Cost-Effectiveness of Hepatitis C Virus Antiviral Treatment for Injection Drug User Populations

Natasha K. Martin,[1,2] Peter Vickerman,[1,2] Alec Miners,[2] Graham R. Foster,[3] Sharon J. Hutchinson,[4,5] David J. Goldberg,[4] and Matthew Hickman[1]

Injecting drug use is the main risk of hepatitis C virus (HCV) transmission in most developed countries. HCV antiviral treatment (peginterferon-α + ribavirin) has been shown to be cost-effective for patients with no reinfection risk. We examined the cost-effectiveness of providing antiviral treatment for injecting drug users (IDUs) as compared with treating ex/non-IDUs or no treatment. A dynamic model of HCV transmission and disease progression was developed, incorporating: a fixed number of antiviral treatments allocated at the mild HCV stage over 10 years, no retreatment after treatment failure, potential reinfection, and three baseline IDU HCV chronic prevalence scenarios (20%, 40%, and 60%). We performed a probabilistic cost-utility analysis estimating long-term costs and outcomes measured in quality adjusted life years (QALYs) and calculating the incremental cost-effectiveness ratio (ICER) comparing treating IDUs, ex/non-IDUs, or no treatment. Antiviral treatment for IDUs is the most cost-effective option in the 20% and 40% baseline chronic prevalence settings, with ICERs compared with no treatment of £521 and £2,539 per QALY saved, respectively. Treatment of ex/non-IDUs is dominated in these scenarios. At 60% baseline prevalence, treating ex/non-IDUs is slightly more likely to be the more cost-effective option (with an ICER compared with no treatment of £6,803), and treating IDUs dominated due to high reinfection. A sensitivity analysis indicates these rankings hold even when IDU sustained viral response rates as compared with ex/non-IDUs are halved. *Conclusion*: Despite the possibility of reinfection, the model suggests providing antiviral treatment to IDUs is the most cost-effective policy option in chronic prevalence scenarios less than 60%. Further research on how HCV treatment for injectors can be scaled up and its impact on prevalence is warranted. (HEPATOLOGY 2012;55:49-57)

Chronic hepatitis C virus (HCV) infection results in over 350,000 deaths per year.[1] In many developed countries, injection drug use is the key HCV transmission risk.[2,3] For example, 90% of infections acquired in the UK are through injections.[4] Treatment and prevention of HCV transmission among injecting drug users (IDUs), therefore, is critical to reducing the burden of liver disease.[2] HCV chronic prevalence within IDU populations varies widely, from below 20% to over 60%.[5] Prevention measures such as opiate substitution therapy and high coverage needle and syringe programs can reduce HCV transmission.[6,7] It is less clear, however, whether current strategies have had a population-level impact.[8,9]

Previous mathematical modeling work suggested HCV antiviral treatment could prevent HCV transmission.[10,11] Current HCV antiviral treatment regimens can achieve a sustained viral response (SVR) in 45% (genotype 1) to 80% (genotype 2/3) of infections and economic evaluations suggest treatment is cost-effective for populations with no risk of reinfection.[12-15]

Abbreviations: HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICER, incremental cost-effectiveness ratio; IDU, injection drug user; NICE, National Institute for Clinical Excellence; OST, opiate substitution therapy; QALY, quality adjusted life year; SVR, sustained viral response.

From the [1]Department of Social Medicine, University of Bristol, Bristol, UK; [2]Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine, London, UK; [3]Queen Marys University of London, Barts and The London School of Medicine, Liver Unit, UK; [4]Health Protection Scotland, Glasgow, UK; [5]Department of Mathematics and Statistics, University of Strathclyde, Glasgow, UK.

Received June 9, 2011; accepted August 18, 2011.

Supported by NCCRCD/NIHR CRDHB, MRC New Investigator Award, Scottish Government Hepatitis C Action Plan.

Address reprint requests to: Natasha Martin, Department of Social Medicine, University of Bristol, Canynge Hall, 39 Whatley Road, Bristol, BS8 2PS, UK. E-mail: Natasha.Martin@bristol.ac.uk; fax: +44 (0)1179287325.

View this article online at wileyonlinelibrary.com.

DOI 10.1002/hep.24656

Potential conflict of interest: Dr. Goldberg advises Merck.

Dr. Foster consults for, advises, is on the speakers' bureau of, and received grants from Roche, Gilead and Janssen. He consults for and is on the speakers' bureau of Bristol-Myers Squibb. He also consults for GlaxoSmithKline and Merck.

Additional Supporting Information may be found in the online version of this article.

