Economically-Efficient Hepatitis C Virus Treatment Prioritization Improves Health Outcomes

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Appendix S1

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SUPPLEMENTAL METHODS

Overview of HCV natural history model

Our natural history model is a modified version of a previously-published Markov model of HCV progression and treatment.[1-3] The model follows the lifetime progression of treatment-naïve individuals with chronic HCV infection stratified by sex, age, and liver fibrosis status described by Metavir score.[4] F0 through F4 (**Figure 1 in the main paper**). Some individuals with F0 fibrosis are non-progressors and some individuals with F0 fibrosis may spontaneously clear their infection without treatment.[5] Age- and sex-specific rates of progression are based on estimates from a previously-published, empirically-calibrated HCV model.[5,6] Sex-, age-, and race-specific mortality rates were estimated using the 2006 US lifetables[7] adjusted for higher non-liver mortality rates observed among individuals infected with HCV in NHANES III (primary NHANES analysis described in Liu et al.[1]). For individuals with advanced disease (F4), there is a risk of decompensated cirrhosis or liver cancer. Treatment for individuals with decompensated cirrhosis and liver cancer may include liver transplant. Parameter values for the natural history of HCV without treatment as well as the costs and utilities associated with HCV health states are presented in **Table 1 (main paper)**.

The HCV natural history model is based on an empirically-calibrated model by Salomon et al.[5] Salomon et al. estimated a single disease progression rate for each stage (i.e., the rate from F1 to F2 is the same as the rate from F2 to F3) stratified by age and gender. The disease progression rates estimated by Salomon et al. are higher for men than women and increase with age, which is consistent with observational data.[8-10] In a high-quality meta-analysis of more than 100 studies, Thein et al.[11] estimated fibrosis-stage specific transition rates. Thein et al. found that the differences in transition rates across fibrosis stages were small (only the transition from F1 to F2 was statistically different from the other transition rates). The rates estimated by Thein et al. are consistent with the rates estimated for ages 40-59 by Salomon et al. Specifically, the annual progression rates Salomon et al. estimated for men aged 40-49 and 50-59 were 5.3% and 11.8%, respectively, and the overall annual progression rates estimated by Thein et al. ranged from 8.5% to 11.7% (the included studies had an average patient age of 43 years with 62% male). The annual progression rates Salomon et al. estimated for women aged 40-49 and 50-59 were 2.8% and 6.3%, respectively, and the annual progression rates estimated by Thein et al. in a subgroup analysis focusing only on women ranged from 4.8% to 7.0% (this analysis only included 4 studies).

Overview of HCV-treatment-budget allocation model

We developed an HCV-treatment-budget allocation model that tracks the US population of chronic HCV infected treatment-naïve and treatment-eligible individuals for 25 years, focusing on those aged 40-79. Prior to treatment, transitions between health states occur in 3-month time-steps based on age-, sex-, race-, and liver-fibrosis-stage-specific rates of disease progression as in the HCV natural history model. As years pass, people from later birth-cohorts enter the treatment-budget allocation model at age 40 based on birth-cohort specific HCV prevalence. People exit the treatment-budget allocation model when they die or are no longer treatment eligible: upon receiving treatment,

spontaneously clearing their HCV infection, reaching the age of 80, or progressing to end-stage liver disease (ESLD) or liver cancer. When individuals exit the model for reasons other than death, the model tallies their remaining lifetime discounted cost, life expectancy, and quality-adjusted life expectancy based on their health state (specific to race, sex, age, and fibrosis stage). These discounted lifetime costs, life expectancy, and quality-adjusted life-expectancy were estimated using the lifetime natural history model.

To support decisions in particular health systems, we provide our Excel model with documentation (**see Appendix S2 for model documentation** and **Appendix S3 for the Excel model**).

Initial fibrosis distribution

We estimated the race-, sex-, age-specific fibrosis-stage distribution in 2015 (presented in **Appendix Table S1**) using our HCV progression model. Each birth cohort's fibrosis-stage distribution will have been influenced by differences in HCV awareness and treatment access and uptake over time.

For each birth cohort, we assumed that the fibrosis-stage distribution at age 40 was that observed among US blood donors identified to have HCV.[12] We then applied disease progression rates, background and liver disease-related mortality rates, historical patterns of disease awareness, and historical treatment uptake rates to determine the fibrosis distribution among treatment-naïve individuals surviving to 2015.[13-16]

For each birth cohort, we assumed treatment became available in the year 2000 around the time that interferon based regimens were approved by the FDA. Based on analysis of NHANES data, we assumed that 49.7% of infected individuals were aware of their infection status,[13] and 61.2% of chronically infected individuals had a pharmacy benefit.[14] Among those with a pharmacy benefit, analysis of a commercial claims database indicated that approximately 20% of patients known to be chronically infected with HCV began treatment each year.[15] This resulted in an overall annual treatment

uptake rate of 6% per year (after year 2000). Just as we do in our forward-looking analysis, we accounted for higher rates of treatment uptake among patients with cirrhosis compared to those without.[16] Combined, these assumptions resulted in historical treatment uptake rates of 4.6% per year in individuals with F0-F2 fibrosis and 8.4% per year in individuals with F3 and F4 fibrosis after treatment became available in year 2000.

As a specific example, consider individuals aged 65-69 years in 2015. These individuals would have been aged 40-44 years in 1990. We assumed that the fibrosis-stage distribution at age 40 was similar to that observed among US blood donors identified to have HCV.[12] From 1990 to 2000, we used our model to apply background and liver-disease-related mortality and HCV disease progression, including the possibility of spontaneous clearance, with no access to treatment. Then, from 2000 until 2015, we applied mortality and HCV disease progression, but also assumed annual treatment initiation of 4.6% per year for individuals with F0-F2 fibrosis and 8.4% per year for individuals with F3 and F4 fibrosis. Among those remaining treatment-naïve in 2015, we recorded the fibrosis distribution. We used the same approach to estimate the fibrosis stage distribution in 2015 for all age groups.

Non-treatment costs and quality-adjusted life-years

We estimated the annual health care costs of the untreated HCV health states based on the average US age-specific baseline health care costs, increased by a factor of 1.37 due to higher-than-average comorbidities in individuals with chronic-HCV infection, and additional fibrosis-stage-specific costs attributable to chronic HCV infection.[2,17,18] We estimated the annual quality-of-life weights of the untreated HCV health states based on the average US age-specific utility weights,[19,20] multiplied by fibrosis-stage-specific weights.[21-25]

When individuals exit the treatment-budget allocation model because they spontaneously clear their HCV infection, reach age 80, progress to decompensated cirrhosis or liver cancer, or receive

treatment, the model counts their age-, race-, sex-, and fibrosis stage specific lifetime discounted costs and QALYs. For example, the lifetime discounted costs and QALYs for progressing to decompensated cirrhosis or liver cancer includes monthly health care costs and utilities associated with these health states, plus the expected lifetime discounted costs of liver transplant. We estimated these remaining lifetime outcomes using the lifetime horizon HCV natural history model based on our previously published Markov model of treatment[1-3] and all input values are presented in the model on the "Inputs" tab of the Excel workbook (**Appendix S3**).

