ORIGINAL ARTICLE

Treatment scale-up to achieve global HCV incidence and mortality elimination targets: a cost-effectiveness model

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ABSTRACT

Aims The WHO's draft HCV elimination targets propose an 80% reduction in incidence and a 65% reduction in HCV-related deaths by 2030. We estimate the treatment scale-up required and cost-effectiveness of reaching these targets among injecting drug use (IDU)-acquired infections using Australian disease estimates.

Methods A mathematical model of HCV transmission, liver disease progression and treatment among current and former people who inject drugs (PWID). Treatment scale-up and the most efficient allocation to priority groups (PWID or patients with advanced liver disease) were determined; total healthcare and treatment costs, quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs) compared with inaction were calculated.

Results 5662 (95% CI 5202 to 6901) courses per year (30/1000 IDU-acquired infections) were required, prioritised to patients with advanced liver disease, to reach the mortality target. 4725 (3278–8420) courses per year (59/1000 PWID) were required, prioritised to PWID, to reach the incidence target; this also achieved the mortality target, but to avoid clinically unacceptable HCV-related deaths an additional 5564 (1959–6917) treatments per year (30/1000 IDU-acquired infections) were required for 5 years for patients with advanced liver disease. Achieving both targets in this way cost $A4.6 ($A4.2–$A4.9) billion more than inaction, but gained 184 000 (119 000–417 000) QALYs, giving an ICER of $A25 121 ($A11 062–$A39 036) per QALY gained.

Conclusions Achieving WHO elimination targets with treatment scale-up is likely to be cost-effective, based on Australian HCV burden and demographics. Reducing incidence should be a priority to achieve both WHO elimination goals in the long-term.

Significance of this study

What is already known on this subject?

- WHO have drafted a set of HCV elimination targets, which include a 65% reduction in HCV-related deaths and an 80% reduction in HCV incidence by the year 2030.
- In most developed settings, people who inject drugs (PWID) are the group at highest risk of infection and transmission; however, slow disease progression means that PWID do not necessarily have the heaviest burden of HCV-related liver disease.
- Achieving elimination targets will involve responses among both PWID and patients with advanced liver disease; however, the feasibility, cost and most cost-effective allocation of treatments between these two groups is unknown.

What are the new findings?

- Approximately 5700 treatment courses per year are required for patients with advanced liver disease to achieve a 65% reduction in HCV-related mortality in Australia by 2030.
- Approximately 4700 treatment courses per year are required for PWID infected with HCV (59/1000 PWID) to achieve an 85% reduction in HCV incidence in Australia by 2030.
- Treating PWID immediately to achieve the incidence target also achieves the 2030 mortality target; however, to avoid clinically unacceptable deaths additional treatments are required for 5 years for patients with advanced liver disease.
- Achieving the WHO mortality and incidence elimination targets is estimated to be cost-effective in Australia.

How might it impact on clinical practice in the foreseeable future?

- Reducing incidence by treating PWID should be a priority in order to achieve HCV elimination targets.

INTRODUCTION

Until recently, HCV elimination seemed an unrealistic public health goal. However, the availability of interferon-free direct-acting antiviral (DAA) treatment regimens with efficacy of over 95%, improved tolerability and delivery, and a comparably short duration of therapy means that elimination is now being considered globally.[1] The WHO have recently drafted a set of hepatitis elimination targets, which include a 65% reduction in HCV-related deaths and a 90% reduction in combined HCV and HBV incidence by the year 2030—further specified as a 95% reduction in HBV incidence and an 80% reduction in HCV incidence.[2] The high cost of DAAs in most countries mean that little is known of the feasibility of achieving these targets, and in particular what they imply for health budgets.

In most developed settings, people who inject drugs (PWID) are the group at highest risk of HCV infection and transmission.[3–6] In Australia, it is estimated that the prevalence of HCV among PWID is 50%,[7] and that >80% of all prevalent HCV infections are attributable to injecting drug use.[8] Despite this concentration of infection and transmission risk among PWID, low treatment uptake[9–11] (in part due to the perceived ineligibility of PWID[11]) and the slow progression of liver disease relative to the average length of injecting career results in a heavier burden of HCV-related liver disease falling upon *former* PWID. This means that to achieve WHO elimination targets using treatment alone, the incidence and mortality goals potentially involve targeting largely disparate groups.

Treating *current* PWID reduces incidence through 'treatment-as-prevention' benefits according to modelling studies.[12] If enough infected individuals are cured, the prevalence of HCV will be reduced sufficiently that transmission and hence the number of new infections is also lowered in a substantive way, with significant positive implications for the future burden of HCV-related liver disease. However, using treatment-as-prevention to reduce liver-related mortality on a 15-year time horizon may be inefficient compared with directly treating patients with advanced liver disease, and may require more total treatments and greater initial spending. Therefore, in order to achieve the WHO elimination targets in the most cost-effective way, resources will need to be effectively allocated between infected PWID to reduce incidence, and patients with advanced liver disease to reduce mortality. This allocation will depend on both the current HCV prevalence and epidemic stage (ie, the proportion of individuals infected with HCV in early vs advanced liver disease). In Australia, it is estimated that in 2013 approximately 66% of PWID had early liver disease (meaning METAVIR score F0/F1).[13] This means that despite transmission declining over the last decade, Australia is yet to experience the full burden of HCV-related liver disease.[13]

In this paper, we aimed to model HCV transmission, liver disease progression and treatment among current and former PWID to estimate the level of treatment scale-up that would be required to achieve the WHO elimination goals. We used data from the Australian epidemic and population to develop our model, which was not dissimilar to other high-income countries.[12 14] We allowed a variable infection/reinfection rate in order to calibrate both the current prevalence and disease burden stage, which also simulated a slowing epidemic as treatments resulted in a declining prevalence. Specifically, the model estimated: (1) the treatment scale-up required among patients with advanced liver disease (both current and former PWID) to achieve the WHO mortality target; (2) the treatment scale-up required among current PWID to achieve the WHO incidence target; (3) the treatment scale-up required and the most effective allocation of treatments between current PWID and patients with advanced liver disease (current and former PWID) to achieve both targets simultaneously and (4) the total healthcare and treatment costs, quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs) of each scenario, compared with a scenario where no action was taken. This will determine the feasibility of achieving the WHO elimination targets in an Australian context.