Table 1. Epidemiological and Disease Progression Parameters

Parameter: Transition Probabilities and Rates	Mean Value [95% Interval]	Distribution	Units	Ref.
Mild to moderate transition probability, TP*	0.025 [0.018-0.033]	Beta (38.086, 1485.3516)	Per year	12
Moderate to cirrhosis TP*	0.037 [0.025-0.052]	Beta (26.905,700.2582)	Per year	12
Cirrhosis to decompensated cirrhosis TP*	0.039 [0.030-0.083]	Beta (14.617,260.1732)	Per year	12
Cirrhosis/decompensated cirrhosis to HCC TP*	0.014 [0.002-0.039]	Beta (1.9326,136.1074)	Per year	12
Decompensated cirrhosis/HCC to transplant TP*	0.03 [0.012-0.056]	Beta (6.5256,210.9945)	Per year	12
Transplant to death TP*	0.21 [0.127-0.307]	Beta (16.276,61.2294)	Per year	12
Post transplant to death TP*	0.057 [0.037-0.082]	Beta (22.902,378.8825)	Per year	12
Decompensated cirrhosis to death TP*	0.13 [0.111-0.150]	Beta (147.03, 983.97)	Per year	12
HCC to death TP*	0.43 [0.372-0.489]	Beta (117.1, 155.23)	Per year	12
Sustained viral response (SVR)				
Genotype 1	0.45	Uniform (0.40,0.50)	–	13,30-32
Genotype 2/3	0.80	Uniform (0.75,0.80)	–	13,30-32
Proportion population genotype 1	0.5	–	–	13
Average lifespan (age 20 in 2010)	76 [75.9-76.1]	Normal (76,0.06)	years	28,43
Average injecting duration†	11 [6.25-15.75]	Uniform (6,16)	years	29,33,44,45
Average excess IDU death rate (excluding HCV related death)	0.01	Poisson	Per year	42
Rate IDUs enter the IDU population	Fit to total population of 1000 injectors	–	Per year	
Infection rate	Fit to give prevalence considered	–	Per year	

All annual rates converted to transition probabilities in model. HCC: hepatocellular carcinoma.

*TP: transition probability.

†Average duration of injecting career until permanent cessation.

Currently, few active injectors are treated, primarily because physicians have concerns over compliance and reinfection.[16,17] Emerging evidence suggests injectors can exhibit similar compliance and response rates to non- or ex-IDUs,[18] and reinfection in the first year is low,[19] leading to many countries (such as the U.S., U.K., and Australia) recommending treatment, regardless of current drug use status.[13,20,21] However, a lack of treatment infrastructure to reach this population, low treatment willingness, and high psychiatric comorbidity may contribute to low treatment rates.

In this study we used a dynamic HCV transmission model among active IDUs (hereafter referred to as IDUs) to determine the cost-effectiveness of providing antiviral treatment to IDUs compared with treating ex- or non-IDUs or no treatment.

Materials and Methods

Model. We utilized an open dynamic model of HCV transmission and antiviral treatment among IDUs, accounting for the prevention effects of antiviral treatment on HCV transmission (schematic in Supporting Materials). New susceptible injectors enter the IDU population and may exit through cessation or death without becoming HCV-infected. Susceptible IDUs become infected at a rate proportional to the number of susceptibles, the fraction of the IDU population infected, and the infection rate. If infected, a proportion (≈26%[22]) spontaneously clear the virus, with the remainder progressing to chronic infection. The model tracks progression through HCV disease states: mild, moderate, cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant, post-transplant, and liver-related death.[12,23-25] Onward infections among IDUs can be averted after successful treatment, but IDUs can also be reinfected, subsequently reentering their previous most advanced HCV disease state. Ex/non-IDUs who are treated have no reinfection risk. Successfully treated IDUs can be reinfected and retreated, but those who fail treatment are ineligible for retreatment.

We randomly sample most epidemiological and disease transition probabilities, costs, and health benefits from probabilistic distributions (Tables 1-3). For each of the 1,000 sampled parameter sets, we simulate three chronic HCV baseline prevalence scenarios in injector populations at equilibrium without treatment (20%, 40%, and 60%), obtaining matched simulations for each prevalence setting and treatment scenario. This gives endemic infection population numbers in each disease category (IDU and ex/non-IDU) given a total population of 1,000 IDUs.

Costs are valued in 2010 UK pounds (£1 = 1.15 Eur = $1.60 USD) and health outcomes are expressed in quality adjusted life years (QALYs). For each treatment scenario we calculate the incremental cost-effectiveness ratio (ICER, the change in costs divided by the change in QALYs), which indicates the cost per QALY gained. An intervention with an ICER falling below a designated government or healthcare provider-defined threshold would be considered cost-effective. Additionally, we present simulation results on a cost-effectiveness plane, a graphical method to display

Table 2. Health Utility Values

Parameter: Utility Values	Mean Yearly Value [95% Interval]	Distribution	Ref.
Uninfected			
Ex/non-IDU	1	N/A	
IDU	0.85	Uniform [0.8-0.9]	33
Mild HCV*	0.77 [0.74-0.80]	Beta (521.238,155.6943)	12,15,24
Moderate HCV*	0.66 [0.60-0.72]	Beta (168.246,86.6723)	12,15,24
Cirrhosis*	0.55 [0.44-0.65]	Beta (47.1021,38.5381)	12,15,24
Decompensated cirrhosis*	0.45 [0.39-0.51]	Beta (123.75,151.25)	12,15,24,46
HCC*	0.45 [0.39-0.51]	Beta (123.75,151.25)	12,15,24,46
Liver transplant*	0.45 [0.39-0.51]	Beta (123.75,151.25)	12,15,24
Post transplant*	0.67 [0.53-0.79]	Beta (32,16)	15,46
On treatment			
Mild*	0.66 [0.59-0.73]	Beta (115.706,59.6063)	12,15,24,46
Moderate*	0.55 [0.44-0.65]	Beta (47.1021,38.5381)	12,15,24,46
SVR			
Mild*,†	0.82 [0.73-0.90]	Beta (65.8678, 14.4588)	12,15,24,46
Moderate*	0.72 [0.62-0.81]	Beta (58.0608, 22.5792)	12,15,24,46

*Value for both IDU and ex/non-IDU.

†For IDU, Mild SVR cannot exceed uninfected IDU utility value. Hence, Mild IDU SVR = minimum utility for mild SVR and utility for uninfected IDU. HCC: hepatocellular carcinoma.

differences in costs and QALYs between healthcare strategies for each simulation undertaken. Costs and health benefits are discounted at 3.5% per year in the base case according to UK National Institute for Clinical Excellence (NICE) guidelines.[26] We use a cycle length of 6 months.

