Annals of Internal Medicine | ORIGINAL RESEARCH

New Protease Inhibitors for the Treatment of Chronic Hepatitis C

A Cost-Effectiveness Analysis

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Background: Chronic hepatitis C virus is difficult to treat and affects approximately 3 million Americans. Protease inhibitors increase the effectiveness of standard therapy, but they are costly. A genetic assay may identify patients most likely to benefit from this treatment advance.

Objective: To assess the cost-effectiveness of new protease inhibitors and an interleukin (IL)–28B genotyping assay for treating chronic hepatitis C virus.

Design: Decision-analytic Markov model.

Data Sources: Published literature and expert opinion.

Target Population: Treatment-naive patients with chronic, genotype 1 hepatitis C virus monoinfection.

Time Horizon: Lifetime.

Perspective: Societal.

Intervention: Strategies are defined by the use of IL-28B genotyping and type of treatment (standard therapy [pegylated interferon with ribavirin]; triple therapy [standard therapy and a protease inhibitor]). Interleukin-28B–guided triple therapy stratifies patients with CC genotypes to standard therapy and those with non-CC types to triple therapy.

Outcome Measures: Discounted costs (in 2010 U.S. dollars) and quality-adjusted life-years (QALYs); incremental cost-effectiveness ratios.

Results of Base-Case Analysis: For patients with mild and advanced fibrosis, universal triple therapy reduced the lifetime risk for hepatocellular carcinoma by 38% and 28%, respectively, and increased quality-adjusted life expectancy by 3% and 8%, respectively, compared with standard therapy. Gains from IL-28B–guided triple therapy were smaller. If the protease inhibitor costs $1100 per week, universal triple therapy costs $102 600 per QALY (mild fibrosis) or $51 500 per QALY (advanced fibrosis) compared with IL-28B–guided triple therapy and $70 100 per QALY (mild fibrosis) and $36 300 per QALY (advanced fibrosis) compared with standard therapy.

Results of Sensitivity Analysis: Results were sensitive to the cost of protease inhibitors and treatment adherence rates.

Limitation: Data on the long-term comparative effectiveness of the new protease inhibitors are lacking.

Conclusion: Both universal triple therapy and IL-28B–guided triple therapy are cost-effective when the least-expensive protease inhibitor are used for patients with advanced fibrosis.

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Hepatitis C virus (HCV) infection is a serious liver disease affecting 180 million persons worldwide (1). In the United States, 2.7 to 3.9 million persons live with chronic HCV infection, approximately 75% of whom are infected with HCV genotype 1 (2, 3). Chronic HCV causes liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) and is the most common cause of liver transplantation (1). Standard therapy for chronic HCV infection is pegylated interferon and ribavirin, which is effective in 40% to 60% of patients with HCV genotype 1 (2, 4).

New viral protease inhibitors, boceprevir (Victrelis, Merck & Co., Whitehouse Station, New Jersey) and telaprevir (Incivek, Vertex Pharmaceuticals, Cambridge, Massachusetts), used in conjunction with standard therapy, significantly increase treatment success in persons infected with genotype 1 and shorten treatment duration (5, 6). These new treatment regimens are more expensive (boceprevir, $1100 per week; telaprevir, $4100 per week) and can cause more severe adverse effects than standard therapy (7). Whether they are best used as first-line therapy for all patients infected with genotype 1 or for the subset of patients with the poorest expected outcomes with standard therapy is unclear.

Interleukin (IL)–28B genotype (CC, CT, or TT type) predicts response to HCV therapy and may prove valuable in targeting protease inhibitors to persons who are least likely to benefit from standard therapy and may also shorten treatment duration (8–11). Patients with non-CC types have a 30% sustained virologic response (SVR) rate with standard therapy and up to a 70% SVR rate when treated with triple therapy (12–14). In contrast, CC types

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Context

Addition of protease inhibitors to standard therapy for hepatitis C improves virologic suppression, but the drugs are expensive. Genetic testing can identify a subgroup of patients who are likely to derive greater relative benefit from the addition of protease inhibitors.

Contribution

In a decision-analytic model, a strategy of adding protease inhibitors to standard therapy for all patients or a targeted treatment strategy based on genetic testing both improved quality-adjusted life expectancy compared with standard therapy alone. Universal treatment led to greater benefit but at higher cost.

Caution

Drugs may not be as effective in real-world practice as in clinical trials.

Implication

Addition of protease inhibitors to standard therapy in hepatitis C is cost-effective.

—The Editors

are more responsive to treatment: 70% achieve SVR with standard therapy and up to 90% achieve SVR with triple therapy.

We performed a model-based cost-effectiveness analysis of treatment strategies for eligible patients infected with chronic HCV genotype 1. We evaluated adding new protease inhibitors to standard therapy in the context of response-guided therapy and the use of IL-28B genotyping to target triple therapy.

METHODS

We used a decision-analytic Markov model of HCV natural history and progression toward advanced liver disease to assess the cost-effectiveness of alternative treatment strategies for treatment-naive patients with genotype 1 chronic HCV monoinfection. Cohorts are defined by age (base case, 50 years), sex, race (white and black), IL-28B genotype (CC and non-CC types), and initial fibrosis stage (Metavir score of F0, F1, F2, F3, or F4). Because a patient's fibrosis stage is not always known, we considered 2 groups: those with mild fibrosis (a mix of F0 to F2) and those with advanced fibrosis (a mix of F2 to F4).

We considered 3 strategies (**Figure 1**): Patients can be treated without IL-28B genotyping with either standard therapy (pegylated interferon with ribavirin) or triple therapy (pegylated interferon with ribavirin and a new protease inhibitor). The IL-28B–guided triple therapy strategy stratifies patients with non-CC types to triple therapy and those with CC types to standard therapy.

Natural History Model

The natural history model is similar to a previously published, empirically calibrated model (15, 16) (**Appendix 1**, available at www.annals.org). In brief, it simulates the lifetime disease progression of persons with chronic HCV infections (**Figure 1**). Progression through fibrosis stages is characterized by the Metavir score, with possible transitions occurring every 12 weeks. Rates of disease progression depend on age and sex. Health states include healthy (no HCV), no fibrosis (F0), portal fibrosis with no septa (F1), portal fibrosis with few septa (F2), numerous septa without cirrhosis (F3), compensated cirrhosis (F4), decompensated cirrhosis, HCC, and liver transplantation. Without treatment, spontaneous clearance of the virus and return to the HCV-negative state is possible only from F0. A proportion of patients who start at F0 do not progress to more severe fibrosis stages. Patients who achieve SVR transition to recovered health states stratified by fibrosis severity. A proportion of patients with decompensated cirrhosis and HCC receive liver transplants. Death can occur from any state.