METHODS

Model description

We used an open deterministic compartmental model of HCV transmission and liver disease progression extending the model from Scott *et al*[15] (figure 1). A detailed model description and methodology is provided in online supplementary appendix A. METAVIR scores were used to classify stages of liver disease, and individuals were distinguished as either: acutely infected (A); chronically infected with liver fibrosis in stage F0–F4; chronically infected with decompensated cirrhosis (DC); chronically infected with hepatocellular carcinoma (HCC); first year or more than 1 year postliver transplant (LT1 and LT2, respectively); chronically infected and in treatment achieving sustained viral response (SVR) (T0–T4—treated from liver fibrosis stage F0–F4, respectively) or susceptible (S0–S4—infection naïve or previously achieving spontaneous clearance or SVR through treatment from liver fibrosis stage F0–F4, respectively). The model was stratified by injecting drug use status (current or former PWID), whether individuals had previously failed treatment or not, and age (using categories 20–24, 25–29, 30–34, 35–44, 45–54, 55–64, 65–74, 75–84, 85+ that were assumed to mix proportionally).

People in the model were able to cease injecting or relapse into injecting drug use at fixed rates η and $r_{relapse}$, respectively. All-cause mortality occurred for each compartment at a rate depending on age and injecting drug use status (see online supplementary appendix B), and mortality rates for the DC, HCC, LT1 and LT2 compartments were increased by $r_{DC\ death}$, $r_{HCC\ death}$, $r_{LT1\ death}$ and $r_{LT2\ death}$, respectively. The total population was held constant by the entry of new PWID assumed to be aged 20 years, susceptible and previously untreated. Reinfection is a significant issue among PWID[16] and was modelled to occur at the same rate as initial infection.

Model calibration

In Australia, an estimated 230 000 people are chronically infected with HCV,[3] and an estimated 184 000 of these individuals acquired their infection through injection drug use.[8] It is also estimated that the prevalence of chronic HCV is 50%[7] among approximately 80 000 current PWID.[8] Therefore, model populations were scaled to represent 40 000 PWID infected with HCV and 144 000 former PWID infected with HCV, as described in online supplementary appendix A. Non-injecting drug use (IDU)-acquired infections and imported infections, for example, from migrants, were not considered in the model (see discussion), but the proportion of all HCV infections that were IDU-acquired was varied in the sensitivity analysis.

Treatment scale-up

We assumed that when treatment programmes were implemented, a fixed total number of treatment courses would be available per year, and that this annual number of treatments would continue to be available for the next 15 years even if not used.[11 17–20] We considered treatment scale-up to be in the range 1000 courses per year (representing 0.5% of IDU-acquired infections or 12.5/1000 PWID) to 10 000 courses per year (representing 5% of IDU-acquired infections or 125/1000 PWID), which is consistent with previous models that have considered treatment scale-up among PWID of 2%–16% of the infected population per year.[11 13 17]

Harm reduction scale-up

In Australia between 2000 and 2010, needle and syringe programmes (NSPs) were estimated to have reduced HCV infections by approximately 15%–43%, for a total cost of

