Van Nuys K, Brookmeyer R, Chou JW, Dreyfus D, Dieterich D, Goldman DP. Broad hepatitis C treatment scenarios return substantial health gains, but capacity is a concern. Health Aff (Millwood). 2015;34(10).

Appendix

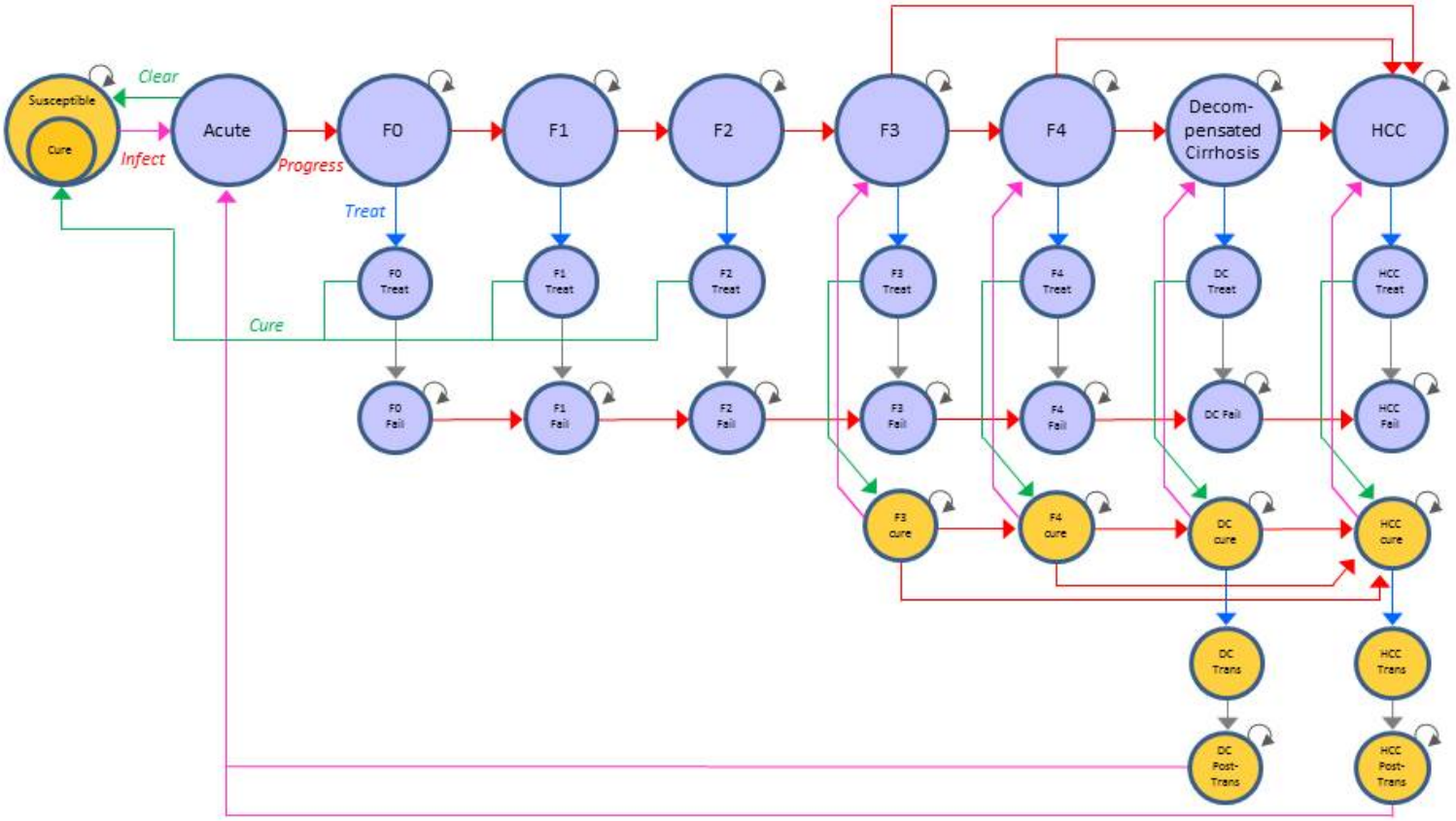
Conceptual Model

The hepatitis C virus (HCV) is a transmissible viral infection that is often asymptomatic in the early stages of the disease, but can progress to serious liver complications including cirrhosis and hepatocellular cancer over years or decades with grave consequences for health and medical costs. (1-3) A discrete time Markov model was developed in Excel to simulate the progression of an HCV-susceptible population through infection, acute, and then chronic HCV, as depicted in Exhibit A1 below. The population in each stage of disease was updated at each time step by cycling the model. The time step (or model cycle duration) was taken to be one year. The Metavir scoring system, designed to quantify the degree of liver fibrosis in patients with liver diseases such as HCV, was used to define disease severity for different stages of the model.(4) The Metavir scoring system is described in Table A1.

Table A1. Metavir Stage Descriptions (4)

Stage	Description
0	No fibrosis
1	Periportal fibrotic expansion
2	Periportal septae (septum)
3	Porto-central septae
4	Compensated cirrhosis

Exhibit A1. Hepatitis C Transmission Simulation Model Schematic



SOURCE Authors' analysis.
NOTES: All states have transitions to "dead." "Trans" = Transplant. Red Arrow = Progression; Blue Arrow = Treat; Green Arrow = Cure; Pink Arrow = Transmission. Blue shading of a shape indicates infectious/infected population. Yellow shading of a shape indicates uninfected and susceptible population.

Upon initial infection, patients enter an "acute" phase which they must leave after one model cycle. They may die, spontaneously clear the disease without treatment, or progress to "chronic" disease, consisting of seven stages of liver damage: Metavir scores F0-F4, decompensated cirrhosis (DC) and hepatocellular carcinoma (HCC). Patients may stay in any disease state except acute for more than one cycle.

Patients in stage F0 or higher may receive HCV treatment during the simulation; if not cured, treated patients may progress or die at the same rates as infected and untreated patients. If HCV is cured in stages F0-F2, patients are no longer infectious and liver damage is assumed to be reversed.(5, 6) These patients return to the susceptible population with healthy livers; if re-infected, they re-commence disease progression at the acute stage.

Patients cured of HCV in stages F3 and higher are no longer infectious, but may progress to additional liver damage more slowly than patients with uncured HCV.(7) They are susceptible for re-infection at the same rate as patients without liver damage, but if re-infected, re-enter the infected population with their existing level of liver damage. Patients with DC or HCC who are cured of HCV are no longer infectious and become eligible for liver transplants. The transplant stage lasts exactly one cycle, after which patients move to a post-transplant state. If these patients are re-infected, they re-enter the infected population with healthy livers at the acute stage. Consistent with current clinical practice, patients who are co-infected with HIV (all patients in the sexual exposure group, more details described below) are not eligible for liver transplants.(8, 9)

Populations Modeled

Three distinct subpopulations are modeled, defined by their HCV exposure route: healthcare (HC), injection drug use (PWID), and sexual (SX). The three exposure groups are modeled independently—an individual can belong to only one exposure group for the duration of the simulation. There is assumed to be no ongoing transmission in the HC exposure group, since effective screening of blood products for HCV was introduced in 1992. Because it is a closed cohort, the HC population shrinks over time, and is assumed to be aging and subject to increasing mortality rates over the course of a simulation. The PWID and SX exposure groups are assumed to have constant mortality rates and experience ongoing entry and exit such that their size remains constant over the simulation.

