Should we treat acute hepatitis C? A decision and cost-effectiveness analysis

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List of Abbreviations
Hepatitis C Virus (HCV)
Direct acting antivirals (DAAs)
People who inject drugs (PWID)
Sustained virologic response (SVR)
Quality-adjusted life years (QALYs)
Quality-of-life (QoL)
Incremental cost effectiveness ratio (ICER)
Hepatocellular carcinoma (HCC)

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ABSTRACT

It is not standard practice to treat patients with acute hepatitis C virus (HCV) infection. However, as the incidence of HCV in the United States continues to rise, it may be time to re-evaluate acute HCV management in the era of direct-acting antiviral agents (DAAs). In this study a microsimulation model was developed to analyze the tradeoffs between initiating HCV therapy in the acute versus chronic phase of infection. By simulating the lifetime clinical course of patients with acute HCV infection, we were able to project long-term outcomes such as quality-adjusted life years (QALYs) and costs. We found that treating acute HCV versus deferring treatment until the chronic phase increased QALYs by 0.02 and increased costs by $483 in patients not at risk of transmitting HCV. The resulting incremental cost effectiveness ratio (ICER) was $19,991 per QALY, demonstrating that treatment of acute HCV was cost-effective using a willingness-to-pay threshold of $100,000 per QALY. In patients at risk of transmitting HCV, treating acute HCV became cost-saving, increasing QALYs by 0.03 and decreasing costs by $3655.

Conclusion: Immediate treatment of acute HCV with DAAs can improve clinical outcomes and be highly cost-effective or cost-saving compared with deferring treatment until the chronic phase of infection. If future studies continue to demonstrate effective HCV cure with shorter 6 week treatment duration, then it may be time to revisit current HCV guidelines to incorporate recommendations that account for the clinical and economic benefits of treating acute HCV in the era of DAAs.

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Hepatitis C virus (HCV) infection remains one of the main causes of chronic liver disease worldwide (1). An estimated 71 million people across the globe are currently infected with the hepatitis C virus (HCV), with approximately 3 to 4 million new infections occurring each year (2, 3). Persons with HCV virus can be classified as being in either the acute or chronic phase of infection. The acute phase of HCV infection is generally defined as occurring from the time of exposure up through six months of infection. If a patient with acute HCV does not spontaneously clear the virus within this six-month time frame, then in the majority of cases chronic infection will subsequently develop (4).

People who inject drugs (PWID) account for the largest portion of acute HCV infections in the United States (5, 6). Up front prevention of virus acquisition is the best way to limit new cases of HCV infection, however despite attempts at targeted interventions, such as needle exchange and opiate substitution programs, the incidence of HCV continues to rise (7). The annual number of reported HCV cases has tripled since 2010, with an estimated 34,000 newly infected Americans in the year 2015 (8). Alongside continued efforts to minimize exposure risks in these populations, it could be worth revisiting current management approaches for patients with acute HCV infection.

Treatment options for HCV infection have undergone a major transformation with the introduction of direct-acting antivirals (DAAs). The success of these new agents has led to significant changes in consensus guidelines and recommended treatment options for patients with chronic HCV (9-11). Of note, these guidelines do not routinely recommend the initiation of therapy in patients with acute HCV infection. Current reasons for deferring treatment to the

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chronic stage are: 1) the desire to avoid treating patients who would have otherwise spontaneously cleared the infection on their own, 2) the limited data on the efficacy of DAAs in the acute phase of HCV infection, and 3) the lack of studies evaluating the cost effectiveness of early treatment strategies (9-11).

During the era of interferon-based regimens, patients being treated for acute HCV infection achieved higher SVR rates with shorter duration therapy (12). A number of recent and ongoing pilot trials evaluating the efficacy of DAAs in acute HCV infection are beginning to demonstrate similar positive results. In particular, two studies – the German HepNet Acute HCV IV Study and the US SLAM C Study, showed 100% sustained virologic response (SVR) with 4 to 6 weeks of treatment with ledipasvir/sofosbuvir (13, 14).

With these recent developments, there is a need to revisit the tradeoffs between the initiation of therapy in the acute versus chronic phase of HCV infection. Because the duration of treatment in the acute phase is potentially shorter (4–6 weeks) compared with treatment in the chronic phase (8–12 weeks), the cost of treatment in the acute phase is lower. An additional benefit of acute HCV treatment is to reduce potential transmission (15, 16). Conversely, if we defer treatment, approximately 25% of patients with acute HCV infection will spontaneously clear the virus (17), creating the opportunity to save on cost by monitoring for clearance and treating only those who develop chronic infection. To evaluate such tradeoffs we conducted a model-based analysis on acute versus chronic HCV treatment, providing some of the first cost-effectiveness data on treating acute HCV infection in the current era of DAA therapy.

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METHODS

We developed a microsimulation (individual-level state-transition) model to compare treating HCV in acute versus chronic phase of the infection. This was done by extending our previously validated model (18) to incorporate recent clinical data on the efficacy of DAAs in treating acute as well as chronic HCV infection. We simulated the clinical course of patients diagnosed with acute HCV infection and projected long-term outcomes such as quality-adjusted life years (QALYs) and costs. A weekly cycle length was utilized in the model. Simulated patients were followed until death.