Lifetime discounted costs and quality-adjusted life-years for patients who receive treatment

There are now nine interferon-free HCV treatments available with efficacies exceeding 90% and with similarly high wholesale prices (**Appendix Table S2**). We estimated the cost and long-term outcomes from a full course of HCV treatment using representative values for the costs, immediate effectiveness, and long-term outcomes of treatment. We estimated the cost of a complete course of treatment using the cost of sofosbuvir/ledipasvir (Harvoni, Gilead Sciences) for the treatment of genotype 1 patients because genotype 1 is the most common genotype (70-75% of chronically infected individuals[26-31]) and because sofosbuvir/ledipasvir represents the largest market share.[32] Total costs were thus calculated using treatment regimen of 8 weeks for patients with F0-F3 fibrosis and 12 weeks for patients with compensated cirrhosis at a weekly costs of $5040 per week accounting for the average reported discount of 46% on sofosbuvir/ledipasvir (full price of $7875/week).[33]

In the treatment-budget allocation model, individuals who receive treatment enter an absorbing state (they exit the population of treatment eligible individuals). The model tallies the average lifetime discounted costs, life years, and QALYs for an individual receiving treatment—a weighted average of individuals who achieve SVR and those who do not—based on their health state (specific to race, sex,

age, and fibrosis stage). These discounted lifetime costs, life expectancy, and quality-adjusted life-expectancy were estimated using the lifetime natural history model.

In the lifetime natural history model, treatment effectiveness was assumed to be 94% which is consistent with the effectiveness of new all-oral direct-acting antiviral treatment options across most genotypes (**Appendix Table S2**). Individuals who do not achieve sustained viral response continue progression with no opportunity for retreatment. Individuals who achieve sustained viral response transitioned to recovered states with no HCV infection. The model does not include a possibility of reinfection. Recovered states are stratified by a history of mild (F0 or F1), moderate (F2 or F3), and severe fibrosis (F4) with lower risks of liver-related morbidity or mortality, non-liver-related mortality, lower health care costs, and higher quality of life than prior to treatment. The amount of reduction in non-liver related mortality after SVR is highly uncertain. In order to increase confidence in our input values, we compared predictions of the lifetime HCV natural history model to the observed reduction in all-cause mortality associated with successful treatment observed in Backus et al.,[34] finding our model predictions to be consistent with those reported by Backus et al. Individuals recovered from F4 fibrosis are assumed to have some residual and irreversible liver damage and so have higher health care costs and lower quality of life than the individuals in the other recovered health states. The higher-than-average population risk of liver-related morbidity and mortality (decompensated cirrhosis and liver cancer) remaining after SVR is not captured explicitly in the model; the consequences of liver cancer and other remaining liver morbidity are captured indirectly through lifelong increased costs and lower quality of life (compared to a population of individuals with no history of HCV).

Optimization Framework

An optimization problem has three components: the objective function, the decisions, and the constraints.

Objective: In our problem, the objective was to maximize the discounted net monetary benefit of the population over the 25-year analytic timeframe considering the benefits and costs over a lifetime to anyone with chronic HCV during this 25-year period. Net monetary benefit (NMB) is the sum of all the discounted benefits multiplied by the willingness-to-pay threshold less then sum of all the discounted costs[35]:

$$NMB = \sum_t \frac{\lambda Q_t - C_t}{(1+r)^t}$$

where λ is the willingness-to-pay threshold, Q_t is the benefits measured in QALYs in year t, C_t is the costs in year t, and r is the annual discount rate (3%). The HCV population model described above calculates Q_t and C_t including the effects of treatment decisions in each cycle. This objective function is nonlinear because the fibrosis-stage distribution in each cycle is dependent on the treatment decisions in the previous cycle. In the base case, we assumed a willingness-to-pay of $100,000 per QALY gained[36] and we varied this assumption in sensitivity analysis.

Decisions: The decisions were which year to prioritize treatment offers to each of the 40 patient subgroups. Patient subgroups were defined on age (40-44, 45-49, … , 75-79) and fibrosis stage (F0, F1, …, F4). For each patient subgroup, the decision alternatives were to prioritize the subgroup immediately (time 0), after 1 year, after 2 years, …, or after 24 years.

Constraints: There were 25 budget constraints, one for each year, stating that the amount spent on HCV treatment could not exceed the annual treatment budget. In the base case, the annual treatment budget was $8.6 billion. We assume that unspent budget from one year is not transferred to future years and permit up to 1% budget overspend in each year.

The decision space for this problem is very large–each of the 40 subgroups has 25 possible values resulting in 8.27×10^{55} possible sets of decisions ($25^{40} = 8.27 \times 10^{55}$). Many of these possible sets of decisions, such as those that immediately prioritize all subgroups, are infeasible because they violate the budget constraints. Furthermore, many feasible sets of decisions leave a large portion of the budget unspent in the first few years. Consistent with cost-effectiveness analyses performed by others,[37-49] our model indicates treatment has a positive incremental net monetary benefit (equivalent to an incremental cost effectiveness ratio of less than $100,000 per QALY gained) for all subgroups compared to either never receiving treatment or waiting to receive treatment later (after reaching a specific age or disease progression) (**Appendix Table S3**). This implies that the optimal solution will include treating all subgroups as early as possible. Therefore, solutions that leave a large portion of the budget unspent in the first few years are easily improved upon by treating one or more subgroups earlier.

In order to search the large number of sets of decisions efficiently and to avoid evaluating solutions which are easily improved upon because they leave unspent budget, we developed an algorithm to focus on searching only feasible sets of decisions which spend nearly all but do not exceed the annual budget constraints using a two-step process. In the first step, we randomly generated the order in which patient subgroups would be considered for prioritization (each subgroup was assigned a number between 1 and 40). In the second step, in the order determined in step 1, we sequentially identified the least possible time to prioritization for each subgroup as to not violate any annual budget constraint.

We used this process to generate a large number (>10,000) of feasible sets of decisions which spend nearly all but do not exceed the annual budget constraints. For each of these candidate sets of decisions, we calculated the lifetime discounted costs, quality-adjusted life-years, and the net monetary benefit. Finally, we identified the set or sets of decisions with the greatest net monetary benefit among

all the candidate sets. We inspected the top 10 sets for consistent policies (i.e., ones with similar patterns in the timing of groups prioritized) as evidence of reaching a global optimum.

Model implementation

The HCV natural history model was implemented in Treeage Pro 2009 Suite (TreeAge Software, Williamstown, Massachusetts). The treatment-budget allocation model was implemented in Microsoft Excel 2013 for Windows and Visual Basic for Applications (VBA) (Microsoft Corporation, Redmond WA). To support decisions in particular health systems, we provide our Excel model with detailed supporting documentation (**see Appendix S2 for model documentation** and **Appendix S3 for the Excel model**). The treatment-budget allocation model can be used as a calculator, to identify the budget impact, health, or health-economic outcomes of a particular set of prioritization decisions, or users can use the optimization framework to identify the set of prioritization decisions that maximize population net monetary benefit. As programmed, the optimization framework only searches integer values (prioritization immediately (time 0), after 1 year, after 2 years, etc.) for the decision variables. However, non-integer values of years until subgroup prioritization (i.e., 1.25 years) are permissible when the model is used as a calculator.

