-responders with currently available treatments (Appendix; online at mja.com.au).

The reduced HCV infection prevalence among PWID remained when baseline HCV prevalence (Box 3) and average duration of injecting (Appendix; online at mja.com.au) varied, although higher baseline prevalences and shorter duration of injecting showed a reduced impact.

Introducing a 5-year scale-up period before reaching full treatment rates reduced the impact of treatment by 10%–14% at 15 years (Box 4, A), but the differences were minimal at 30 years (Box 4, B). If new treatments increased SVR to 80% and decreased treatment duration to 24 weeks for both genotypes after 5 years, the estimated impact would increase by 20%–26% at 15 years, and 17%–38% by 30 years, depending on the scale-up strategy.

A benefit was predicted from new treatments resulting in higher SVR with shorter treatment durations when uptake was increased from 5/1000 to 20/1000 after 5 years (Box 5); the projected HCV infection prevalence was nearly half the baseline prevalence by 30 years. Maintaining the treatment rate at 5/1000 showed minimal impact (prevalence of 47% at 5 years and 46% at 30 years).

Discussion
Our modelling suggests that modest rates of HCV treatment among people who currently inject drugs could halve HCV infection prevalence among PWID in 30 years in Victoria. Although this is particularly relevant to Victoria, as the Victorian Government has recently funded ten HCV treatment nurses to work in community-based clinics in urban and regional Victoria, similar impacts on HCV infection prevalence are possible elsewhere in Australia. Our findings suggest that structuring clinics and nurses’ roles to improve timely access to HCV treatment and to support adherence and treatment completion for PWID could produce considerable population-level reductions in HCV transmission. Moreover, new HCV treatment therapies are likely to become available soon, including

![Graph 1: Estimated reduction in chronic HCV infection prevalence among PWID over time through initiating antiviral treatment at different rates](image1)

**Graph 1: Estimated reduction in chronic HCV infection prevalence among PWID over time through initiating antiviral treatment at different rates**

**Graph 2: Estimated effect of treatment rate on relative reduction in chronic HCV infection prevalence among PWID at 15 and 30 years**

**Graph 2: Estimated effect of treatment rate on relative reduction in chronic HCV infection prevalence among PWID at 15 and 30 years**
regimens that are not based on pegylated interferon. Treatment outcomes (SVR rates) will improve for all patients, irrespective of viral genotype and their previous response to therapy. Treatment length will decrease, as will drug side effects, further increasing the projected impact of treatment on HCV infection prevalence.

In the past, concerns about treating PWID have included lack of compliance with therapy, associated drug resistance, and the potential for reinfection. These concerns may discourage clinicians from recommending HCV treatment and deter health service bureaucrats from funding clinics that are appropriately located and structured to meet the complex health needs of PWID. A recent Australian study of HCV treatment uptake and deferral, using data from the Australian Chronic Hepatitis C Observational Study, identified factors related to drug and alcohol use rather than clinical factors as the major influences on treatment uptake. A recent systematic review of HCV treatment for PWID found adequate levels of adherence in this population and low levels of reinfection after successful treatment, and a subsequent study of treatment of acute and early chronic hepatitis C reported high levels of adherence regardless of reported injecting behaviour. Internationally, several studies in a range of settings have demonstrated that successful treatment of current injectors is possible; one study reports high treatment adherence, irrespective of injecting drug use before or during therapy. Additionally, the rate of reinfection after treatment has been shown to be low.

Knowledge about HCV diagnosis and management in the primary care setting in Australia is poor, and considerable work is needed to ensure primary care clinics can appropriately manage HCV infection in PWID. However, Australian primary health care practitioners have considerable experience in managing complex chronic diseases affecting patients with multiple and complex health needs — for example, diabetes, HIV and problems with mental health. With appropriate training and adequate resourcing it should be feasible for them to manage HCV infection in PWID, particularly if systems are developed to facilitate shared-care and timely referral of complex patients to HCV specialists.

The model’s prediction that treating people who currently inject drugs will reduce prevalence and HCV transmission despite risk of reinfection suggests that it is worthwhile funding the treatment of HCV infection in PWID, even if managing this group is resource-intensive. Such a policy would involve locating HCV nurses in primary care services attended by a high proportion of PWID and ensuring that other support services are available, including mental health, drug and alcohol, social welfare, housing and peer support.

Our study has limitations. While estimates for the model parameters...
were generated from multiple data sources, injecting drug use is a highly stigmatised and typically hidden behaviour, so the number of PWID in Victoria and mean duration of injecting are uncertain. Our findings are based on a predictive model rather than experimental evidence or observations in other communities, and assumes that, after scale-up, treatment rates will be constant for 30 years (for example, 625 PWID treated annually); however, as HCV infection prevalence decreases, so may demand for HCV treatment. Conversely, increasing awareness and improvement of treatment may lead to increased treatment uptake. We assumed that the rate of initiation to injecting remains constant over time. The population of PWID may increase due to general population growth or decrease due to changing drug-use patterns, although numbers in Victoria have been stable over the past 15 years.

Finally, the model assumes that risky injecting behaviours and HCV infection prevalence are homogenously distributed among PWID and that all infected PWID have equal probability of HCV acquisition, treatment access, and treatment success. Assuming population heterogeneity in HCV risk and treatment accessibility may lead to the model overestimating the impact of treating 625 PWID annually.

PWID are at greatest risk of acquiring and transmitting HCV infection, but very few are being treated. Because of the high risk of onward transmission, even modest increases in treatment rates in this group may lead to considerable population-level reductions in HCV infection prevalence. Particularly when considered in combination with the value of treatment to individuals, this finding suggests there are real benefits in investing additional resources in treating PWID.

Acknowledgements: We thank Soenke Trumper (General Practice Victoria), Joe Sasadeusz (Royal Melbourne and Alfred Hospitals), Jacqui Richmond (St Vincent’s Hospital), Kate Mellor (St Vincent’s Hospital), Sally von Bibra (Alfred Hospital), Anna Wilkinson (Alfred Hospital) for expert input that informed our parameter estimates. Margaret Hellard was supported by a National Health and Medical Research Council (NHMRC) Research Fellowship. Rachael Sacks-Davis was supported by an NHMRC PhD scholarship. Peter Higgs was supported by an NHMRC Research Post Doctoral Fellowship. Natasha Martin was supported by Health Protection Scotland. Peter Vickerman was supported by the Medical Research Council, UK. Rebecca Jenkinson and Mark Stoove were supported by Centre for Research Excellence into Injecting Drug Use Fellowships.

Competing interests: No relevant disclosures.

Received 31 Jul 2011, accepted 24 Jan 2012.


22. Foster GR. Injecting drug users with chronic hepatitis C: should they be offered antiviral therapy? Addiction 2008; 103. 1412-1413.