Within each exposure group, the three HCV genotypes most common in the US (genotypes 1, 2 and 3) are modeled.(10) This permits us to model HCV prevalence and transmission with greater nuance, and to account for the fact that different genotypes respond differently to treatment; (11) may progress at different rates; (12, 13) and involve different mortality risks.(14) Patients may only be infected with one genotype at a time, but once cured, a patient can be re-infected with any of the three genotypes.

Transmission Function

In the PWID and SX exposure groups, for each genotype, the rate at which individuals are infected is modeled dynamically as a function of the number in the exposure group who are currently infected with the given genotype. Individuals who are uninfected (susceptible) at the beginning of a year t are at risk of becoming HCV infected and the probability of becoming infected during year t (i.e., the annual incidence rate) is given by:

$$Pr(infected_{t+1}|susceptible_t) = K \times \frac{N_t^{infected}}{N_t^{infected} + N_t^{susceptible}} \quad (1)$$

where t is the year, $N_t^{infected}$ is the number of people infected at the beginning of year t, and $N_t^{susceptible}$ is the number of people susceptible at the beginning of year t. The transmission model specified by equation (1) assumes that the incidence rate is proportional to the fraction of individuals in an exposure group who are infected. The proportionality constant K is calibrated to ensure that the incidence rate (the left side of equation 1) matches the empirical estimate of disease incidence rate at model start (t=0):

$$K = \frac{(incidence\ rate)(N_{t0}^{infected} + N_{t0}^{susceptible})}{N_{t0}^{infected}}, \quad (2)$$

The incidence rates and proportionality constants K for each exposure group by genotype are reported in Table A2.

Table A2. Starting Annual Incidence Rates and Values of K

	Annual Incidence Rate	Calculated *K*
Healthcare Exposure		
Genotype 1	0	0
Genotype 2	0	0
Genotype 3	0	0
Injection Drug Use		
Genotype 1	0.016	0.039
Genotype 2	0.0036	0.039
Genotype 3	0.0027	0.039
Sexual Transmission		
Genotype 1	0.0065	0.040
Genotype 2	0.0014	0.040
Genotype 3	0.0011	0.040

SOURCE Williams et al. (2011) (15) and authors' calculations.

Treatment Scenarios

Four treatment scenarios are modeled, as described in the main article. They differ in terms of both which and how many patients are treated, and the treatments used. The Baseline scenario assumes that HCV treatment consists of the most effective regimen available prior to the introduction of direct-acting antivirals (DAA), which is pegylated interferon alpha plus ribavirin (PR). Regimens consisting of PR plus a first generation DAA such as telaprevir or boceprevir were also considered for the baseline scenario but ultimately rejected for several reasons: They have significantly worse side effect and adverse event profiles, cannot be used by large segments of the population due to potential interactions with many common drugs (statins, sulfonylureas, benzodiazepines, etc.), and are unlikely to be cost-effective vs. PR in the US among patients with severe liver disease

such as those treated in the baseline scenario. In addition, both boceprevir and telaprevir have been withdrawn from the US market.

The other three scenarios assume that HCV treatment consists of the most effective regimen currently available. The Baseline and Treat Advanced scenarios are inspired by state Medicaid programs that limit access to newer treatments by requiring patients to meet clinical criteria — often requiring patients to undergo liver biopsy to establish that their liver disease severity has reached F3 or higher — to gain prior authorization. (16-20)

Regimen drugs, duration, efficacy and costs differ by infection genotype, as detailed in Table A3.

Table A3. Regimens, Duration and Efficacy for Four Treatment Scenarios Modeled

<table>
<tr><th></th><th colspan="3">Baseline</th><th colspan="3">Treat Advanced</th><th colspan="2">Treat All Diagnosed</th><th colspan="2">Treat 5%</th></tr>
<tr><td>Population treated</td><td colspan="3">All diagnosed patients with F3 or greater</td><td colspan="3">Same as Baseline</td><td colspan="2">All diagnosed patients with F0 or greater</td><td colspan="2">5% of patients with F0 or greater</td></tr>
<tr><td>Drugs used</td><td colspan="3">PR 48 weeks for GT1
PR 24 weeks for GT2/3</td><td colspan="3">sofosbuvir + ledipasvir 12 wks for GT1
sofosbuvir + ribavirin 12 weeks for GT2
sofosbuvir + ribavirin 24 weeks for GT3</td><td colspan="2">Same as Treat Advanced</td><td colspan="2">Same as Treat Advanced</td></tr>
<tr><td colspan="11">Regimen Cost</td></tr>
<tr><td></td><td colspan="3"></td><td>Yr 1
(21-23)</td><td>Yrs 2-14
(21-23)</td><td>Yrs 15+
(21-23)</td><td colspan="2"></td><td colspan="2"></td></tr>
<tr><td>Genotype 1</td><td colspan="3">$35,000(24)</td><td>$100,000(25)</td><td>$64,000</td><td>$21,000</td><td colspan="2" rowspan="3">Same as Treat Advanced</td><td colspan="2" rowspan="3">Same as Treat Advanced</td></tr>
<tr><td>Genotype 2</td><td colspan="3">$17,000(24)</td><td>$100,000(25)</td><td>$64,000</td><td>$21,000</td></tr>
<tr><td>Genotype 3</td><td colspan="3">$17,000(24)</td><td>$200,000
(21, 22, 25)</td><td>$128,000</td><td>$42,000</td></tr>
<tr><td colspan="11">Cure (SVR12) rates by disease stage</td></tr>
<tr><td>Genotype</td><td>F0-F2</td><td>F3</td><td>F4, DC, HCC</td><td>F0-F3</td><td colspan="2">F4, DC, HCC</td><td>F0-F3</td><td>F4, DC, HCC</td><td>F0-F3</td><td>F4, DC, HCC</td></tr>
<tr><td>1</td><td>0.60
(26)</td><td>0.51
(26)</td><td>0.33
(26)</td><td>0.99
(27-29)</td><td colspan="2">0.99
(27-29)</td><td colspan="2" rowspan="3">Same as Treat Advanced</td><td colspan="2" rowspan="3">Same as Treat Advanced</td></tr>
<tr><td>2</td><td>0.76
(26)</td><td>0.61
(26)</td><td>0.57
(26)</td><td>0.97
(27-29)</td><td colspan="2">0.91
(27-29)</td></tr>
<tr><td>3</td><td colspan="3">Same as GT2(26)</td><td>0.94
(27-29)</td><td colspan="2">0.92
(27-29)</td></tr>
</table>

The scenarios involve treating some fixed proportion of the prevalent population in *each* model cycle. The Treat All and Treat Advanced scenarios treat all prevalent patients who have been diagnosed with HCV in particular disease stages, which likely represents the maximum possible treatment group since only diagnosed patients can be treated. Current estimates of HCV diagnosis rates cluster around 50%.(30, 31) Once treated in the first model cycle, many of the currently diagnosed patients are cured and removed from the prevalent population, yet in subsequent model cycles, the same proportion of the remaining prevalent patients are treated. Thus, these aggressive treatment scenarios implicitly assume that prevalent patients continue to be diagnosed such that the diagnosis rate remains constant and the same proportion of prevalent patients is available for treatment.