Patient cohort

Our base case cohort was representative of the acute HCV patient population in the United States. Patient age at the start of the analysis was 26 (4). All patients were assumed to be genotype 1 as this was the genotype included in the currently available studies investigating the efficacy of DAAs in the acute phase of HCV infection (13, 14).

Treatment strategies

We simulated and compared two management strategies: 1) immediately treat acute HCV infection (referred to as "*treat acute HCV*" arm), versus 2) wait for six months and treat only those who develop chronic HCV infection (referred to as "*treat chronic HCV*" arm) (Figure 1). All patients received an HCV RNA test and genotype test at initial diagnosis. In the "*treat acute HCV*" arm, after the diagnostic tests, patients received immediate treatment with 6 weeks of ledipasvir/sofosbuvir (13). Although two pilot studies showed 100% SVR with 4 to 6 weeks of treatment with ledipasvir/sofosbuvir (13, 14), these were small trials and we did not want to over-estimate SVR efficacy by incorporating rates of 100%. We therefore made the assumption

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that the SVR rate in acute HCV treatment would at a minimum be equivalent to the SVR rate in chronic treatment, and utilized SVR values from published studies on chronic HCV therapy (11, 19).

In the "*treat chronic HCV"* arm, patients were followed for six months before receiving a second HCV RNA test to determine if spontaneous clearance had occurred. For our base case analysis we used a 25% spontaneous clearance rate obtained from a systematic review (17), and further conducted sensitivity analysis on a wide range of spontaneous clearance values (0-60%) (11, 20). If patients demonstrated spontaneous clearance then no further treatment was needed. Patients with a positive HCV RNA test after 6 months were deemed to have developed chronic HCV infection and were subsequently treated with 8 weeks of ledipasvir/sofosbuvir, as recommended by the American Association for the Study of Liver Disease (AASLD-IDSA) guidance (11). All patients in our base case were treated for 8 weeks, acknowledging that there may be subset of patients in whom 12 weeks of therapy is still the recommended treatment duration based on drug therapy choice. In both arms, patients who failed to achieve SVR were eligible for retreatment, and those who failed second line therapy were assumed to follow the natural history of HCV. SVR status was confirmed by an RNA test 12 weeks following therapy completion.

Natural history of HCV infection

To account for the higher risk of non-liver-related death in the acute HCV patient population, we adjusted the background mortality with sex-specific hazard ratios (2.58 for men and 1.97 for women) (21-23). Patients who failed to achieve SVR started at F0 fibrosis stage and progressed through different stages of liver fibrosis (F0 to F4). Patients with F4 fibrosis stage or

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compensated cirrhosis could further progress to decompensated cirrhosis, hepatocellular carcinoma (HCC), or death from liver-related mortality (18). The rate of fibrosis progression, decompensation, HCC, and liver-related death were estimated from published systematic reviews (24) and observational studies (25, 26). Patients with decompensated cirrhosis and HCC had higher excess mortality (26, 27) and were eligible for liver transplantation (28, 29). The likelihood of liver transplantation was estimated from previous studies (18, 30).

Cost and quality of life estimates

Our analysis was conducted from a third-party payers' perspective and included only direct medical costs. The recent listing of the highly effective glecapravir/pibrentasvir is $3,300 per week; to ensure our model cost input reflected the current DAA price environment we used a 50% discount on the wholesale acquisition costs for ledipasvir/sofosbuvir of $7,875 per week (i.e. $3,937.50) for our base case analysis (31). We also conducted one-way sensitivity analysis on drug price by further applying an additional discount up to 50% on top of our base case drug price. The cost of HCV genotype and RNA testing were $435 and $98, respectively (32). We estimated health state-specific costs from our previously published studies (30, 33) and conservatively assumed no additional costs for the acute HCV state. All cost estimates were converted to 2016 US dollar values using the healthcare component of the Consumer Price Index (34).

We assigned health-related quality-of-life (QoL) utility values to each health state in the model; utilities were bounded between a minimum value of 0 (denoting death) and a maximum value of 1 (denoting perfect health). All utility weights were extracted from previously published studies

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that used the EuroQol-5D instrument (35, 36). We assumed the QoL for the acute phase of HCV was equivalent to that for the F0 fibrosis state, and the QoL for post-SVR patients was equivalent to that of the general population. We also normalized all utilities with age-gender specific QoL weights representative of the United States population.

Effect of acute HCV treatment on HCV transmission

We examined the potential impact of acute HCV treatment on preventing HCV transmission (15, 16, 37). In particular, we considered a cohort of patients who are at high risk of transmitting HCV, such as PWIDs, who account for the largest portion of acute HCV infections in the United States. It is possible that immediate treatment of acute HCV in these patients (versus waiting until the chronic phase) can reduce potential HCV transmission. We conducted an analysis by assuming that an untreated acute HCV person could infect other 0.2 (range: 0-1.0) persons during the acute phase of the infection. We made this conservative assumption given that the equivalent estimates based on published parameters are typically greater than 0.5 (38-43). Our assumption implied that treating 5 people with acute HCV could prevent one new HCV infection.

