Supplementary appendix: Cost-effectiveness of hepatitis C treatment for patients in early stages of liver disease

Contents of Supplementary Appendix

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Appendix A. Natural mortality probabilities

Since the cost-effectiveness model uses a single-year time-step, five-year probabilities (P_{5yr}) for natural mortality at a given age group were taken from literature[1] and converted to annual probabilities (P_{1yr}) according to the following:

[1] $P_{1yr} = 1 - (1 - P_{5yr}) \wedge (1/5)$

These one-year probabilities are then associated with patients belonging to a particular age group (Table A1).

Table A1. Annual probabilities of a natural mortality given a patient's age.*

Age Group	Probability
18-20	0.000
20-25	0.001
26-30	0.001
31-35	0.001
36-40	0.001
41-45	0.002
46-50	0.003
51-55	0.005
56-60	0.007
60-65	0.010
66-70	0.015
71-75	0.024
76-80	0.038
81-85	0.062
86-90	0.107
91-95	0.174
96-120	0.263

* Source of mortality rates is National Vital Statistics Reports.[1]

Appendix B. Fibrosis progression rate estimation

State transitions between stages of liver disease have been estimated in the literature many times.[2-5] We chose to estimate progression rates from the Chronic Hepatitis Cohort Study (CHeCS)[6] because the CHeCS cohort contains a relatively large number of hepatitis C mono-infected individuals from the US who are born between 1945 and 1965, which is the population of greatest interest to our study. Simple statistics about the biopsy records from CHeCS are presented in Table B1.

Table B1. Descriptive statistics of biopsy scores among hepatitis C patients from the Chronic Hepatitis Cohort Study (CHeCS) by fibrosis level.

Fibrosis stage	N	Portion
0	466	0.199
1	614	0.263
2	414	0.177
3	234	0.100
4	611	0.261
All	2339	1.000

Mean biopsy score:	1.96
Mean patient age:	49.59

The procedure used to estimate the progression rates from biopsy scores is described in detail by Yi et al.[2] Our implementation of the Yi et al.[2] estimation procedure carries two assumptions worth additional discussion. First, for a given sample of biopsies the average infection period is assumed to be the same for all biopsy scores. For this reason, we only estimate progression rates from CHeCS using each patient's first biopsy. Using the second and third biopsies would not be reasonable given the estimation procedure's necessary assumption of a single, average infection period. The second assumption is that initial fibrosis levels (fibrosis at the time of infection) is assumed to be F0. And by extension, this assumption imposes progression-only direction of disease development (i.e., any fibrosis regression cannot be accommodated). Estimation results are presented in Table B2.

Table B2. Stage-specific fibrosis progression transition probabilities estimated from hepatitis C patients in the Chronic Hepatitis Cohort Study (CHeCS) using the maximum likelihood method described by Yi et al.[2] *

Assuming infection period is 25 years

Liver Disease Stage Transition Parameter	Estimated transition probability	SE	Approximate 95% Confidence Interval	
			Low	High
F0 to F1	0.065	0.003	0.059	0.070
F1 to F2	0.081	0.005	0.071	0.091
F2 to F3	0.128	0.011	0.106	0.149
F3 to F4	0.214	0.025	0.165	0.262

* These estimations assume an average infection period of 25 years. The average age of biopsied patients in CHeCS is 49.6 years. SE refers to standard error.

As a check on the use of progression rates estimated from CHeCS, Table B3 presents annual transition probabilities between liver disease stages, calculated from CHeCS-based progression rates and also from recent sources from a meta-analysis of stage transition probabilities by Thein et al.[3] The CHeCS-based rates are comparable to those developed in the literature. For this study, neither the disease progression rates from CHeCS nor those from the literature are adjusted for any characteristics, such as gender, age, or alcohol consumption. In this way, the disease progression rates estimated from CHeCS include the effects of all patient-level characteristics that may influence disease progression.

Table B3 ensures us that CHeCS-based rates are reasonable given previous estimates from the literature. We also evaluate the cost-effectiveness model with CHeCS-based rates and literature-based rates to investigate whether the rates imply any economically-significant differences in outcomes. Those model results are presented in Table B4. The most important outcome in Table B4 is that the values are similar when comparing scenarios that utilize CHeCS-based transition probabilities and transition probabilities based on the "Mid" values from Thein et al.[3] Since the CHeCS-based rates are slightly lower than the "Mid" values from the literature, the cost effectiveness ratios using the

progression rates calculated from CHeCS data are slightly higher. In our model, lower rates of disease progression produce lower disease burdens and thereby yield higher (i.e., less desirable) cost-effectiveness ratios with respect to early treatment. This pattern can be observed in the "Low" and "High" progression rate-based scenarios. The greatest cost effectiveness ratios are produced using the lowest progression rate assumptions ("Low" from Thein et al.), and the smallest cost-effectiveness ratios are produced using the most rapid progression rate assumptions ("High" from Thein et al.). Notice in all but the "High" scenario, comparing treatment at F1 to F2 results in a dominated strategy when a patient starts at F0.