The treatments used in the non-Baseline scenarios include drugs that are currently protected under patent, but that have seen stiff price competition from recent market entrants. To account for these pricing dynamics, the model reduces treatment costs by 46% (22) in years 2-14, to account for branded competition, and a further reduction of 33% in year 15, for a total reduction upon patent expiration of 79%, assumed to be the marginal cost of producing the drugs.(21)

Starting Populations

At model start, the size of the total infected population in the model across all disease stages is 2,700,000 people.(32) This includes 21,870 incident patients,(33) who are distributed across the three exposure groups according to estimates from Williams et al.,(15) and within each exposure group across three genotypes according to the prevalence of each genotype in the overall population, as estimated by Manos et al (2012).(10) These incident patients make up the populations in the acute phases at the start of the simulation. The remaining 2,678,130 non-incident infected population at model start are then distributed across exposure groups and genotypes following the same logic. These patients are then further distributed across disease stages as in Hagan (2014).(34-36) The distribution of the infected population by exposure group, genotype, and disease stage is given in Table A4.

Table A4. Size and distribution of model populations at start of simulation

		Healthcare Exposure	PWID	Sexual Exposure
Uninfected/Susceptible		74,415,696 (37)	777,354 (38)	461,600 (39)
Genotype 1	*Acute*	0	12,754	2,992
	F0	181,764	119,438	13,532
	F1	374,220	272,160	34,020
	F2	235,224	171,072	21,384
	F3	149,688	108,864	13,608
	F4	64,152	46,656	5,832
	DC	32,076	23,328	2,916
	HCC	32,076	23,328	2,916
Genotype 2	*Acute*	0	2,834	665
	F0	40,392	26,542	3,007
	F1	83,160	60,480	7,560
	F2	52,272	38,016	4,752
	F3	33,264	24,192	3,024
	F4	14,256	10,368	1,296
	DC	7,128	5,184	648
	HCC	7,128	5,184	648
Genotype 3	*Acute*	0	2,127	498
	F0	30,294	19,905	2,256
	F1	62,370	45,360	5,670
	F2	39,204	28,512	3,564
	F3	24,948	18,144	2,268
	F4	10,692	7,776	972
	DC	5,346	3,888	486
	HCC	5,346	3,888	486

SOURCE Authors' analysis and CDC (2014);(40) Manos (2012);(10) Williams (2011);(15) and Hagan (2014)(35)

Model Outputs

Each year, the model produces the number of people in every disease state. These disease-state populations are then multiplied by published estimates of annual per-person values for quality-adjusted life years (QALYs) in each disease state; each QALY is valued at $150,000 to generate the total value of QALYs produced by a treatment scenario.(41) Other annual per-person estimates of economic measures including treatment costs and non-treatment medical expenditures are similarly applied to disease-state populations to generate population-wide estimates. These estimates are assumed to be constant over the duration of the simulation. Dollar values are discounted at 3% per year to produce present discounted values of future value streams.(42)

Patients who die within a cycle are assumed to transition out of the simulation following a uniform probability distribution with a mean of six months. Model outputs for such patients are calculated as half the values as for those who don't die during the cycle.

Model Parameters

Model parameters are taken from the published literature, with efforts made to find exposure group- and genotype-specific values wherever possible. The Healthcare exposure group was defined to be US residents born between 1945 and 1965, and contains the largest number of HCV-infected patients. It is modeled with a mortality rate that increases at 8% per year as the closed cohort ages over time.(43) Model parameters for the healthcare exposure cohort and their sources are provided in Table A5.

The PWID exposure group has the highest incidence rate, reflecting the greater transmission among this population. The PWID cohort also has the highest starting mortality rates for both the infected and uninfected populations.(44) Model parameters for the PWID cohort and their sources are provided in Table A6.

The Sexual exposure group is characterized by co-infection with HIV, which affects the progression of HCV (45), and in our analysis is principally composed of men who have sex with men. Model parameters for the Sexual exposure group and their sources are provided in Table A7.

Annual Mortality Rates

Disease stage-, exposure group-, and genotype-specific annual mortality rates were calculated as follows: the annual mortality rate for each exposure group was taken from the literature (37, 44, 46) and used for the background mortality rate for the uninfected population in that group. Since the healthcare exposure group is a closed cohort whose average age increases over the simulation, we assume that the background mortality rate grows at 8% per year in this group.(43) For the other two exposure groups, we assume a stable age distribution, or that the exiting of older individuals is offset by ongoing entry of younger individuals into these exposure groups, and assume a constant background mortality. While it is possible that improved treatments may lead to slight aging of these two exposure groups, those effects could be offset by younger ages at entry into the groups (e.g., younger age at initiation of drug use or sexual activity). Accordingly, in the absence of clear trends on the ages of initiation for these risk behaviors, we have opted for the simplest plausible assumption of a stable (stationary) age distribution in the PWID and sexual exposure groups over the time span of our forecasts.

To calculate the annual mortality rates for HCV-infected individuals with genotype 1 in stages acute-F2 in each exposure group, the group's background mortality rate was multiplied by 2.37, the ratio of the all-cause mortality rate of the HCV infected relative to the non-HCV infected based on the Third National Health and Nutrition Examination Survey.(47) To calculate the F3-F4 mortality rates for genotype 1 in each group, the F2 mortality rate was multiplied by 3.77, the ratio of mortality at fibrosis stages F3-F4 versus F2 from McCombs et al. (2014). (14) Annual mortality rate estimates for decompensated cirrhosis and hepatocellular carcinoma for genotype 1 in each exposure group were taken from Younossi et al. (2014).(48)

These genotype 1 mortality rate estimates were multiplied by 0.85 and 0.94 to create similar estimates for genotypes 2 and 3, respectively, based on the relative ratios for each genotype, from McCombs et al. (2014).(14)

Table A5. Model Parameters for the Healthcare Exposure Group, Genotypes 1-3 (citation numbers in parentheses)

	Genotype 1	Genotype 2	Genotype 3
Annual Mortality Rate			
Susceptible (Background)	0.006 (37)		
Acute, F0-F2	0.0142(47)	0.0121(14, 47)	0.0134(14, 47)
F3, F4	0.0536(14, 47)	0.0456(14, 47)	0.0504(14, 47)
DC	0.135(48-50)	0.1148(14, 48-50)	0.1269 (14, 48-50)
HCC	0.427(48, 51, 52)	0.363(14, 48, 51, 52)	0.4014 (14, 48, 51, 52)
Transplant[a]	0.165(53)		
Post-Transplant[b]	0.0226(14, 37)		
Annual Background Mortality Growth Rate	.08 (43)		
Annual Transition Probability			
Acute → Spontaneous Clearance	0.18 (54)		
F0 → F1	0.076 (36, 55, 56)		
F1→ F2	0.095 (36, 55, 56)		
F2 → F3	0.108 (36, 55, 56)		
F3 → F4	0.134 (36, 55, 56)		
F3 → HCC	0.008 (48, 57)	0.008 (48, 57)	0.0144 (12, 48, 57)
F4 → DC	0.039 (48, 49, 58)	0.0265 (12, 48, 58)	0.0507 (12, 48, 58)
F4 → HCC	0.025 (48, 49)	0.0138 (12, 48, 49)	0.045 (12, 48, 49)
DC → HCC	0.025 (48, 49)	0.0138 (12, 48, 49)	0.045 (12, 48, 49)
DC → Transplant	0.031 (59, 60)		
HCC → Transplant	0.103 (58, 59)		
F3 Cure → F4 Cure	0.0375 (7)		
F3 Cure → HCC Cure	0.0029 (7)		
F4 Cure → DC Cure	0.0109 (7)		
F4 Cure → HCC Cure	0.009 (7)		
DC Cure → HCC Cure	0.007 (7)		
QALY Weights			
Susceptible, Acute	0.86 (59, 61)		
F0-F1	0.84 (60, 61)		