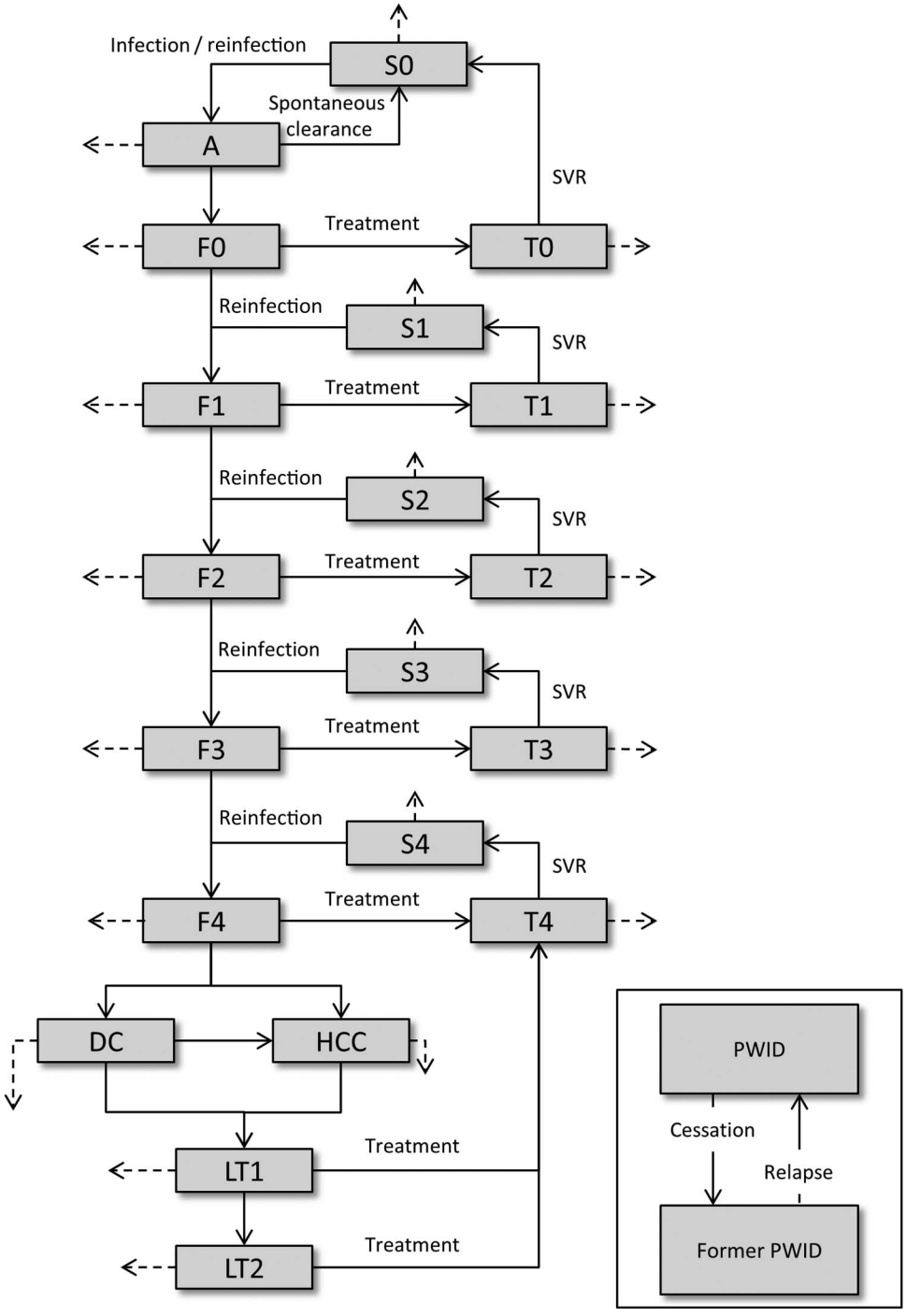

Figure 1 Model schematic. DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT1 and LT2, first year or more than 1 year postliver transplant; PWID, people who inject drug; SVR, sustained viral response.

$A245 million.[21] Moreover, modelling studies indicate that further scale-up of harm reduction interventions such as NSPs and opioid substitution therapy (OST) could reduce HCV prevalence by up to a third.[22] For this analysis, a more modest scale-up of NSP and OST programmes was assumed, which would reduce the risk of new infections by 10%.[21 22] This was implemented by scaling the infection rate parameter from 2015 onwards to 90% of its pre-2015 value (see online supplementary appendix A) for all scenarios, including the base case of no treatment. Therefore, the (non-healthcare) costs of this scale-up were not included in the analysis.

Parameters

Population, HCV-related, health-related and cost parameters are provided in online supplementary appendix B. As the cost of DAAs remains uncertain, we assumed a base scenario and tested upper and lower bounds in the sensitivity analysis. The base value was taken to be $A30 000 (for 12 weeks of treatment) for genotypes 1 and 2, and $A60 000 (for 24 weeks of treatment) for genotype 3, averaged over the Australian genotype distribution (see online supplementary appendix B). The upper and lower bounds tested in the sensitivity analysis were $A15 000 and $A40 000 for 12 weeks of therapy, respectively (and double for 24 weeks of therapy).

Scenarios

Base case (best supportive care)

No treatments were available. Total discounted cost and QALYs were calculated separately for current and former PWID, before being combined.

Reaching the mortality target by treating advanced liver disease

The model was repeatedly run with the annual number of treatments available for patients with liver fibrosis stage F3 or worse incrementally increased from 1000 per year until the total number of liver-related deaths in 2030 was <35% of the total liver-related deaths in 2015. Where the number of treatments available was greater than the number of patients with advanced liver disease, they were allocated to patients with early liver disease (proportionally across current and former PWID).

Reaching the incidence target by treating current PWID

The model was repeatedly run with the annual number of treatments available to current PWID incrementally increased from 1000 per year until the total number of incident cases in 2030 was <20% of the total incident cases in 2015. Where the number of treatments available was greater than the number of PWID infected with HCV, they were allocated to former PWID.

Allocating treatment resources to reach both targets

For each fixed number of treatments, separate scenarios were run with the proportion of treatments allocated to patients with advanced liver disease, increased from 0 to 1. If no allocation was able to reach both WHO targets, then the total available number of treatments was increased and the process repeated. When treatment numbers were sufficient that both WHO targets were reached, the allocation achieving this was noted, and the total costs and QALYs accrued between 2015 and 2030 were calculated analogously to the base case.

Sensitivity analysis

A Monte Carlo uncertainty analysis was conducted to get CIs for the number of treatments required to reach the WHO elimination targets, and the associated total costs and QALYs. Uncertainties of health utilities and annual disease transition probabilities were assumed to be normally distributed (and hence uncertainties in disease transition *rates* were log-normally distributed), using mean and variance estimates from the literature (see online supplementary appendix B). These uncertainties were parameterised as probability distributions and 1000 simulations were undertaken using random, independent parameter draws; 95% CIs were taken as the 2.5th and 97.5th percentiles of the resulting outputs.

One-way sensitivity analyses were also undertaken to test the impact when the cost of treatment was $A15 000–$A80 000; initial chronic HCV prevalence was set to either 40% or 60% instead of 50%; the discounting rate was increased from 3% to 5%; the SVR rate was 90% or 99% instead of 95%; the length of injecting career was halved from 17 to 8.5 years; treatment duration was 8 or 48 weeks for all genotypes; either 60% or 90% of HCV infections in Australia were IDU-acquired instead of 80%; the number of PWID in Australia was 60 000 or 100 000 instead of 80 000 (ie, 0.25% or 0.42% of the population, instead of 0.33%) and when additional harm reduction was not introduced or was scaled up to reduce incidence by 20% instead of 10%.

RESULTS

Treatment numbers required to reach the WHO elimination targets

To achieve an 80% reduction in HCV incidence by 2030 required treating a minimum of 4725 IDU-acquired infections per year for the next 15 years, regardless of liver disease stage, if treatments were preferentially given to current PWID. This scale-up corresponds to a treatment rate of 59/1000 PWID per year. In a setting with 50% initial prevalence among PWID, reaching the WHO incidence target would require rapidly controlling the epidemic rather than steadily increasing treatment for PWID, as when only moderate treatment numbers were used those who were not treated immediately were able to reinfect patients attaining SVRs, allowing the epidemic to continue. For example, if 59 treatments were available per 500 PWID infected with HCV per year (ie, 59/1000 PWID total), then within 15 years the PWID infected with HCV population would become exhausted—even with some population turnover—and in later years, the remaining treatments were allocated to former PWID (figure 2), but with fewer treatments available, the incidence target could not be reached. Figure 3, left shows that if the same number of treatments were instead allocated preferentially to patients with advanced liver disease, only minimal reductions in incidence would be achieved.

To achieve a 65% reduction in HCV-related mortality by 2030 required treating 5662 IDU-acquired infections (30/1000 IDU-acquired infections) per year for the next 15 years, regardless of injecting drug use status, if treatments were prioritised to patients with advanced liver disease. However, if this number of treatments were instead prioritised to current PWID, then the epidemic could be controlled by approximately 2025, and a 65% reduction in mortality by 2030 could also be achieved (figure 3, right). Hence, when the WHO incidence target was achieved by prioritising treatments to current PWID, the WHO mortality target was also reached.