Treatment Options and Specifics. For each baseline chronic prevalence (20%, 40%, and 60%) we compare the following scenarios: 1. No treatment (best supportive care) among both IDUs and ex/non-IDUs. 2. Treatment (peginterferon + ribavirin) at a mild stage for only IDUs. 3. Treatment (peginterferon + ribavirin) at a mild stage for only ex/non-IDUs.

We define best supportive care as a care package that does not involve an antiviral treatment, but includes inpatient/outpatient services, investigations, procedures, and blood tests (details in Supporting Materials). In our base analysis, we considered a fixed and realistic treatment number (10 per year in our population of 1,000 injectors) for a program of 10 years. To account for prevention benefits, we calculate costs and QALYs for a further 40 years giving a total time horizon of 50 years (leading to conservative cost-effectiveness estimates, as not all future prevention benefits are included).

Transition Probabilities. Transition probabilities between HCV disease states are taken from previous economic analyses and empirical studies (Table 1).[12,15,24,25] New injectors enter the model at 20 years old, and injectors have an elevated chance of death (due to overdose, etc.) compared with the ex/non-IDU population,[27] who have an average lifespan of 76 years.[28] UK-specific death rates are assumed.[27,29]

We sampled from published antiviral treatment (peginterferon-α + ribavirin) SVR probabilities,[13,30-32] and assumed a distribution of 50% genotype 1 and 50% genotype 2/3 infections.[13] We employed current NICE guidelines for treatment duration by responder type and genotype.[13] Preliminary studies suggest that SVR rates are equal between IDU and ex/non-IDUs,[18] so we assumed this in our base case.

Utilities. Health utilities (measured in QALYs) for each disease state for ex/non-IDUs were taken from previous economic analyses and the mild HCV trial (Table 2).[12,15] In line with previous analyses, we assume the baseline (uninfected) IDU health utility is less than for non/ex-IDUs (uniformly sampled from 0.8-0.9).[33] Lacking data on IDU HCV utility values, we assumed equal utility values for infected IDUs as ex/non-IDUs. As a result, the subsequent utility loss upon infection is lower for IDUs than ex/non-IDU. Thus, the benefit of preventing an IDU infection is less than for the noninjection population. Additionally, we assume an uninfected utility value for non/ex-IDUs of 1.0.

Costs. We adopt a healthcare provider perspective on costs, with all results inflated to 2010 UK pounds using the hospital community health services pay and prices index. Antiviral treatment (peginterferon-α + ribavirin) costs were taken from the British National Formulary[34] (mean cost £5,406 for 24 weeks, sampled uniformly between £4,806-£6,418, and halved/

Table 3. Cost Inputs

Parameter: Costs	Mean 2003-2004 Value**	Distribution	Units	Ref.
HCV infection-related costs*				
Annual Mild HCV	138	Gamma (25.7,5.3698)	£ per year	12,15
Annual Moderate HCV	717	Gamma (88.85,8.0698)	£ per year	12,15
Annual Cirrhosis	1138	Gamma (24.234,46.984)	£ per year	12,15
Annual HCC	8127	Gamma (18.108,448.8045)	£ per year	12
Annual Decompensated cirrhosis	9120	Gamma (36.0249,253.1582)	£ per year	12,15
Liver transplant	27330	Gamma (89.7536,304.5004)	£ per transplant	12
Hospital costs year of transplant	9458	Gamma (13.7788,686.4168)	£ per year	12
Annual Post transplant	1385	Gamma (15.2189,91.0053)	£ per year	12
Annual Mild SVR	259	Gamma (28.8141, 8.9887)	£ per year	12
Annual Moderate SVR	717	Gamma (89.004,8.0557)	£ per year	12
Annual Cirrhosis SVR	1138	Gamma (25.81,44.091)	£ per year	12
Antiviral treatment delivery costs†				
Outpatient evaluation†				
Staff	35.59	Varied by staff cost variation‡	£ per treatment	12
Tests	201.31	Varied by test cost variation§		
Outpatient further investigation visit†				
Staff	29.64	Varied by staff cost variation‡	£ per treatment	12
Tests	606.32	Varied by test cost variation§		
First treatment appointment†				
Staff	44.43	Varied by staff cost variation‡	£ per treatment	12
Tests	166.31	Varied by test cost variation§		
Basic assessments (total for weeks 1,2,4)†				
Staff	47.17	Varied by staff cost variation‡	£ per treatment	12
Tests	34.92	Varied by test cost variation§		
Extended assessments (total for weeks 4,8)†				
Staff	31.45	Varied by staff cost variation‡	£ per treatment	12
Tests	28.09	Varied by test cost variation§		
Detailed assessment week 12†				
Staff	19.59	Varied by staff cost variation‡	£ per treatment	12
Tests	179.61	Varied by test cost variation§		
Basic assessments (total for weeks 16, 20)†				
Staff	31.45	Varied by staff cost variation‡	£ per treatment	12
Tests	23.28	Varied by test cost variation§		
Detailed assessment week 24†				
Staff	23.45	Varied by staff cost variation‡	£ per treatment	12
Tests	39.98	Varied by test cost variation§		
Basic assessments (total for weeks 28,32,40,44)†				
Staff	62.89	Varied by staff cost variation‡	£ per treatment	12
Tests	47.56	Varied by test cost variation§		
Detailed assessment week 36†				
Staff	19.59	Varied by staff cost variation‡	£ per treatment	12
Tests	26.03	Varied by test cost variation§		
Detailed assessment week 48†				
Staff	23.45	Varied by staff cost variation‡	£ per treatment	12
Tests	39.98	Varied by test cost variation§		
SVR surveillance (total for weeks 4, 12, 24 post treatment)†				
Staff	42.2	Varied by staff cost variation‡	£ per treatment	12
Tests	95.76	Varied by test cost variation§		
IDU extra nurse time				
12 weeks of treatment	104.89	Varied by staff cost variation‡	£ per treatment	Little data¶
24 weeks of treatment	129.73	and IDU staff time variation‖		
48 weeks of treatment	179.41			