	Genotype 1	Genotype 2	Genotype 3
F2, F3, F3 Cure	0.79,(60, 61)		
F4, F4 Cure	0.76 (59, 62)		
DC, DC Cure	0.69 (59, 62)		
DC Transplant[a]	0.50 (59, 62)		
DC Post-Transplant[b]	0.71 (9, 63)		
HCC, HCC Cure	0.67 (59, 62)		
HCC Transplant[a]	0.5 (59, 62)		
HCC Post-Transplant[b]	0.71 (9, 63)		
Annual Medical Expenditures			
Susceptible	$6,894 (64)		
Acute, F0, F1, F2, F3	$16,792 (65)		
F0 Fail, F1 Fail, F2 Fail, F3 Fail	$10,915 (65, 66)		
F4	$19,919 (65)		
F4 Fail	$15,138 (65, 66)		
DC	$55,649 (65)		
DC Fail	$38,954 (65, 66)		
DC Transplant[a]	$160,040 (65)		
DC Post-Transplant[b]	$ 160,040 (65)		
HCC	$123,405 (65)		
HCC Fail	$86,384 (65, 66)		
HCC Transplant[a]	$160,040 (65)		
HCC Post-Transplant[b]	$160,040 (65)		

NOTE [a]Year of liver transplant; [b]All subsequent years after liver transplant;

Table A6. Model Parameters for the PWID Exposure Group, Genotypes 1-3 (citation numbers in parentheses)

	Genotype 1	Genotype 2	Genotype 3
Annual Mortality Rate			
Susceptible	0.0264 (44)		
Acute, F0-F2	0.0626 (44, 47)	0.0532 (14, 44, 47)	0.0588 (14, 44, 47)
F3, F4	0.2359 (14, 44, 47)	0.2005 (14, 44, 47)	0.2217 (14, 44, 47)
DC	0.135 (48-50)	0.1148 (14, 48-50)	0.1269 (14, 48-50)
HCC	0.427 (48-50)	0.363 (14, 48-50)	0.4014 (14, 48-50)
Transplant[a]	0.1650 (53)		
Post-Transplant[b]	0.0995 (14, 44)		
Annual Transition Probability			
Acute → Spontaneous Clearance	0.18 (67)		
F0 → F1	0.116 (36, 68-73)		
F1 → F2	0.085 (36, 68-73)		
F2 → F3	0.085 (36, 68-73)		
F3 → F4	0.13 (36, 68-73)		
F3 → HCC	0.008 (48, 57)	0.008 (48, 57)	0.0144 (12, 48, 57)
F4 → DC	0.039 (48, 49, 58)	0.0265 (12, 48, 58)	0.0507 (12, 48, 58)
F4 → HCC	0.025 (48, 49, 58)	0.0138 (12, 48, 49)	0.045 (12, 48, 49)
DC → HCC	0.025 (48, 49, 58)	0.0138 (12, 48, 49)	0.045 (12, 48, 49)
DC → Transplant	0.031 (59, 60)		
HCC → Transplant	0.103 (58, 59)		
F3 Cure → F4 Cure	0.0364 (7)		
F3 Cure → HCC Cure	0.0029 (7)		
F4 Cure → DC Cure	0.0109 (7)		
F4 Cure → HCC Cure	0.009 (7)		
DC Cure → HCC Cure	0.007 (7)		
QALY Weights	Same as for healthcare exposure group. See Table A5 for values.		
Annual Medical Expenditures	Same across exposure groups and genotype. See Table A5 for values.		

NOTE [a]Year of liver transplant; [b]All subsequent years after liver transplant

Table A7. Model Parameters for the Sexual Exposure Group, Genotypes 1-3 (citation numbers in parentheses)

	Genotype 1	Genotype 2	Genotype 3
Annual Mortality Rate			
Susceptible	0.0001 (46)		
Acute, F0-F2	0.0003 (46, 47)	0.0002 (14, 46, 47)	0.0003 (14, 46, 47)
F3, F4	0.001 (14, 46, 47)	0.0009 (14, 46, 47)	0.001 (14, 46, 47)
DC	0.135 (48-50)	0.1148 (14, 48-50)	0.1269 (14, 48-50)
HCC	0.427 (48-50)	0.363 (14, 48-50)	0.4014 (14, 48-50)
Transplant[a]	0.137 (74, 75)		
Post Transplant[b]	0.052 (74, 75)		
Annual Transition Probability			
Acute → Spontaneous Clearance	0.13 (76)		
F0 → F1	0.122 (45)		
F1 → F2	0.115 (45)		
F2 → F3	0.124 (45)		
F3 → F4	0.115 (45)		
F3 → HCC	0.016 (9, 48, 57, 77)	0.016 (9, 48, 57, 77)	0.0288 (12, 48, 57, 77)
F4 → DC	0.078 (9, 48, 49, 58, 78)	0.053 (12, 48, 49, 58, 78)	0.1014 (48, 49, 58, 78)
F4 → HCC	0.05 (9, 48, 49, 77)	0.0275 (12, 48, 49, 77)	0.09 (48, 49, 77)
DC → HCC	0.05 (9, 48, 49, 77)	0.0275 (12, 48, 49)	0.09 (48, 49)
DC → Transplant	0 (9)		
HCC → Transplant	0 (9)		
F3 Cure → F4 Cure	0.0322 (7)		
F3 Cure → HCC Cure	0.0058 (7)		
F4 Cure → DC Cure	0.0218 (7)		
F4 Cure → HCC Cure	0.018 (7)		
DC Cure → HCC Cure	0.014 (7)		
QALY Weights			
Susceptible, Acute	0.87 (8, 74)		
F0-F1	0.85 (8, 60, 74)		
F2, F3, F3 Cure	0.80 (8, 60, 74)		
F4, F4 Cure	0.68 (8, 74)		
DC, DC Cure	0.48 (8, 74)		
DC Transplant[a]	0.81 (8, 74)		
DC Post-Transplant[b]	0.81 (8, 74)		
HCC, HCC Cure	0.23 (8, 74)		
HCC Transplant[a]	0.81 (8, 74)		

	Genotype 1	Genotype 2	Genotype 3
HCC Post-Transplant[b]	0.81 (8, 74)		
Medical Expenditures	Same across exposure groups and genotype. See Table A5 for values.		

NOTE [a]Year of liver transplant; [b]All subsequent years after liver transplant

Sensitivity Analyses

We conducted sensitivity analyses along several dimensions, exploring the impact of changes in key variables on social value, total infected population after 50 years, and the time needed for the infected population to fall below 200,000, the threshold at which HCV would be considered a rare disease in the US.(79) These results are presented in Tables A8 and A9.

