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Cost-effectiveness of treating chronic hepatitis C virus with direct-acting antivirals in people who inject drugs in Australia

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Key words
cost-effectiveness, direct-acting antivirals, hepatitis C virus, people who inject drugs.

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Abstract

Background and Aim: Reducing the burden of hepatitis C virus (HCV) related liver disease will require treating people who inject drugs (PWID), the group at most risk of infection and transmission. We determine the cost-effectiveness of treating PWID with interferon-free direct-acting antiviral therapy in Australia.

Methods: Using a deterministic model of HCV treatment and liver disease progression, including a fixed rate of re-infection, the expected healthcare costs and quality-adjusted life years (QALYs) of a cohort of newly HCV-infected PWID were calculated for: no treatment; treatment after initial infection ("early-treatment"); and treatment prior to developing compensated cirrhosis ("late-treatment"). Incremental cost-effectiveness ratios (ICERs) were used to compare scenarios.

Results: Late-treatment was cost-effective compared to no treatment, with a discounted average gain of 2.98 (95%confidence interval 2.88–5.22) QALYs per person for an additional cost of $15 132 ($11 246–18 922), giving an ICER of $5078 ($2847–5295) per QALY gained. Compared to late-treatment, early-treatment gained a further discounted average of 2.27 (0.58–4.80) QALYs per person for $38 794 ($34 789–41 367), giving an ICER of $17 090 ($2847–63 282), which was cost-effective in approximately 90% of Monte-Carlo uncertainty simulations. For every 100 newly HCV-infected PWID, there were an estimated 40 (39–56) eventual liver-related deaths without treatment, compared to 7 (6–11) and 8 (7–13) with early-treatment and late-treatment available respectively.

Conclusions: Treating HCV-infected PWID with new therapies is cost-effective and could prevent a significant number of liver-related deaths. Although late-treatment was the most cost-effective option, the cost per QALY gained for early-treatment compared to late-treatment is likely to be below unofficial Australian willingness to pay thresholds.

Introduction

Hepatitis C virus (HCV) is a major global health problem affecting approximately 170 million people worldwide.[1] In Australia there are an estimated 230 000 people chronically infected with HCV,[2] and as with most developed countries, people who inject drugs (PWID) remain the group at greatest risk of infection.[1–3] The prevalence of HCV antibodies among PWID varies globally, ranging from 10% to 97%;[4,5] however this may be up to 25% higher than the prevalence of current HCV infection[6] which is rarely determined in epidemiological studies. Nevertheless, the prevalence of HCV infection in PWID is high in many countries,[4,5] and treating PWID of their infection has been identified as having the most significant impact on the overall future burden of disease.[7,8]

The considerable side effects and low cure rates of interferon-based HCV treatments[9,10] have contributed to persistently low treatment amongst PWID globally. In Australian residents, uptake is estimated at only 2000–3500 individuals annually; less than 2% of all chronically infected individuals.[11–13] Most chronic HCV infections are asymptomatic for many years; however prolonged untreated infection poses a substantial risk of progression to advanced liver disease.[14] Continued poor uptake of treatment is likely to result in a substantial future healthcare burden as those who are chronically infected age.[15] In particular as the risk of primary liver cancer is ten-fold higher in people aged 45–64 years than in those aged 25–44 years.[16]

The advent of highly effective direct-acting antiviral treatment (DAAs), with 90% cure rates, improved tolerability, and a comparably short duration of therapy (up to 12 weeks)[17–19] has shifted attitudes towards treatments. However, even in countries like Australia that have a well-resourced health system, DAAs as currently priced are yet to be approved either in full or part for subsidy on the Pharmaceutical Benefits Scheme (PBS) and will place

a substantial burden on government medication outlays if and when they are listed. Despite their clear benefits, particularly among PWID, few studies have determined their cost-effectiveness in this population. Data relating to a country's healthcare system must be weighed against local treatment costs and re-infection probabilities to provide useful evidence for health policy.

Many models of the cost-effectiveness of DAAs are not applicable to PWID,[20] given their significant rates of HCV re-infection[21] and differences in mortality and quality of life compared to the general population.[22] Previous models have been used to determine the cost-effectiveness of treating PWID with older generation therapies, using a fixed rate of re-infection[23,24] or a dynamic transmission model including prevention benefits.[25] In this paper we use a similar approach by assuming a fixed rate of re-infection (calibrated by baseline prevalence) to determine the cost-effectiveness of treating PWID with DAAs in Australia. In particular, we compare treating PWID at the onset of their infection or delaying treatment until their liver disease has progressed to moderate fibrosis. Treatments have proven to be equally effective at this stage of liver disease and delaying treatment may potentially save on costs, in particular because the slow progression of liver disease means that a proportion of PWID will have ceased injecting drug use by the time they are eligible for late-treatment, reducing re-infection and re-treatment rates.