Treatment Model

Patients initiate treatment at the outset of the model. The goal of treatment is SVR—the absence of HCV RNA from serum 24 weeks after discontinuation of treatment. Both standard therapy and triple therapy use specific response-guided protocols (**Appendix Figures 1** and **2**, available at www.annals.org) (1, 5, 6, 17, 18). Those who experience no response, partial response, and relapse resume fibrosis progression after treatment failure because no retreatment is offered. Retreatment scenarios are explored in **Appendix 1**.

Because no randomized, controlled trials directly compare the 2 protease inhibitors and their reported efficacies are similar, we considered a general protease inhibitor whose effectiveness was similar and then explicitly modeled costs, treatment durations, and response-guided rules specific to each drug. In scenario analyses, we explicitly compared the 2 protease inhibitors under a range of effectiveness and cost scenarios.

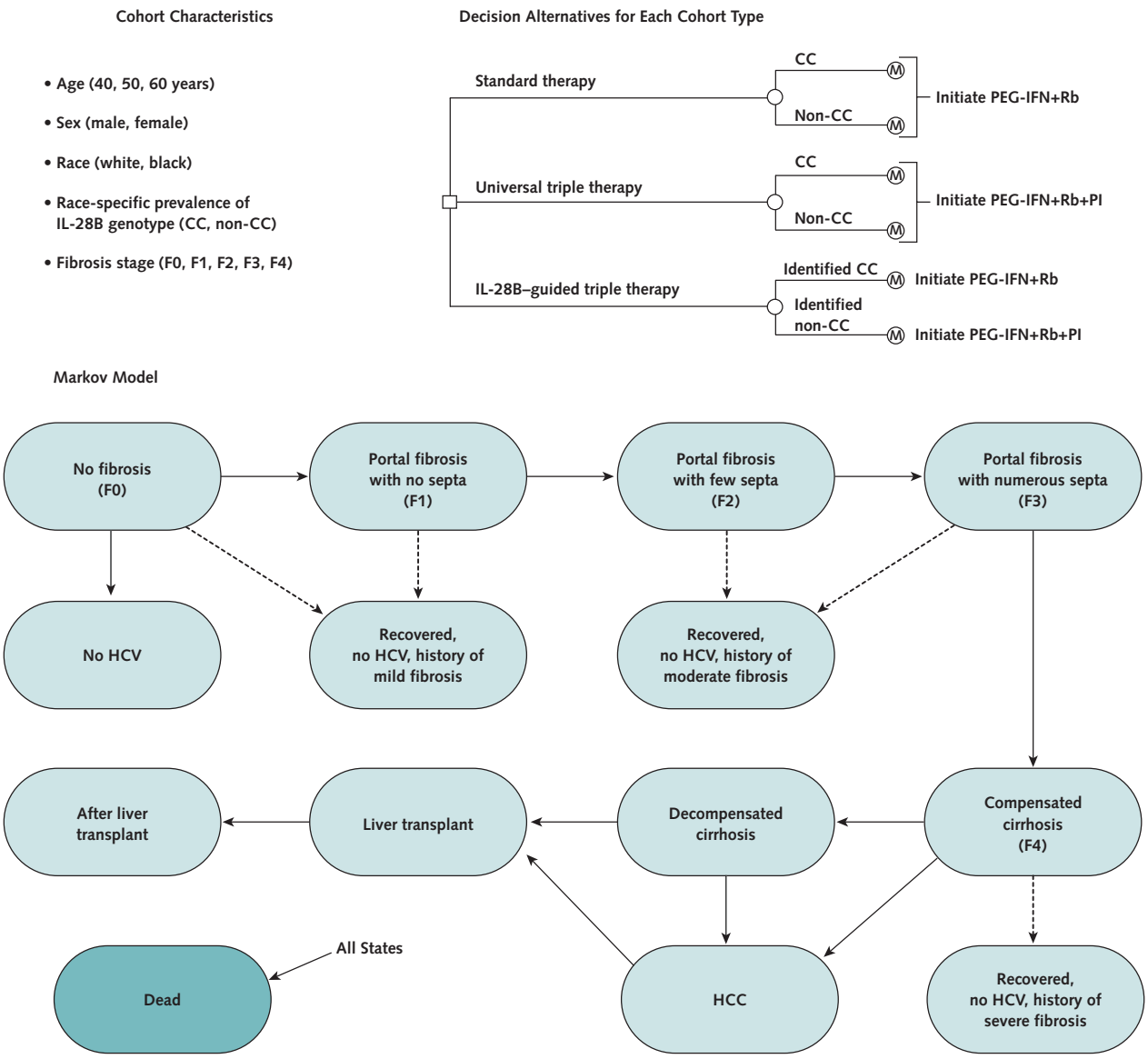
Data and Sources

Tables 1 and **2** show the data and sources.

Background Mortality

Sex-, age-, and race-specific mortality rates from causes other than HCV are from the 2006 U.S. life tables (23). Patients with chronic HCV have higher risks for death from other causes. We increased the relevant non–liver-related mortality rates by using sex- and race-specific factors (1.9 to 2.75) estimated from NHANES III (Third National Health and Nutrition Examination Survey) (**Appendix 1**). Patients who achieved SVR are no longer at higher risk for liver-related death, but they continue to be at higher risk for non–liver-related death.

Figure 1. **Model schematics.**



The small square represents the decision to implement a policy of standard therapy, universal triple therapy, or IL-28B–guided triple therapy. The small circle with inset "M" indicates the Markov model. During each 12-wk cycle of the model, all persons face a risk for death, depending on their age, sex, race, and health state. Persons begin the model receiving treatment, and if treatment is successful (the patient achieves sustained virologic response), the patient may transition along one of the dashed arrows to a fibrosis stage—stratified, recovered state. Treatment effectiveness is determined by type of treatment, race, fibrosis stage, and IL-28B genotype. If treatment is not successful, the person continues progressing through the natural history of HCV (*solid arrows*). Death can occur from any health state in the Markov model. HCC = hepatocellular carcinoma; HCV = hepatitis C virus; IL-28B = interleukin-28B; PEG-IFN = pegylated interferon; PI = protease inhibitor; Rb = ribavirin.

Fibrosis

A patient's fibrosis stage can be assessed by using liver biopsy—although due to the risk for complication and potential sampling error, other noninvasive methods are also frequently used to coarsely stage patients as having mild or advanced fibrosis (46–48). We considered 2 representative patient cohorts (**Table 1**): patients with mild fibrosis and patients with advanced fibrosis (20). The F2 stage appeared in both groups because of the high likelihood of misclassification from noninvasive staging methods (46–48). In scenario analyses, we considered clinical situations in which fibrosis stage is known and evaluated cohorts of each fibrosis stage separately.