Table A8: Infected Population Results of Sensitivity Analyses on Key Model Parameters

	Model Outcome							
	Number Infected in Year 50				Years Until Rare Disease Status[7]			
Base Case Results	**Treat 5%** **38,759**	**Baseline** **206,618**	**Treat Advanced** **102,912**	**Treat All Diagnosed** **1,371**	**Treat 5%** **26**	**Baseline** **50+**	**Treat Advanced** **36**	**Treat All Diagnosed** **7**
Sensitivity Analyses	**Treat 5%**	**Baseline**	**Treat Advanced**	**Treat All Diagnosed**	**Treat 5%**	**Baseline**	**Treat Advanced**	**Treat All Diagnosed**
Increase starting infected population to 3.2 million	39,467	217,447	112,180	1,555	27	50+	38	N/C
QALYs valued at $50K	N/C	N/C	N/C	N/C	N/C	50+	N/C	N/C
QALYs valued at $100K	N/C	N/C	N/C	N/C	N/C	50+	N/C	N/C
QALYs valued at $200K	N/C	N/C	N/C	N/C	N/C	50+	N/C	N/C
Allow retreatment in Baseline scenario[1]	N/C	191,736	N/C	N/C	N/C	48	N/C	N/C
Increase diagnosis rate[2,3]	N/C	N/C	N/C	N/C	N/C	50+	N/C	6
Reduce treatment rate[3,4]	N/C	210,945	119,626	1,772	N/C	50+	37	11
No branded discounts[5]	N/C	N/C	N/C	N/C	N/C	50+	N/C	N/C
Reduce quality of life in F0-F1[6]	N/C	N/C	N/C	N/C	N/C	50+	N/C	N/C

Source: Authors' Analysis
NOTES:
[1]Implemented by improving the cure rate for PR therapy by 10-20% and cost of PR therapy by 27-44% (80)
[2]Diagnosis rate among healthcare exposure group increased to 75% to account for recent introduction of recommendations for universal screening among baby boomers(81)
[3]Change implemented in all but Treat 5% scenario
[4]In each group receiving treatment, treatment applied to only 50% of those who are infected and diagnosed
[5]No drug discounts until year 15 when drug prices fall by 79% due to loss of patent protection (21-23)
[6]QALY weights are lower for F0-F2, per McEwan et al. (59)
[7]The US Rare Diseases Act of 2002 defines a rare disease as "any disease or condition that affects less than 200,000 people in the United States" (82)(85)(83)(83)[8383]
Abbreviations: N/C = no change from Base Case; QALY = Quality adjusted life year; F0-F2 = fibrosis scores F0-F2 on the Metavir scale.

Table A9: Social Value Results of Sensitivity Analyses on Key Model Parameters

	Social Value Net of Baseline ($bil)					
	Treat 5%		Treat Advanced		Treat All Diagnosed	
	Lower Bound	Upper Bound	Lower Bound	Upper Bound	Lower Bound	Upper Bound
Base Case Results	**347**	**349**	**126**	**131**	**1,188**	**1,222**
	Treat 5%		Treat Advanced		Treat All Diagnosed	
Sensitivity Analyses	Lower Bound	Upper Bound	Lower Bound	Upper Bound	Lower Bound	Upper Bound
Increase starting infected population to 3.2 million	407	410	149	154	1,403	1,442
QALYs valued at $50K	170	172	39	44	578	611
QALYs valued at $100K	258	260	83	87	883	916
QALYs valued at $200K	435	437	170	175	1,493	1,527
Allow retreatment in Baseline scenario[1]	321	323	101	105	1,162	1,196
Increase diagnosis rate[2,3]	333	334	143	147	1,247	1,281
Reduce treatment rate[3,4]	380	387	93	97	1,016	1,047
No branded discounts[5]	382	384	156	161	1,242	1,276
Reduce quality of life in F0-F1[6]	374	377	130	134	1,266	1,300

Source: Authors' Analysis

NOTES:

[1]Implemented by improving the cure rate for PR therapy by 10-20% and cost of PR therapy by 27-44% (80)

[2]Diagnosis rate among healthcare exposure group increased to 75% to account for recent introduction of recommendations for universal screening among baby boomers(81)

[3]Change implemented in all but Treat 5% scenario

[4]In each group receiving treatment, treatment applied to only 50% of those who are infected and diagnosed

[5]No drug discounts until year 15 when drug prices fall by 79% due to loss of patent protection (21-23)

[6]QALY weights are lower for F0-F2, per McEwan et al. (59)

Abbreviations: N/C = no change from Base Case; QALY = Quality adjusted life year; F0-F2 = fibrosis scores F0-F2 on the Metavir scale

Starting Infected Population

There is no consensus regarding the prevalence of HCV (detected + undetected) among the US population—widely cited estimates range from 2.7 million (32) to 3.2 million (1). We use the more conservative figure in the main analysis, but explore in a sensitivity analysis on how our results would change if the starting infected population were 3.2 million instead.

Value of a QALY

Estimates of the value of a quality-adjusted life-year (QALY) from the value of life literature vary widely.(41) The cost-effectiveness literature often cites values of $50,000–100,000,(83) while labor economics, product safety, and workplace safety literature publish estimates that center around $300,000 (in 2000 dollars).(84) Similar values are reported in studies that use out-of-pocket payment decisions by patients and prescribing decisions by physicians.(85) More recently, researchers have questioned the continued use of the $50,000 figure, given its "murky origins" more than 20 years ago, lack of adjustment for inflation or economic growth, and suggest that values of $100,000-$150,000 are more appropriate.(86) We value QALYs at $150,000 for the baseline analysis, and consider values ranging from $50,000 to $200,000 in sensitivity analyses.

Re-treatment

For model tractability, we assume that patients are treated at most once per infection. However, patients who fail initial treatment with PR have sometimes been re-treated (80), despite treatment guidelines that recommend against it due to the low probability of cure and significant side effects associated with PR treatments (4). To explore the impact that re-treatment of patients who fail initial PR treatment could have on model results, we conducted a sensitivity analysis in which the SVR rate and cost for PR therapy were increased under the assumption that 65% of patients who fail initial treatment are re-treated with 48 additional weeks of PR with a lower probability of attaining SVR than treatment naïve patients. SVR rates were increased by 10-20% and costs were increased by 27-44% (depending on genotype and fibrosis stage).(80)

Diagnosis and Treatment Rates

The maximum proportion of infected patients in any disease state that can be treated is limited by the rate of diagnosis among the population, as well as the available treatment capacity. To explore the impact that changes in each of these factors would have on our model results, we change the proportion of patients who receive treatment, as a fraction of those infected, in three of our four treatment scenarios: Baseline, Treat Advanced, and Treat All Diagnosed. The Treat 5% treatment scenario is assumed to simply treat 5% of all infected patients in each disease state; the 5% does not vary by diagnosis rate or treatment capacity. Current estimates of HCV diagnosis rates tend to cluster around 50%.(30, 31)

For the diagnosis rate sensitivity analysis, we assume that recent recommendations for universal screening among baby boomers (81) increases the diagnosis rate in our healthcare exposure group from 50% to 75% (it remains at 50% in the other two exposure groups). For the treatment rate sensitivity analysis, we assume that, among patients in a

disease state targeted for treatment, only 50% of those infected and diagnosed receive treatment in any period.(31)

QALY Decrement

For utility weights associated with a life-year spent in each model disease state, the main analysis follows Salomon et al. (60) and reduces the utility of the uninfected state by 2% for mild disease (Acute-F1) and by 6% for moderate disease (F2-F3). QALY weights for F4 and higher are taken from McEwan et al.(59) in the base analysis. In a sensitivity analysis, we employed QALY weights from McEwan for all disease states, which are lower than those from Salomon for mild to moderate disease.