Model outcomes

Our model simulated the life-time clinical course of the "treat acute HCV" and "treat chronic HCV" strategies and projected expected average QALYs and costs for the base case cohort. We then calculated the incremental cost-effectiveness ratio (ICER) of treating acute versus chronic HCV infection. All future QALYs and costs were discounted at 3% per year. To reduce the effect of the first-order uncertainty the model was run 100,000 times.

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Scenario analysis

We conducted several scenario analyses to evaluate model outcomes under different clinical settings. First, we considered 4- and 6-week treatment durations in acute HCV and 8- and 12-week treatment durations in chronic HCV infection. Second, we included the possibility of loss to follow-up in both the acute and chronic treatment arms. Due to limited evidence for this variable, we varied the probability of loss to follow up from 0% to 90%.

Sensitivity analysis

We performed one-way sensitivity analysis to assess the impact of uncertainty in transition probabilities, QoL weights, costs, initial age, model time horizon, and background mortality on model outcomes (Table 1). As both spontaneous viral clearance rate and DAA efficacy in acute HCV infection are two key parameters in our model, we conducted two-way sensitivity analysis by evaluating different combinations of these parameters. We also performed probabilistic sensitivity analysis to simultaneously account for uncertainty in all model parameters. We used the recommended statistical distributions for each parameter (Table 1) and conducted the analysis using 10,000 second-order samples (and 100,000 first-order samples).

RESULTS

Cost-effectiveness of treating acute HCV

In patients who are not at risk of transmitting HCV, treating acute HCV increased QALYs by 0.02 and increased total costs by $483 as compared to deferring treatment to the chronic phase

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(Table 2). The resulting ICER was $19,991/QALY, substantially below the $100,000/QALY willingness-to-pay threshold, demonstrating that treatment of acute HCV is cost-effective.

In patients at risk of transmitting HCV, using a per-person transmission rate estimate of 0.2, and therefore implying that treating 5 people with acute HCV could prevent one new HCV infection, QALYs increased by 0.03 and costs decreased by $3655, demonstrating that treatment of acute HCV was cost-saving (Table 2). Indeed, treating acute HCV was cost-saving even when the number of new infections transmitted was as low as 0.02 (eFigure 1). Greater cost-saving was achieved as the number of new infections transmitted by people with acute HCV infection increased.

In the scenario analyses, evaluation of a range of acute and chronic treatment durations continued to demonstrate that acute HCV treatment remained either cost-effective or cost-saving (Table 2). In addition, we assessed possible scenarios in which patients may not adhere to treatment for acute HCV, or fail to return for chronic HCV therapy after the 6-month monitoring period. Treating acute HCV remained cost-effective with a loss to follow-up probability as high as 90% (eFigure 2).

Sensitivity analysis

One-way sensitivity analysis showed that for patients not at risk of transmitting HCV, the ICER was most sensitive to the spontaneous clearance rate, the QoL utility values of the acute HCV state and the post-SVR state, and the probability of lost to follow-up (Figure 2A). When the drug price was changed by ±50% of the base case value, the ICER of treating acute versus chronic

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HCV ranged from $9,000-30,000/QALY. For patients at risk of transmitting HCV, treatment in acute HCV was found to be cost-saving across all parameter ranges except for high values of the spontaneous clearance rate and probably of lost to follow-up (Figure 2B). Model results were not sensitive to the starting age and the model time horizon (eTable 1).

Figure 3 shows a two-way sensitivity analysis for the spontaneous clearance rate and the SVR rate in acute HCV treatment. Displayed on the graph are the regions in which varying combinations of these two parameters lead to cost-effective or cost-saving results. For instance, at 98% SVR, treating acute HCV is cost-effective/saving if the rate of spontaneous clearance is below 31% for patients not at risk of transmitting HCV (Figure 3A), and below 44% for patients at risk of transmitting HCV (Figure 3B).

Probabilistic sensitivity analysis showed that treating acute HCV was either cost-effective or cost-saving with a very high probability of 98.6% using a willingness-to-pay threshold of $100,000/QALY (eFigure 3).

DISCUSSION

In clinical practice the treatment of acute HCV infection remains controversial. Current guidelines recommend deferring treatment to the chronic stage, or monitoring patients with acute HCV for at least 12–24 weeks prior to initiating therapy. One of the driving factors in the decision to delay treatment is the desire to avoid needlessly administering therapy to patients who would have otherwise spontaneously cleared the virus. This was particularly true in the era of interferon based HCV treatment regimens, when the risks associated with therapy were far greater than what we now see with the advent of highly effective and well-tolerated DAAs. In

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addition, because of the high cost of DAAs, payers are equally concerned about providing unnecessary treatment to patients who may ultimately not require therapy. No prior analyses have looked specifically at weighing the savings associated with monitoring for spontaneous HCV clearance against the clinical benefits and cost reduction seen with shorter duration therapy in the treatment of acute HCV infection.