IL-28B Genotypes

Among study participants who were IL-28B genotyped (12), CT and TT types had similar treatment re-

Table 1. **Model Parameter Values and Ranges**

Variable	Base Case (Range)	Reference
Model assumptions		
Discount rate (annual)	0.03 (0–0.05)	19
Time horizon	Lifetime	
Perspective	Societal	
Cohort characteristics		
Cohort age, *y*	50 (40–60)	
Stage of fibrosis distribution (mild/advanced)*		20
No fibrosis (F0)	0.30/0	
Portal fibrosis (F1)	0.41/0	
Periportal fibrosis (F2)	0.29/0.29	
Bridging fibrosis (F3)	0/0.23	
Compensated fibrosis (F4)	0/0.48	
Proportion with IL-28B genotype, CC-type polymorphism (vs. non–CC type)		
White	0.37 (0.28–0.46)	12
Black	0.14 (0.11–0.18)	
HCV natural history		
Proportion of patients with no fibrosis (F0) who do not progress	0.24 (0.20–0.33)	21
Annual probability of spontaneous remission from no fibrosis (F0) health state	0.012 (0.007–0.017)	15, 21
Fibrosis progression (annual probability)		15, 21
Males		
Age 40–49 y	0.05 (0.03–0.09)	
Age 50–59 y	0.12 (0.07–0.14)	
Age 60–69 y	0.20 (0.12–0.30)	
Age ≥70 y	0.26 (0.14–0.38)	
Females		
Age 40–49 y	0.03 (0.01–0.06)	
Age 50–59 y	0.06 (0.03–0.11)	
Age 60–69 y	0.11 (0.04–0.21)	
Age 70–79 y	0.14 (0.08–0.24)	
Age ≥80 y	0.20 (0.08–0.30)	
Cirrhosis to decompensated cirrhosis	0.04 (0.03–0.05)	
Cirrhosis (both F4 and decompensated cirrhosis) to HCC	0.02 (0.017–0.03)	
Liver transplant (annual probability)		
Decompensated cirrhosis to liver transplant	0.05 (0–0.40)	22
HCC to liver transplant	0.15 (0.05–0.40)	22
Hazard ratio for sex-, race-, and age-specific mortality from nonliver causes in patients with chronic HCV infection		23
White, male	2.56 (1.80–3.30)	NHANES III
White, female	1.90 (1.30–2.50)	NHANES III
Black, male	2.75 (1.90–3.60)	NHANES III
Black, female	2.48 (1.70–3.20)	NHANES III
Liver-related mortality (annual probability)		
Liver transplant	0.14 (0.134–0.150)	24
After liver transplant	0.05 (0.049–0.051)	24
Decompensated cirrhosis	0.26 (0.12–0.33)	21
HCC		25
First year	0.72 (0.58–0.80)	
Subsequent year	0.25 (0.16–0.30)	
Treatment-related mortality	0.005 (0.0005–0.011)	26
Effectiveness of treatment in treatment-naive patients (CC/non-CC)		
Standard therapy (PEG-INF+Rb)		4, 12, 27
Mild fibrosis (F0/F1/F2), white		
Probability of EVR (assessed at 12 wk)	0.90/0.66	
Probability of virologic response at 24 wk, conditional on EVR	0.92/0.75	
Probability of SVR, conditional on completed treatment (48 wk)	0.83/0.64	
Overall probability of SVR†	0.46 (0.42–0.49)	
Mild fibrosis (F0/F1/F2), black		
Probability of EVR (assessed at 12 wk)	0.76/0.45	
Probability of virologic response at 24 wk, conditional on EVR	0.95/0.78	
Probability of SVR, conditional on completed treatment (48 wk)	0.67/0.40	
Overall probability of SVR†	0.19 (0.13–0.24)	
Triple therapy (PEG-INF+Rb+PI)‡		5, 13, 14, 28–30
Adherence to triple therapy	0.70 (0.50–0.70)	
Mild fibrosis (F0/F1/F2), white		

Continued on following page

Table 1—**Continued**

Variable	Base Case (Range)	Reference
Probability of EVR (assessed at 12 wk)	0.98/0.90	
Probability of treatment failure at 24 wk	0.10/0.15	
Probability of treatment completion at either 24 or 28 wk	0.62/0.43	
Probability of continuing treatment until 48 wk	0.28/0.42	
Probability of SVR, conditional on completed treatment (24 or 28 wk)	0.98/0.95	
Probability of SVR, conditional on completed treatment (48 wk)	0.75/0.65	
Overall probability of SVR†	0.68 (0.60–0.72)	
Mild fibrosis (F0/F1/F2), black		
Probability of EVR (assessed at 12 wk)	0.80/0.60	
Probability of treatment failure at 24 wk	0.14/0.14	
Probability of treatment completion at 24–28 wk	0.48/0.48	
Probability of continuing treatment until 48 wk	0.38/0.38	
Probability of SVR, conditional on completed treatment (24–28 wk)	0.95/0.89	
Probability of SVR, conditional on completed treatment (48 wk)	0.70/0.60	
Overall probability of SVR†	0.42 (0.24–0.47)	
Reduction in SVR for advanced fibrosis stage (F3 and F4)	0.80 (0.70–1.00)	
Effectiveness of retreatment		
Proportion of patients who do not achieve SVR who subsequently seek retreatment	0.80 (0.50–1.00)	Expert opinion
Overall SVR after retreatment with triple therapy		31
White race		
No response	0.35 (0.28–0.39)	
Partial response	0.64 (0.51–0.70)	
Relapse	0.86 (0.69–0.95)	
Black race		
No response	0.26 (0.21–0.28)	
Partial response	0.47 (0.37–0.52)	
Relapse	0.63 (0.50–0.69)	

EVR = early virologic response; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; IL-28B = interleukin-28B; NHANES III = Third National Health and Nutrition Examination Survey; PEG-IFN = pegylated interferon; PI = protease inhibitor; Rb = ribavirin; SVR = sustained virologic response.
* The fibrosis stage distribution from Siddiqui and colleagues (20) is 18% for F0, 24% for F1, 17% for F2, 13% for F3, and 28% for F4. To obtain the distribution of F0, F1, and F2 in the mild fibrosis group: F0 = 18/(18 + 24 + 17), F1 = 24/(18 + 24 + 17), and F2 = 17/(18 + 24 + 17). For the distribution of F2, F3, and F4 in the advanced fibrosis group: F2 = 17/(17 + 13 + 28), F3 = 13/(17 + 13 + 28), and F4 = 28/(17 + 13 + 28).
† Calculated final SVR for the full cohort stratified by race, but not by IL-28B genotypes.
‡ The reported triple therapy effectiveness used in the base-case analysis is similar to boceprevir. In the scenario analysis of telaprevir, we increased the overall probability of SVR to represent the effectiveness reported in the telaprevir ADVANCE (A New Direction in HCV Care: A Study of Treatment-Naive Hepatitis C Patients with Telaprevir) trial, white patients (SVR, 75%) and black patients (SVR, 61%).

sponse rates; therefore, we combined them into a single category, non-CC. We used race-specific IL-28B genotype distributions: 37% of white patients and 14% of black patients had the CC genotype. Additional studies have estimated IL-28B genotype distributions and provide similar estimates of CC prevalence (35% to 37%) (13, 14).