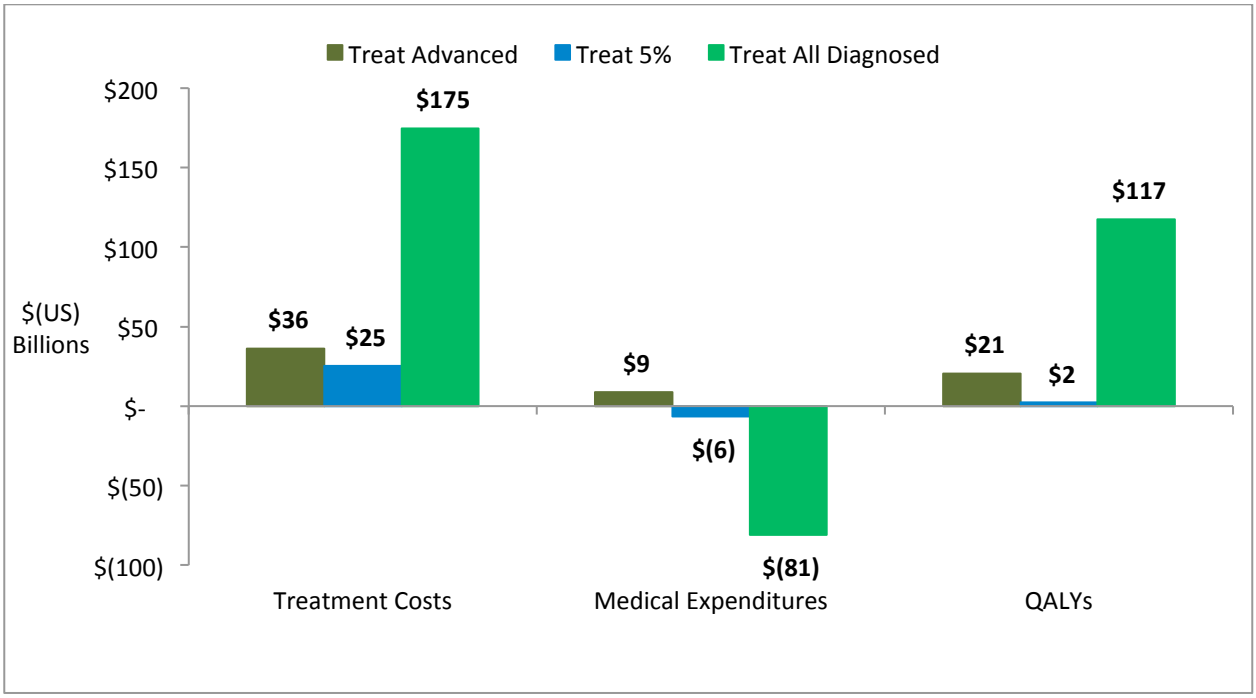
Price Discounts

The main analysis assumes that branded drugs used for treatment cost their full price in the first year, are discounted by 46% in years 2-14 due to entry from other branded competitors, and are discounted by 79% in years 15+ after loss of patent protection.(21-23) In this sensitivity analysis, we explore what happens if no branded entry occurs and treatments remain at their list price until patent expiration.

Time Horizon

The discounted cumulative results reported in Exhibit 3 in the manuscript are based on a 50-year time horizon; if a ten-year horizon is used instead, treatment costs, medical expenditures and value from QALYs all have the same general shape as in the 50-year case, but only the Treat All scenario has total benefits exceeding treatment costs after ten years. The ten year results are presented in Exhibit A2 below:

Exhibit A2. Discounted costs and benefits for alternative treatment strategies net of Baseline over a 10-year period



SOURCE Authors' analysis

NOTE "Baseline" treatment scenario treats all of the HCV infected and diagnosed population with advanced disease (F3 and higher) every period with old agents; "Treat Advanced" treats the same population as Baseline with new agents; "Treat 5%" treats 5% of the total HCV infected population (F0 and above) every period with new agents; "Treat All Diagnosed" treats all of the HCV infected and diagnosed population (F0 and above) every period with new agents. All model parameters are taken from the literature. QALYs are valued at $150,000 each (41); discount rate = 3% (42).

References

1. Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med. 2006;144(10):705-14.
2. Biggins SW, Bambha KM, Terrault NA, Inadomi J, Shiboski S, Dodge JL, et al. Projected future increase in aging hepatitis C virus-infected liver transplant candidates: a potential effect of hepatocellular carcinoma. Liver Transpl. 2012;18(12):1471-8.
3. Centers for Disease Control. Hepatitis C information for health professionals. 2014 [cited 2015 January 20]; Available from: http://www.cdc.gov/hepatitis/HCV/.
4. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology. 2009;49(4):1335-74.
5. Friedman SL, Bansal MB. Reversal of hepatic fibrosis -- fact or fantasy? Hepatology. 2006;43(2 Suppl 1):S82-8.
6. Wright TL. Treatment of patients with hepatitis C and cirrhosis. Hepatology. 2002;36(5 Suppl 1):S185-94.
7. Kabiri M, Jazwinski AB, Roberts MS, Schaefer AJ, Chhatwal J. The changing burden of hepatitis C virus infection in the United States: model-based predictions. Ann Intern Med. 2014;161(3):170-80.
8. Kuehne FC, Bethe U, Freedberg K, Goldie SJ. Treatment for hepatitis C virus in human immunodeficiency virus-infected patients: clinical benefits and cost-effectiveness. Arch Intern Med. 2002;162(22):2545-56.
9. Saab S, Gordon SC, Park H, Sulkowski M, Ahmed A, Younossi Z. Cost-effectiveness analysis of sofosbuvir plus peginterferon/ribavirin in the treatment of chronic hepatitis C virus genotype 1 infection. Aliment Pharmacol Ther. 2014;40(6):657-75.
10. Manos MM, Shvachko VA, Murphy RC, Arduino JM, Shire NJ. Distribution of hepatitis C virus genotypes in a diverse US integrated health care population. J Med Virol. 2012;84(11):1744-50.
11. Tice JA, Ollendorf DA, Pearson SD. The comparative clinical effectiveness and value of simperevir and sofosbuvir in the treatment of chronic hepatitis c infection. California Technology Assessment Forum; 2014 [cited 2014 October 8]; Available from: http://ctaf.org/sites/default/files/assessments/CTAF_Hep_C_Apr14_final.pdf.
12. Kanwal F, Kramer JR, Ilyas J, Duan Z, El-Serag HB. HCV genotype 3 is associated with an increased risk of cirrhosis and hepatocellular cancer in a national sample of U.S. Veterans with HCV. Hepatology. 2014;60(1):98-105.
13. Probst A, Dang T, Bochud M, Egger M, Negro F, Bochud PY. Role of hepatitis C virus genotype 3 in liver fibrosis progression--a systematic review and meta-analysis. J Viral Hepat. 2011;18(11):745-59.
14. McCombs J, Matsuda T, Tonnu-Mihara I, Saab S, Hines P, L'Italien G, et al. The risk of long-term morbidity and mortality in patients with chronic hepatitis C: results from an analysis of data from a Department of Veterans Affairs Clinical Registry. JAMA Intern Med. 2014;174(2):204-12.
15. Williams IT, Bell BP, Kuhnert W, Alter MJ. Incidence and transmission patterns of acute hepatitis C in the United States, 1982-2006. Arch Intern Med. 2011;171(3):242-8.