In this study, we performed a modeling-based analysis and demonstrated that treatment with DAA therapy in acute HCV infection can be a cost-effective, and in fact cost-saving strategy in the majority of scenarios. We sought to incorporate conservative estimates throughout our model to prevent overestimation of acute HCV treatment benefits. We used low values for SVR rates in acute treatment, and did not take into account the decrement in quality of life that can be experienced by patients with acute HCV when therapy is not offered. In addition, all patients in our base cohort that developed chronic HCV were treated with 8 weeks of DAA therapy, despite a subset for which 12 weeks of therapy may still be recommended under current guidelines (44).

Our study has several limitations. First, the duration of treatment in acute HCV infection was based on data obtained from a small number of pilot studies evaluating the treatment of acute HCV monoinfection with DAAs. However, given the robust data available on the efficacy seen with DAAs in chronic HCV, and the historic evidence that treatment of acute HCV results in higher SVR rates with shorter duration therapy, we anticipate that future investigations will find results that are comparable to the values used in our computations. Second, our analysis focused on a specific DAA regimen. We used price information for ledipasvir/sofosbuvir as model input, as this was the regimen utilized in the available studies evaluating DAAs in patients with acute

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genotype 1 HCV infection (13, 14). We realize that alternatives, such as highly-effective pan-genotypic treatment options, may prove to be the therapy of choice for many patients, including genotype 3 infections found commonly in PWID. These regimens will have their own price profile that could impact model inputs, however our sensitivity analysis on a wide range of drug prices did not alter study conclusions. If the duration of therapy difference holds true – 4 to 6 weeks in acute infection versus 8 to 12 weeks in chronic infection – then the cost-effectiveness argument supporting treatment in acute HCV can still be generalized to other drugs.

Identifying patients with acute HCV remains challenging in clinical practice. Most patients remain asymptomatic during this phase, and the diagnosis of acute HCV infection requires both active testing to identify seroconversion and repeated testing over time. This task is often difficult at baseline, without considering the added hurdle of accessing and retaining some of the more marginalized populations that are not well connected to health or social services. Nevertheless, these challenges should not deter discussions on treatment initiation in patients with acute HCV infection who do present to care. Additionally, our study results provide important data that can be used to further support the development of strategies aimed at enhancing early HCV detection.

The treatment of HCV infection continues to be a rapidly evolving field. Most studies to date focus on the treatment of patients with chronic infection, however further investigations into the treatment of acute HCV are needed. Furthermore, elimination of HCV is a stated objective made by the World Health Organization and the National Academy of Medicine in 2016 (45, 46). Important to this goal will be recognizing that in the United States this virus is not just

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concentrated among baby boomers, but also spreading rapidly in a new generation of Americans (47-50). Our results suggest that incorporation of acute HCV treatment in those who drive the bulk of transmission should be considered as part of the management algorithm in HCV infection.

Conclusion

Our modeling-based analysis finds that treatment of acute HCV infection can improve outcomes and be highly cost-effective or cost-saving compared with deferring treatment to the chronic phase. Given the need to halt the rising incidence of HCV infection, if future studies demonstrate that effective acute HCV cure can be achieved with shorter treatment durations, then it may be time to revisit treatment guidelines to incorporate recommendations that account for the clinical and economic benefits of acute HCV treatment in the era of DAAs.

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FIGURE LEGENDS

Figure 1. State-transition diagram for a microsimulation model evaluating acute versus chronic HCV treatment. At any given time a patient occupies one of the health states represented by rectangles/circles/ovals. Arrows between states represent possible transitions based on probabilities. As time progresses, patients can transition to other states and acquire costs and health-utilities associated with that state. The model stops when all patients transition to a death state. A patient can transition to a death state from any of the above states as the result of background mortality (these transitions are not shown in the figure for clarity).

Abbreviations: HCV, hepatitis C virus; DAA, direct-acting antiviral; SVR, sustained virologic response; F0–F4, METAVIR fibrosis score; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LRD, liver related death; LT, liver transplant.

Figure 2: Tornado diagrams for one-way sensitivity analyses of the incremental cost-effectiveness ratio (ICER). (A) Analysis for patients who are not at risk of transmitting HCV. (B) Analysis for patients who are at risk of transmitting HCV.

Abbreviations: p, probability; q, quality of life utility; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years; HCV, hepatitis C virus; DAA, direct-acting antiviral; SVR, sustained virologic response; F0–F4, METAVIR fibrosis score.

Figure 3. Two-way sensitivity analysis of the probability of spontaneous clearance and sustained virologic response (SVR) rates in acute HCV treatment. Displayed on the graphs are the regions in which varying combinations of these two parameters lead to cost-effective or cost-saving results. (A) Analysis for patients who are not at risk of transmitting HCV. (B) Analysis for patients who are at risk of transmitting HCV.

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years; HCV, hepatitis C virus; SVR, sustained virologic response.