Treatment Effectiveness

Complete virologic response profiles for the duration of treatment stratified by race and IL-28B genotype are not available from clinical trials. For standard therapy effectiveness, we used data from the intention-to-treat IL-28B analysis of cohorts from the IDEAL (Individualized Dosing Efficacy vs. Flat Dosing to Assess Optimal Pegylated Interferon Therapy) study (4, 8, 12). For the effectiveness of treatments that include the new protease inhibitors, we used data reported from the phase 3 clinical trials for telaprevir (ADVANCE [A New Direction in HCV Care: A Study of Treatment-Naive Hepatitis C Patients with Telaprevir]) and boceprevir (SPRINT-2 [Serine Protease Inhibitor Therapy 2]) (5, 13, 14, 29). We inferred missing subgroup estimates stratified by race and IL-28B genotype, consistent with the reported SVRs (**Appendix Tables 1** and **2**, available at www.annals.org).

Treatment Adherence

In the base-case analysis, we assumed that treatment adherence was similar for standard therapy and triple therapy (that is, approximately 70% patients were adherent, defined as taking ≥80% of both pegylated interferon and ribavirin [12]). Comparable adherence metrics were not reported in the protease inhibitor trials, although experience suggests that adherence in real-world settings can be lower than that in clinical trials. Therefore, in sensitivity analyses, we reduced adherence for triple therapy from 70% to 50% for all patients receiving triple therapy.

Health Outcomes

Age-specific quality-of-life weights were derived from the Medical Expenditure Panel Survey (32, 33). Quality-of-life reductions associated with chronic HCV infection were estimated by combining several published studies (15, 34–37) (**Appendix 1**). Utility decrements were −0.110 for

Table 2. **Utilities and Costs**

Variable	Base Case (Range)	Reference
Quality of life*		
Age-specific QALY weights		32, 33
HCV-specific weights		15, 34–37
HCV mild fibrosis (F0, F1)	0.980 (0.700 to 1.000)	
SVR after mild fibrosis	1.000 (0.740 to 1.000)	
HCV moderate fibrosis (F2, F3)	0.850 (0.660 to 1.000)	
SVR after moderate fibrosis	0.933 (0.710 to 1.000)	
Compensated cirrhosis (F4)	0.790 (0.460 to 1.000)	
SVR after cirrhosis	0.933 (0.600 to 1.000)	
Decompensated cirrhosis	0.720 (0.257 to 0.913)	
HCC	0.720 (0.150 to 0.950)	
Liver transplant (during or after)	0.825 (0.636 to 1.000)	
Standard therapy annualized decrement†	−0.110 (−0.200 to 0.000)	
Triple therapy annualized decrement†	−0.165 (−0.400 to 0.000)	
Liver transplant annualized decrement†	−0.200 (−0.364 to 0.000)	
Cost (2010 U.S. dollars), $		
Age-specific baseline health care costs		38
IL-28B testing	371 (186 to 557)	
Treatment (drug and medical care)		
PEG-INF+Rb (F0 to F3, 48 wk)	32 692 (12 002 to 49 460)	39, 40
PEG-INF+Rb (F4, 48 wk)	35 814 (15 123 to 52 582)	39, 40
PIs (per week)‡	1100 (781 to 1430)	7, 41
AEs, standard therapy	1920 (1344 to 2496)	42
AEs, standard therapy, PI	2586 (1810 to 3361)	42
Retreatment (48 wk)§	83 677 (48 176 to 115 742)	
Annual care‖		
HCV mild fibrosis (F0, F1)	1404 (152 to 4194)	15, 40, 43–45
HCV portal fibrosis (F2)	1404 (152 to 4194)	
HCV bridging fibrosis (F3)	1404 (152 to 4194)	
Compensated cirrhosis (F4)	4194 (152 to 4194)	
Decompensated cirrhosis	11 109 (5560 to 16 669)	
HCC	44 224 (22 117 to 66 341)	
Liver transplant, first year	145 640 (72 825 to 218 455)	
Liver transplant, subsequent	25 430 (12 715 to 38 156)	
Recovered states from F0 to F3	406 (0 to 702)	Assumed¶
Recovered states from F4	811 (0 to 2097)	

AE = adverse event; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; IL-28B = interleukin-28B; PEG-INF = pegylated interferon; PI = protease inhibitor; QALY = quality-adjusted life-year; Rb = ribavirin; SVR = sustained virologic response.

* The total quality-of-life weight for a given age and HCV disease state is computed as the product of the mean age-specific quality weight obtained from published data (32, 33) and the utility associated with the HCV disease state, less any utility decrements for events that occurred during the cycle, such as receiving treatment or a liver transplant.

† Unlike other utilities in this table, these utility decrements are for short-term states (that is, receiving HCV treatment or a liver transplant). The QALY decrement for receiving HCV treatment involves multiplying the annual utility decrement by the time on treatment, which can vary given the response-guided therapy rules of each strategy. For example, the utility decrement of −0.11 is reported in terms of QALYs lost per year while receiving standard therapy. For a person receiving standard therapy for 12 wk, the loss of QALYs from treatment is −0.0254 (−0.11 × 12/52). Similarly, for the 12 wk surrounding the liver transplant, the loss of QALYs from transplantation is −0.0462 (−0.20 × 12/52).

‡ The PI cost is added to the standard therapy cost while receiving triple therapy.

§ Base-case retreatment cost is the sum of the costs of 48-wk standard therapy and 44-wk PI therapy at $1100/wk, similar to boceprevir. In the telaprevir case, retreatment cost is the sum of the costs of 48-wk standard therapy and 12-wk PI therapy at $4100/wk.

‖ The total costs for a given age and HCV disease state is computed as the sum of the mean age-specific health care costs (38) and the HCV-specific health state plus any costs of IL-28B testing, HCV treatment, or liver transplant that occurred in the cycle.

¶ We assumed costs in the recovered states are 50% of the hepatitis C–related care costs in the year before diagnosis of the corresponding states (43).

1 year of standard therapy (equal to a loss of 40 quality-adjusted days) (34) and −0.165 for 1 year of triple therapy (equal to a loss of 60 quality-adjusted days). Decrements were scaled by the actual time receiving treatment, which can be shorter in response-guided triple therapy (**Table 2**).

Costs

Age-specific baseline health care costs included patients' out-of-pocket expenses (38). We also included additional fibrosis stage–specific costs attributable to chronic HCV infection derived from HCV-related medical expenditures from the year after HCV diagnosis (43). Ongoing fibrosis stage–specific patient costs were halved for patients who achieved SVR after treatment (40, 43), an assumption that we varied widely in sensitivity analyses (**Table 2**) (15, 40, 43–45).