SUPPLEMENTAL RESULTS

Supplemental base case results

Appendix Table S3 presents the incremental cost effectiveness ratio (ICER) in dollars per QALY-gained for immediate HCV treatment compared to the next-best non-dominated alternative for each subgroup. For each subgroup, we considered the following treatment prioritization strategies: Never treatment; Treatment prioritization after progression to each possible fibrosis stage more severe than the subgroup's current health; Treatment prioritization after aging to each possible age group older than the subgroup's current age; and Immediate treatment prioritization. People aged 40-44 years with fibrosis stage F1 have the lowest ICER ($17,600 per QALY gained). For younger age categories, individuals with F1 fibrosis have the lowest ICER for immediate treatment, typically followed by fibrosis stages F2, F3, F4 (compensated cirrhosis). For older age-categories, individuals with F2 or F3 fibrosis have the lowest ICERs for immediate treatment. For people with F0 fibrosis, strategies of delaying treatment until disease progression appear on the efficient frontier indicating that at some treatment prices, it may be cost-effective to delay treatment. This is intuitive because, in addition to being the furthest from the long-term disease complications of decompensated cirrhosis and liver cancer, a fraction of F0 do not appear to progress and there remains a possibility of spontaneous viral clearance from this health state. However, at the base case prices considered in our analysis, immediate treatment prioritization for patients with F0 fibrosis compared to delaying treatment until progression to F1 fibrosis costs between $33,000 per QALY-gained (for ages 40-44) and $75,400 per QALY-gained (for ages 75-79) indicating that immediate treatment is cost-effective for all patient subgroups at a willingness-to-pay threshold of $100,000 per QALY-gained. Within each fibrosis-stage, younger individuals have lower ICERs for immediate treatment compared to no treatment due to lower competing mortality risks.

Appendix Table S4 presents the average time (in years) to receive treatment for the 3 million individuals in the initial cohort stratified their initial fibrosis stage. The average time to receive

treatment across the entire population is similar for all prioritization schedules. This is consistent with standard queuing theory where the average wait time is unchanged by the order in which people in line are served (called queue discipline).[50] Queue discipline only influences the distribution of wait times across individuals in the line. The variation in average waiting time observed across the schedules is because, as an implementation rule in all of the schedules except FCFS, priority is not assigned to a subgroup until all of the expected demand from that subgroup can be accommodated. This has the greatest effect on the schedule focused only on severity where treatment is not offered to anyone in a fibrosis subgroup until the entire expected demand from the subgroup (10% of the population each year) can be offered treatment.

Average waiting times vary across fibrosis stages for FCFS due to differential rates of censoring (becoming treatment ineligible). First, people with less severe disease are more likely to be young and so are less likely to die from other age-related causes or to 'age-out' of the model by reaching age 80. Second, individuals with less severe disease are less likely to progress to end-stage liver-disease before they receive treatment.

Appendix Figure S1 presents the proportion of individuals in the initial cohort (of 3 million people aged 40-79) who received treatment over the first 15 years stratified by their initial fibrosis stage. Reasons for not receiving treatment within 15 years include transition to remission (from F0 only), transition to end-stage liver disease (decompensated cirrhosis or liver cancer), reaching age 80, death, or having not yet demanding treatment (in the base case, we assume 10% average annual demand among prioritized groups).

Over the first 15 years, FCFS and the schedule based only on optimization treated 62% of the initial cohort of people with F0 fibrosis, whereas the other schedules only treated between 51% and 54% of the initial cohort with F0 fibrosis. Conversely, FCFS and the schedule based only on optimization

treated 51% of the initial cohort with F4 fibrosis (whereas all other schedules treated 56% of the initial cohort with F4 fibrosis).

Sensitivity analysis: optimal treatment prioritization

Appendix Figure S2 presents the prioritization sequence identified by optimization exploring the effects of price reductions. Price reductions enable more people to receive treatment and so faster prioritization of subgroups. If drug prices decrease at a rate of 10% per year, an additional 86,143 people will receive treatment over the first five years and patient subgroups can be prioritized approximately one year earlier than in the base case (**Appendix Figure S2B**). If drug prices fall more dramatically, as has been seen in Europe,[51] all patient subgroups can be prioritized two years earlier and all groups will be prioritized within the first 3 years (**Appendix Figure S2C**).

If dramatic reductions in cost occur simultaneously with higher patient demand for treatment, the fundamental trade-off remains in place and the optimal patient prioritization sequence is consistent with the base case (**Appendix Figure S2D**). That said, in a scenario with dramatically reduced prices and higher demand individual and population health benefits improve: nearly 500,000 more patients receive treatment and 25,700 fewer individuals progress to ESLD over the first 5 years (comparing the outcomes of the optimized schedule in both scenarios).

Appendix Figure S3 presents the prioritization sequence identified by optimization exploring the effects of higher prices, higher demand, changes in the fibrosis-stage-specific demand, and changes in the initial fibrosis distribution. In addition to those shown, we performed sensitivity analysis on the total number of HCV infected individuals, age and fibrosis distributions, demand rates, fibrosis-stage-specific baseline health care costs, treatment budgets, and combinations of these parameters.

In the base case, the optimized schedule prioritized treatment sooner to those with more advanced fibrosis and those who are younger relative to those with less advanced fibrosis and those who are older. This pattern of prioritization was robust to changes in assumptions such as the age distribution of individuals with chronic HCV (not shown), fibrosis distribution (**Appendix Figure S3F**), differences in demand across fibrosis stages (**Appendix Figure S3E**), disease progression rates (**Appendix Figure S3G and S3H**), and baseline health care costs for patients with more advanced disease (not shown. While the general pattern of subgroup prioritization remained the same, the time until each patient subgroup was offered treatment lengthened with smaller annual budgets, higher patient demand, and higher treatment price (**Appendix Figure S3A-D**).

We also performed sensitivity analysis on the willingness-to-pay threshold. When the willingness-to-pay threshold was reduced below the incremental cost effectiveness ratio of treating a specific subgroup compared to either never treating them or waiting to treat them later (after progression), the optimal policy is to never offer treatment to that group. The groups for whom it is most costly to gain additional QALYs (i.e., with the highest ICERs) are older individuals and individuals with the least advanced disease (F0 and F1). These groups are already prioritized for later treatment in the base case analysis. Therefore, changing the willingness-to-pay threshold did not substantially change the order in which subgroups would be prioritized (results not shown).

Sensitivity analysis: higher demand and higher cost of treatment

Appendix Figure S4 presents the prioritization schedules for a scenario analysis which assumed a higher demand for treatment and a higher cost of treatment (but with the same total treatment budget). Specifically, demand for treatment was 11.8% per year for individuals with F0 to F2 fibrosis and 21.5% per year for individuals with F3 and F4 (compared to 7.9% per year for individuals with F0 to F2 fibrosis and 14.3% per year for individuals with F3 and F4 fibrosis in the base case) and the average cost of treatment increased to $51,800 for F0-F3 and $77,300 for F4 (compared to $40,320 and $60,480 in the base case). FCFS provided treatment to only one-third of those who request it in the first two years. After 5 years, the proportion of the demand which was satisfied increased to 50%. The schedule which prioritizes on disease severity without stratification by age, prioritized all individuals with F4 fibrosis immediately. One of the assumptions of this schedule is that priority cannot be assigned to the next fibrosis severity level unless all the expected demand can be satisfied. As a result, individuals with F3 fibrosis were not able to be prioritized until year 9. In contrast, the schedules which assign priority based on disease severity with age stratification prioritized all individuals with F4 fibrosis immediately and all individuals with F3 fibrosis within 5 years. The schedule which optimized the lifetime net monetary benefit of the population subject to the treatment budget, prioritized subgroups with F2-F4 fibrosis younger than age 60 immediately and prioritized all subgroups with F1-F4 fibrosis younger than age 70 within six years. In the schedule which first prioritized patients with F4 fibrosis and then used optimization to identify the priority sequence, younger patients (<65 years) with moderate-to-severe disease (F2 and F3) are prioritized for treatment in the first five years, but older patients and those with less severe disease wait 8 or more years for prioritization. In the schedule that first prioritized patients with F4 fibrosis followed by patients with F3 fibrosis, most patients with F3 fibrosis could not be prioritized in the first year. All patient groups with F3 fibrosis were prioritized within the first 6 years.