Table B3. Annual transition probabilities for liver disease stages from CHeCS and literature sources.[3]

Liver disease stage transition parameter	Thein et al. (2008) [3]			
	CHeCS	Mid	Low	High
F0 to F1	0.065	0.117	0.041	0.155
F1 to F2	0.081	0.085	0.044	0.111
F2 to F3	0.128	0.120	0.092	0.201
F3 to F4	0.214	0.116	0.068	0.187

Table B4. Cost-effectiveness results for treatment of hepatitis C patients in early stages of liver disease using different estimates for transition probabilities for liver disease stages.

Source of liver disease stage transitions		*Incremental CE Ratios ($/QALY)*					
		Patients starting at F0			Patients starting at F1		Patients starting at F2
		Tx at F2 vs. F3	Tx at F1 vs. F2	Tx at F0 vs. F2	Tx at F2 vs. F3	Tx at F1 vs. F2	Tx at F2 vs. F3
CHeCS		97,891	[a]	242,856	59,482	174,104	37,349
Thein et al. (2008)[3]	Mid	136,338	[a]	232,327	97,385	197,306	64,929
	Low	274,335	[a]	288,057	180,824	251,072	112,339
	High	54,549	164,701	196,140 [b]	39,096	133,667	26,365

[a.] Treating at F1 vs F2 is weakly dominated in this scenario by treating at F0 vs F1, so the appropriate ICER to calculate compares treatment at F0 vs F2.
[b.] This ICER represents treatment at F0 vs F1 because for these assumptions on liver disease stage transitions, treatment at F0 vs F1 did not dominate treatment at F1 vs F2.

Appendix C. The effect of HCV-infection status on developing ESLD

Recent studies have investigated the effect of HCV-infection status on the development of end stage liver disease, in particular hepatocellular carcinoma[7,8] and decompensated cirrhosis.[8] To adjust the transition probability from compensated cirrhosis to ESLD for HCV-uninfected patients, we calculate the proportional difference in published transition probabilities between infected and uninfected patients from Morgan et al. for liver cancer[7] and van der Meer et al. for decompensated cirrhosis.[8] This proportional difference is applied to the transition probabilities calculated from HCV-infected patients in CHeCS, which is described in Appendix C to produce the model parameter for the probability of transitioning from compensated cirrhosis (F4) to one of the ESLD states.

Table C1. Annual transition probabilities from compensated cirrhosis to end stage liver disease used to calculate the effect of a sustained virologic response

Annual transition probabilities from decompensated cirrhosis to hepatocellular carcinoma			
Infected	Uninfected (SVR)	Proportional Difference	Source
0.178	0.042	0.764	[7]
Annual transition probabilities from compensated to decompensated cirrhosis			
Infected	Uninfected (SVR)	Proportional Difference	Source
0.036	0.003	0.913	[8]

Appendix D. Effect of HCV status and ESLD on quality adjusted life years

In the base case scenario, HCV-infected patients are subjected to a reduction in quality of life of 2% relative to HCV-uninfected (Table D1). This is implemented in the model by using a multiplier of 0.98 on QALYs for HCV-infected individuals; which is to say, 0.98 is multiplied by the HCV-uninfected QALY value associated with a given liver disease stage. An assumption that HCV infection status confers reductions in quality of life is consistent with previously published cost-effectiveness studies[9,10,11] as well as previous studies that measure health related quality of life.[12-14] In particular, our model is a clinical model, where HCV infection status is presumed to be known by the patient. So even though some studies have found negligible quality of life reductions associated with HCV-infected patients when the patient's HCV infection status is unknown to them,[15] our model only considers patients who have been diagnosed. As diagnosed patients, they may incur physical as well as psychological reductions in their quality of life due to either the knowledge of their HCV infection status, or the physical symptoms of infection, or both. Studies have documented the harmful effects of HCV infection on a patient's psychological well-being[16] as well as reductions in health related quality of life measurements following a positive diagnosis.[17] Furthermore, a portion of the reductions in quality of life from hepatitis C have been documented to rebound, or recover, following successful treatment and a patient's achieving a sustained virologic response.[18]

Table D1. Parameter values for quality adjusted life years.