(Continued)

TABLE 3. (Continued)

Parameter: Costs	Mean 2003-2004 Value**	Distribution	Units	Ref.
IDU extra basic assessments				
12 weeks of treatment			£ per treatment	Little data¶
Staff	47.16	Varied by test cost variation§		
Tests	34.92	Varied by staff cost variation‡		
24 weeks of treatment		and IDU staff time variation‖		
Staff	78.60			
Tests	58.20			
48 weeks of treatment				
Staff	141.48			
Tests	104.76			
IDU psychiatric visits***				
Staff	41.94	Varied by staff cost variation‡ and IDU staff time variation‖	£ per treatment	Little data¶

*Used for best supportive care costs for each disease stage.

**Costs were updated from 2003/04 to 2009/10 prices using the Hospital and community health pay and prices index;

***Two visits comprising of 20 min nurse (grade H assumed) and 10 min consultant doctor.

†For a detailed breakdown of staffing time/salaries, tests, and test costs see Shepherd et al.[12]

‡Staff value calculated by multiplying mean staff cost by a staff cost variation parameter, uniformly sampled between 0.8 and 1.2.

§Test value calculated by multiplying mean test cost with a test cost variation parameter, uniformly sampled between 0.8 and 1.2.

‖IDU staff cost value calculated by multiplying mean staff cost by a staff cost variation parameter and an extra IDU staff time variation parameter (both uniformly sampled between 0.8 and 1.2).

¶Estimated by Graham Foster. Nurse time/salary calculated from Shepherd et al.[12]

doubled for treatment durations of 12/48 weeks). Costs for HCV disease states (used for best supportive care costs) and antiviral treatment delivery (excluding drug costs) are shown in Table 3. Although HCV-infected IDUs may incur additional supportive care costs when compared with infected ex/non-IDU, we assumed no difference in costs. We itemized treatment delivery costs by appointment, separated into staff and test costs; a detailed breakdown can be found in Shepherd et al.[12]

We assumed treating IDUs accrues additional treatment delivery costs (two psychiatric sessions prior to treatment, double the number of basic assessments during treatment, and 50% additional nursing time at each hospital visit; Graham Foster, pers. commun.). Due to difficulty assessing the uncertainty around costs, we sampled staff and test costs, and additional IDU staff time parameters from 80%-120% of the baseline estimate, and used these to vary the baseline cost estimates for treatment delivery.

Sensitivity Analysis. We performed a linear regression analysis of covariance (ANCOVA) analysis on the ICER comparing treatment of IDUs to no treatment (at 40% prevalence) and calculated the proportion of the sum of squares contributed by each parameter to estimate the importance of individual parameters to the overall uncertainty.[35] We also performed a one-way sensitivity analysis to identify whether specific model assumptions have a large effect on the 40% prevalence scenario analysis, and whether these alter the most cost-effective policy decision. We varied the IDU SVR rate (half or three-quarters of non/ex-IDU SVR), genotype (all genotype 1 or all genotype 2/3), time horizon (extending it to 100 or 200 years), discount rate (0% health discounting), treatment number (5 or 20 treatments per year), treatment duration (5 or 20 years), and treatment delivery costs (staff time and test costs required for undertaking treatment, excluding fixed antiviral drug costs) for IDU (equal or double the mean cost for an ex/non-IDU). We also explored a scenario where ex-IDU uninfected utility values are reduced (from 1 to 0.9) and average lifespan for both IDU and ex-IDU is reduced by 7 years (in addition to overdose-related and other mortality risks during injection). Finally, we examined treatment at a moderate stage instead of a mild stage.

Results

Cost-Effectiveness Analysis. Table 4 presents the costs, QALYs, and ICERs for no treatment (best supportive care), antiviral treatment for IDU (10 treatments per 1,000 IDU annually for 10 years), and antiviral treatment for ex/non-IDU (10 treatments annually for 10 years). Results are shown for three baseline chronic HCV prevalence scenarios among IDUs (20%, 40%, and 60%).

Table 4. Economic Evaluation Results with Treatment at a Mild Stage Versus no Treatment (Best Supportive Care) for 20%, 40%, and 60% Baseline Chronic HCV Prevalences

Scenario	Mean Total Costs (in 1000 of £) [95% Interval]	Mean Total QALYs [95% Interval]	Mean ICER [95% Interval]
20% prevalence			
No treatment	£20,010 [£12,654-£32,344]	137,066 [96,704-206,932]	
Treat IDUs	£20,163 [£12,986-£32,246]	137,360 [96,916-207,307]	£521* [£-408-£1,839]
Treat ex/non-IDUs	£20,552 [£13,243-£32,788]	137,146 [96,762-207,057]	dominated†
40% prevalence			
No treatment	£40,774 [£26,053-£65,483]	123,053 [87,031-185,394]	
Treat IDUs	£41,119 [£26,536-£65,873]	123,217 [87,191-185,618]	£2,539* [£1,262-£4,822]
Treat ex/non-IDUs	£41,316 [£26,610-£66,035]	123,133 [87,129-185,488]	dominated†
60% prevalence			
No treatment	£61,475 [£39,424-£98,863]	109,084 [76,883-163,857]	
Treat ex/non-IDUs	£62,017 [£39,969-£99,413]	109,163 [76,979-163,972]	£6,803* [£-16,007-£38,570]
Treat IDUs	£62,066 [£40,048-£99,456]	109,161 [76,978-163,961]	dominated†

All costs given in 2010 GBP. QALYs: quality-adjusted life years.