Treatment costs include drugs and medical care (**Table 2**). We assumed that patients received 150 mcg once weekly of pegylated interferon alfa-2b ($584 per week [PegIntron, Schering Corp., a subsidiary of Merck & Co.]) or, similarly, 180 mcg once weekly of pegylated interferon alfa-2a ($580 per week [Pegasys, Roche, Basel, Switzerland]), plus ribavirin, 1000 mg daily ($370.87 per week [Rebetol, Schering Corp., a subsidiary of Merck & Co.])

(39, 49). We converted average wholesale prices to best prices by using a conversion factor of 0.64, consistent with the Congressional Budget Office estimates (50). The prices for boceprevir and telaprevir are $1100 and $4100 per week, respectively (7). Given the divergent treatment duration and costs of the 2 protease inhibitors, we assumed the cost for the short treatment course of a general protease inhibitor to be $26 400 applied during the first 28 weeks of treatment (24 weeks of boceprevir cost) and $35 200 for the long treatment course (32 weeks of boceprevir cost). In scenario analyses, we increased the cost for a general protease inhibitor to $49 200 during the first 12 weeks of treatment (12 weeks of telaprevir cost). Annual medical care costs during HCV treatment were based on medical claims data for chronic HCV, estimated to be $3122 for patients with scores of F0 to F3 and $6244 for those with a score of F4 (40). We included additional costs from adverse effects because triple therapy may be associated with differentially higher rates or severity of these events (42).

When necessary, costs were inflation-adjusted to 2010 U.S. dollars by using the U.S. Consumer Price Index (51).

Analysis

Outcomes included lifetime discounted costs, quality-adjusted life-years (QALYs) gained, and incremental cost-effectiveness ratios (ICERs) of the 3 treatment strategies. Results are presented as weighted averages over race and sex based on the distribution observed in patients with chronic HCV from NHANES III data (51% white male, 23% white female, 17% black male, and 9% black female).

We followed the recommendations of the U.S. Panel on Cost-Effectiveness in Health and Medicine, adopting a societal perspective, considering costs and benefits over a lifetime horizon, and discounting future costs and health benefits at 3% annually (19). Given the multiplicity of sources used, we performed deterministic sensitivity analyses for all variables and probabilistic sensitivity analyses to examine the effect of uncertainty on policy recommendations.

Role of the Funding Source

The study was funded primarily from a Stanford Graduate Fellowship from Stanford University (awarded to Ms. Liu). The funding source had no role in the design, conduct, or reporting of this analysis, or in the decision to submit the manuscript for publication.

RESULTS

Using new protease inhibitors as part of triple therapy for all patients chronically infected with genotype 1 HCV or targeted to those who are most likely to benefit from IL-28B, genotyping improves health outcomes compared with current standard 2-drug therapy (**Table 3**). For patients with advanced fibrosis, universal triple therapy increases the proportion achieving SVR to 51% compared with 32% SVR for standard therapy. This increase in SVR results in reductions in the lifetime risk for decompensated cirrhosis (from 23.0% to 16.5%), HCC (from 13.2% to 9.5%), and liver transplant (from 4.6% to 3.3%). For pa-

Table 3. **Lifetime Discounted Costs and Health Benefits of Treatment Strategies, by Severity of Fibrosis Stage***

Strategy	SVR, %	Lifetime Risk, %			Cost, $	QALYs	ICER, $/QALY	ICER Excluding IL-28B, $/QALY†
		Decompensated Cirrhosis	HCC	Liver Transplant				
Base case (boceprevir scenario)								
Mild fibrosis‡								
Standard therapy	38	8.4	4.7	1.5	160 456	10.97	–	–
IL-28B–guided triple therapy	57	5.7	3.2	1.0	177 152	11.24	62 900	–
Universal triple therapy	61	5.1	2.9	0.9	183 257	11.30	102 600	70 100
Advanced fibrosis§								
Standard therapy	32	23.0	13.2	4.6	161 312	8.84	–	–
IL-28B–guided triple therapy	48	17.6	10.1	3.6	179 090	9.38	32 800	–
Universal triple therapy	51	16.5	9.5	3.3	185 447	9.51	51 500	36 300
Telaprevir scenario								
Mild fibrosis‡								
Standard therapy	38	8.4	4.7	1.5	160 456	10.97	–	–
IL-28B–guided triple therapy	63	4.9	2.8	0.9	191 559	11.33	86 800	–
Universal triple therapy	70	3.9	2.2	0.7	203 285	11.44	102 400	91 000
Advanced fibrosis§								
Standard therapy	32	23.0	13.2	4.6	161 312	8.84	–	–
IL-28B–guided triple therapy	54	15.9	9.1	3.2	193 805	9.56	45 300	–
Universal triple therapy	60	14.4	8.0	2.8	206 010	9.78	54 100	47 400

HCC = hepatocellular carcinoma; ICER = incremental cost-effectiveness ratio; IL-28B = interleukin-28B; QALY = quality-adjusted life-year; SVR = sustained virologic response.

* Results are weighted averages over race and sex and are based on relative prevalence of these groups for patients with chronic hepatitis C virus from NHANES III (Third National Health and Nutrition Examination Survey) data (white male, 51%; white female, 23%; black male, 17%; and black female, 9%).

† If IL-28B genotyping is unavailable, ICER compares universal triple therapy with standard therapy.

‡ F0, 30%; F1, 41%; and F2, 29%.

§ F2, 29%; F3, 23%; and F4, 48%.

tients with mild fibrosis, universal triple therapy increases SVR from 38% to 61% and reduces the lifetime risk for decompensated cirrhosis (from 8.4% to 5.1%), HCC (from 4.7% to 2.9%), and liver transplant (from 1.5% to 0.9%) compared with standard therapy. Interleukin-28B–guided triple therapy achieved SVR in 48% of patients with advanced fibrosis and 57% of patients with mild fibrosis. Reductions in lifetime decompensated cirrhosis and HCC obtained with IL-28B–guided triple therapy were approximately 83% of those achieved with universal triple therapy.

For patients with advanced fibrosis, IL-28B–guided triple therapy and universal triple therapy increased discounted quality-adjusted life expectancy by 0.54 and 0.67 years, respectively, compared with standard therapy; and for patients with mild fibrosis, the increases were 0.27 and 0.33 years, respectively.

If the protease inhibitor costs $1100 per week, universal triple therapy improves outcomes but also substantially increases total costs ($24 135 for advanced fibrosis and $22 801 for mild fibrosis compared with standard therapy). Compared with IL-28B–guided triple therapy, universal triple therapy costs $51 500 per QALY for patients with advanced fibrosis and $102 600 per QALY for patients with mild fibrosis (**Figure 2,** *A* and *B*). The more favorable cost-effectiveness results for patients with advanced fibrosis are due largely to the greater health gains achieved by universal triple therapy for patients at roughly equal increases in costs.