Parameter description	Relevant fibrosis or ESLD stage(s)	Values: Base case	Low	High	Source(s)
Annual QALY values					
HCV-uninfected patients	0, 1, 2, 3	0.88	0.72	1.00	[9,19]
	4	0.73	0.55	0.89	
HCV-infected patients	0, 1, 2, 3	0.86	0.72	0.95	
	4	0.73	0.55	0.89	
Patients with end stage liver disease	HCC	0.38	0.09	0.81	
	DC	0.60	0.45	0.81	
	LT	0.66	0.45	0.86	
Adjustment to QALYs relative to HCV-uninfected patients					
HCV-infected patients	0, 1, 2, 3	0.98	0.72	1.00	Computed from above
	4	0.98	0.62	1.00	
Patients with end stage liver disease	HCC	0.52	0.10	0.91	
	DC	0.82	0.51	0.91	
	LT	0.90	0.51	0.97	

Appendix E. Cost-effectiveness calculations

Cost-effectiveness analysis has been used to evaluate health care interventions for decades.[20] This study applies these standard methods to a set of HCV-related treatment policies. The HCV treatment policies were characterized by the stage of liver fibrosis that a patient initiates HCV treatment. Those stages were defined as being at F0, F1, F2, F3, or F4. After costs and health outcomes were estimated with the model, any pair of policies could be evaluated using the formula for incremental (or marginal) cost effectiveness:[21,22]

[1] $(Cost_A - Cost_B)/(Outcomes_A - Outcomes_B)$.

Policy A and policy B could be, for example, initiating therapy at F2 and initiating therapy at F3. The costs and outcomes used in equation 1 were estimated in the model using equations 2 and 3:

[2] $Cost_A = \sum_t \left(\left(\sum_{f,p} \left(F_{f,p} Cost_{f,p} \right) + \sum_v (V_v Cost_v) + \sum_{tx} (Tx_{tx} Cost_{tx}) \right) (1+d)^{-t} \right)$.

The per-person non-treatment-related medical costs ($Cost_{f,p}$) at each stage of liver disease, *f*, in each population compartment, *p*, were multiplied by the population level ($F_{f,p}$) in each stage and compartment. Similarly, the per-person non-treatment-related medical costs ($Cost_v$) associated with of the end stage liver disease states (*v*) were multiplied by the appropriate population size (V_v). Per-person treatment costs ($Cost_{tx}$) were multiplied the number of patients in treatment (Tx_{tx}) in each of the two possible treatment compartments, represented by tx. These three values were summed together for every year (*t*) and adjusted to present values terms according to the discount rate (*d*).

[3] $QALY_A = \sum_t \left(\left(\sum_{f,p} \left(F_{f,p} QALY_{f,p} \right) + \sum_v (V_v QALY_v) \right) (1+d)^{-t} \right)$.

Equation 3 sums up the QALYs from all the population compartments (*p*), early stage liver disease states (*f*), and end stage liver disease states (*v*). These annual amounts were discounted every

year (*t*) at the discount rate (*d*). The costs and QALY values for comparator policy, such as policy B represented in equation 1, were calculated using the same equations as 2 and 3.

For this cost-effectiveness study, we used a societal perspective, which included all medical costs regardless of who incurred the costs and the quality of life of the patients. For this study, we did not include productivity costs, patient time or travel costs, for which data were not available. All future outcomes, including costs and QALYs were discounted at 3%. All costs were adjusted to US$2012 using the health care component of the Personal Consumption Expenditure index.[23]

Appendix F. Comparing immediate treatment to no treatment

Some clinicians may be interested in results that represent a situation where delaying treatment is not an option. In such a case, the choice must be made to initiate HCV treatment at diagnosis or forego treatment altogether. Table F1 presents results centered on this possibility. Average cost-effectiveness ratios are calculated comparing treatment at a given fibrosis level to a no-treatment scenario.

Table F1. Base case results from cost effectiveness model for a 55 year old HCV patient where treatment at a given fibrosis stage is compared to no treatment at all in US$2012.