*Compared to no treatment.

†Indicating the alternative treatment scenario has fewer incremental costs and more incremental QALYs.

Treating IDUs is the most cost-effective policy option at 20% and 40% chronic prevalence, with ICERs (compared with no treatment) of £521 and £2,539 per QALY, respectively. Treatment of ex/non-IDUs is dominated by treatment of IDUs at these prevalences (i.e., more costly and less effective). At 60% chronic prevalence, treatment of ex/non-IDUs is slightly more cost-effective than treating IDUs, with an ICER (compared with no treatment) of £6,803 per QALY, in line with previous economic evaluations of HCV treatment for this group.[12,14] The cost-effectiveness acceptability curves in Figs. 1 and 2 show that at 20% and 40% prevalence, treatment of IDUs is the most cost-effective option using the NICE threshold for cost-effective interventions (£20,000-£30,000 per QALY gained). In contrast, at 60% prevalence, Fig. 3 suggests that it is 57%-60% likely that treating ex/non-IDUs is the more cost-effective option, but both options are below the NICE threshold.

In all prevalence settings, providing treatment (to IDUs or ex/non-IDUs) results in additional costs and QALYs compared with no treatment (best supportive care), indicating that treatment is unlikely to be cost-saving. This is illustrated in Supporting Figs. 2-4, which show the cost-effectiveness plane for each prevalence scenario, with most simulations falling within the upper right-hand quadrant. In the 20% and 40% prevalence IDU treatment scenarios, total costs are lower than in the ex/non-IDU scenario because of reductions in onward infections (leading to higher QALYs and reduced HCV-associated medical costs). The lower the baseline prevalence, the higher the QALY gain when treating IDUs, as treatments result in a larger relative reduction in prevalence. In the 60% prevalence setting, costs are higher for treating IDU than ex/non-IDU; any beneficial prevention effects are offset by increased reinfection.

Sensitivity/Uncertainty Analysis. The ANCOVA analysis in Supporting Fig. 5 shows that most variability (55%) in the ICER at 40% prevalence results from uncertainty in the cost parameters associated with care in the different HCV progression states. Additional variability is related to uncertainty in the mild SVR utility value (6%) and the transition probabilities from mild to moderate (6%), moderate to cirrhosis (12%),

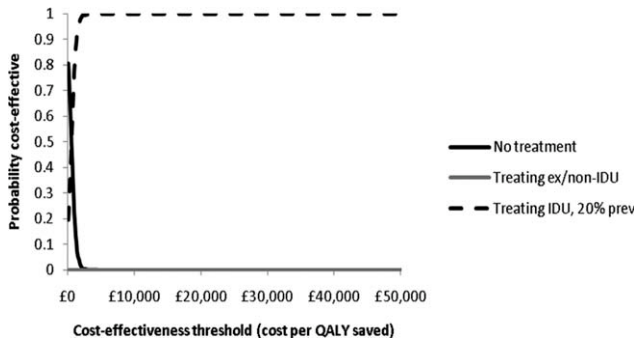

Fig. 1. Cost-effectiveness acceptability curves for the 20% chronic prevalence scenario.

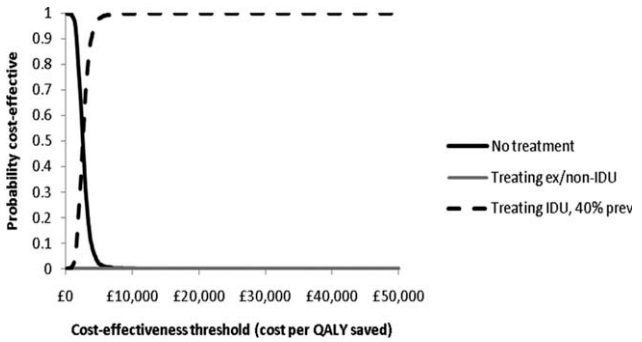

Fig. 2. Cost-effectiveness acceptability curves for the 40% chronic prevalence scenario.

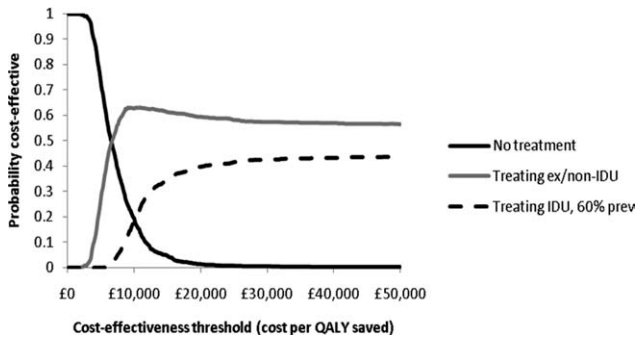

Fig. 3. Cost-effectiveness acceptability curves for the 60% chronic prevalence scenario.

cirrhosis to decompensated cirrhosis (5%), and IDU death (7%). Uncertainty in the uninfected IDU utility value and costs related to antiviral treatment contributes little to the variability in projections.