Achieving the mortality target in this way required fewer total treatments, but resulted in a greater total number of HCV-related deaths (see also table 1), which would be clinically unacceptable. Therefore, an additional scenario was run, where 4725 IDU-acquired infections were treated each year for 15 years, prioritised to current PWID (ie, 59/1000 PWID) to reach the incidence (and hence also the mortality) target; however, additional treatments were available for the first 5 years for patients with advanced liver disease. This reflects the reality of a backlog of patients with advanced liver disease who are currently waiting for treatment or retreatment when DAAs become available. In this scenario, an additional 5564 treatments per year (30/1000 IDU-acquired infections) were required for 5 years to ensure that both the WHO targets were reached and the total number of HCV-related deaths was no greater than when the mortality target was reached by prioritising treatment to patients with advanced liver disease.

Estimated burden of disease

Scaling up treatments in order to reach the WHO incidence target (or the combined WHO targets) resulted in a dramatic decline in HCV prevalence among PWID (figure 4, top left panel and bottom left panel, dashed line) up until 2025, and a subsequent reduction in the burden of disease. Beyond 2025, although the HCV prevalence among PWID continued to decline, it did so at a slower rate, as treatments began to be allocated to former PWID (figure 2).

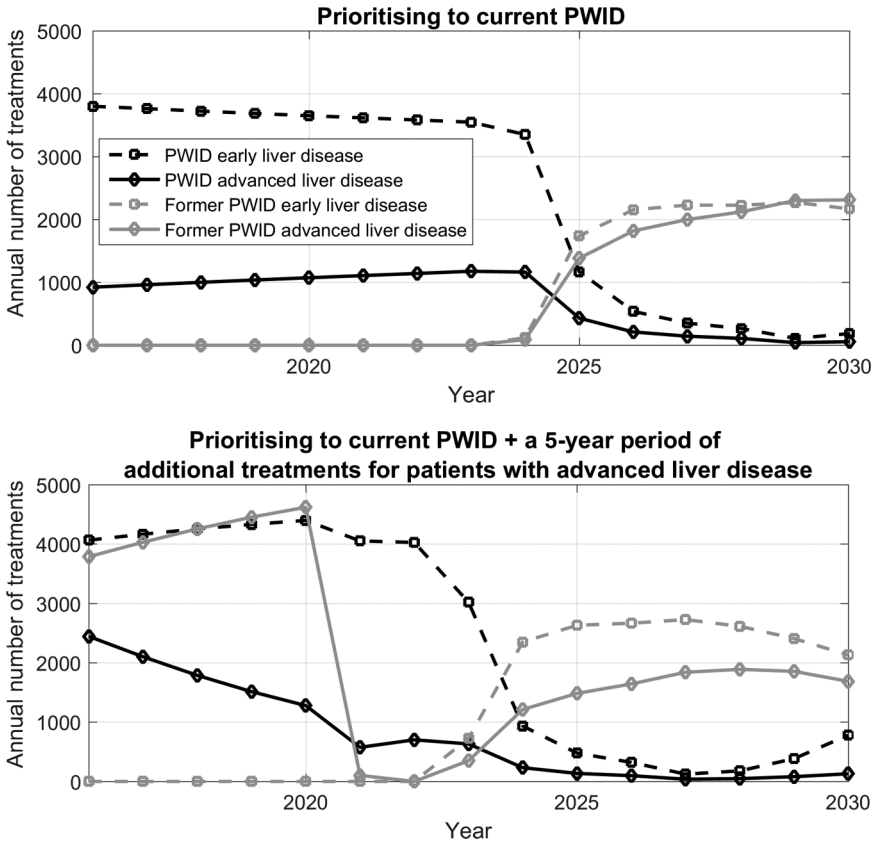

Figure 2 Actual treatment allocation in scenarios that achieve both the WHO targets. Top panel: 4725 treatments per year prioritised to people who inject drug (PWID); beyond 2025 the PWID infected with HCV population is exhausted and treatments are allocated to former PWID. Bottom panel: 4725 treatments prioritised to PWID, plus an additional 5564 treatments per year allocated to pateints with advanced liver disease for 5 years.

Cost-effectiveness of reaching elimination targets

Using a willingness to pay threshold of $A50 000 per QALY gained, it was cost-effective to achieve the WHO mortality and incidence targets by scaling up treatment.

Scaling up treatment to reach the mortality target cost an additional $A3.551 (95% CI $A2.998 to $A4.171) billion over the next 15 years compared with inaction, but gained an additional 88 000 (54 000–224 000) QALYs, giving an ICER of $A40 468 ($A16 413–$A65 977) per QALY gained. Scaling up treatment to reach the incidence target cost an additional $A3.895 ($A1.154–$A4.664) billion compared with inaction, but gained an additional 132 000 (38 000–357 000) QALYs, giving an ICER of $A29 614 ($A9187–$A52 626) per QALY gained. Scaling up treatment to reach both targets and providing additional treatments for 5 years to reduce cumulative HCV-related deaths cost an additional $A4.618 ($A4.205–$A4.880) billion