In this scenario, if budgets are limited to $8.6 billion per year, all prioritization schedules considered would consume the budget entirely for the first ten years. **Appendix Figure S5** presents the main health outcomes for the scenario with higher demand and higher treatment costs. Schedules that prioritize disease severity prevented more cases of ESLD than FCFS and optimization: approximately 30,000 more cases prevented over 5 years and 60,000 more cases prevented over 10 years. After 2 years, there were nearly 100,000 fewer people with F4 fibrosis under schedules that prioritized disease severity than under FCFS and optimization. After 5 years, there were 130,000 fewer people with F4 fibrosis under schedules the prioritized based on severity and stratified by age (Severity+Older and Severity+Younger) than under FCFS and optimization. As in the base case, optimization yielded the most QALYs and the greatest population net monetary benefit.

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APPENDIX TABLE S1. Number of individuals and fibrosis stage distribution of the initial cohort

Cohort	Number of people*	Fibrosis stage				
		F0	F1	F2	F3	F4
White males						
40-44	84,372	33.0%	34.6%	17.8%	12.4%	2.2%
45-49	188,865	27.0%	33.4%	22.8%	12.8%	4.1%
50-54	300,328	20.5%	28.8%	27.1%	15.8%	7.8%
55-59	432,580	15.3%	21.6%	28.3%	20.3%	14.5%
60-64	387,047	12.4%	13.6%	24.2%	23.1%	26.7%
65-69	151,960	11.8%	6.9%	16.9%	21.5%	42.9%
70-74	41,566	13.3%	3.1%	9.8%	16.0%	57.7%
75-79	21,313	16.5%	1.1%	4.5%	9.3%	68.6%
White females						
40-44	61,764	33.0%	34.6%	17.8%	12.4%	2.2%
45-49	139,299	29.6%	34.9%	21.1%	11.7%	2.7%
50-54	216,758	25.1%	33.5%	24.9%	12.5%	4.0%
55-59	191,790	20.4%	30.1%	28.4%	15.0%	6.2%
60-64	139,640	16.2%	24.5%	29.5%	18.9%	10.8%
65-69	51,698	13.2%	18.2%	28.2%	22.4%	17.9%
70-74	15,439	11.8%	12.7%	24.7%	23.9%	26.9%
75-79	12,361	11.8%	8.2%	19.7%	23.1%	37.2%
Black males						
40-44	6,353	33.0%	34.6%	17.8%	12.4%	2.2%
45-49	22,433	27.0%	33.4%	22.8%	12.8%	4.1%
50-54	50,425	20.5%	28.8%	27.1%	15.8%	7.8%
55-59	78,590	15.4%	21.6%	28.3%	20.3%	14.5%
60-64	87,916	12.4%	13.6%	24.3%	23.1%	26.6%
65-69	57,494	11.8%	7.0%	16.9%	21.5%	42.8%
70-74	24,146	13.4%	3.1%	9.9%	16.0%	57.6%
75-79	9,802	16.6%	1.1%	4.5%	9.3%	68.5%
Black females						
40-44	11,054	33.0%	34.6%	17.8%	12.4%	2.2%
45-49	21,141	29.6%	34.9%	21.1%	11.7%	2.7%
50-54	43,528	25.1%	33.5%	24.9%	12.5%	4.0%
55-59	72,439	20.5%	30.1%	28.4%	14.9%	6.2%
60-64	58,127	16.2%	24.5%	29.5%	18.9%	10.8%
65-69	25,451	13.2%	18.2%	28.3%	22.4%	17.9%
70-74	12,296	11.9%	12.7%	24.7%	23.9%	26.8%
75-79	10,724	11.8%	8.2%	19.7%	23.1%	37.1%
TOTAL (n)	**3,028,700**	**573,878**	**710,615**	**740,361**	**532,214**	**471,631**

***** Estimated by the number of HCV-infected individuals in the non-institutionalized US population (3.1 million) stratified by age, race, and sex using the National Health and Nutrition Examination Survey (NHANES) (1999-2010) multiplied by 98% of all chronic HCV-infected individuals eligible for new treatments. [52,53]

APPENDIX TABLE S2. Direct-acting antivirals with FDA approval to treat HCV genotypes 1-4, wholesale cost of treatment, and effectiveness (probability of achieving sustained virologic response).

Genotype	Frequency [26-31]	Treatment regimen	Estimated full cost of treatment*	Effectiveness
1	1a: 50-70% 1b: 10-30%	sofosbuvir/ledipasvir	F0-F3: $63,000 F4: $94,500	F0-F3 [54,55]: 94-100% F4 [54]: 94-100%
		ombitasvir/paritaprevir/ ritonavir/dasabuvir + ribavirin	1a, F0-F3: $84,700 1a, F4: $168,000 1b, F0-F3:$83,300 1b, F4: $84,700	1a, F0-F3 [56,57]: 95-97% 1a, F4 [58]: 92% 1b, F0-F3 [56,57]: 98-99% 1b, F4 [58]: 100%
		sofosbuvir/simeprevir	$150,000	F0-F3 [59]: 97% F4 [60,61]: 88%-94%
		sofosbuvir/daclatasvir + ribavirin	$63,000	F0-F3 [62]: 93-95% F4 [63]: 82%
		elbasvir/grazoprevir	$54,600	F0-F3 [64]: 92-99% F4 [64]: 97%
		sofosbuvir + ribavirin	$84,700	1a, F0-F3 [65]: 92% 1b, F0-F3 [65]: 82% F4 [65]: 80%
		glecaprevir/pibrentasvir	$26,400	F0-F3 [66]: 97 (90-100%) F4 [67]: 96% (82-99%)
		sofosbuvir/velpatasvir	$74,760	F0-F3 [68]: 99% (98-100%) F4 [68,69]: 99% (95-100%)
2	9-22%	sofosbuvir + ribavirin	$84,700	F0-F3 [65,70]: 97%-100% F4 [65]: 80%
		glecaprevir/pibrentasvir	$26,400	F0-F3 [66]: 96 (80-100%)
		sofosbuvir/velpatasvir	$74,760	F0-F3 [68]: 100% (96-100%) F4 [68,69]: 100% (96-100%)
3	5-12%	sofosbuvir/daclatasvir + ribavirin	$63,000	F0-F3 [62,71]: 89-95% F4 [63,71,72]: 73-88%
		glecaprevir/pibrentasvir	$26,400	F0-F3 [66]: 93 (80-97%) F4 [67]: 96% (82-99%)
		sofosbuvir/velpatasvir	$74,760	F0-F3 [73]: 97% (94-99%) F4 [69,73]: 91% (90-97%)

4	<2%	sofosbuvir/ledipasvir	F0-F3: $63,000-94,500 F4: $94,500	F0-F4 [74-76]: 93-100%
		ombitasvir/paritaprevir/ritonavir +ribavirin	F0-F3: $76,700 F4: $102,300	F0-F3 [77,78]: 90-100% F4 [78,79]: 91-98%
		elbasvir/grazoprevir	$54,600	F0-F3 [64,80]: 92-99% F4 [64,80]: 97%
		glecaprevir/pibrentasvir	$26,400	F0-F3 [66]: 90-100%
		sofosbuvir + ribavirin	$84,700	F0-F3 [65]: 96% F4 [65]: 80%
		sofosbuvir/velpatasvir	$74,760	F0-F3 [68]: 100% (96-100%) F4 [68,69]: 100% (94-100%)