	Patients starting at F0		Patients starting at F1		Patients starting at F2	
	No Tx	Tx at F0	No Tx	Tx at F1	No Tx	Tx at F2
Non-treatment costs ($)	13,651	7,855	20,173	7,977	30,479	8,820
Discounted treatment costs ($)	-	105,293	-	105,180	-	104,731
Total costs ($)	13,651	113,149	20,173	113,157	30,479	113,551
Liver disease-related deaths	0.05	0.00	0.14	0.00	0.28	0.01
QALYs	15.45	16.37	14.37	16.35	12.34	16.22
Treatment policies compared:		Tx at F0 vs. No Tx		Tx at F1 vs.No Tx		Tx at F2 vs. No Tx
Average CE Ratio ($/Averted death)		1,839,778		675,307		309,680
Average CE Ratio ($/QALY)		108,774		47,014		21,409

Appendix G: Additional sensitivity analyses

In addition to the sensitivity analyses presented in the main text, we also conducted additional multi-way sensitivity analyses which are presented in this appendix. We varied all epidemiologic parameters simultaneously such that all epidemiologic parameters were assumed to be favorable to treatment or unfavorable to treatment. Broad ranges were found between the ICERs values calculated from scenarios assuming high and low (or favorable and unfavorable) parameter assumptions when both economic and epidemiologic parameters were varied together. For the scenarios where patients were diagnosed and treated at F0, the largest ranges were found when the following parameter groups were varied: quality of life assumptions ($14,300/QALY and $211,782,000/QALY), treatment costs ($77,100/QALY and $793,500), and the discount rate ($34,200/QALY and $693,600/QALY) (Table G1).

Table G1. Results of multi-way sensitivity analyses on health economic parameters stratified by scenarios that are favorable and unfavorable with respect to the epidemiologic parameters.*

		Scenarios on all epidemiologic parameters					
		Epidemiologic parameters favors Tx			Epidemiologic parameters disfavors Tx		
Parameter group varied	Parameter scenario	Patients with F0, Tx at F0 vs. F1	Patients with F1, Tx at F1 vs. F2	Patients with F2, Tx at F2 vs. F3	Patients with F0, Tx at F0 vs. F1	Patients with F1, Tx at F1 vs. F2	Patients with F2, Tx at F2 vs. F3
All health economic parameters	Base case	158,666	79,638	10,983	527,383†	457,926	207,340
Medical costs for chronic liver disease	Low	156,100	78,464	10,860	524,308†	455,131	208,118
	High	118,838	55,218	Cost-saving	480,310†	409,470	141,634
Medical costs for ESLD	Low	159,112	81,110	13,118	527,407†	458,023	208,400
	High	158,034	77,556	7,962	527,350†	457,791	205,855
Treatment costs	Low	77,061	37,855	3,891	261,259†	226,458	100,240
	High	240,270	121,421	18,075	793,507†	689,394	314,440
Quality of life assumptions‡	Favors Tx	14,340†	12,755	5,546	38,097†	34,233	28,137
	Disfavor Tx	1,036,709	158,019	14,091	211,782,018	9,116,268	390,328
Discount rate	Low	34,209	16,896	559	300,598†	214,998	56,554
	High	251,099	137,546	22,660	693,627†	632,865	332,285

* This table presents the incremental cost effectiveness ratios comparing two scenarios under a variety of parameter assumptions. For example, the first value in the row labeled "Liver disease stage transitions / Low" is $288,100, which states the incremental cost per QALY attained (the incremental cost-effectiveness ratio) for a patient with a starting fibrosis level of F0 is $288,100 when comparing initiating treatment at F0 versus initiating treatment at F1 (i.e., Tx at F0 vs. F1). Sensitivity analyses are organized by parameter group, assuming a 55-year-old hepatitis C patient, with treatment of hepatitis C characterized by a generalized all-oral, direct-acting antiviral. All costs are in US$2012. To simplify presentation, all numbers were rounded to nearest hundred. F0, F1, F2, and F3 = stages of liver disease; ESLD = end stage liver disease; QALY = quality-adjusted life-year; Tx = treatment.

† In these scenarios, treatment at F1 is dominated by treatment at F0 so the ICERs presented compare treatment at F0 with treatment at F2.

‡ Within the "Quality of life assumptions" scenarios, the favorable scenario uses the high values for QALY (Table 1) associated with being HCV-uninfected and uses the low value for the QALY multiplier (Table 1), thereby maximizing the difference between quality of life among infected and uninfected populations.