In situations where IL-28B–guided therapy is unavailable, universal triple therapy costs $36 300 per QALY for patients with advanced fibrosis and $70 100 per QALY for patients with mild fibrosis compared with standard therapy (**Table 3**).

Chronic HCV is a slowly progressing disease that can take 30 years to cause end-stage liver disease. Meanwhile, patients may die of non–liver-related causes. Therefore, initial fibrosis stage affects the cost-effectiveness of treatment strategies. We considered clinical treatment scenarios in which a patient's specific fibrosis stage had been determined via biopsy (**Appendix Figure 3**, available at www.annals.org). In general, universal triple therapy provides relatively more benefit per dollar spent for patients with more advanced liver fibrosis than those with less advanced fibrosis (ICERs below $50 000 per QALY for patients with F4 fibrosis increasing to >$150 000 per QALY for those with no fibrosis).

Treatment Costs

The treatment cost of the 2 protease inhibitors differs, and the cost considered in our base-case analysis was that of boceprevir ($1100 per week for 24 to 32 weeks). If the price of the protease inhibitor were higher—equal to telaprevir ($4100 per week for 12 weeks)—and the effectiveness was that of telaprevir reported in the ADVANCE trial, the ICERs of universal triple therapy versus IL-28B–guided triple therapy are $54 100 per QALY for patients with advanced fibrosis and $102 400 per QALY for patients with mild fibrosis— similar to the results for a protease inhibitor, such as boceprevir (**Figure 2**, *C* and *D*). In situations where IL-28B–guided therapy is unavailable, universal triple therapy costs $47 400 per QALY for patients with advanced fibrosis and $91 000 per QALY for patients with mild fibrosis compared with standard therapy (**Table 3**).

Comparing the 2 drugs, the effectiveness of universal triple therapy using telaprevir needs to be substantially greater than that observed in the ADVANCE trial to yield an ICER below $50 000 per QALY compared with universal triple therapy using boceprevir (**Appendix Figure 4**, available at www.annals.org), although differences, including patterns of adverse effects, and uncertainties about adherence and effectiveness make a definitive comparison difficult.

Prices for brand-name drugs vary substantially between purchasing institutions. For example, the Veterans Health Administration may purchase drugs at the Federal Supply Schedule price. In that case, the ICERs for universal triple therapy compared with IL-28B–guided triple therapy are $41 100 per QALY gained for advanced fibrosis and $81 300 per QALY gained for mild fibrosis, although specific estimates depend on the price levels and relative prices of standard therapy and new protease inhibitors (**Appendix Table 3**, available at www.annals.org).

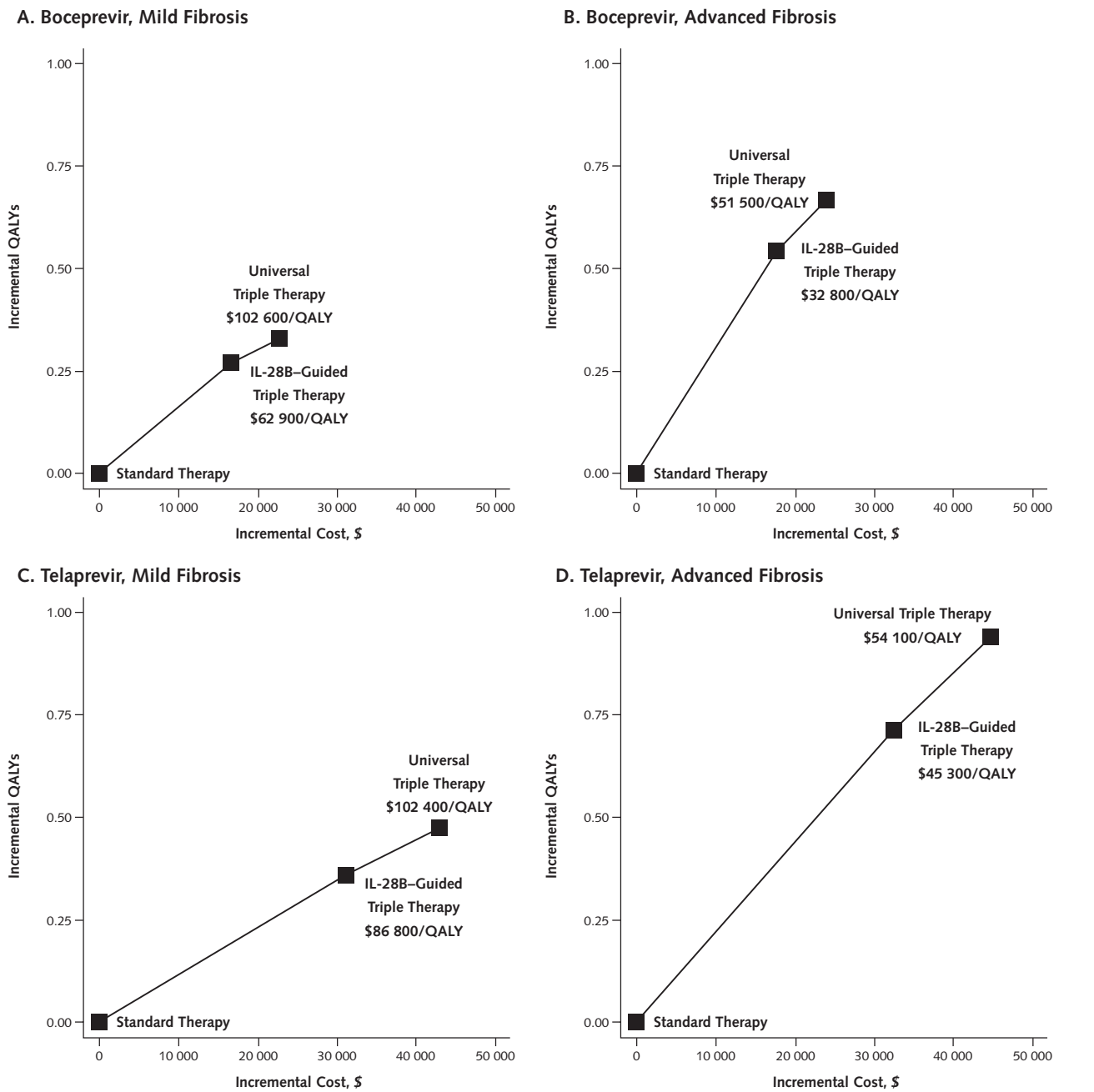
Adverse Events From Therapy

Adverse effects from triple therapy are more frequent and potentially more severe than those from standard therapy, which include anemia, depression, rash, and flu-like symptoms. Higher rates and severity of adverse effects may undermine the cost-effectiveness of universal triple therapy. We performed a threshold analysis to determine how severe the adverse effect profile would need to be for the ICER to exceed $100 000 per QALY for patients with advanced fibrosis (**Appendix Table 4**, available at www.annals.org). We found that it did not exceed this threshold, even when the costs of adverse effects were tripled ($7500) and the disutility of adverse effects were doubled (equal to a disutility of −0.36 QALYs per year with triple therapy).