* Wholesale acquisition cost including ribavirin if required. Actual costs vary substantially due to local manufacturer-provider or manufacturer-payer agreements

APPENDIX TABLE S3. Incremental cost effectiveness ratio (ICER) ($ per QALY-gained) for immediate HCV treatment prioritization compared to the next-best non-dominated strategy for each subgroup. For each subgroup, we considered the following treatment prioritization strategies: Never treatment; Treatment prioritization after progression to each possible fibrosis stage more severe than the subgroup's current health; Treatment prioritization after aging to each possible age group older than the subgroup's current age; and Immediate treatment prioritization. Only strategies on the efficient frontier are shown. If only one ICER is shown, it is the ICER of immediate treatment prioritization compared to never treatment; in these cases, all other treatment prioritization timings were dominated. (Detailed incremental costs and QALYs for all strategies are available from the authors on request.)

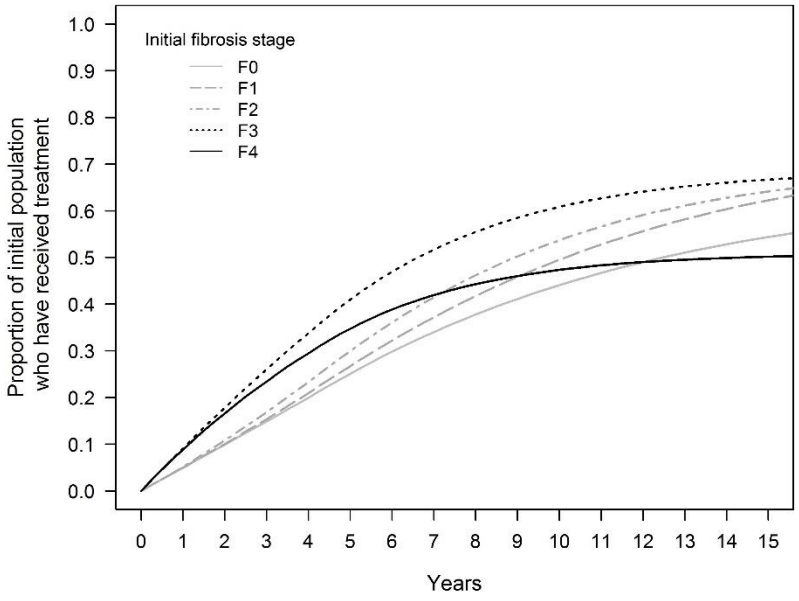
Age	Fibrosis stage				
	F0	F1	F2	F3	F4
40-44	F1: 22,100 Now: 33,000	17,600	18,100	18,300	19,900
45-49	F1: 23,800 Now: 34,000	19,500	20,000	20,200	21,900
50-54	F1: 26,000 Now: 37,200	22,000	22,200	22,400	24,200
55-59	F1: 28,900 Now: 41,500	25,000	25,100	25,100	27,200
60-64	F1: 34,000 Now: 50,500	29,900	29,600	29,400	31,500
65-69	F1: 40,800 Now: 68,300	38,600	37,700	36,700	39,200
70-74	F3: 44,800 F1: 46,500 Now: 77,300	48,200	46,900	45,100	48,500
75-79	F3: 47,000 F1: 50,200 Now: 75,400	F3: 52,600 Now: 55,000	F3: 51,300 Now: 54,200	49,900	55,300

APPENDIX TABLE S4. Average time (in years) to receive treatment among individuals in the initial cohort by their initial fibrosis stage (not necessarily the stage at which they received treatment).

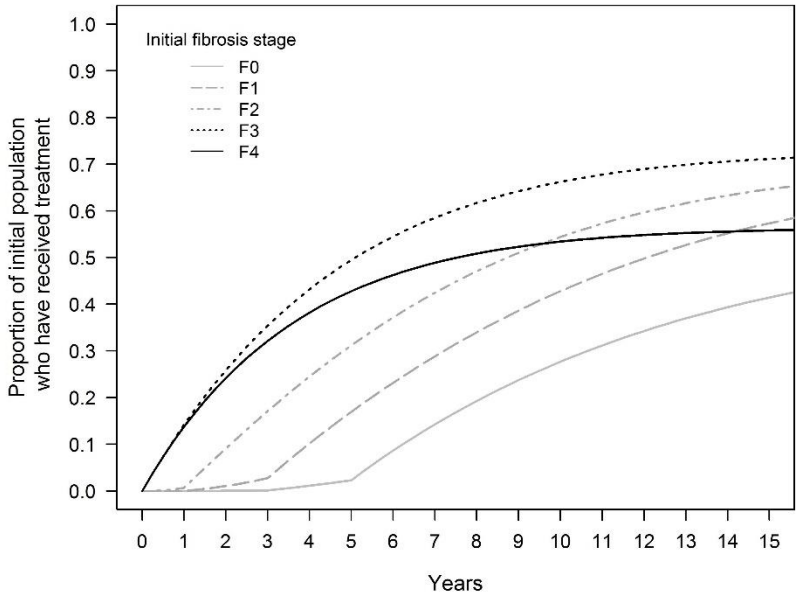
Initial fibrosis stage	Number of individuals	Prioritization schedule						
		FCFS	Severity	Severity+ Older	Severity+ Younger	Optimization	F4+ Optimization	F4+F3+ Optimization
F0	573,878	7.4	10.5	9.7	9.8	9.6	9.6	9.5
F1	710,615	7.6	8.9	8.6	8.6	7.3	7.9	8.0
F2	740,361	6.6	6.6	6.4	6.3	6.1	6.3	6.5
F3	532,214	4.8	4.1	4.1	4.1	4.3	4.3	4.1
F4	471,631	4.0	3.3	3.3	3.3	3.8	3.3	3.3
Total	**3,028,700**	**6.3**	**6.9**	**6.6**	**6.7**	**6.4**	**6.5**	**6.5**

APPENDIX FIGURE S1. Proportion of initial population who received treatment over time stratified by initial fibrosis stage (not necessarily the stage at which they received treatment).

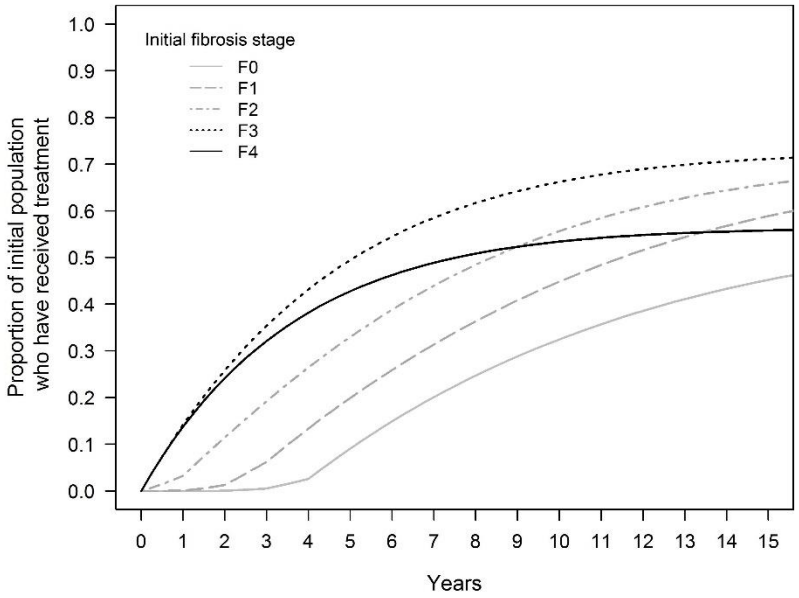
(A) First-come first-served. Patients from all subgroups receive treatment on a first-come first-served basis until the annual budget is exhausted or annual treatment is satisfied.