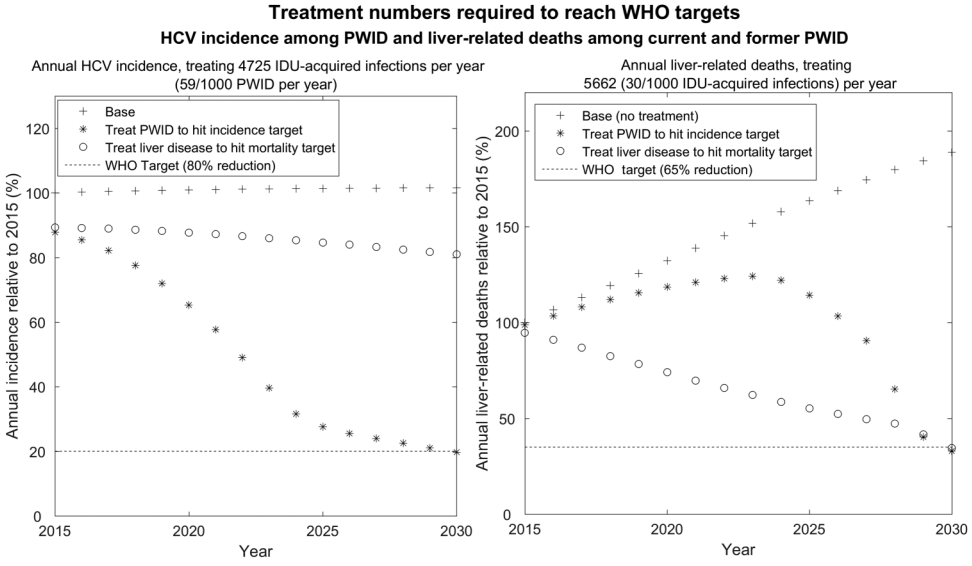

Figure 3 Estimated HCV incidence and liver-related deaths among current and former people who inject drug (PWID), 2015–2030. Left panel: minimum treatment numbers to reach the WHO incidence target. Right panel: minimum treatment numbers to reach the WHO mortality target. No treatments (+); preferentially treating current PWID (*) and preferentially treating advanced liver disease (○). IDU, injecting drug use.

Table 1 Treatment scale-up, costs and QALYs associated with using treatment to reach the WHO HCV elimination targets

Point estimate (95% CI)	No treatment	Incidence target	Mortality target	Both targets	Both targets with minimal total deaths
Treatments numbers required for priority groups to reach target					
Treatments prioritised to current injectors*	0	4725 (3278 to 8420)	0	4725 (4248 to 8420)	4725 (4248 to 8420)
Treatments prioritised to patients with advanced liver disease†	0	0	5662 (5202 to 6901)	0	5564 (1959 to 6917)
Model outcomes					
Reduction in incidence in 2030	Baseline	80% (80 to 81%)	20% (18 to 25%)	80% (80 to 86%)	82% (80 to 88%)
Reduction in mortality in 2030	Baseline	67% (66 to 74%)	65% (65 to 70%)	67% (66 to 82%)	70% (81 to 86%)
Cumulative deaths 2015–2030	17 736 (17 458–32 339)	12 849 (9305 to 26 171)	8326 (7901 to 15 766)	12 849 (9293 to 24 098)	8267 (7534 to 15 652)
Prevalence among PWID in 2030	48% (47%–48%)	6% (5.9 to 6.2%)	34% (30 to 36%)	6% (4 to 6%)	6% (4 to 6%)
Total discounted cost (billion $A)	$2.434 ($2.334–3.407)	$6.329 ($3.790 to 7.576)	$5.984 ($5.603 to 7.224)	$6.329 ($5.943 to 7.576)	$7.052 ($6.848 to 7.906)
Total discounted QALYs (million)	4.777 (4.286–4.947)	4.908 (4.510 to 5.034)	4.865 (4.488 to 5.026)	4.908 (4.545 to 5.037)	4.961 (4.677 to 5.076)
ICER ($A per QALY gained)	–	$29 614 ($9187 to 52 626)	$40 468 ($16 413 to 65 977)	$29 614 ($12 378 to 64 466)	$25 121 ($11 062 to 39 036)

*Treated proportionally over liver disease stage.
†Treated proportionally over injecting drug use status.
ICER, incremental cost-effectiveness ratio; PWID, people who inject drug; QALY, quality-adjusted life year.

compared with inaction, but gained 184 000 (119 000–417 000) QALYs, giving an ICER of $A25 121 ($A11 062–$A39 036) per QALY gained (table 1).

Sensitivity analysis

With the exception of when there were more or less patients to treat, the estimated treatment scale-up to reach the WHO *mortality* target was robust to changes in parameter values, but the treatment scale-up required to reach the WHO *incidence* target was sensitive to changes in the average length of injecting career, the amount of additional harm reduction available, initial prevalence among PWID and treatment efficacy (table 2). For the length of injecting career, this is because a greater infection parameter is required to calibrate the same initial prevalence when there is a faster population turnover,[18] giving a higher incidence rate and meaning that treatment-as-prevention needs a far greater scale-up to be effective. A higher initial prevalence also requires a greater infection parameter for calibration, and for an initial prevalence of above approximately 58% the WHO incidence target could not be reached unless the SVR rate was also increased to 99%. Similarly, more or less harm reduction through OST and NSPs directly affected the infection parameter. The model sensitivity to changes in treatment efficacy is an indication that the incidence target may be hard to meet in practice. In particular, when treatment efficacy was reduced to below approximately 92%, the WHO incidence target could not be reached with any level of scale-up, because the number of patients failing treatment who continued to transmit infection, combined with infected former PWID relapsing into injecting, became sufficient that incidence did not reduce by >80% in 2030. It should be noted that 'failing treatment' means failing multiple treatment courses. Therefore, retaining patients in care, offering retreatment, exploring multiple combination therapies for 'hard-to-cure' patients and providing additional harm reduction measures will be critical to achieving HCV elimination targets.

The cost-effectiveness of reaching both the WHO targets was robust to changes in the parameters tested, and remained below the unofficial threshold of $A50 000 per QALY gained in Australia for all scenarios. The most significant increases in *total costs* were when DAAs were more expensive or when there were more IDU-acquired infections to treat. Even when DAAs were more expensive—the least cost-effective scenario—achieving the WHO elimination targets remained cost-effective.

In all scenarios, achieving the incidence target also achieved the mortality target, but with a greater number of total deaths than when treatments were prioritised to patients with advanced liver disease.

DISCUSSION

Using a model of HCV transmission, liver disease progression and treatment, we determined that it is cost-effective to achieve the WHO elimination targets by scaling up treatment. In Australia, this would require approximately 5700 treatments per year (30/1000 IDU-acquired infections) for patients with advanced liver disease in order to reach the WHO mortality target, and approximately 4700 treatments per year (59/1000 PWID) for PWID in order to reach the WHO incidence target. Further, if treatment were directed initially only to PWID, our models predict that this would both minimise incidence and reach the mortality target with fewer total treatments. This finding indicates that reducing incidence should be a priority if Australia is to achieve both the WHO elimination goals. Beyond these targets, it is clinically unacceptable not to treat patients with advanced liver disease.