Figure 4 shows that none of the univariate sensitivity analyses on the ICER (treatment of IDUs as compared with no treatment) for the 40% prevalence scenario changed the optimal policy choice of treating IDU. Reducing the SVR among IDUs by one-quarter or half increases the ICER by nearly 50% and 150%, respectively. Treatment of an all genotype 1 population results in a higher ICER (+50%) due to a lower SVR, whereas treating all genotype 2/3 reduces the ICER (−60%). Lowering the uninfected ex-IDU utility value (to 0.9) and average lifespan by 7 years results in an increase in ICER (+40%) for treating IDUs and the ICER for treating ex-IDUs also increases. Using a health discount rate of 0% instead of 3.5% per year substantially reduces the ICER to just below zero (cost saving) due to increased savings from future infections averted. Treatment at a moderate stage is more cost-effective than treating at a mild stage, with an ICER of £1,082. Increasing the time horizon to 100 years reduces the ICER by nearly 50% due to further prevention and treatment benefits, with reductions stabilizing at 200 years due to discounting. The ICER for treatment of ex/non-IDUs as compared with no treatment stabilizes at about £4,200 for long time horizons. Changes in IDU treatment delivery costs, treatment rate, or treatment duration do not alter the ICER substantially.

Discussion

Our results suggest treating chronic HCV infection among injectors and ex- or noninjectors is cost-effective, but treating injectors may be more cost-effective when the chronic HCV prevalence among IDU is below 60% (about 80% antibody prevalence). In these scenarios, treating injectors results in more QALYs gained through the prevention of onward transmission than are lost from reinfection. The model projections suggest that this policy decision holds even if SVR rates among injectors are half of those published for ex/non-IDUs, although it is unclear if clinicians would be willing to treat IDUs with response rates as low as this. Our analysis provides evidence that HCV treatment among injectors should not be restricted because of concerns over reinfection, but should be prioritized as HCV treatment services expand.

Strengths and Weaknesses. We present model projections, not empirical evidence. Interpretation must be cautious, as models can only raise and corroborate hypotheses rather than directly test them. Key limitations relate to the simplifying assumptions of the model and uncertainty around several parameters.

First, there is a lack of information on expected treatment costs and SVRs for providing HCV treatment to injectors in the community. Indeed, current studies of SVR in injectors, although encouraging, are generally small and among self-selected patients, who may have higher SVR rates than the IDU population in general.[18] The presence of favorable factors (younger age or milder liver disease) may balance IDU-factors that reduce

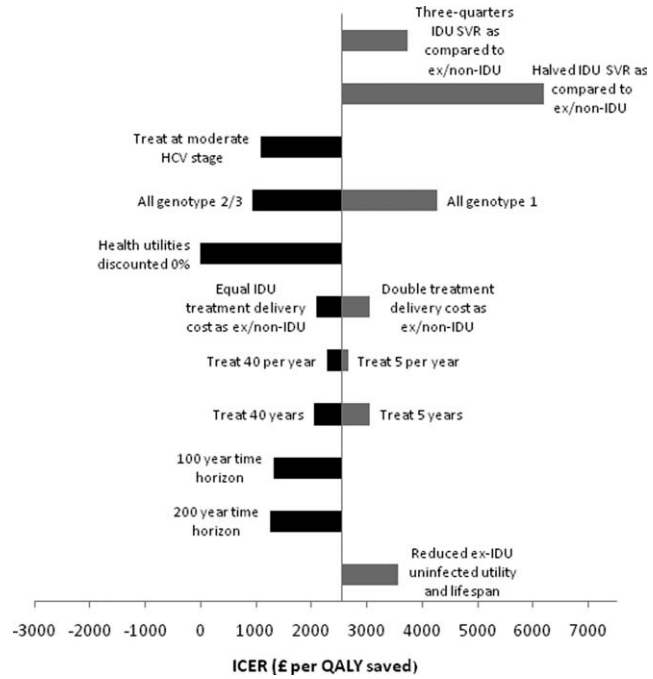

Fig. 4. Results of the one-way sensitivity analysis showing the incremental cost-effectiveness ratio (treating IDUs as compared with no treatment) for the 40% baseline prevalence scenario. The axis is centered on the ICER for the baseline analysis (£2,539 per QALY saved) and the figure simulates 1,000 parameter sets for each individual parameter change. In all simulations the optimal policy decision remained as in the baseline analysis (treating IDUs is most cost-effective).

treatment response; however, data on this are lacking. The results of our sensitivity analysis are encouraging because they suggest the findings are robust to a large drop in SVR; however, larger studies are needed to establish SVR rates among injectors. Extra training costs for treating IDUs (in primary care, prison, and/or specialist treatment agencies) are likely, in addition to the extra clinic visits included in our analysis. We did not include costs of drug treatment/opiate substitution treatment (OST) as part of the HCV treatment, although most injectors entering HCV treatment are likely to be on OST. Adding OST costs does not necessarily reduce the cost-effectiveness of HCV treatment because OST has other benefits such as reducing crime costs and drug-related mortality, and possibly increasing HCV treatment compliance.[33,36] In the UK and many countries with developed OST programs there are substantial numbers of untreated patients, hence OST could be an important point of contact for treatment recruitment. Initially, the limiting step to scaling-up treatment, therefore, is availability of hepatitis nurses to deliver treatment, which is growing in a number of sites[36,37] that have achieved high uptake rates.[37]

Second, there are a lack of data related to IDU and ex-IDU utility values and lifespan either with or without chronic HCV infection, and after successful treatment.[15,38] Previous evaluations on HCV utility values and costs have been performed in a mixed population of non-IDUs and those with an injection history. It is likely former IDUs would have lower uninfected utility values and shorter lifespans than those who have never injected, but specific values were unavailable.