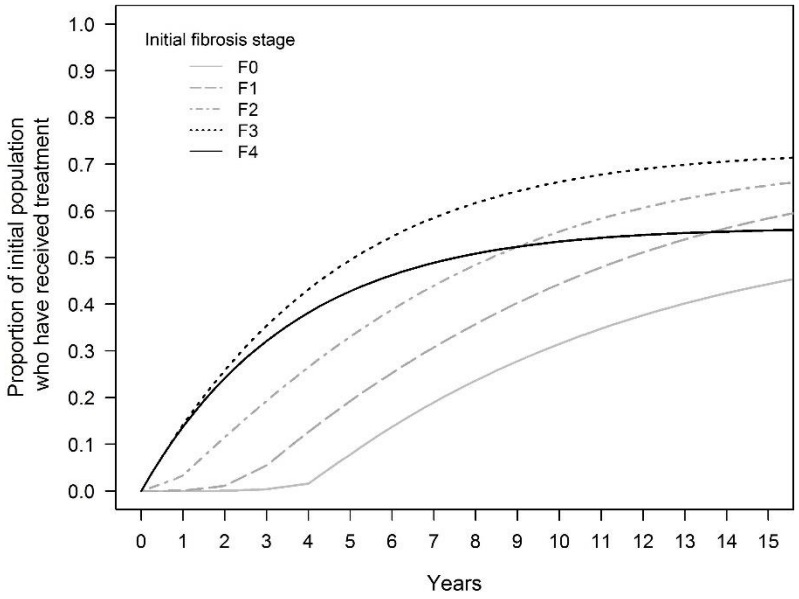
(B) Priority to patients with the most severe disease (without stratification by age). Patients are prioritized by fibrosis stage only. Priority can only be opened to the next fibrosis-stage subgroup if the expected demand from all age categories in that subgroup can be satisfied in the coming year.



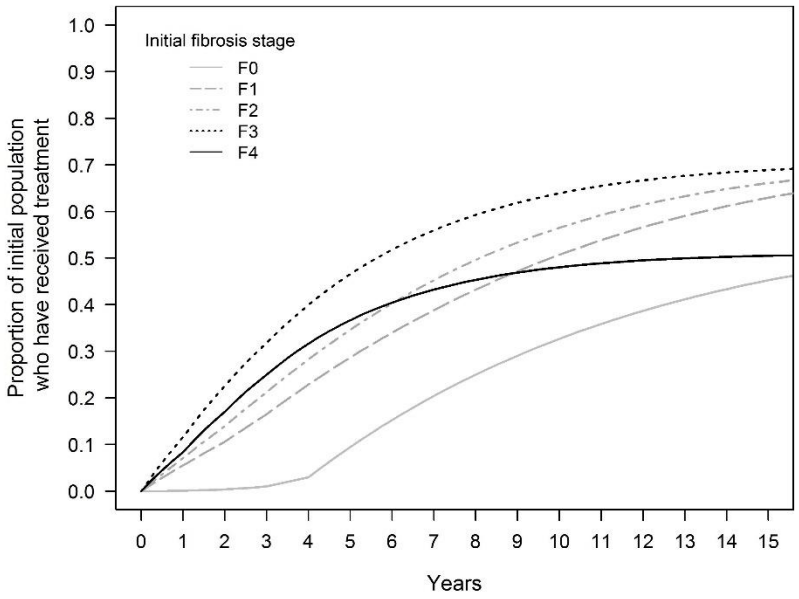
(C) Priority to patients with the most severe disease and older patients. Patients with most severe disease (F4) and who are in the oldest age category (75-79) are given first priority, followed by those with severe disease in the next age (age 65-69), and so on as long as the expected demand from the next subgroup can be satisfied in that year. Priority is opened to patients with F3 fibrosis in the oldest age category after all patients with F4 fibrosis are prioritized.



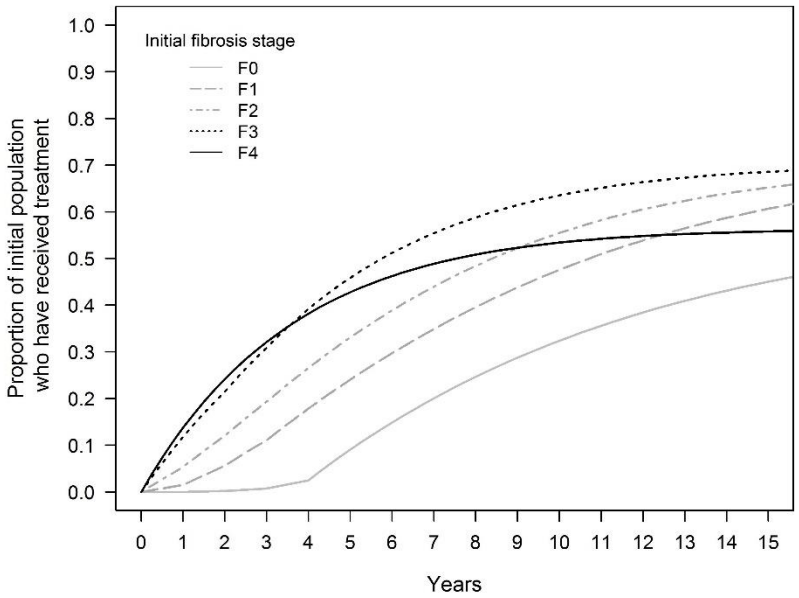
(D) Priority to patients with the most severe disease and younger patients. Patients with most severe disease (F4) and who are in the youngest age category (40-44) are given first priority, followed by those with severe disease in the next age (age 45-49), and so on as long as the expected demand from the next subgroup can be satisfied in that year. Priority is opened to patients with F3 fibrosis in the youngest age category after all patients with F4 fibrosis are prioritized.



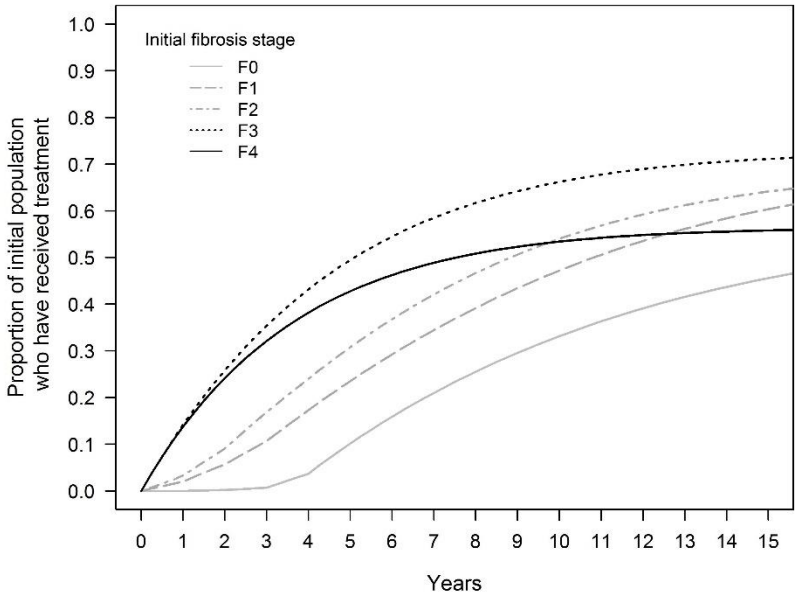
(E) Priority based on optimization. The prioritization schedule is determined via searching across feasible prioritization rules (those that do not exceed the treatment budget for any year) for one that maximizes lifetime population net monetary benefit.