Methods

Model description. We used a closed compartmental model of liver disease progression and treatment with a fixed rate of HCV re-infection (Fig. 1).

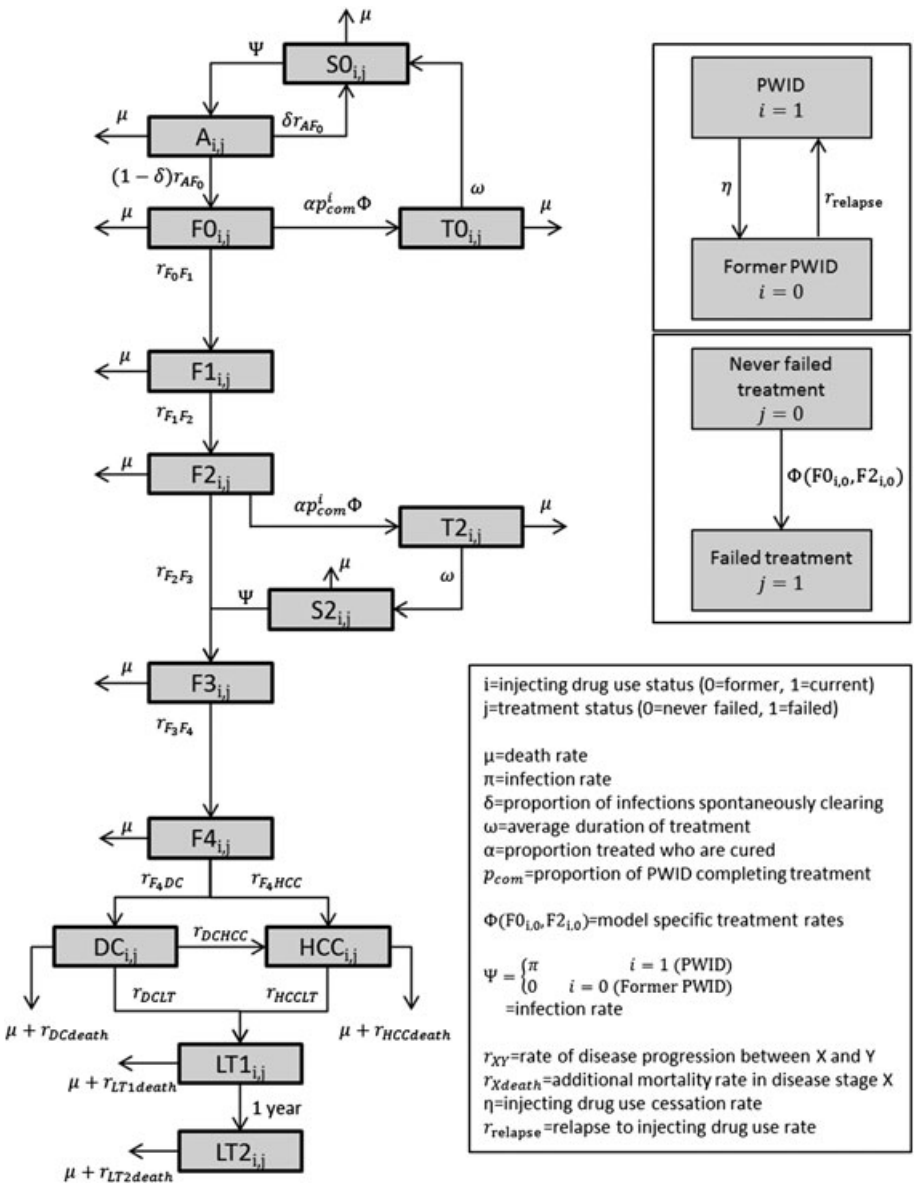

Figure 1 Model schematic.