Third, the current model does not include heterogeneity in infection risk and treatment accessibility. The presence of "high risk, high transmitter" subpopulations that could be less likely to enter or comply with HCV treatment could reduce the prevention impact and cost-effectiveness. Conversely, those who access and complete treatment may subsequently be less likely to transmit the disease. However, the natural history of injection and potential impact of such heterogeneity is complex.[39] Higher risk subpopulations are not necessarily fixed, with IDUs having periods of higher and lower risk at different times during their injection career. Other models have suggested that high risk in the first year of injection or the presence of high-risk groups can limit primary prevention.[40] The lack of age-structure in the current model also means that we cannot accurately utilize age-specific death rates.[41,42] These limitations need to be addressed by incorporating more complexity in future model projections and undertaking empirical research to determine the conditions, patient characteristics, and timing under which HCV treatment can be delivered and any associated changes in SVR.

Comparison with Other Studies. The cost-effectiveness of HCV antiviral treatment in terms of reducing morbidity and future liver disease to the individual is established, and our ex/non-IDU model predictions are consistent with these estimates (£3,000-£10,000 per QALY gained depending on treatment regime).[12,15] No other studies, to our knowledge, have examined the cost-effectiveness of treating injectors including the prevention effect, or compared the cost-effectiveness of different clinical/policy decisions on whether it is justified to treat injectors as well as non-injecting populations, which requires a dynamic model as presented here.

Implications and Future Research. Hepatitis C transmission risk remains high among injectors in most populations, even when there is high coverage of prevention interventions such as needle and syringe programs and OST.[8,9] Our research indicates HCV treatment could play a role in prevention among the IDU population,[10,11] and treating IDUs is likely to be cost-effective across a wide range of prevalences. Empirical studies examining the treatment of IDUs and measuring the effects on prevalence are warranted.

References

1. Perz JF, Armstrong GL, Farrington LA, Hutin YJF, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol 2006;45:529-538.
2. ACMD. The Primary Prevention of Hepatitis C Among Injecting Drug Users, 2009.
3. Hepatitis C Virus Projections Working Group. Estimates and projections of the hepatitis C virus epidemic in Australia 2006. http://www.nchecr.unsw.edu.au/NCHECRweb.nsf/resources/HCVPWG2006/$file/HCVPWGRepAug06.pdf; 2006.
4. De Angelis D, Sweeting M, Ades AE, Hickman M, Hope V, Ramsay M. An evidence synthesis approach to estimating hepatitis C prevalence in England and Wales. Stat Methods Med Res 2009;18:361-379.
5. Vickerman P, Hickman M, May M, Kretzschmar M, Wiessing L. Can hepatitis C virus prevalence be used as a measure of injection-related human immunodeficiency virus risk in populations of injecting drug users? An ecological analysis. Addiction 2009;105:311-318.
6. Van Den Berg C, Smit C, Brussel GV, Coutinho R, Prins M. Full participation in harm reduction programmes is associated with decreased risk for human immunodeficiency virus and hepatitis C virus: evidence from the Amsterdam Cohort Studies among drug users. Addiction 2007;102:1454-1462.
7. Turner K, Hutchinson S, Craine N, Hope V, Palmateer N, Vickerman P, et al. The impact of needle and syringe provision and opiate substitution therapy on the incidence of Hepatitis C virus in injecting drug users: pooling of UK evidence. Addiction 2011; doi: 10.1111/j.1360-0443.2011.03515.x [Epub ahead of print].
8. Palmateer N, Kimber J, Hickman M, Hutchinson S, Rhodes T, Goldberg D. Evidence for the effectiveness of sterile injecting equipment provision in preventing hepatitis C and human immunodeficiency virus transmission among injecting drug users: a review of reviews. Addiction 2010;105:844-859.