Appendix H. Additional threshold analyses

In this appendix, additional threshold analyses were conducted, where important assumptions in the model were varied. In particular, we solved for the threshold treatment cost, as was done in Figure 2 of the main text, while assuming high and low values for specific parameter groups and using two different ICER targets. The two ICER targets are $50,000/QALY and $100,000/QALY. From these results, a large range of treatment cost thresholds is observed. When just the QALY parameter values are varied, the treatment cost threshold ranges from $2,427 to $259,694 among the scenarios yielding $50,000/QALY. The results that yielded $100,000/QALY (final column in Table H1) produce greater threshold treatment cost values because the ICER target has doubled from $50,000/QALY to $100,000/QALY.

Table H1. Results of threshold analyses to identify the treatment cost necessary to yield a incremental cost-effectiveness ratio of $50,000/QALY and $100,000/QALY for the treatment of a patient with liver fibrosis of F0, assuming high and low values of several parameter groups.*

Parameter group varied		Threshold treatment cost ($US2012) ICER = $50,000/QALY	Threshold treatment cost ($US2012) ICER = $100,000/QALY
None	Base case[a]	22,210	42,378
Epidemiological parameters			
Liver disease stage transitions	Low[a]	18,724	35,795
	High	27,352	52,208
Treatment effectiveness	Low	12,383	23,663
	High[a]	24,467	46,695
ESLD transitions	Low[a]	21,904	41,797
	High	22,929	43,825
Disease-induced deaths	Low[a]	22,178	42,246
	High[a]	22,241	42,477
Health economic parameters			
Non-treatment medical costs	Low[a]	23,232	43,400
	High	41,352	61,651
ESLD medical costs	Low[a]	22,133	42,301
	High[a]	22,334	42,502
Quality of life assumptions	Favor Tx[a]	259,694	517,347
	Disfavor Tx	2,427	2,878
Discount rate	Low[a]	47,280	90,172
	High	15,735	30,076

* All costs are presented as US$2012. For example, in the row labeled "Treatment effectiveness" / "Low" the value 12,383 indicates a treatment cost of $12,383 per year (or per complete dose) yields a incremental cost effectiveness ratio of $50,000/QALY for the treatment of patients in F0 relative to F2 for a hepatitis C patient who is 55 years old. F0, F1, F2, F3, F4 = stages of liver disease; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year.

[a.] Treatment policies being compared are F0 vs. F2, because treatment at F0 dominates treatment at F1. In all other cases, the policies being compared are F0 vs. F1.

We also investigated the treatment cost thresholds under different levels of fibrosis and patient ages (Table H2). The treatment cost thresholds among patients diagnosed with F2 liver fibrosis are greater than the corresponding treatment cost thresholds for patients diagnosed at F1 or F0. In general, a patient diagnosed in a later stage of liver disease (e.g., diagnosed at F1 or F2 relative to diagnosed at F0) are more likely to progress to end stage liver disease sequelae. Therefore, the benefits to a successful

treatment are greater and the treatment cost that yields a given cost-effectiveness threshold are greater. These results indicate that the range treatment costs that yield a particular cost-effective threshold vary substantially across fibrosis level, patient age, and the assumed cost-effectiveness threshold.

Table H2. Results of threshold analyses to identify the treatment cost necessary to yield a incremental cost-effectiveness ratio of $50,000/QALY and $100,000/QALY for the treatment of a patient with liver fibrosis of F0, F1, F2, F3, and F4, where patients are also stratified by age groups.*

ICER = $50,000/QALY

Patient fibrosis level	35 year old	45 year old	55 year old	65 year old
Fibrosis at F0, treated at F0	30,201	26,843	22,210 [a]	15,907 [a]
Fibrosis at F1, treated at F1	47,281	39,678	30,866	21,392
Fibrosis at F2, treated at F2	237,599	184,633	128,835	76,089
Fibrosis at F3, treated at F3	1,254,419	994,841	713,556	433,003
Fibrosis at F4, treated at F4	331,725	277,236	214,241	146,588

ICER = $100,000/QALY

Patient fibrosis level	35 year old	45 year old	55 year old	65 year old
Fibrosis at F0, treated at F0	57,727	51,305	42,378	30,362
Fibrosis at F1, treated at F1	90,066	75,519	58,719	40,699
Fibrosis at F2, treated at F2	450,769	349,162	242,802	142,927
Fibrosis at F3, treated at F3	2,380,306	1,880,715	1,342,951	810,722
Fibrosis at F4, treated at F4	655,590	544,758	417,378	281,868

* All costs are presented as US$2012. For example, in the row labeled "Fibrosis at F1, treated at F1" the value 47,281 indicates a treatment cost of $47,281 per year (or per complete dose) yields an incremental cost effectiveness ratio of $50,000/QALY for the treatment of patients in F1 relative to treatment in F2 for a hepatitis C patient who is 35 years old. F0, F1, F2, F3, F4 = stages of liver disease; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year.
[a.] Treatment policies being compared are F0 vs. F2, because treatment at F0 dominates treatment at F1. In all other cases, the policies being compared are F0 vs. F1.