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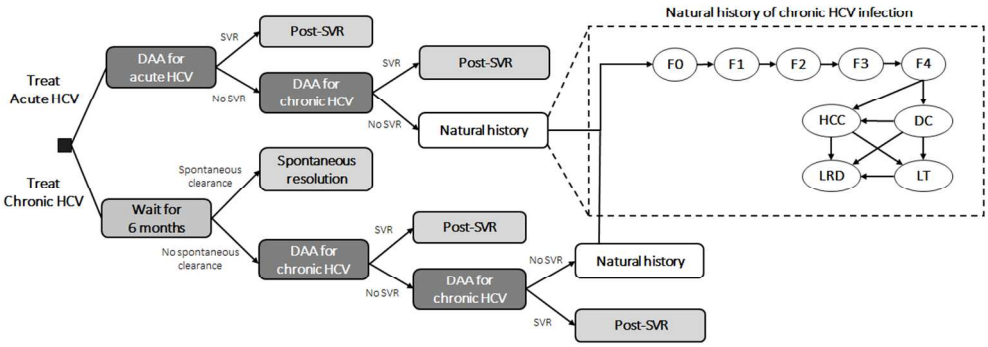

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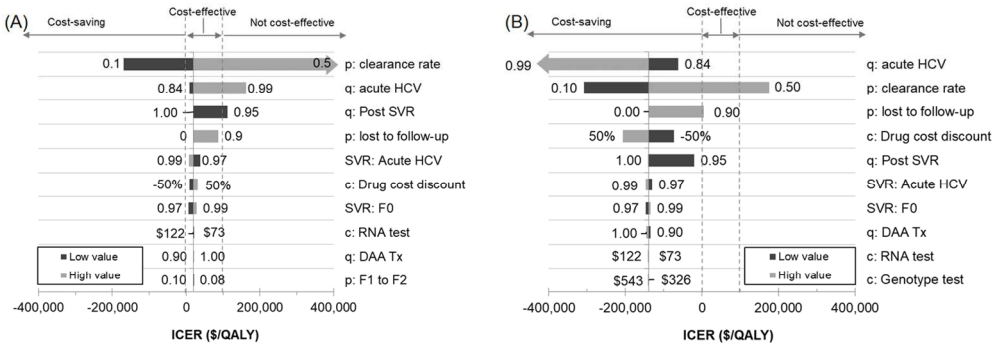

Figure 2: Tornado diagrams for one-way sensitivity analyses of the incremental cost-effectiveness ratio (ICER). (A) Analysis for patients who are not at risk of transmitting HCV. (B) Analysis for patients who are at risk of transmitting HCV. Abbreviations: p, probability; q, quality of life utility; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years; HCV, hepatitis C virus; DAA, direct-acting antiviral; SVR, sustained virologic response; F0–F4, METAVIR fibrosis score.

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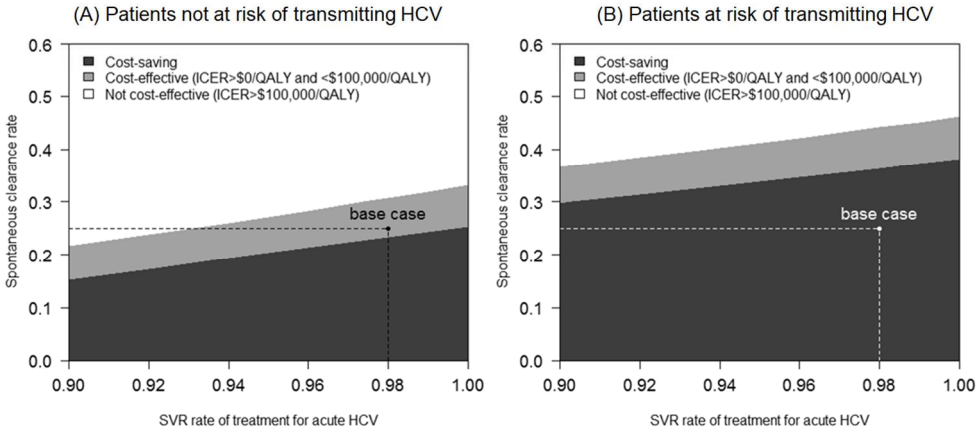

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Table 1: Model parameters: Baseline values, ranges, and distributions.