Table 1 Demographic, HCV infection, and HCV treatment model parameters

Demographic information	Estimate	Symbol	References and comments
Mean age at first injection	17 years		[26]
Estimated time to first infection	6.5 years		Using incidence of 15.5 per 100 person years (range 3–12 years).[21]
Estimated age of cohort to start model	23.5 years		From above.
Duration of injecting career	17 years	$1/\eta$	[33]
Annual probability of drug relapse to IDU	0.027	$1-\exp(-r_{relapse})^{\dagger}$	[24,34]
Mortality ratios			
Annual non-liver-related mortalities for cohort PWID (per 1000 person years)			
25–29 years old[‡]	0.96	$1-\exp(-\mu_1)$	[35]
30–34 years old	1.12	$1-\exp(-\mu_2)$	[35]
35–44 years old	0.18	$1-\exp(-\mu_3)$	[35]
45-54 years old	0.22	$1-\exp(-\mu_4)$	Assumed to equal the general Australian population. Values from Victoria life tables,[36] assuming 60% male PWID.[37]
55-64 years old	0.53	$1-\exp(-\mu_5)$	
65-74 years old	1.38	$1-\exp(-\mu_6)$	
75-84 years old	4.28	$1-\exp(-\mu_7)$	
85+ years old	14.96	$1-\exp(-\mu_8)$	
HCV infection			
Annual probability of PWID re-infection	0.11	$1-\exp(-\pi)$	Calibrated based on 50% chronic HCV prevalence (Appendix A). Range 0.08–0.16, corresponding to 40% and 60% chronic HCV prevalence tested in sensitivity analysis.
Spontaneous clearance	0.26	δ	[6] Range 0.22–0.29. Uniform distribution assumed for uncertainty analysis.
Genotype distribution in Australia			
Genotype 1	55%		[38]
Genotype 2	7%		[38]
Genotype 3	38%		[38]
Treatment			
Probability of PWID completing treatment	0.892	p_{com}	[39]
Genotype weighted SVR probability			
Mild chronic HCV	0.9	α	For Genotype 1[17–19,40]; assumed equally efficacious across genotypes.
Moderate chronic HCV	0.9	α	Assumed equally efficacious for mild and moderate liver disease stages.
Treatment duration			
Genotype 1 and 2	12 weeks		[17–19,41]
Genotype 3	24 weeks		
Australian weighted average	16.56 weeks	$52/\omega$	

[†]Annual transition probabilities are converted to rates.

[‡]Extended to include individuals aged between 23.5 and 25 year olds.

HCV, hepatitis C virus; IDU, injection drug use; PWID, people who inject drugs; SVR, sustained viral response.

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 one year post liver transplant (LT1 and LT2 respectively); chronically infected and in treatment achieving sustained viral response (SVR) (T0 and T2—treated from liver fibrosis stage F0 and F2 respectively); or susceptible (S0—achieving spontaneous clearance or SVR spontaneously from the acute stage or through treatment from liver fibrosis stage F0; S2—achieving SVR from treatment in liver fibrosis stage F2). Individuals were also classified by injecting drug use status ($i = 1$ indicating current PWID, $i = 0$ indicating former PWID) and whether they had previously failed treatment ($j = 0$ indicating never failed, $j = 1$ indicating previously failed).

The model was started with a cohort of newly infected PWID who had not previously failed treatment ($F0_{1,0} = 100$), who were assumed to be 23.5 years old—the mean age of first injection[26] + the average time to infection,[21] see Table 1. People in the model moved between identical compartments of the i stratification because of cessation or relapse into injecting drug use at fixed rates η and $r_{relapse}$ respectively. All-cause mortality occurred for each compartment at an age dependent rate μ (Table 1), and mortality rates for the DC, HCC, LT1, and LT2 compartments were increased by $r_{DCdeath}$, $r_{HCCdeath}$, $r_{LT1death,}$ and $r_{LT2death}$ respectively. Liver disease progressed at rates obtained from the literature (Table 2), and average liver transplant wait times were $1/r_{DCLT}$ and $1/r_{HCCLT}$ from the DC and HCC stages respectively.

The availability of treatment was scenario dependent (see Scenarios section), but when available, a proportion p_{com} of PWID who were offered treatment were assumed to adhere, so that for a given treatment efficacy α, the proportions α and αp_{com} of former PWID and current PWID respectively achieved SVR when offered treatment. Individuals who were assumed to achieve SVR moved to the treatment compartment matching their liver fibrosis stage (T0 or T2) and after a period ω, achieved SVR and moved to the corresponding susceptible compartment (S0 or S2). The remaining proportions of current and former PWID ($1 - \alpha$ and $1 - \alpha p_{com}$ respectively) who failed treatment were moved to the $j = 1$ stratification and where they continued liver disease progression without any re-treatment. The increasing number of fixed-dose combination therapies on the market means that alternate options are likely to be available in the future to cure these patients in an extended treatment regimen, resulting in a higher treatment efficacy; both extended treatment duration and higher efficacy treatments are tested in the sensitivity analysis.

PWID who achieved SVR could become re-infected at a fixed rate π, which was calculated using a separate model where incidence was estimated based on prevalence and other model parameters (Appendix A). PWID who became re-infected after successful early-treatment spent a period $1/r_{AF0}$ in the acute stage before a proportion δ spontaneously cleared infection and became susceptible, while the remaining $(1 - \delta)$ became chronically infected and entered the F0 compartment. PWID who became re-infected after successful late-treatment entered the F2 compartment, and were assumed to not spontaneously clear infection. Spontaneous clearance following re-infection has been observed,