16. Viohl & Associates. The Sovaldi® squeeze: high costs force tough state decisions. MHPA; 2014 [cited 2015 January 20]; Available from: http://www.mhpa.org/_upload/SovaldiSqueeze-Oct2014.pdf.
17. Arkansas Department of Human Services. AR Medicaid DUR Board edits approved at the April 16, 2014 meeting. 2014 [cited 2014 October 7]; Available from: https://www.medicaid.state.ar.us/InternetSolution/provider/docs/pharmacy.aspx.
18. Colorado Department of Health Care Policy and Financing. Preferred Drug List (PDL): Effective October 1, 2014. 2014 [cited 2014 October 7]; Available from: https://www.colorado.gov/pacific/sites/default/files/PDL%2010-1-2014.pdf.
19. Oregon Health Authority. Oregon Medicaid pharmaceutical services prior authorization criteria. 2014 [cited 2014 October 7]; Available from: http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/pa-criteria.pdf.
20. Alaska Medicaid. Prior authorization criteria: Direct acting agents for hepatitis C. 2014 [cited 2015 January 19]; Available from: http://dhss.alaska.gov/dhcs/Documents/pharmacy/pdfs/HCV-DAA_PA_Criteria.pdf.
21. Grabowski HG, Vernon JM. Brand loyalty, entry, and price competition in pharmaceuticals after the 1984 Drug Act. J Law Econ. 1992;35(2):331-50.
22. Tirrell M. Pricing wars heat up over hepatitis C drugs. 2015; Available from: http://www.cnbc.com/id/102396903.
23. Hill A, Khoo S, Fortunak J, Simmons B, Ford N. Minimum costs for producing hepatitis C direct-acting antivirals for use in large-scale treatment access programs in developing countries. Clin Infect Dis. 2014;58(7):928-36.
24. Tungol A, Rademacher K, Schafer JA. Formulary management of the protease inhibitors boceprevir and telaprevir for chronic hepatitis C virus. J Manag Care Pharm. 2011;17(9):685-94.
25. Staton T. Balky payers, beware: Gilead eyes $95K-or-so price for Sovaldi combo pill. 2014 [cited 2014 October 9]; Available from: http://www.fiercepharma.com/story/balky-payers-beware-gilead-eyes-95k-or-so-price-sovaldi-combo-pill/2014-09-15?utm_medium=nl&utm_source=internal.
26. Lee SS, Bain VG, Peltekian K, Krajden M, Yoshida EM, Deschenes M, et al. Treating chronic hepatitis C with pegylated interferon alfa-2a (40 KD) and ribavirin in clinical practice. Aliment Pharmacol Ther. 2006;23(3):397-408.
27. Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. 2014;370(20):1889-98.
28. Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med. 2013;368(20):1878-87.
29. Zeuzem S, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. N Engl J Med. 2014;370(21):1993-2001.
30. Denniston MM, Klevens RM, McQuillan GM, Jiles RB. Awareness of infection, knowledge of hepatitis C, and medical follow-up among individuals testing positive for hepatitis C: National Health and Nutrition Examination Survey 2001-2008. Hepatology. 2012;55(6):1652-61.
31. Volk ML, Tocco R, Saini S, Lok ASF. Public health impact of antiviral therapy for hepatitis C in the United States. Hepatology. 2009;50(6):1750-5.

32. Denniston MM, Jiles RB, Drobeniuc J, Klevens RM, Ward JW, McQuillan GM, et al. Chronic hepatitis C virus infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010. Ann Intern Med. 2014;160(5):293-300.
33. Centers for Disease Control and Prevention. Surveillance for viral hepatitis - United States, 2012. 2015 [cited 2015 January 16]; Available from: http://www.cdc.gov/hepatitis/Statistics/2012Surveillance/Commentary.htm#hepC.
34. Coffin PO, Scott JD, Golden MR, Sullivan SD. Cost-effectiveness and population outcomes of general population screening for hepatitis C. Clin Infect Dis. 2012;54(9):1259-71.
35. Hagan LM, Sulkowski MS, Schinazi RF. Cost analysis of sofosbuvir/ribavirin versus sofosbuvir/simeprevir for genotype 1 hepatitis C virus in interferon-ineligible/intolerant individuals. Hepatology. 2014;60(1):37-45.
36. Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology. 2008;48(2):418-31.
37. U.S. Census Bureau. Annual estimates of the resident population by single year and sex for the Unites States: April 1, 2010 to July 1, 2013. 2013; Available from: http://factfinder2.census.gov. .
38. Mathers BM, Degenhardt L, Phillips B, Wiessing L, Hickman M, Strathdee SA, et al. Global epidemiology of injecting drug use and HIV among people who inject drugs: a systematic review. Lancet. 2008;372(9651):1733-45.
39. Centers for Disease Control and Prevention. Monitoring selected national HIV prevention and care objectives by using HIV surveillance data—United States and 6 dependent areas—2011. 2013 [cited 2015 January 16]; Available from: http://www.cdc.gov/hiv/library/reports/surveillance.
40. Centers for Disease Control. Viral hepatitis statistics & surveillance. 2014 [cited 2014 October 10]; Available from: http://www.cdc.gov/hepatitis/Statistics/2012Surveillance/index.htm.
41. Hirth RA, Chernew ME, Miller E, Fendrick AM, Weissert WG. Willingness to pay for a quality-adjusted life year: in search of a standard. Med Decis Making. 2000;20(3):332-42.
42. Gold MR, Siegel J, Russell L, Weinstein M. Cost-effectiveness in health and medicine: report of the panel on cost-effectiveness in health and medicine. New York: Oxford Univ Pr. 1996.
43. Arias E. United States Life Tables, 2009. 2014 Contract No.: 7.
44. Mathers BM, Degenhardt L, Bucello C, Lemon J, Wiessing L, Hickman M. Mortality among people who inject drugs: a systematic review and meta-analysis. Bull World Health Organ. 2013;91(2):102-23.
45. Thein HH, Yi Q, Dore GJ, Krahn MD. Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis. AIDS. 2008;22(15):1979-91.
46. Centers for Disease Control and Prevention. HIV surveillance report, 2011, vol 23. 2013 [cited 2014 July 25]; Available from: http://www.cdc.gov/hiv/topics/surveillance/resources/reports/.
47. El-Kamary SS, Jhaveri R, Shardell MD. All-cause, liver-related, and non-liver-related mortality among HCV-infected individuals in the general US population. Clin Infect Dis. 2011;53(2):150-7.