Appendix I. Additional notes

Recent cost-effectiveness analyses have looked at HCV screening practices[24,25] and the implications of the latest generation of HCV pharmaceuticals, known as direct acting antivirals or protease inhibitors.[26-29] Although we know of no other study to assess the cost-effectiveness of HCV treatment by liver disease stage at diagnosis using treatment cost and treatment effectiveness parameter values relevant to the newer generation pharmaceuticals for HCV treatment, our results are generally consistent with other recent assessments of the cost-effectiveness of HCV treatment scenarios.[27,30,31] For example, the incremental cost-effectiveness of triple therapy using direct-acting antivirals (without stratifying for liver disease stage) was between $29,200 and $88,900 per QALY when comparing triple therapy to dual therapy, assuming a lower treatment cost than we posit for current all-oral therapies.[27] Another recent study finds the cost effectiveness of triple therapy to be between $62,900 and $102,600 per QALY when comparing triple therapy to dual therapy among mildly fibrotic patients, and between $32,800 and $54,100 per QALY when comparing triple therapy to dual therapy among patients with advanced fibrosis.[31] In similar fashion, a study that compares all-oral therapy to conventional therapy (dual therapy for genotypes 2/3 and triple therapy for genotype 1) does so without specific regard to the incremental cost effectiveness of treatment at different fibrosis level.[26] In their base case, they find the cost effectiveness of all oral therapy versus triple therapy to be $44,500 per QALY.[26] Their study assumes an all-oral therapy regimen is similar in cost and in some cases less expensive than triple therapy, which would contribute lower cost-effectiveness ratios than would be produced using our base case assumptions. Both studies[26,31] differ from our study because they evaluate different therapy types (comparing all-oral therapy to triple therapy or comparing triple therapy to dual therapy) while assuming a given distribution of fibrosis levels for their modeled population. Our study assumes a generalized

treatment type (characterized by treatment cost and effectiveness) and evaluates the scheduling of this treatment with respect to liver disease progression.

The progression rates we used carry the assumptions that liver fibrosis regression does not occur among HCV-infected or HCV-uninfected patients, and that fibrosis progression does not occur among HCV-uninfected patients. Evidence for fibrosis regression, particularly among HCV-uninfected patients, is growing.[32,33] Including the possibility of fibrosis regression among HCV-uninfected patients would make HCV treatment even more beneficial and might have improved the relative cost-effectiveness of earlier initiation of treatment. Evidence is also growing for mortality associated with HCV-infected individuals for causes other than liver-related diseases.[34] The current model assumes HCV-related deaths occur only during the most advanced stages of liver diseases. If HCV infection causes or contributes to premature deaths from non-liver-related causes among patients, then our model's estimates of disease-related deaths are low and treatment cost-effectiveness may be underestimated. Finally, due to the focus of this study on the US baby-boomer cohort, this model considers neither the potential for re-acquiring infection (through on-going drug use) nor any herd-immunity effects among sustained responders who continue to inject drugs. The magnitude of these forces remains the subject of discussion[35-37] and may also vary between the context, location, and scope of a given study. As with the omission of fibrosis regression and additional non-liver-related mortalities, inclusion of herd immunity effects may make treatment more beneficial and thereby improve treatment cost-effectiveness. Since the threshold analysis assumes a given cost-effectiveness ratio and estimates a cost-effective level for a given model parameter (i.e., treatment cost), by underestimating treatment cost-effectiveness (via omitting of fibrosis regression, excess mortality, and herd immunity) we may under-estimate the corresponding threshold levels of treatment cost. Since fibrosis regression and excess mortality are emerging ideas in hepatitis C research, there was no

widespread consensus on possible parameter values, therefore we judged the inclusion of these aspects in the cost-effectiveness model would be too tenuous until further consensus developed. In the case of herd-immunity, this aspect of viral hepatitis seemed to be an inappropriate assumption for our population of interest, who are older in age and presumed to be no longer susceptible to re-infection because either their risk behaviors have changed since their initial infection or the conduit for their infection (i.e., contaminated blood transfusion) has been resolved.

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