Table 2 Liver disease and health state progression rates

Annual health state transition probabilities	Estimate	Distribution for uncertainty analysis	Standard deviation	Rate parameter†	Refs.
Acute infection to mild (F0)‡	52/12	52/TNormal[1,26]§	52/2	$1 - \exp(-r_{AF0})$	42
F0 to F1					
Former PWID	0.106	TNormal(0.094,0.205)	0.028	$1 - \exp(-r_{F0F1})$	43
Current PWID	0.116	TNormal(0.059,0.228)	0.042	$1 - \exp(-\hat{r}_{F0F1})$	43
F1 to F2					
Former PWID	0.074	TNormal(0.064,0.175)	0.028	$1 - \exp(-r_{F1F2})$	43
Current PWID	0.085	TNormal(0.065,0.110)	0.011	$1 - \exp(-\hat{r}_{F1F2})$	43
F2 to F3					
Former PWID	0.106	TNormal(0.092,0.187)	0.033	$1 - \exp(-r_{F2F3})$	43
Current PWID	0.085	TNormal(0.049,0.147)	0.025	$1 - \exp(-\hat{r}_{F2F3})$	43
F3 to F4					
Former PWID	0.105	TNormal(0.092,0.187)	0.024	$1 - \exp(-r_{F3F4})$	43
Current PWID	0.130	TNormal(0.053,0.319)	0.067	$1 - \exp(-\hat{r}_{F3F4})$	43
F4 to DC	0.037	TNormal(0.030,0.092)	0.016	$1 - \exp(-r_{F4DC})$	44
F4 to HCC	0.010	TNormal(0.009,0.038)	0.007	$1 - \exp(-r_{F4HCC})$	44
DC to HCC	0.068	TNormal(0.041,0.099)	0.015	$1 - \exp(-r_{DCHCC})$	44
DC to liver transplant	0.033	TNormal(0.017,0.049)	0.008	$1 - \exp(-r_{DCLT})$	44
DC to death	0.138	TNormal(0.074,0.202)	0.032	$1 - \exp(-r_{DCdeath})$	44
HCC to liver transplant	0.100	TNormal(0.050,0.180)	0.033	$1 - \exp(-r_{HCCLT})$	44
HCC to death	0.605	TNormal(0.545,0.676)	0.033	$1 - \exp(-r_{HCCdeath})$	44
Liver transplant to death in year 1	0.169	TNormal(0.127,0.210)	0.021	$1 - \exp(-r_{LT1death})$	44
Liver transplant to death in years 2+	0.034	TNormal(0.024,0.043)	0.005	$1 - \exp(-r_{LT2death})$	44

†Annual transition probabilities are converted to rates; normally distributed parameters are converted to log-normal parameters.
‡Mean time in acute phase 12 weeks; range 1 week–6 months; standard deviation 2 weeks.
§TNormal(a,b), Normal distribution truncated between a and b.
DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; PWID, people who inject drugs.

Table 3 Health utilities and the annual and one-off costs associated with managing chronic HCV infection and treatment for various stages of liver disease

Health state utilities	Estimate	Distribution for uncertainty analysis	Standard deviation	Symbol	Refs.
Spontaneous viral clearance, never infected	0.93	TNormal(0.928,0.932)	0.01	q_S	[44]
Sustained virological response					
After early-treatment (F0)	0.93	TNormal(q_F012,q_S)	0.01	q_svr0	[45–47]
After late-treatment (F2–F3)	0.93	TNormal(q_F012,q_S)	0.01	q_svr2	Assumed to improve following SVR[48,49]
Acute HCV	0.77	TNormal(0,q_S)	0.12	q_A	
Mild chronic HCV (F0/F1/F2)	0.77	TNormal(0,q_S)	0.12	q_F012	[45–47]
Moderate chronic HCV (F3)	0.66	TNormal(0,q_F012)	0.15	q_F3	[45–47]
Compensated cirrhosis (F4)	0.55	TNormal(0,q_F3)	0.24	q_F4	[45–47]
Decompensated cirrhosis/liver failure	0.45	TNormal(0,q_F4)	0.14	q_DC	[45–47]
Hepatocellular carcinoma	0.45	TNormal(0,q_F4)	0.14	q_HCC	[45–47]
Liver transplantation year 1	0.45	TNormal(q_HCC,1)	0.14	q_LT1	[45–47]
Liver transplantation year 2+	0.67	TNormal(q_LT1,1)	0.14	q_LT2	[45–47]
During treatment					
Early-treatment	0.77	TNormal(q_F012,q_S)	0.12	q_T0	Assumed
Late-treatment	0.66	TNormal(q_F3,q_S)	0.15	q_T2	Assumed