48. Younossi ZM, Singer ME, Mir HM, Henry L, Hunt S. Impact of interferon free regimens on clinical and cost outcomes for chronic hepatitis C genotype 1 patients. J Hepatol. 2014;60(3):530-7.
49. Rein DB, Smith BD, Wittenborn JS, Lesesne SB, Wagner LD, Roblin DW, et al. The cost-effectiveness of birth-cohort screening for hepatitis C antibody in U.S. primary care settings. Ann Intern Med. 2012;156(4):263-70.
50. Planas R, Balleste B, Alvarez MA, Rivera M, Montoliu S, Galeras JA, et al. Natural history of decompensated hepatitis C virus-related cirrhosis. A study of 200 patients. J Hepatol. 2004;40(5):823-30.
51. Singer ME, Younossi ZM. Cost effectiveness of screening for hepatitis C virus in asymptomatic, average-risk adults. Am J Med. 2001;111(8):614-21.
52. Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology. 1997;112(2):463-72.
53. Best JH, Veenstra DL, Geppert J. Trends in expenditures for Medicare liver transplant recipients. Liver Transpl. 2001;7(10):858-62.
54. Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. J Viral Hepat. 2006;13(1):34-41.
55. Shin JL, Teitel J, Swain MG, Bain VG, Adams PC, Croitoru K, et al. A Canadian multicenter retrospective study evaluating transjugular liver biopsy in patients with congenital bleeding disorders and hepatitis C: is it safe and useful? Am J Hematol. 2005;78(2):85-93.
56. Hamada H, Yatsuhashi H, Yano K, Daikoku M, Arisawa K, Inoue O, et al. Impact of aging on the development of hepatocellular carcinoma in patients with posttransfusion chronic hepatitis C. Cancer. 2002;95(2):331-9.
57. Dienstag JL, Ghany MG, Morgan TR, Di Bisceglie AM, Bonkovsky HL, Kim HY, et al. A prospective study of the rate of progression in compensated, histologically advanced chronic hepatitis C. Hepatology. 2011;54(2):396-405.
58. McGarry LJ, Pawar VS, Panchmatia HR, Rubin JL, Davis GL, Younossi ZM, et al. Economic model of a birth cohort screening program for hepatitis C virus. Hepatology. 2012;55(5):1344-55.
59. McEwan P, Ward T, Yuan Y, Kim R, L'Italien G. The impact of timing and prioritization on the cost-effectiveness of birth cohort testing and treatment for hepatitis C virus in the United States. Hepatology. 2013;58(1):54-64.
60. Salomon JA, Weinstein MC, Hammitt JK, Goldie SJ. Cost-effectiveness of treatment for chronic hepatitis C infection in an evolving patient population. JAMA. 2003;290(2):228-37.
61. Chong CA, Gulamhussein A, Heathcote EJ, Lilly L, Sherman M, Naglie G, et al. Health-state utilities and quality of life in hepatitis C patients. Am J Gastroenterol. 2003;98(3):630-8.
62. Thein HH, Krahn M, Kaldor JM, Dore GJ. Estimation of utilities for chronic hepatitis C from SF-36 scores. Am J Gastroenterol. 2005;100(3):643-51.
63. McLernon DJ, Dillon J, Donnan PT. Health-state utilities in liver disease: a systematic review. Med Decis Making. 2008;28(4):582-92.

64. Davis KL, Mitra D, Medjedovic J, Beam C, Rustgi V. Direct economic burden of chronic hepatitis C virus in a United States managed care population. J Clin Gastroenterol. 2011;45(2):e17-24.
65. Gordon SC, Pockros PJ, Terrault NA, Hoop RS, Buikema A, Nerenz D, et al. Impact of disease severity on healthcare costs in patients with chronic hepatitis C (CHC) virus infection. Hepatology. 2012;56(5):1651-60.
66. Gordon SC, Hamzeh FM, Pockros PJ, Hoop RS, Buikema AR, Korner EJ, et al. Hepatitis C virus therapy is associated with lower health care costs not only in noncirrhotic patients but also in patients with end-stage liver disease. Aliment Pharmacol Ther. 2013;38(7):784-93.
67. Villano SA, Vlahov D, Nelson KE, Cohn S, Thomas DL. Persistence of viremia and the importance of long-term follow-up after acute hepatitis C infection. Hepatology. 1999;29(3):908-14.
68. Benhamou Y, Bochet M, Di Martino V, Charlotte F, Azria F, Coutellier A, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. Hepatology. 1999;30(4):1054-8.
69. Cournot M, Glibert A, Castel F, Druart F, Imani K, Lauwers-Cances V, et al. Management of hepatitis C in active drugs users: experience of an addiction care hepatology unit. Gastroenterol Clin Biol. 2004;28(6-7 Pt 1):533-9.
70. Grando-Lemaire V, Goisset P, Sorge F, Trinchet JC, Castera L, Roulot D, et al. [Hepatitis C virus screening in drug users in an addiction out-patient unit]. Gastroenterol Clin Biol. 2002;26(12):1091-6.
71. Puoti M, Bonacini M, Spinetti A, Putzolu V, Govindarajan S, Zaltron S, et al. Liver fibrosis progression is related to CD4 cell depletion in patients coinfected with hepatitis C virus and human immunodeficiency virus. J Infect Dis. 2001;183(1):134-7.
72. Rai R, Wilson LE, Astemborski J, Anania F, Torbenson M, Spoler C, et al. Severity and correlates of liver disease in hepatitis C virus-infected injection drug users. Hepatology. 2002;35(5):1247-55.
73. Wilson LE, Torbenson M, Astemborski J, Faruki H, Spoler C, Rai R, et al. Progression of liver fibrosis among injection drug users with chronic hepatitis C. Hepatology. 2006;43(4):788-95.
74. Hornberger J, Torriani FJ, Dieterich DT, Brau N, Sulkowski MS, Torres MR, et al. Cost-effectiveness of peginterferon alfa-2a (40kDa) plus ribavirin in patients with HIV and hepatitis C virus co-infection. J Clin Virol. 2006;36(4):283-91.
75. Forman LM, Lewis JD, Berlin JA, Feldman HI, Lucey MR. The association between hepatitis C infection and survival after orthotopic liver transplantation. Gastroenterology. 2002;122(4):889-96.
76. Schnuriger A, Dominguez S, Guiguet M, Harfouch S, Samri A, Ouazene Z, et al. Acute hepatitis C in HIV-infected patients: rare spontaneous clearance correlates with weak memory CD4 T-cell responses to hepatitis C virus. AIDS. 2009;23(16):2079-89.
77. Razavi H, Elkhoury AC, Elbasha E, Estes C, Pasini K, Poynard T, et al. Chronic hepatitis C virus (HCV) disease burden and cost in the United States. Hepatology. 2013;57(6):2164-70.
78. Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings LW. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. Gastroenterology. 2010;138(2):513-21, 21 e1-6.

79. U.S. Rare Diseases Act of 2002. Public Law 107-280.
80. Poynard T, Colombo M, Bruix J, Schiff E, Terg R, Flamm S, et al. Peginterferon alfa-2b and ribavirin: effective in patients with hepatitis C who failed interferon alfa/ribavirin therapy. Gastroenterology. 2009;136(5):1618-28 e2.
81. U.S. Preventive Services Task Force. Final recommendation statement: hepatitis C screening. 2014 [cited 2015 January 23]; Available from: http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/hepatitis-c-screening.
82. El Khoury AC, Vietri J, Prajapati G. The burden of untreated hepatitis C virus infection: a US patients' perspective. Dig Dis Sci. 2012;57(11):2995-3003.
83. Ubel PA, Hirth RA, Chernew ME, Fendrick AM. What is the price of life and why doesn't it increase at the rate of inflation? Arch Intern Med. 2003;163(14):1637-41.
84. Aldy JE, Viscusi WK. Adjusting the value of a statistical life for age and cohort effects. Rev Econ Stat. 2008;90(3):573-81.
85. Nadler E, Eckert B, Neumann PJ. Do oncologists believe new cancer drugs offer good value? Oncologist. 2006;11(2):90-5.
86. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness — the curious resilience of the $50,000-per-QALY threshold. N Engl J Med. 2014;371(9):796-7.