Input	Base Case	Range	Distribution	Parameter 1[a]	Parameter 2[b]
Study population					
Initial age (year) (4)	26				
Male % (4, 18)	64%				
Transition Probabilities (annual)					
F0 to F1 (24)	0.117	0.104–0.130	Beta	285.98	2158.26
F1 to F2 (24)	0.085	0.075–0.096	Beta	239.77	2581.00
F2 to F3 (24)	0.120	0.109–0.133	Beta	351.88	2580.45
F3 to F4 (24)	0.116	0.104–0.129	Beta	304.40	2319.73
F4 to DC (25)	0.039	0.010–0.079	Beta	4.87	120.08
F4 to HCC (25)	0.014	0.010–0.079	Beta	0.64	44.75
Post F4-SVR to DC (46)	0.008	0.002–0.036	Beta	0.87	107.97
Post F4-SVR to HCC (46)	0.005	0.002–0.013	Beta	3.28	653.57
DC to HCC (26)	0.068	0.030–0.083	Beta	24.48	335.51
DC to transplantation (29, 47)	0.023	0.010–0.062	Beta	3.04	128.93
DC (first year) to death from liver disease (26)	0.182	0.065–0.190	Beta	27.56	123.89
DC (subsequent year) to death from liver disease (26)	0.112	0.065–0.190	Beta	11.29	89.55
HCC to transplantation (27, 48)	0.040	0.000–0.140	Beta	1.21	29.13
HCC to death from liver disease (25)	0.427	0.330–0.860	Beta	5.52	7.41
Liver transplantation (first year) to death from liver disease (28)	0.116	0.060–0.420	Beta	1.35	10.31
Post-Liver transplantation to death from liver disease (28)	0.044	0.024–0.110	Beta	3.96	86.04
Spontaneous clearance rate (17)	0.25	0.1-0.5	Beta	4.44	13.31
Probability of lost to follow-up	0	0.0-1.0	Uniform	0.0	1.0
Number of transmission per person	0	0-0.2	Uniform	0.0	0.2

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Costs estimates					
Health state cost (annual)					
F0, F1 (33, 49)	775	±25%	Gamma	64.00	12.12
F2 (33, 49)	785	±25%	Gamma	64.00	12.12
F3 (33, 49)	1594	±25%	Gamma	64.00	12.27
Compensated Cirrhosis (33)	1859	±25%	Gamma	64.00	24.90
DC (33)	20,653	±25%	Gamma	64.00	29.04
HCC (33)	37,980	±25%	Gamma	64.00	322.71
Liver transplant (first year) (33)	109,826	±25%	Gamma	64.00	322.71
Post Liver transplant (33)	28,822	±25%	Gamma	64.00	593.44
Testing and treatment					
DAA drug cost per week (31)	7875				
RNA test cost (32)	98	±25%	Gamma	64.00	1.53
Genotype test cost (32)	435	±25%	Gamma	64.00	6.79
Health State Quality-of-Life Weights					
Multiplier for DAA treatment	0.95	0.90–1.00	Beta	71.25	3.75
Acute HCV [c]	0.93	0.84–0.99	Beta	42.12	3.17
F0, F1 (35)	0.93	0.84–0.99	Beta	42.12	3.17
F2, F3 (35)	0.93	0.84–0.99	Beta	42.12	3.17
Compensated Cirrhosis (35)	0.90	0.81–0.99	Beta	39.10	4.34
DC (35)	0.80	0.57–0.99	Beta	10.81	2.70
HCC (35)	0.79	0.54–0.99	Beta	9.57	2.54
Post Liver transplant (35)	0.84	0.77–0.93	Beta	69.72	13.28
Post SVR	1.00	0.95–1.00	Beta	61.74	0.62
SVR					
Treatment for chronic HCV (11)	0.981	0.968-0.990	Beta	603.48	11.69
Treatment for acute HCV [d]	0.981	0.968-0.990	Beta	603.48	11.69
SVR decrement (for sensitivity	0%	0%–15%	Uniform	--	--

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analysis) (50)

Abbreviations: SVR, sustained virologic response; F0–F4, METAVIR fibrosis score; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; F4-SVR, post-SVR state of cirrhotic patient; IFN, interferon; oSOC, old standard of care; SOF, sofosbuvir; LDV, ledipasvir

[a] Parameter 1 corresponds to α parameter for beta distribution and k (shape) parameter for gamma distribution

[b] Parameter 2 corresponds to β parameter for beta distribution and θ (scale) parameter for gamma distribution

[c] Assume the same quality of life weight as F0 state.

[d] Assume that the SVR rates were the same for treating chronic and acute HCV.

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Table 2. Cost-effectiveness results of treating hepatitis C virus in the acute versus chronic phase of infection

Outcomes for patients who are not at risk of transmitting HCV				
		Duration for acute HCV treatment		
		4 weeks	6 weeks	8 weeks
Duration for chronic HCV treatment		Incremental ICER ($/QALY)		
	6 weeks	-62,448	268,808	701,056
	8 weeks	-260,128	**19,991**	401,679
	12 weeks	-615,549	-413,060	-131,617
		Incremental QALY		
	6 weeks	0.03	0.02	0.02
	8 weeks	0.03	**0.02**	0.02
	12 weeks	0.03	0.03	0.02
		Incremental Cost ($)		
	6 weeks	-1,620	6,226	14,070
	8 weeks	-7,382	**483**	8,322
	12 weeks	-18,851	-10,996	-3,159

Outcomes for patients who are at risk of transmitting HCV				
		Duration for acute HCV treatment		
		4 weeks	6 weeks	8 weeks
Duration for chronic HCV treatment		Incremental ICER ($/QALY)		
	6 weeks	-161,146	84,074	383,327
	8 weeks	-343,622	**-139,548**	123,366
	12 weeks	-678,589	-529,308	-326,480
		Incremental QALY		
	6 weeks	0.03	0.03	0.02
	8 weeks	0.03	**0.03**	0.02
	12 weeks	0.03	0.03	0.03
		Incremental Cost ($)		
	6 weeks	-4,424	2,114	8,650
	8 weeks	-10,209	**-3,655**	2,878
	12 weeks	-21,728	-15,183	-8,651

Base case results – comparing 6 weeks of acute HCV treatment with 8 weeks of chronic HCV treatment – are highlighted in grey in the above table. Abbreviations: HCV, hepatitis C virus; QALY, quality adjusted life year; ICER, incremental cost effectiveness ratio.