Type of cost		Value (2014 Australian dollars)	Refs.
Annual costs of managing chronic HCV			[27,28]
Mild chronic HCV (F0–F2)		$446.70	[27,28]
Moderate chronic HCV (F3)		$690.85	[27,28]
Compensated cirrhosis (F4)		$935.05	[27,28]
Decompensated cirrhosis (DC)			
	Hepatic encephalopathy	*$20 053.03*	[27,28]
	Diuretic sensitive ascites	*$3792.38*	[27,28]
	Refractory ascites	*$29 264.28*	[27,28]
	Variceal hemorrhage	*$68 567.43*	[27,28]
	Weighted average	$15 202.43	
Hepatocellular carcinoma (HCC)		$10 759.75	[27,28]
One-off costs of transition between states			
Initial diagnosis of HCV		$936.63	[27,28]
Achieving SVR from treatment		$303.55	[27,28]
Transition to F4		$565.67	[27,28]
Transition to HCC		$970.20	[27,28]
Liver transplant		$145 565.00	[50]

(Continues)

Table 3 (Continued)

Type of cost		Value (2014 Australian dollars)	Refs.
Costs associated with treatment			
Mild or moderate HCV			27,28
	Genotype 1 or 2	*$51 779.60*	
	Genotype 3	*$102 377.15*	27,28
	Weighted average	$71 006.67	
Other costs			
Additional annual costs of care for PWID with chronic HCV		$34.22	27,28

HCV, hepatitis C virus; PWID, people who inject drugs; SVR, sustained viral response.

however at a reduced rate that is currently unclear, and this assumption will lead to slightly higher estimates of re-infection for this group and conservative estimates of cost-effectiveness. Where re-infection occurred, individuals were able to be re-treated.

Parameters. As the cost of DAAs is currently unclear in Australia, we assumed a base scenario of $50 000 (for 12 weeks of treatment) for genotype 1 and 2, and $100 000 (for 24 weeks of treatment) for genotype 3—averaged over the Australian genotype distribution (Table 1)—and tested upper and lower bounds of $100 000 for all genotypes and $10 000 for all genotypes in the sensitivity analysis. Healthcare and other costs associated with disease management or treatment were determined in consultation with hepatology and infectious diseases experts (Table 3). For a typical patient in each liver disease stage, specialist and general practitioner consultation frequency, as well as the frequency that tests and procedures would be requested were agreed upon for the current standard of care. The costs of each consultation, test, or procedure were then taken from the Medicare Benefits Scheme[27] and the PBS.[28] A further breakdown is provided in Appendix B.

Scenarios. *No antiviral treatment.* No treatments were available. The average discounted person-years spent in each compartment by a cohort member (i.e. a newly infected PWID) was calculated by integrating the size of each compartment over time for the first 100 years, discounted with a continuously compounding rate of 3% per annum (the lower bound recommended in Australia,[29] with an upper bound of 5% also tested) and then dividing by the cohort size. Discounted average costs and quality-adjusted life years (QALYs) per infected PWID were calculated by multiplying the average discounted person-years spent in each compartment by the associated annual costs and heath utilities (Table 3).

Early-treatment. Early-treatment was defined as treatment from the F0 stage in order to give an upper bound on cost-effectiveness —without treatment these patients have the most delayed and therefore discounted healthcare costs. This was implemented by initially offering the entire cohort treatment, and for the purposes of determining the cost-effectiveness of treating at this stage it was assumed that everyone initially commenced treatment: a proportion αp_{com} were moved to the $T0_{1,1}$ compartment, while the remaining $(1-\alpha p_{com})$ failed treatment and stayed in the $F0_{1,1}$ compartment. The model was run, and costs and QALYs were calculated, including the discounted costs of initial and subsequent treatments.

Late-treatment. Late-treatment (to prevent advanced liver disease) was defined as treating on transition from F2 to F3, as limitations in the accuracy of the Fibroscans typically used to identify disease stage mean that a later cut-off would fail to prevent some cases. This was implemented by offering the entire cohort treatment as they moved from liver fibrosis stage F2 to F3 (again assuming everyone commenced): when making the transition from F2 to F3 a proportion αp_{com} were moved to the T2 compartment, while the remaining $(1-\alpha p_{com})$ failed treatment and continued

liver disease progression to the F3 compartment. The model was run, and costs and QALYs were calculated.

Sensitivity analysis. To test model robustness, a Monte Carlo uncertainty analysis was conducted. Using the uncertainties of individual parameters—parametrized as probability distributions (Tables 2, 3)—1000 simulations were undertaken using random, independent parameter draws. Ninety-five percent confidence intervals (95%CIs) for the discounted cost per infected person, QALYs per infected person, life expectancy, liver-related deaths, and incremental cost-effectiveness ratio (ICER) estimates were taken as the central 95 percentiles of the resulting 1000 outputs. Henceforth, outcomes presented are from point estimate parameters, and 95%CIs have been taken from the uncertainty analysis results.