(F) First priority to patients with the most severe disease (F4) followed by priority based on optimization. Patients with most severe disease (F4) are given first priority. The remainder of the prioritization schedule is determined via searching across feasible prioritization rules (those that do not exceed the treatment budget for any year) for one that maximizes lifetime population net monetary benefit.



(G) First priority to patients with the most severe disease (F4, then F3) followed by priority based on optimization. Patients with most severe disease (F4) are given first priority, followed by those with F3 fibrosis. The remainder of the prioritization schedule is determined via searching across feasible prioritization rules (those that do not exceed the treatment budget for any year) for one that maximizes lifetime population net monetary benefit.



APPENDIX FIGURE S2. Time to subgroup prioritization using the patient prioritization schedule based on optimization with the objective of maximizing population net monetary benefit subject to an annual treatment budget of $8.6 billion for scenarios exploring price reductions.

Legend

	Time to prioritization
	Immediate
	1 year
	2 years
	3-4 years
	5-6 years
	7-8 years
	>8 years

(A) Base case scenario

Age category	Liver fibrosis stage				
	F0	F1	F2	F3	F4
40-44	3	3			
45-49	3				
50-54	4				
55-59	4				
60-64	4	2			
65-69	4	3	2	1	1
70-74	4	3	2	3	2
75-79	4	3	3	3	3

(B) Drug cost decreases at 10% per year until the price falls to 50% of the base case

Age category	Liver fibrosis stage				
	F0	F1	F2	F3	F4
40-44	2				
45-49	2				
50-54	2	1			
55-59	2				
60-64	2				
65-69	3	2	1	1	1
70-74	3	2	1	1	2
75-79	3	2	2	2	2

(C) Drug cost decreases at 25% per year until the price falls to 25% of the base case

Age category	Liver fibrosis stage: F0	F1	F2	F3	F4
40-44	1				
45-49	1				
50-54	2	1			
55-59	1				
60-64	2				
65-69	2				
70-74	2	1	1	1	1
75-79	2	1	1	1	1

(D) Drug cost decreases at 25% per year until the price falls to 25% of the base case and higher demand (11.8% per year for individuals with F0 to F2 fibrosis and 21.5% per year for individuals with F3 and F4)

Age category	Liver fibrosis stage: F0	F1	F2	F3	F4
40-44	3	2	0	0	0
45-49	3	2	2	0	0
50-54	3	2	1	0	0
55-59	3	2	2	0	0
60-64	3	2	2	1	0
65-69	3	2	2	1	1
70-74	3	3	3	3	3
75-79	3	3	3	3	3

APPENDIX FIGURE S3. Time to subgroup prioritization using the patient prioritization schedule based on optimization with the objective of maximizing population net monetary benefit subject to an annual treatment budget of $8.6 billion for scenarios exploring higher prices, higher demand, changes in the fibrosis-stage-specific demand, and changes in the initial fibrosis distribution.

Legend

	Time to prioritization
	Immediate
	1 year
	2 years
	3-4 years
	5-6 years
	7-8 years
	>8 years

(A) Base case scenario

Age category	Liver fibrosis stage: F0	F1	F2	F3	F4
40-44	3	3			
45-49	3				
50-54	4				
55-59	4				
60-64	4	2			
65-69	4	3	2	1	1
70-74	4	3	2	3	2
75-79	4	3	3	3	3

(B) Higher drug cost: Drug cost is $51,800 for F0-F3 and $77,300 for F4 (compared to $40,320 and $60,480 in the base case)

Age category	Liver fibrosis stage: F0	F1	F2	F3	F4
40-44	6				
45-49	6	1			
50-54	6	2			
55-59	7	2			
60-64	7	3	1		
65-69	7	6	1	3	4
70-74	7	6	5	5	5
75-79	7	6	5	5	6

(C) Higher demand: Demand for treatment is 11.8% per year for individuals with F0 to F2 fibrosis and 21.5% per year for individuals with F3 and F4 (compared to 7.9% per year for individuals with F0 to F2 fibrosis and 14.3% per year for individuals with F3 and F4 fibrosis in the base case).

Age category	Liver fibrosis stage: F0	F1	F2	F3	F4
40-44	5	2			
45-49	6				
50-54	6	2			
55-59	6	4			
60-64	7	2	2		1
65-69	7	6	4	4	3
70-74	7	6	5	5	5
75-79	7	5	5	4	6

(D) Higher demand and higher drug cost: Drug cost is $51,800 for F0-F3 and $77,300 for F4 and demand for treatment is 11.8% per year for individuals with F0 to F2 fibrosis and 21.5% per year for individuals with F3 and F4.

Age category	Liver fibrosis stage: F0	F1	F2	F3	F4
40-44	8	1			
45-49	9	4			
50-54	9	4			
55-59	9	4			
60-64	9	5	2	1	3
65-69	9	5	2	5	6
70-74	9	8	7	8	7
75-79	9	8	8	8	8

(E) Equal demand across fibrosis stages: Demand for treatment is 10% per year for all fibrosis stages.

Age category	Liver fibrosis stage: F0	F1	F2	F3	F4
40-44	3				
45-49	3				
50-54	4				
55-59	3				
60-64	4	1			
65-69	4	2	2		1
70-74	4	2	2	2	2
75-79	4	2	2	2	2

(F) Initial fibrosis distribution shifted towards more patients with severe disease: Absolute reduction of 1% in the age-specific proportion of patients with fibrosis stages F0-F3; 4% absolute increase in the age-specific proportion of patients F4 fibrosis.

Age category	Liver fibrosis stage				
	F0	F1	F2	F3	F4
40-44	4				
45-49	4				
50-54	4				
55-59	4	1			
60-64	4	1			
65-69	4	2	1	1	2
70-74	5	2	3	3	3
75-79	4	2	2	2	3

(G) Slower disease progression rates: 65% reduction in the base case progression rates for all stages of disease progression including progression from F4 to HCC and ESLD

Age category	Liver fibrosis stage				
	F0	F1	F2	F3	F4
40-44	3				
45-49	3				
50-54	3				
55-59	3				
60-64	3				1
65-69	4				2
70-74	4	2	2	1	4
75-79	4	2	2	2	4

(H) Faster disease progression rates: 65% increase in the base case progression rates for all stages of disease progression and a 100% increase in the progression from F4 to HCC and ESLD.

Age category	Liver fibrosis stage				
	F0	F1	F2	F3	F4
40-44	4	2			
45-49	3	2			
50-54	4				
55-59	4				
60-64	4				
65-69	4	2	1	2	1
70-74	4	3	2	2	3
75-79	4	3	3	3	3

APPENDIX FIGURE S4. Prioritization schedules assuming demand for treatment is 11.8% per year for individuals with F0 to F2 fibrosis and 21.5% per year for individuals with F3 and F4 (compared to 7.9% per year for individuals with F0 to F2 fibrosis and 14.3% per year for individuals with F3 and F4 fibrosis in the base case) and the average cost of treatment increases to $51,800 for F0-F3 and $77,300 for F4 (compared to $40,320 and $60,480 in the base case).