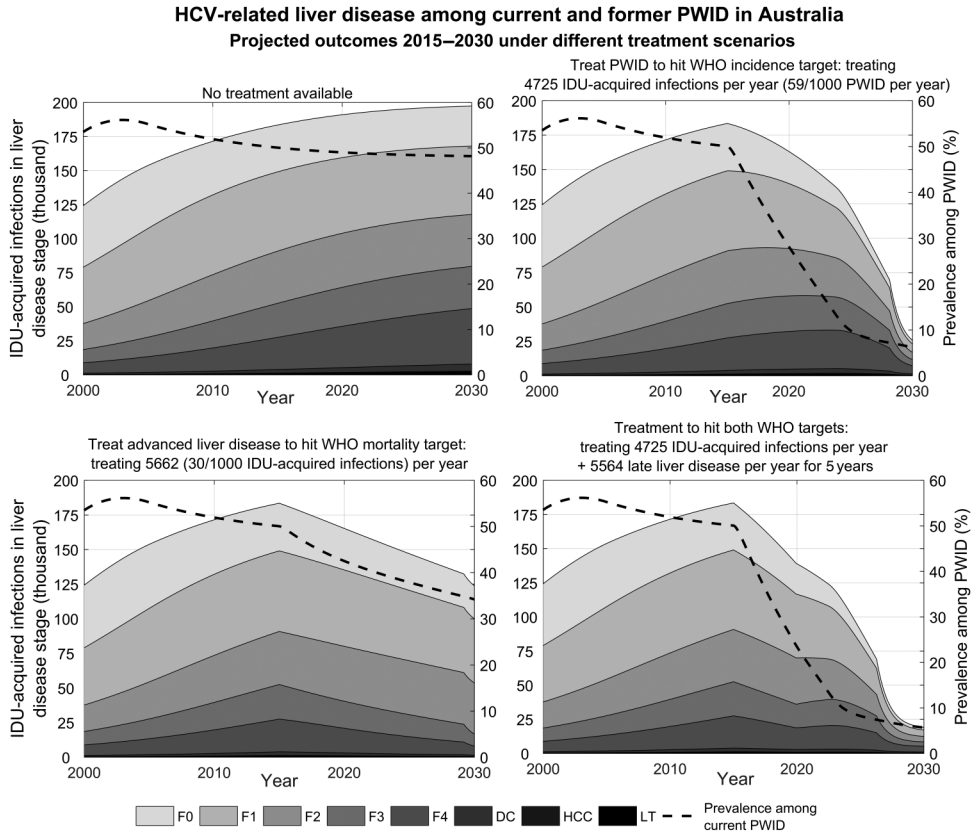

Figure 4 Estimated burden of HCV-related liver disease 2000–2030. Top left panel: no treatment. Top right panel: treating 4725 injecting drug use (IDU)-acquired infections (59/1000 people who inject drug (PWID)) per year prioritised to current PWID—the minimum to reach the WHO incidence target. Bottom left panel: treating 5662 IDU-acquired infections (30/1000 IDU-acquired infections) prioritised to patients with advanced liver disease per year—the minimum to reach the WHO mortality target. Bottom right panel: treating 4725 IDU-acquired infections per year prioritised to current PWID to achieve both the WHO targets plus 5564 additional treatments per year for 5 years to minimise cumulative HCV-related deaths. In all panels, the initial peak in prevalence among PWID is a result of changes to Australian drug markets (see online supplementary appendix A). DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplant.

Therefore, the backlog of patients in Australia who are currently postponing treatment or retreatment until DAAs become available must be managed; in order to achieve both the WHO targets *and* to avoid unacceptable HCV-related deaths, an additional short term scale-up of treatments is required, prioritised to patients with advanced liver disease.

These scale-up numbers are consistent with Martin *et al*,[11] who estimated that treatment numbers of 40/1000 and 54/1000 PWID per year in this setting could achieve 50% and 75% *prevalence* reductions after 15 years. By comparison, our model suggests that annual treatment numbers of 59/1000 PWID (plus a 10% reduction in incidence through harm reduction scale-up) would reduce prevalence by 94% after 15 years (table 1).

The fact that the incidence target was difficult to achieve—requiring a significant scale-up of treatment among a relatively small subset of IDU-acquired infections in order to rapidly control the epidemic—highlights the importance of ongoing harm reduction programmes (OST and NSP). Changes in the level of harm reduction modelled produced substantive effects on the treatment scale-up required to achieve the incidence target, and in particular, without any additional harm reduction 50% more treatment courses were required. Furthermore, it reinforces the potential benefit an even partially effective vaccine would provide in limiting reinfection.[17] In our sensitivity analysis, when initial prevalence was increased above 60%, treatment alone was insufficient to meet the WHO incidence target; the small percentage who did not achieve SVR following treatment continued to transmit enough infection to prevent the WHO target from being reached. Even a modest improvement in herd immunity, which could be provided by a vaccine, would lower reinfection and could have significant implications for this scenario. This is particularly relevant given the likely heterogeneity of HCV prevalence among PWID in different geographical areas of Australia, which could plausibly be greater than 60% in some regions.

Achieving elimination targets by scaling up treatment is likely to come with a large cost investment, even though the model suggests it is cost-effective. For context, the estimated additional $A4.6 billion required over the next 15 years to achieve both the WHO targets represents 9.5% of Australia's 2015/2016 $A48.3 billion 1-year health budget. However, in December 2015 the Australian government announced a commitment to invest more than $A1 billion to subsidise DAA treatments, with no restrictions on eligibility, effective from March 2016.[23 24] With this subsidy, patient copayments are expected to be as little as $A37.70 or $A6.10 for concession holders.[23] This is a major step towards achieving elimination, and although short of the estimated $A4.6 billion, it is likely that treatment costs will reduce substantially over time, that the high tolerability profile of interferon-free DAAs will lead to cheaper, nurse-led models of care,[25] and that additional investment may occur within the next 15 years. Furthermore, the estimated $A4.6 billion is conservatively high. Healthcare costs associated with patients who have DC or HCC in our model were underestimates based on

Table 2 Sensitivity of treatment scale-up, costs and QALYs and ICERs as key parameters are varied