One-way sensitivity analyses were also undertaken to test the impact on ICERs when: the cost of treatment was either $100 000 for all genotypes or $10 000 for all genotypes; the annual probability of re-infection was 0.08 or 0.16 instead of 0.11 (corresponding to chronic HCV prevalence of 40% or 60% respectively, instead of 50%—see Appendix A); the discounting rate was increased from 3% to 5%; no re-treatment was allowed; the SVR rate was changed from 90% to either 70% or 99%; the length of injecting career was halved from 17 to 8.5 years; former PWID were unable to relapse into active injecting; former PWID were unable to relapse into active injecting *and* the length of injecting career was halved; treatment duration was set to 12 or 24 weeks for all genotypes instead of the 16 week weighted average; and the health utility following late-treatment was 0.770 instead of 0.930.

Results

Cost-effectiveness estimates. Compared to no treatment, late-treatment was the most cost-effective option; however, early-treatment was the most effective option in terms of quality of life years gained (Table 4). Late-treatment resulted in a discounted average gain of 2.98 (95%CI 2.88–5.22) QALYs per person for an additional cost of $15 132 (95%CI $11 246–18 922) compared to no treatment—giving an ICER of $5078 (95%CI $2847–5295) per QALY gained. In contrast, early-treatment resulted in a discounted average gain of 5.25 (95%CI 3.94–9.33) QALYs per person for an additional cost of $53 926 (95%CI $51 115–55 781) compared to no treatment—giving an ICER of $10 272 (95%CI $5689–13 690) per QALY gained.

Compared to late-treatment, early-treatment gained a further discounted average of 2.27 (95%CI 0.58–4.80) QALYs per person for $38 794 (95%CI $34 789–41 367), giving an ICER of $17 090 (95%CI $2847–63 282). For a willingness to pay threshold of $50 000 per QALY gained this was cost-effective in approximately 90% of Monte Carlo uncertainty analysis simulations (Fig. 2, bottom left), but was not cost-effective in some simulations, and so this result is not statistically significant at the 95% level (see Discussion).

For every 100 newly HCV-infected PWID, there were an estimated 40 (95%CI 39–56) eventual liver related deaths when no treatment was available, compared to 7 (95%CI 6–11) and 8

Table 4 Modeled costs, QALYs, life expectancies, and ICERs for treating PWID with chronic HCV. Point estimates represent outcomes using point estimate parameters; ranges represent 95% confidence intervals (CIs) from the Monte Carlo uncertainty analysis

Point estimates (95%CIs)	Cost per infected person	QALYs per infected person	Life expectancy of an infected person	ICER compared to no treatment	ICER compared to next best case	Liver related deaths expected per 100 newly infected PWID
Base case (no antiviral treatment)	$21 877 ($20 618–27 294)	16.45 (11.19–18.13)	67.97 (63.55–68.27)	Reference case		40 (39–56)
Late-treatment	$37 009 ($34 754–43 772)	19.43 (15.84–21.44)	74.14 (73.11–74.44)	$5078 ($2847–5295)	No treatment *versus* late-treatment $5078 ($2847–5295)	8 (7–13)
Early-treatment	$75 803 ($75 410-79 335)	21.70 (20.58-22.09)	74.47 (73.58-74.56)	$10 272 ($5689–13 690)	Early *versus* late-treatment $17 090 ($7926–63 282)	7 (6–11)

HCV, hepatitis C virus; ICERs, incremental cost-effectiveness ratios; PWID, people who inject drugs; QALYs, quality-adjusted life years.