Legend

	Time to prioritization
	Immediate
	1 year
	2 years
	3-4 years
	5-6 years
	7-8 years
	>8 years

(A) First-come first-served.

Year	Proportion of demand satisfied
0	31%
1	34%
2	37%
3	40%
4	44%
5	49%
6	56%
7	64%
8	74%
9	89%
10+	100%

(B) Priority to patients with the most severe disease (without stratification by age).

Age category	Liver fibrosis stage				
	F0	F1	F2	F3	F4
40-44	13	12	11	9	
45-49	13	12	11	9	
50-54	13	12	11	9	
55-59	13	12	11	9	
60-64	13	12	11	9	
65-69	13	12	11	9	
70-74	13	12	11	9	
75-79	13	12	11	9	

(C) Priority to patients with the most severe disease and older patients.

Age category	Liver fibrosis stage				
	F0	F1	F2	F3	F4
40-44	10	9	8	5	
45-49	10	9	7	5	
50-54	10	9	7	5	
55-59	10	9	7	4	
60-64	10	8	6	2	
65-69	10	8	6	1	
70-74	9	8	5		
75-79	9	8	5		

(D) Priority to patients with the most severe disease and younger patients.

Age category	Liver fibrosis stage				
	F0	F1	F2	F3	F4
40-44	9	7	5		
45-49	9	8	5	1	
50-54	9	8	5	1	
55-59	10	8	6	2	
60-64	10	9	7	3	
65-69	10	9	7	4	
70-74	10	9	7	5	
75-79	10	9	7	5	

(E) Priority based on optimization.

Age category	Liver fibrosis stage: F0	F1	F2	F3	F4
40-44	8	1			
45-49	9	4			
50-54	9	4			
55-59	9	4			
60-64	9	5	2	1	3
65-69	9	5	2	5	6
70-74	9	8	7	8	7
75-79	9	8	8	8	8

(F) First priority to patients with the most severe disease (F4) followed by priority based on optimization.

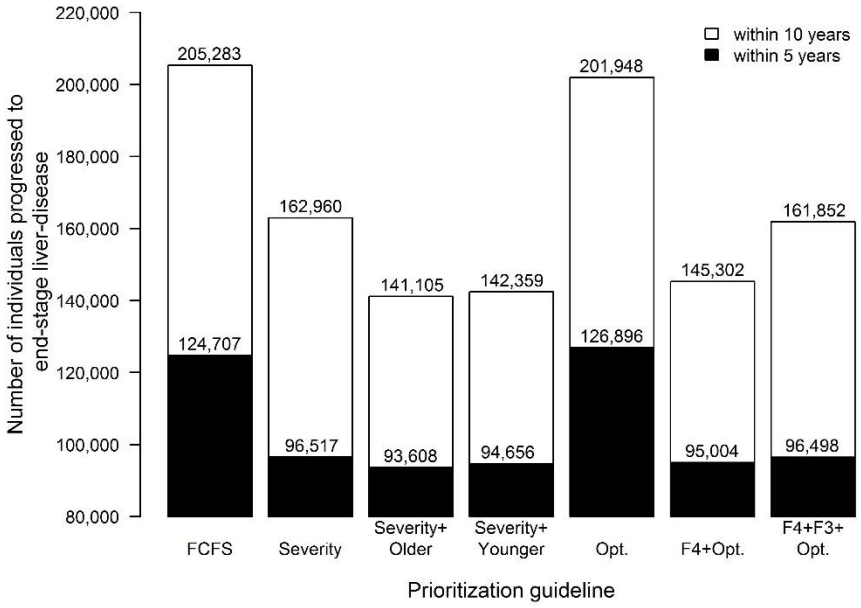
Age category	Liver fibrosis stage: F0	F1	F2	F3	F4
40-44	10	7	2	1	
45-49	10	7	3		
50-54	10	7	3	1	
55-59	9	8	6	2	
60-64	10	8	6	4	
65-69	10	8	7	5	
70-74	10	9	9	9	
75-79	10	9	9	8	

(G) First priority to patients with the most severe disease (F4, then F3) followed by priority based on optimization.

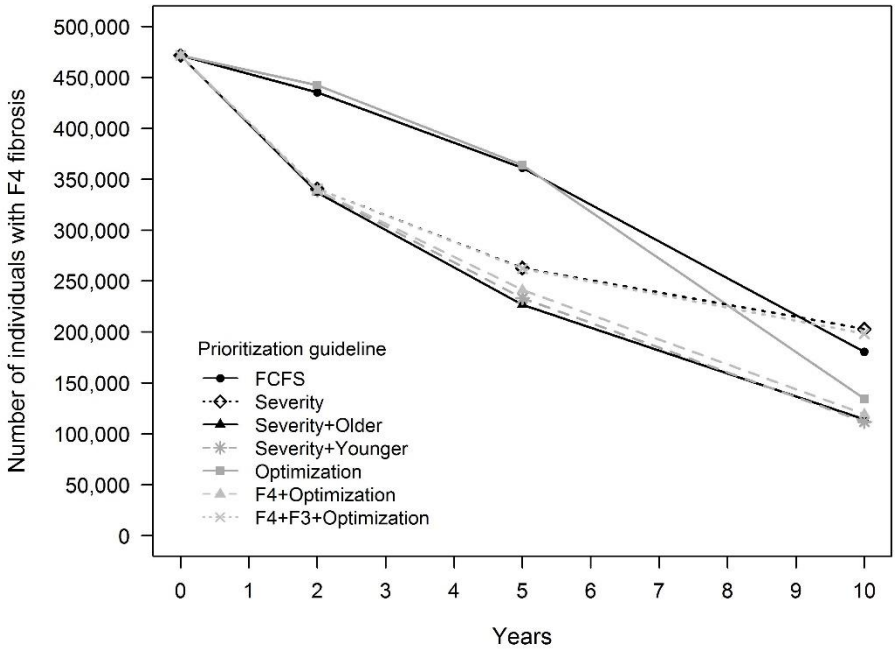
Age category	Liver fibrosis stage: F0	F1	F2	F3	F4
40-44	9	6	5		
45-49	8	6	5	1	
50-54	8	6	6	1	
55-59	9	7	9	2	
60-64	10	7	8	4	
65-69	10	8	9	5	
70-74	10	10	10	5	
75-79	10	10	10	5	

APPENDIX FIGURE S5. Comparison of the seven prioritization schedules assuming demand for treatment is 11.8% per year for individuals with F0 to F2 fibrosis and 21.5% per year for individuals with F3 and F4 (compared to 7.9% per year for individuals with F0 to F2 fibrosis and 14.3% per year for individuals with F3 and F4 fibrosis in the base case) and the average cost of treatment increases to $51,800 for F0-F3 and $77,300 for F4 (compared to $40,320 and $60,480 in the base case).

(A) The cumulative number of individuals who develop end-stage liver disease (liver cancer or decompensated cirrhosis) over the next 5 years and 10 years.



(B) The number of individuals in liver fibrosis stage F4 over the next 10 years.



(C) The lifetime discounted quality-adjusted life-years (QALYs) for the total population of individuals who are chronically HCV infected over 25 years.