	Treatments per year required to hit the WHO incidence target	Treatments per year required to hit the WHO incidence target (per 1000 PWID)	Treatments per year required to hit the WHO mortality target	Treatments per year required to hit both the WHO targets with minimal total deaths	Total discounted cost over 15 years (billion $A)	Total discounted QALYs over 15 years (thousand)	ICER (both targets with minimal total deaths)
Point estimate	4725 (0%)	59/1000 PWID	5662 (0%)	10 289 (0%)	$7.052 (0%)	4961 (0%)	$25 121 (0%)
Injecting career halved from 17 to 8.5 years.	6316 (34%)	79/1000 PWID	5430 (−4%)	11 913 (16%)	$7.068 (0%)	4445 (−10%)	$22 294 (−11%)
Discounting factor increased from 3% to 5%.	4725 (0%)	59/1000 PWID	5662 (0%)	10 289 (0%)	$6.160 (−13%)	4325 (−13%)	$27 030 (8%)
No harm reduction instead of reducing 10% of incidence.	7221 (53%)	90/1000 PWID	5760 (2%)	9174 (−11%)	$7.125 (1%)	4990 (1%)	$21 998 (−12%)
Harm reduction increased from reducing 10% of incidence to reducing 20% of incidence.	3566 (−25%)	45/1000 PWID	5662 (0%)	10 306 (0%)	$6.999 (−1%)	4949 (0%)	$26 460 (5%)
Initial prevalence decreased from 50% to 40%.	2773 (−41%)	35/1000 PWID	5878 (4%)	9768 (−5%)	$6.962 (−1%)	6768 (36%)	$24 311 (−3%)
Initial prevalence increased from 50% to above 58%.	Not achieved						
Initial prevalence increased from 50% to 60% and SVR increased from 95% to 99%.	5936 (26%)	74/1000 PWID	5618 (−1%)	10 730 (4%)	$7.206 (2%)	3741 (−25%)	$28 945 (15%)
SVR reduced from 95% to below 92%.	Not achieved						
SVR decreased from 95% to 90% and harm reduction increased from reducing 10% additional incidence to reducing 20% additional incidence.	5438 (15%)	68/1000 PWID	10 836 (91%)	13 277 (29%)	$8.336 (18%)	5017 (1%)	$24 530 (−2%)
SVR increased from 95% to 99%.	3477 (−26%)	43/1000 PWID	5564 (−2%)	10 217 (−1%)	$6.952 (−1%)	4952 (0%)	$25 802 (3%)
Price of DAAs reduced from $30k/60k to $15k/30k for 12/24 weeks of treatment.	4725 (0%)	59/1000 PWID	5662 (0%)	10 289 (0%)	$4.245 (−40%)	4961 (0%)	$9856 (−61%)
Price of DAAs increased from $30k/60k to $40k/80k for 12/24 weeks of treatment.	4725 (0%)	59/1000 PWID	5662 (0%)	10 289 (0%)	$8.922 (27%)	4961 (0%)	$35 297 (41%)
Treatment duration decreased from a genotype-weighted average of 16.56 to 8 weeks.	4725 (0%)	59/1000 PWID	5760 (2%)	10 485 (2%)	$7.084 (0%)	4960 (0%)	$25 409 (1%)
Treatment duration increased from a genotype-weighted average of 16.56 to 48 weeks.	4547 (−4%)	57/1000 PWID	5662 (0%)	10 404 (1%)	$7.011 (−1%)	4951 (0%)	$26 314 (5%)
Percentage of HCV infections that were IDU-acquired decreased from 80% to 60%	4725 (0%)	59/1000 PWID	4160 (−27%)	8669 (−16%)	$5.362 (−24%)	3658 (−26%)	$24 354 (−3%)
Percentage of HCV infections that were IDU-acquired increased from 80% to 90%	4725 (0%)	59/1000 PWID	6473 (14%)	11 087 (8%)	$7.896 (12%)	5600 (13%)	$27 019 (8%)
Number of PWID in Australia decreased from 80 000 to 60 000.	3544 (−25%)	59/1000 PWID	6006 (6%)	9652 (−6%)	$7.020 (0%)	5026 (1%)	$25 619 (2%)
Number of PWID in Australia increased from 80 000 to 100 000.	5906 (25%)	59/1000 PWID	5552 (−2%)	11 171 (9%)	$7.116 (1%)	4883 (−2%)	$26 632 (6%)

DAA, direct-acting antiviral; ICER, incremental cost-effectiveness ratio; IDU, injecting drug use; PWID, people who inject drug; QALY, quality-adjusted life year; SVR, sustained viral response.

minimum recommendations.[14] In the scenario of inaction, a far greater proportion of individual infected with HCV will progress to these liver disease stages compared with when treatment is available, meaning that baseline costs are likely to be higher than we have calculated. This also means that the costs per QALY calculated are likely to be overestimates, and achieving elimination may be even more cost-effective than we have estimated.

This study has only considered people who acquired their HCV infection through injecting drug use. In Australia, this is estimated to be 80% of the infected population, with other infections being attributed migrants from countries with high HCV prevalence and iatrogenic spread before the screening of blood products was introduced in 1990.[26–29] The high standard of healthcare currently available in Australia means that the risk of transmission from this population is minimal and unlikely to affect the treatment scale-up required to achieve the WHO incidence target. However, depending on the distribution of liver disease stages among this population, additional treatments may be required in order to achieve the WHO mortality target. Nevertheless, when the percentage of HCV infections that were IDU-acquired was increased in the sensitivity analysis, the number of extra treatments required was small relative to the number that we had estimated. In particular, we noted that treatment with DAAs (among the non-injecting drug user population) was cost-effective,[30] and so although these additional treatments may change total costs and QALYs, our conclusions about the cost-effectiveness of reaching the WHO targets will remain the same.

This study has several limitations. First, as with all modelling studies, these outcomes are based on a theoretical model and there is uncertainty in model parameters. However, the Monte Carlo uncertainty analysis (providing the CIs in table 1) has allowed us to estimate these ranges, which seem modest. Second, we have considered reinfection and initial infection to occur at the same rates, when in reality there may be behavioural differences between PWID who have achieved an SVR and infection-naïve PWID. Third, we have not considered practical limitations to scaling up treatment. The illicit nature and stigmatisation of injecting drug use and the low engagement of PWID with healthcare are likely to be barriers that will need to be overcome. In particular, many healthcare providers currently exclude PWID from treatment due to perceived ineligibilities,[10] despite evidence that they can be successfully treated.[31] It is hoped that the high tolerability of new treatments will create a greater level of acceptance among this population and improve the levels of care received.