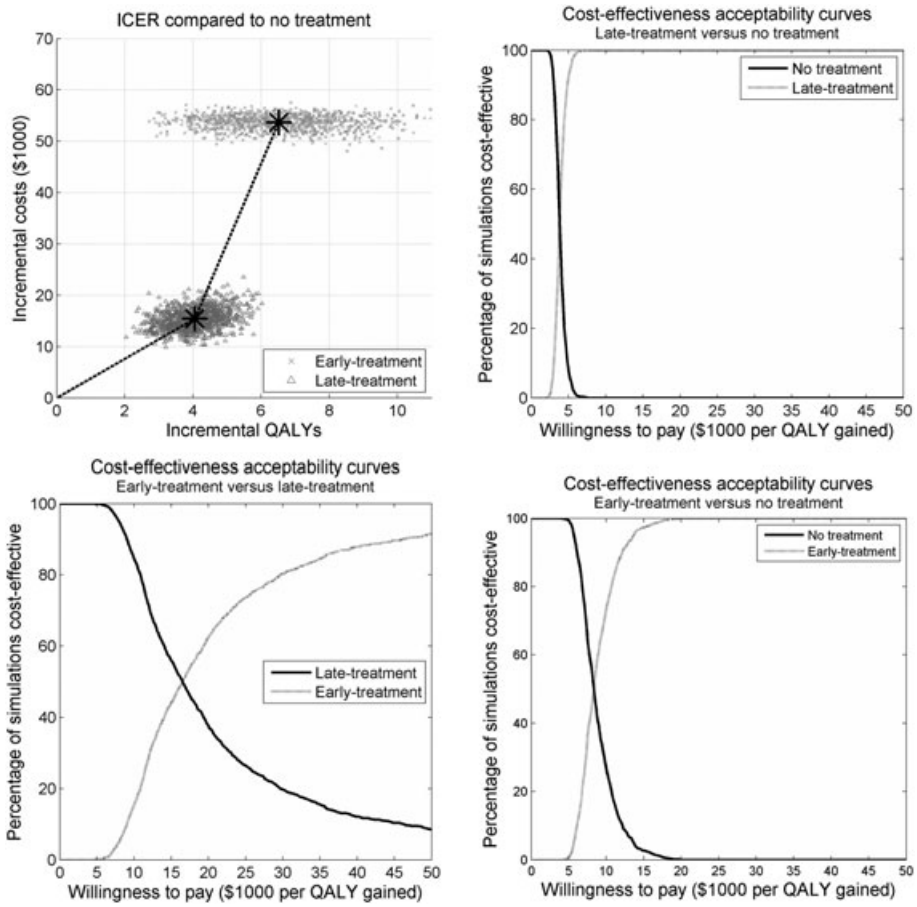

Figure 2 Cost-effectiveness plane showing simulation results and averages for early- and late-treatment compared to no treatment (top left); and cost-effectiveness acceptability curves for late-treatment compared to no treatment (top right), early-treatment compared to late-treatment (bottom left), and early-treatment compared to no treatment (bottom right).

(95%CI 7–13) when early-treatment and late-treatment were available respectively.

Sensitivity analysis. Changes to the cost of DAAs had the largest effect on cost-effectiveness estimates, but even at $100 000 per treatment course the ICERs for early- *versus* late-treatment and late *versus* no treatment ($37 778 and $13 259 per QALY gained respectively) were below the unofficial Australian willingness to pay threshold of $50 000 per QALY gained. Further, when the cost of DAAs was reduced to $10 000 for all genotypes, both early- and late-treatment were more effective and less costly than no treatment, and early-treatment had an ICER of only $1365 per QALY gained compared to late-treatment.

Excluding the potential for former PWID to relapse into active injecting is a conservative assumption,[30] which increased ICER estimates by 97% (from $17 090 to $37 714) for early-treatment compared to late-treatment, but only increased ICER estimates by 2% (from $5078 to $5188) for late-treatment compared to no treatment. This is because if HCV-infected former PWID cannot relapse into the pool of injectors, then a greater infection parameter π is required to calibrate prevalence, leading to higher re-infection rates amongst current PWID. For the early-treatment scenario, this means that more of the cured PWID are likely to become re-infected, requiring additional treatment costs and facing the possibility of failing treatment and experiencing poorer health outcomes; however conversely, for the late-treatment scenario, by the time advanced liver disease (and hence treatment) is obtained, most PWID have ceased injecting and with no chance of relapse or re-infection will experience similar outcomes. For the same reasons, when the length of injecting career was halved the ICER increased for early-treatment and decreased for late-treatment (although by less than 10% in each case), and these effects compounded when the length of injecting career was halved *and* former PWID were unable to relapse.

If the annual probability of re-infection was increased from 0.11 to 0.16 (initial prevalence increased from 50% to 60%), ICERs for the early- *versus* late-treatment and late-treatment *versus* no treatment scenarios increased by 24% (by $4119) and 26% (by $1297) respectively, again as a result of a greater infection parameter. Conversely, if the annual probability of re-infection was decreased from 0.11 to 0.08 (initial prevalence decreased from 50% to 40%), ICERs for early- *versus* late-treatment and late-treatment *versus* no treatment decreased by 17% (by $2874) and 18% (by $895) respectively.

Variations in the ICERs for early- *versus* late-treatment and late-treatment *versus* no treatment as a result of changes to the discounting rate, re-treatment availability, treatment efficacy, treatment duration,