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Supplementary Materials

eFigure 1. Sensitivity analysis on the number of infections during the acute HCV phase for patients who are at risk of transmitting HCV.

eTable 1. Sensitivity analysis on initial age and model horizon.

eFigure 2. Scenario analysis on the probability of lost to follow-up.

eFigure 3. Cost-effectiveness acceptability curve for probabilistic sensitivity analysis.

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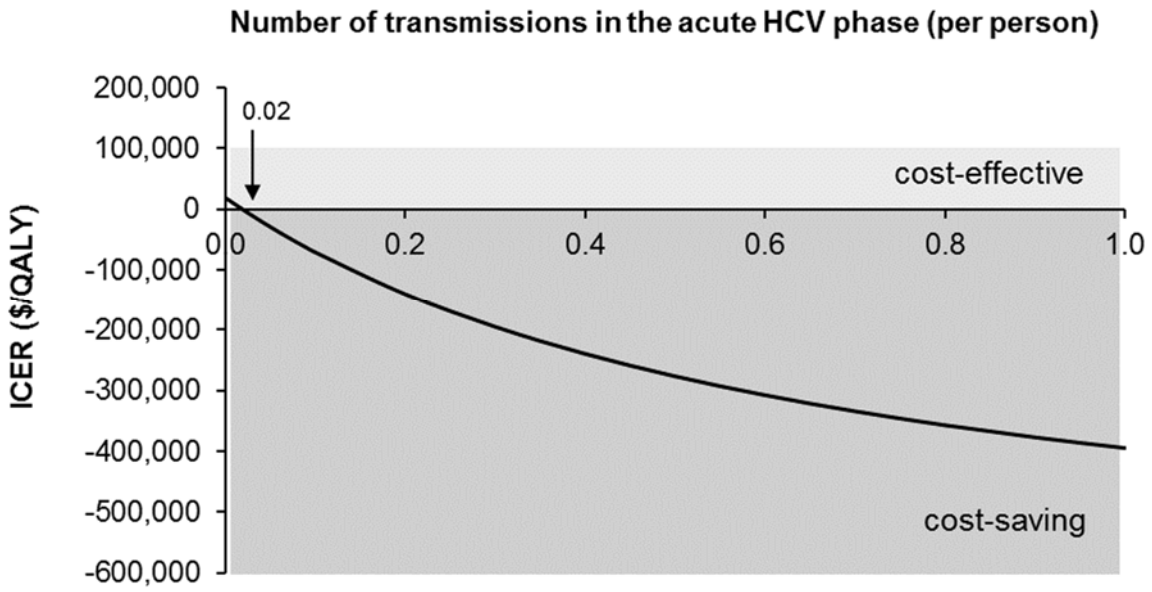

eFigure 1. Sensitivity analysis on the number of infections during the acute HCV phase for patients who are at risk of transmitting HCV. Treating acute HCV versus deferring treatment until the chronic phase was cost-saving even when the number of new infections transmitted was as low as 0.02, and greater cost-saving was achieved as the number of new infections transmitted by people with acute HCV infection increased.

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years; HCV, hepatitis C virus; SVR, sustained virologic response.

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eTable 1. Sensitivity analysis on initial age and model horizon

	Treatment for chronic HCV (F0)		Treatment for acute HCV				
	QALY	Cost ($)	QALY	Cost ($)	Incremental QALY	Incremental Cost ($)	ICER ($/QALY)
Initial age (year)							
20	22.04	24,347	22.07	24,830	0.025	483	19,118
30	19.56	24,342	19.58	24,826	0.029	484	16,891
40	16.37	24,309	16.39	24,820	0.027	511	18,810
50	12.99	24,215	13.01	24,803	0.022	589	27,040
60	9.65	24,033	9.67	24,776	0.019	743	39,470
Model horizon							
1	0.89	24,332	0.91	24,810	0.02	477	22,281
5	4.21	24,333	4.24	24,811	0.02	478	19,731
10	7.78	24,334	7.81	24,813	0.02	479	20,295
20	13.24	24,338	13.27	24,817	0.02	480	19,953
30	16.88	24,340	16.91	24,820	0.02	480	19,523
40	19.10	24,342	19.13	24,824	0.03	482	19,247
Life time (base case)	20.66	24,344	20.68	24,827	0.02	483	19,991
Background mortality							
Base case*	20.66	24,344	20.68	24,827	0.024	483	19,991
10% increase	20.38	24,339	20.41	24,826	0.025	487	19,833
20% increase	20.12	24,334	20.14	24,825	0.024	491	20,471
50% increase	19.42	24,322	19.45	24,823	0.026	502	19,577
100% increase	18.47	24,301	18.49	24,820	0.025	518	21,082
150% increase	17.68	24,282	17.71	24,816	0.024	534	21,943

* For the base case analysis, hazard ratio of 2.58 for men and 1.97 for women were used to account for higher background mortality in the acute HCV patient population compared to the general US population.