9. Sweeting M, Hope V, Hickman M, Ncube F, Ramsay M, De Angeles D. Hepatitis C infection among injecting drug users in England and Wales 1992-2006: there and back again? Am J Epidemiol 2009;170:352-60.
10. Martin NK, Vickerman P, Foster GR, Hutchinson SJ, Goldberg DJ, Hickman M. Can antiviral therapy for hepatitis C reduce the prevalence of HCV among injecting drug user populations? A modelling analysis of its prevention utility. J Hepatol 2011;54:1137-1144.
11. Martin NK, Vickerman P, Hickman M. Mathematical modelling of hepatitis C treatment for injecting drug users. J Theor Biol 2011;274:58-66.
12. Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N. Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation. Health Technol Assess 2007;11:1-224.
13. NICE. Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C. Technol Appraisal Guidance 106: National Institute for Health and Clinical Excellence; 2006.
14. Sroczynski G, Esteban E, Conrads-Frank A, Schwarzer R, Mühlberger N, Wright D, et al. Long-term effectiveness and cost-effectiveness of antiviral treatment in hepatitis C. J Viral Hepat 2010;17:34-50.
15. Wright M, Grieve R, Roberts J, Main J, HC T. Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. Health Technol Assess 2006;10:21.
16. Edlin BR, Seal KH, Lorvick J, Kral AH, Ciccarone DH, Moore LD, et al. Is it justifiable to withhold treatment for hepatitis C from illicit-drug users? N Engl J Med 2001;345:211-214.
17. Foster GR. Injecting drug users with chronic hepatitis C: should they be offered antiviral therapy? Addiction 2008;103:1412-1413.
18. Hellard M, Sacks-Davis R, Gold J. Hepatitis C treatment for injection drug users: a review of the available evidence. Clin Infect Dis 2009;49:561-573.
19. Dalgard O. Follow up studies of treatment for hepatitis C virus infection among injection drug users. Clin Infect Dis 2005;40:S336-S338.
20. NIH. Management of Hepatitis C. 2002. NIH Consensus Statement. In: (NIH) NIoH, editor, 2002.
21. Australian Government Department of Health and Aged Care. Schedule of pharmaceutical benefits for approved pharmacists and medical practitioners. Canberra: Department of Health and Aged Care and Medicare Australia, Pharmaceutical Benefits Scheme; 2001.
22. Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following hepatitis C infection: a systematic review of longitudinal studies. J Viral Hepat 2006;13:34-41.
23. Shepherd J, Brodin H, Cave C, Waugh N, Price A, Gabbay J. Pegylated interferon α-2a and -2b in combination with ribavirin in the treatment of chronic hepatitis C: a systematic review and economic evaluation. Health Technol Assess 2004;8:39.
24. Grieve R, Roberts J, Wright M, Sweeting M, DeAngelis D, Rosenberg W, et al. Cost effectiveness of interferon α or peginterferon α with ribavirin for histologically mild chronic hepatitis C. Gut 2006;55:1332-1338.
25. Castelnuovo E, Thompson-Coon J, Pitt M, Cramp M, Siebert U, Price A, et al. The cost-effectiveness of testing for hepatitis C in former injecting drug users. Health Technol Assess 2006;2006:32.
26. NICE. Guide to the Methods of Technology Appraisal, 2008.
27. Hickman M, Hope V, Coleman B, Parry J, Telfer M, Twigger J, et al. Assessing IDU prevalence and health consequences (HCV, overdose and drug-related mortality) in a primary care trust: implications for public health action. J Public Health 2009:1-9.
28. Government Actuary's Department. Interim life tables 1980-82 to 2004-06: Office for National Statistics.
29. Sweeting MJ, De Angelis D, Ades AE, Hickman M. Estimating the prevalence of ex-injecting drug use in the population. Stat Methods Med Res 2009;18:381-395.
30. Hadziyannis SJ, Sette H, Morgan TR, Balan V, Diago M, Marcellin P, et al. Peginterferon-β±2a and ribavirin combination therapy in chronic hepatitis C. Ann Intern Med 2004;140:346-355.
31. McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. N Engl J Med 2009;361:580-593.
32. Shiffman ML, Suter F, Bacon BR, Nelson D, Harley H, Sola R, et al. Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. N Engl J Med 2007;357:124-134.
33. Vickerman P, Miners A, Williams J. Assessing the cost-effectiveness of interventions linked to needle and syringe programmes for injecting drug users. In: NICE, editor. London, 2008.
34. British Medical Association. British National Formulary. 2010;59.
35. Briggs A, Claxton K, Sculpher M. Decision Modelling for Health Economic Evaluation. Oxford: Oxford University Press; 2006.
36. Waizmann M, Ackermann G. High rates of sustained virological response in hepatitis C virus-infected injection drug users receiving directly observed therapy with peginterferon alpha-2a (40KD) (PEGASYS) and once-daily ribavirin. J Subst Abuse Treat 2010;38:338-345.
37. Grebely J, Genoway K, Khara M, Duncan F, Viljoen M, Elliott D, et al. Treatment uptake and outcomes among current and former injection drug users receiving directly observed therapy within a multidisciplinary group model for the treatment of hepatitis C virus infection. Int J Drug Policy 2007;18:437-443.
38. Dietze P, Stoové M, Miller P, Kinner S, Bruno R, Alati R, et al. The self-reported personal wellbeing of a sample of Australian injecting drug users. Addiction 2010;105:2141-2148.
39. Kimber J, Copeland L, Hickman M, Macleod J, McKenzie J, De Angelis D, et al. Survival and cessation in injecting drug users: prospective observational study of outcomes and effect of opiate substitution treatment. BMJ 2010;340:c3172.
40. Vickerman P, Hickman M, Judd A. Modelling the impact on Hepatitis C transmission of reducing syringe sharing: London case study. Int J Epidemiol 2007;36:396-405.
41. Degenhardt L, Bucello C, Mathers B, Briegleb C, Ali H, Hickman M, et al. Mortality among regular or dependent users of heroin and other opioids: a systemic review and meta-analysis of cohort studies. Addiction 2011;106:32-51.
42. Cornish R, Macleod J, Strang J, Vickerman P, Hickman M. Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK General Practice Research Database. BMJ 2010;341.
43. Toson B, Baker A. Life expectancy at birth: methodological options for small populations. National Statistics Methodological Series No. 33; Office for National Statistics, 2003.
44. Nordt C, Stohler R. Incidence of heroin use in Zurich, Switzerland: a treatment case register analysis. The Lancet 2006; 367(9525):1830–1834.
45. Sweeting MJ, DeAngelis D, Hickman M, Ades AE. Estimating hepatitis C prevalence in England and Wales by synthesizing evidence from multiple data sources. Assessing data conflict and model fit. Biostat 2008;9:715–734.
46. Sutton AJ, Edmunds WJ, Sweeting MJ, Gill ON. The cost-effectiveness of screening and treatment for hepatitis C in prisons in England and Wales: a cost-utility analysis. J Viral Hepat 2008;15797–808.