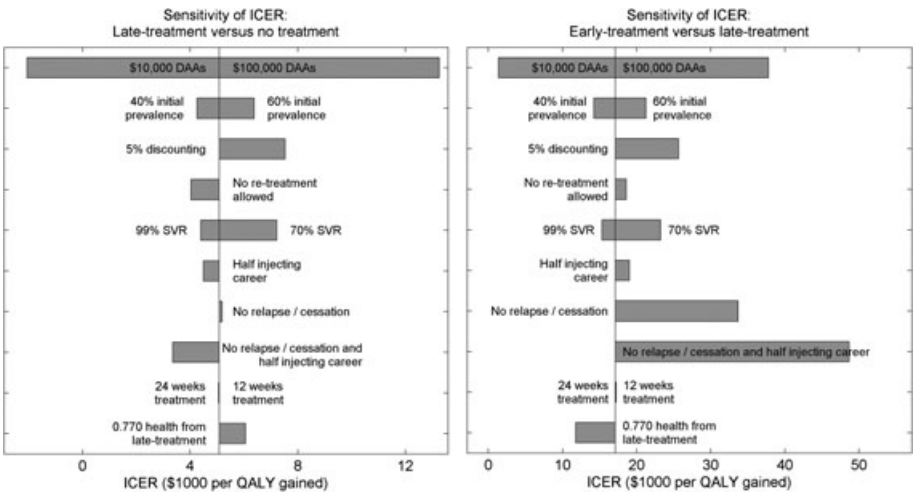

Figure 3 Sensitivity of the ICER for early-treatment compared to no treatment (left); and early-treatment compared to late-treatment (right), to changes in: the cost of DAAs, initial prevalence (re-infection rate), the discounting rate, re-treatment availability, the percentage who achieve a sustained viral response (SVR) from treatment, the average length of injecting career, the potential for former PWID to relapse into active injecting, treatment duration, and the health utility following late-treatment.

and health utility following late-treatment were logical and within sensible limits (Fig. 3).

Discussion

Using a cohort model of HCV treatment, liver disease progression, and re-infection we have determined that it is cost-effective to treat PWID with DAAs in Australia. Late-treatment was the most cost-effective option, with an ICER of $5078 per QALY gained compared to no treatment, while early-treatment had an ICER of $10 272 per QALY gained compared to no treatment and $17 090 per QALY gained compared to late-treatment.

As the time taken for liver disease to progress to an advanced stage was comparable to the length of injecting career, re-infection rates were lower after late-treatment than after early-treatment because of cessation of injecting. PWID that were treated early therefore had an increased likelihood of becoming re-infected, failing re-treatment, and progressing to advanced liver disease. For some combinations of parameters in the uncertainty analysis this resulted in early-treatment gaining only slightly more QALYs than late-treatment, while costing substantially more (Fig. 2, top and bottom left). As a result, in approximately 10% of parameter combinations in our uncertainty analysis, early-treatment had an ICER greater the $50 000 per QALY gained compared to late-treatment, owing to sensitivities in the model parameters for the length of injecting career and rates of relapse into injecting drug use among former PWID.

These estimates are likely to be conservative, and treating PWID with DAAs in Australia may be even more cost-effective than predicted. First, the costs associated with patients who have DC or HCC in our model are underestimates: healthcare management costs associated with these disease stages were based on *minimum* requirements agreed upon by specialists (Appendix 2). In the scenario of no treatment, a far greater proportion of HCV-infected PWID progress to these liver disease stages compared to when treatment is available, meaning that the baseline average cost per newly HCV-infected individual may be higher and the ICERs lower than we have calculated. Second, we have not captured the benefits of reduced transmission—namely that treating an increasing number of PWID will reduce the HCV prevalence among PWID and also the infection/re-infection rate. Modeling suggests that by treating 40/1000 PWID per year, HCV prevalence can be halved within 15 years.[31,32] This is likely to have a significant impact on total costs, as an increasing number of new infections are prevented and the epidemic is slowed, and is also likely to increase the cost-effectiveness of early-treatment compared to late-treatment, because early-treatment is more likely to occur before injecting cessation and would therefore have the most effect on the prevention of further transmissions. Further work should be undertaken to account for the effects of a dynamic infection rate on the cost-effectiveness of treatment.

Conclusion

Treating HCV-infected PWID with new therapies is cost-effective, and could prevent a significant number of liver related deaths. Although late-treatment was the most cost-effective option, the cost per QALY gained for early-treatment compared to late-treatment is likely to be below unofficial Australian willingness to pay thresholds. The low cost per QALY for early-treatment in our model in Australia suggests the early-treatment of PWID may be similarly cost-effective in other jurisdictions.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix A. Equations
Appendix B. Costs
Table B1. Costs associated with initial diagnosis of HCV.
Table B2. Annual costs of mild and moderate (F0-F3) stages of HCV related liver disease, the cost of developing compensated cirrhosis and the annual costs of compensated cirrhosis.
Table B3. The cost of developing hepatocellular carcinoma, annual costs of managing hepatocellular carcinoma and the cost of a liver transplant.
Table B4. The cost of treatment from mild/moderate HCV related liver disease (genotype 1/2 or genotype 3).
Table B5. The costs incurred post-successful treatment.
Table B6. The costs of decompensated cirrhosis (hepatic encephalopathy diuretic, sensitive ascites, refractory ascites and variceal haemorrhage), and the probability of developing each condition.
Table B7. Additional costs associated with treating PWID.