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years; HCV, hepatitis C virus.

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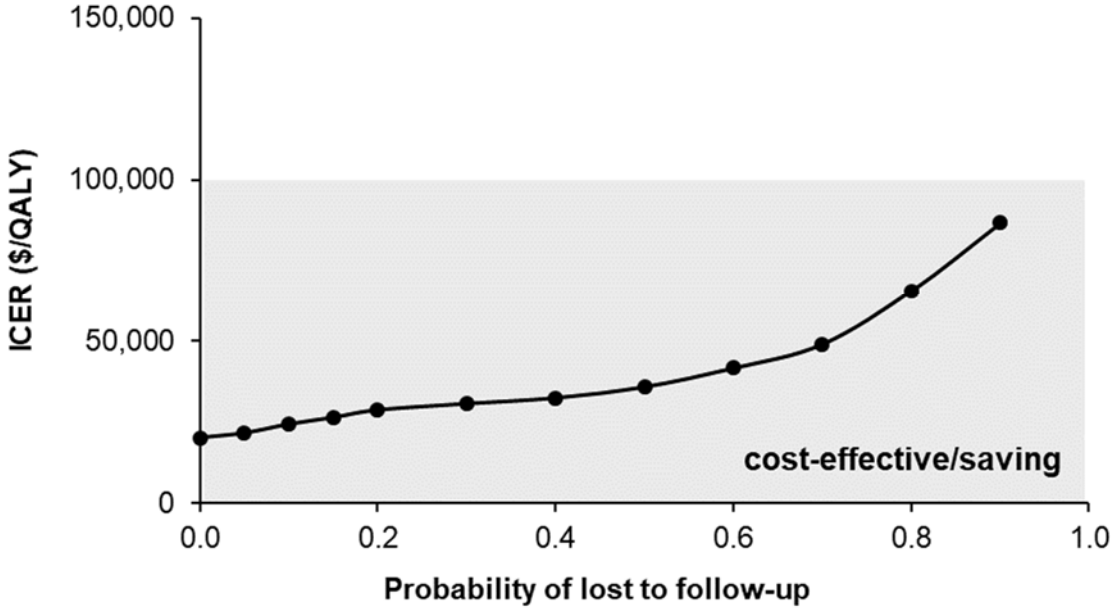

eFigure 2. Scenario analysis on the probability of lost to follow-up. Treating acute HCV remained cost-effective/saving with a loss to follow-up probability as high as 90%

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years; HCV, hepatitis C virus; SVR, sustained virologic response.

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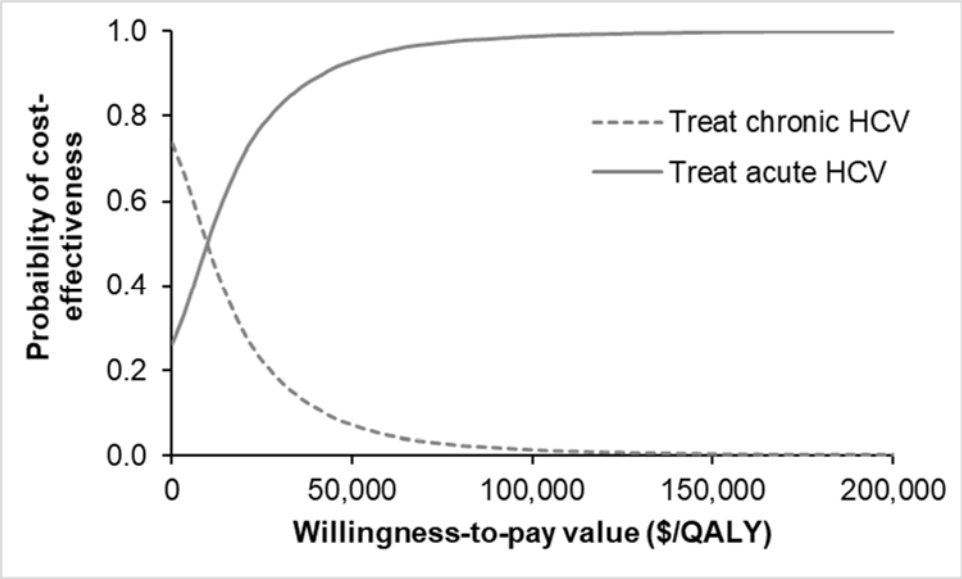

eFigure 3: Cost-effectiveness acceptability curve for probabilistic sensitivity analysis. Treating acute HCV was either cost-effective or cost-saving with a probability of 98.61% using a willingness-to-pay threshold of $100,000 per quality-adjusted life years.

Abbreviations: QALY, quality adjusted life years; HCV, hepatitis C virus

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