Adherence

In our base-case analysis, we assumed equal adherence for standard therapy and triple therapy (70% of patients taking ≥80% of their HCV medications). In a threshold analysis, we found that if adherence to standard therapy remained at 70% but was as low as 50% for triple therapy, then universal triple therapy is more costly but achieves no additional benefit compared with IL-28B–guided triple therapy and was consequently not cost-effective for patients with either mild or advanced fibrosis (**Appendix Table 5**, available at www.annals.org). However, when compared with standard therapy with 70% adherence for those with advanced fibrosis, universal triple therapy, even with 50% adherence, cost $73 200 per QALY. For mild fibrosis,

Figure 2. **Cost-effectiveness results: incremental costs incurred and QALYs for each intervention.**



The graph plots the incremental discounted QALYs (*y*-axis) and incremental discounted total expected lifetime costs (*x*-axis) for each treatment strategy separately for cohorts of patients with mild and advanced fibrosis. The solid lines represent the cost-effectiveness frontier, those strategies that are potentially cost-effective depending on one's willingness to pay per unit of health benefit gained, expressed as an incremental cost-effectiveness ratio (defined as the ratio of the additional costs of an intervention and its additional effects compared with the next-best alternative). IL-28B = interleukin-28B; QALY = quality-adjusted life-year.

universal triple therapy for this scenario cost more than $150 000 per QALY compared with standard therapy.

Risk for HCC

Limited evidence suggests a risk for HCC from more advanced fibrosis stages, even after achieving SVR. To explore this, we conducted a sensitivity analysis in which we assumed that patients with F4 fibrosis who were successfully treated had an annual rate of developing HCC that was 20% of that for F4 before treatment. The results did not alter the main conclusions (**Appendix Table 6**, available at www.annals.org).

Other Sensitivity Analyses

Appendix Tables 7 to **10** (available at www.annals.org) show additional sensitivity analyses considering non–liver-related mortality and retreatment and subgroup analyses by race, sex, age, IL-28B genotype, and fibrosis stage.

Probabilistic Sensitivity Analyses

In probabilistic sensitivity analyses, we used the boceprevir cost (**Appendix Figure 5**, available at www.annals.org). For patients with advanced fibrosis, using either universal triple therapy or IL-28B–guided triple therapy was optimal 98% of the time at a willingness-to-pay threshold of $50 000 per QALY or 100% at a threshold of $100 000 per QALY, respectively. For patients with mild fibrosis, the corresponding values were 18% and 95%. Conversely, at a threshold of $50 000 per QALY, standard therapy was optimal 82% of the time for mild fibrosis but only 2% of the time for advanced fibrosis.

DISCUSSION

For treatment-naive patients with chronic genotype 1 HCV monoinfection, universal triple therapy yields greater health benefits than both standard therapy and IL-28B–guided triple therapy. Although it also increases total costs, universal triple therapy provides reasonable value for money, costing approximately $50 000 per QALY compared with IL-28B–guided triple therapy for patients with advanced fibrosis, if the protease inhibitor added to standard therapy is available for $1100 per week. Universal triple therapy becomes less cost-effective when the cost of the protease inhibitors is higher, or when adherence rates are substantially lower for triple therapy than for standard therapy. For patients with mild fibrosis, universal triple therapy at a cost of $1100 per week is not cost-effective, even at $100 000 per QALY, but IL-28B–guided triple therapy costs $62 900 per QALY compared with standard therapy.

Because of the high cost and risk for adverse effects with protease inhibitors, some health systems may consider reserving them for second-line rather than first-line treatment, especially for patients with less severe fibrosis. However, for patients with advanced fibrosis, in our main analyses we found that universal, first-line triple therapy reaches conventional levels of cost-effectiveness. We explored the cost-effectiveness of treating all patients with standard therapy and reserving protease inhibitors for second-line treatment and found that this strategy is less effective and more costly than other strategies that use triple therapy as a first-line treatment for at least some patients (**Appendix 2**, available at www.annals.org).

Despite the highly anticipated benefits of the new protease inhibitors, tailoring HCV treatment to specific patient characteristics has garnered interest in the medical community. We find that IL-28B genotype may be useful for such stratification, and our findings are consistent with the recommendations on IL-28B genotyping in the 2011 American Association for the Study of Liver Diseases treatment guidelines (17).

Our main analysis did not directly compare boceprevir with telaprevir. We considered a general protease inhibitor in comparison with standard 2-drug therapy and IL-28B–guided triple therapy. We varied the costs of the general protease inhibitor, treatment algorithms, and effectiveness to be similar to either boceprevir or telaprevir. It is important to note that key differences, especially the difference in cost, are relevant for health systems that are considering whether to include 1 or both new drugs in their formularies. The weekly cost of telaprevir is 4 times greater than that of boceprevir, and depending on treatment duration, the total drug cost for a complete course of telaprevir can be 140% to 190% of the cost of boceprevir. The effectiveness of telaprevir seems higher than boceprevir in separate clinical trials (SVR of 75% vs. 68%), although the populations represented in the studies may not be comparable, because the observed effectiveness also differed in the respective control groups. The difference between the 2 drugs has not been evaluated in a head-to-head comparison. The types and rates of adverse effects differ between the 2 drugs, but the overall costs from adverse effects seem to be similar. Modeled as a general protease inhibitor, universal triple therapy was found to be cost-effective compared with standard therapy for patients with advanced fibrosis (costing approximately $50 000 per QALY or less). However, when the 2 drugs are directly compared, the increase in the effectiveness of telaprevir relative to that of boceprevir needed to achieve conventional levels of cost-effectiveness may well be substantially higher than that observed in the ADVANCE trial (6). Clinical trials directly comparing the 2 drugs are needed to address comparative effectiveness. A head-to-head evaluation of the cost-effectiveness of these drugs would need to include more detailed modeling of adverse events, which would, in turn, require substantially more information about treatment patterns in real-world clinical practice.

Because the protease inhibitors we evaluated were only recently approved by the U.S. Food and Drug Administration, the feasibility of implementation of response-guided therapy recommendations in routine practice, the treatment effectiveness, and adherence to treatment are unknown. Adherence is especially important to treatment effectiveness and cost-effectiveness. If adherence to triple therapy is lower than that of standard therapy, IL-28B–guided therapy may be the optimal strategy.