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Contributors NS performed the modelling and drafted the manuscript. MEH, JSD and NS conceived and coordinated the study. EMB and AT critically revised the modelling and clinical aspects of the study, respectively. All authors were involved in revising the manuscript and have approved the final version.

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REFERENCES

1 Burki T. Elimination on the agenda for hepatitis C. *Lancet Infect Dis* 2014;14:452–3.
2 World Health Organisation. Draft global health sector strategy on viral hepatitis, 2016–2021—the first of its kind. 2015. http://wwwwhoint/hepatitis/news-events/strategy2016-2021/en/
3 The Kirby Institute. HIV, viral hepatitis and sexually transmissible infections in Australia Annual Surveillance Report 2014. The University of New South Wales, Sydney NSW 2052, 2014.
4 Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. *Lancet Infect Dis* 2005;5:558–67.
5 Hajarizadeh B, Grebely J, Dore GJ. Epidemiology and natural history of HCV infection. *Nat Rev Gastroenterol Hepatol* 2013;10:553–62.
6 Nelson PK, Mathers BM, Cowie B, *et al*. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. *Lancet* 2011;378:571–83.
7 Iversen J, Maher L. Australian Needle and Syringe Program National Data Report 2008–2012. The Kirby Institute, University of New South Wales. ISBN: 1448-5915, 2013.
8 Ministerial Advisory Committee on AIDS Sexual Health and Hepatitis. Hepatitis C Virus Projections Working Group: Estimates and Projections of the Hepatitis C Virus Epidemic in Australia. 2006.
9 Dore GJ. The changing therapeutic landscape for hepatitis C. *Med J Aust* 2012;196:629–32.
10 Walsh N, Lim M, Hellard M. Using a surveillance system to identify and treat newly acquired hepatitis C infection. *J Gastroenterol Hepatol* 2008;23:1891–4.
11 Grebely J, Oser M, Taylor LE, *et al*. Breaking down the barriers to hepatitis C virus (HCV) treatment among individuals with HCV/HIV coinfection: action required at the system, provider, and patient levels. *J Infect Dis* 2013;207(Suppl 1):S19–25.
12 Martin NK, Vickerman P, Grebely J, *et al*. Hepatitis C virus treatment for prevention among people who inject drugs: Modeling treatment scale-up in the age of direct-acting antivirals. *Hepatology* 2013;58:1598–609.
13 Sievert W, Razavi H, Estes C, *et al*. Enhanced antiviral treatment efficacy and uptake in preventing the rising burden of hepatitis C-related liver disease and costs in Australia. *J Gastroenterol Hepatol* 2014;29(Suppl 1):1–9.
14 Hellard ME, Jenkinson R, Higgs P, *et al*. Modelling antiviral treatment to prevent hepatitis C infection among people who inject drugs in Victoria, Australia. *Med J Aust* 2012;196:638–41.
15 Scott N, Iser D, Thompson A, *et al*. Cost-effectiveness of treating chronic hepatitis C virus with direct-acting antivirals in people who inject drugs in Australia. *J Gastroenterol Hepatol* 2015.[online ahead of print] doi:10.1111/jgh.13223
16 Simmons B, Saleem J, Hill A, *et al*. Risk of late relapse or reinfection with hepatitis C virus after achieving a sustained virological response: a systematic review and meta-analysis. *Clin Infect Dis* 2016;62:683–94.
17 Scott N, McBryde E, Vickerman P, *et al*. The role of a hepatitis C virus vaccine: modelling the benefits alongside direct-acting antiviral treatments. *BMC Med* 2015;13:198.
18 Scott N, Hellard M, McBryde E. Modelling hepatitis C virus transmission among people who inject drugs: assumptions, limitations and future challenges. *Virulence* 2016;7:201–8.
19 Martin NK, Vickerman P, Hickman M. Mathematical modelling of hepatitis C treatment for injecting drug users. *J Theor Biol* 2011;274:58–66.
20 Vickerman P, Martin N, Hickman M. Can Hepatitis C virus treatment be used as a prevention strategy? Additional model projections for Australia and elsewhere. *Drug Alcohol Depend* 2011;113:83–5; discussion 86–7.
21 Kwon JA, Anderson J, Kerr CC, *et al*. Estimating the cost-effectiveness of needle-syringe programs in Australia. *Aids* 2012;26:2201–10.
22 Vickerman P, Martin N, Turner K, *et al*. 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;107:1984–95.
23 Australian Government Department of Health. https://www.health.gov.au/internet/ministers/publishing.nsf/Content/health-mediarel-yr2015-ley154.htm (December 2015).
24 Pharmaceutical Benefits Advisory Committee (PBAC). November 2015. Positive Recommendations, http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/recommendations-pbac-november-2015
25 Wade AJ, Macdonald D, Doyle JS, *et al*. Successful community based treatment of hepatitis C in people who inject drugs. *PLoS ONE* 2015;10.
26 Archer G, Buring M, Clark B, *et al*. Prevalence of hepatitis C virus antibodies in Sydney blood donors. *Med J Aust* 1992;157:225–7.
27 Ismay SL, Thomas S, Fellows A, *et al*. Post-transfusion hepatitis revisited. *Med J Aust* 1995;163:74–7.
28 Mison L, Young I, O'Donoghue M, *et al*. Prevalence of hepatitis C virus and genotype distribution in an Australian volunteer blood donor population. *Transfusion* 1997;37:73–8.
29 Wong P, Dodd R, Kiely P, *et al*. Characteristics of hepatitis C-positive blood donors in Victoria, Australia. *Transfus Med* 1999;9:15–19.
30 Leidner AJ, Chesson HW, Xu F, *et al*. Cost-effectiveness of hepatitis C treatment for patients in early stages of liver disease. *Hepatology* 2015;61:1860–9.
31 Hellard M, Sacks-Davis R, Gold J. Hepatitis C treatment for injection drug users: a review of the available evidence. *Clin Infect Dis* 2009;49:561–73.