Although the main analysis focuses on initial treatment of chronic HCV infections, important questions remain about retreating patients whose initial treatment fails. Our analysis does not primarily address this topic, but data and studies of effectiveness in this setting are forthcoming. We explored this issue and found that IL-28B–guided triple therapy with retreatment of patients in whom initial treatment with standard therapy failed is cost-effective in the advanced fibrosis group (**Appendix 2**). However, given the lack of evidence, we did not consider strategies involving retreatment with triple therapy after initial failure with triple

therapy. Clinicians will require a strategy for managing patients whose triple therapy fails, especially if failure results from poor adherence or toxicities. Of note, HCV viral resistance to protease inhibitors can also alter the effectiveness in retreatment, although data on this are still emerging.

Our analysis has several limitations. Interleukin-28B genotyping is a relatively new approach to predicting patients' response to standard HCV therapy. Additional studies will provide further confidence of the predictive value of IL-28B. We did not include reductions in HCV transmission due to successful treatment and, thus, may have underestimated the benefits associated with improving SVR rates, such as those from triple therapy. A substantial minority of patients infected with chronic HCV is also coinfected with hepatitis B virus, HIV, or both. Our results are limited to persons who are monoinfected and should be interpreted only in the context of this population because studies evaluating the effectiveness of new protease inhibitors in persons coinfected with HIV are ongoing. In addition, challenges with standard HCV–HIV drug interactions are already known, and HCV protease inhibitor interactions are emerging (52, 53). Future analyses should address the complex management issues surrounding treatment decisions for patients with coinfections.

New HCV protease inhibitors show promise in increasing treatment effectiveness for patients infected with HCV genotype 1, even though their additional benefits come with increased adverse effects and treatment costs. Our study supports the important role of protease inhibitors in treating chronic HCV for patients with advanced fibrosis as part of a first-line regimen. Management of chronic HCV in the United States could be improved by a shift toward response-guided triple-drug strategies, provided that the price of protease inhibitors and adherence to taking them are maintained at reasonable levels.

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Appendix 1: Supplemental Information on Data and Methods

Model Implementation

We implemented the model in TreeAge Pro 2009 Suite (TreeAge Software, Williamstown, Massachusetts) and Microsoft Excel 2007 (Microsoft, Redmond, Washington).

Hepatitis C Virus Natural History

The hepatitis C virus (HCV) natural history model is based on Salomon and colleagues' model (15, 21). We made 2 changes from their model. We increased the non–liver-related background mortality rates for patients with chronic HCV by using data from NHANES III, because these patients are at higher risk for death from comorbid conditions and lifestyle risks than the general population. We also allowed patients with both decompensated cirrhosis and HCC to receive liver transplants. We validated our model against the model developed by Salomon and colleagues. For a cohort of persons aged 40 years, the 30-year cumulative probability of developing compensated cirrhosis (F4) is 25% for men and 8% for women from our model. These are similar to the mean results obtained by Salomon and colleagues, which were 30% and 9%, respectively; and within their confidence bounds, 13% to 46% for men and 1% to 29% for women.

Response-Guided Therapy

Standard Therapy

Standard therapy includes pegylated interferon alfa (2a or 2b) and ribavirin for 48 weeks. Virologic response is assessed at 12, 24, and 48 weeks. Patients who do not achieve an early virologic response (EVR) (defined as a $\geq$2-$\log_{10}$/mL reduction or complete absence of serum HCV RNA at week 12 of treatment compared with the baseline level), discontinue treatment and are considered nonresponsive in accordance with the American Association for the Study of Liver Diseases 2009 and the European Association for the Study of the Liver 2011 guidelines (1, 18). Patients with detectable serum HCV RNA at 24 weeks discontinue treatment and are considered partially responsive; otherwise, patients continue treatment for a total of 48 weeks. Patients who do not achieve SVR at the end of treatment are considered to have relapse (**Appendix Figure 1**).

Triple Therapy

The characteristics of triple therapy are estimated on the basis of both HCV drugs recently approved by the U.S. Food and Drug Administration, telaprevir and boceprevir. Given the differences in study populations and the broad overlaps in their effectiveness estimates, we considered a single protease inhibitor. However, we modeled different costs and treatment durations for boceprevir and telaprevir according to U.S. Food and Drug Administration–approved response-guided therapy rules for each drug. In the base-case analysis similar to boceprevir, we assumed that patients receive a course of triple therapy during the first 28 weeks (4 weeks of pegylated interferon and ribavirin lead-in followed by 24 weeks of triple therapy). Patients who do not achieve EVR at week 12 of treatment discontinue therapy and are considered nonresponsive. At week 24, treatment is again discontinued in some patients because of nonresponse. However, among patients who respond to treatment, a proportion will stop treatment early because they meet completion criteria at week 28. The remaining patients continue an 8 additional weeks of triple therapy followed by pegylated interferon and ribavirin alone until 48 weeks. We modeled the treatment completion criteria for short therapy versus long therapy as follows: undetectable HCV RNA at weeks 4 and 12, assessed at week 24 for telaprevir; and undetectable HCV RNA between weeks 8 and 24, assessed at week 28 for boceprevir (**Appendix Figure 2**). We also explored a telaprevir scenario, in which patients receive a course of triple therapy during the first 12 weeks and then continue pegylated interferon and ribavirin to week 24. At week 24, a proportion of patients meet early treatment completion criteria, and the rest of patients continue pegylated interferon and ribavirin therapy alone until 48 weeks (**Appendix Figure 2**).

Death From Nonliver Causes

Sex-, age-, and race-specific mortality rates were derived from 2006 U.S. life tables (23). As patients with chronic HCV have higher risks for death from other causes as well, we increased the appropriate age-, sex-, and race-specific background mortality rate by sex- and race-specific factors (1.9 to 2.75) estimated from NHANES III.

We used the NHANES III–linked mortality for persons aged 17 years or older in which HCV status was assessed from 1988 to 1994 with mortality follow-up of the same persons through 2006 (n = 15 892). We followed the methods described in El-Kamary and colleagues' study (54) to generate Cox models to estimate the mortality rate ratio for all-cause and non–liver-related death in persons with chronic HCV (n = 268) compared with those with no HCV antibodies (n = 15 624). Our cohort for analysis differed from the work of El-Kamary and colleagues in that we did not exclude persons from the analysis for having

missing or incomplete data on variables of marital status; education; poverty income ratio; alcohol consumption; smoking status; lifetime drug use; lifetime number of sexual partners; body mass index; and comorbid conditions, such as cancer, diabetes, or hepatitis A infection. We stratified the population by race (white and black) and sex (male and female) to generate mortality rate ratios adjusted only for age category (17 to 29, 30 to 44, 45 to 59, or ≥60 years).

Backus and colleagues (55) found that SVR reduced all-cause mortality among patients infected with HCV of genotype 1 (hazard ratio, 0.7) with a median follow-up of 3.8 years. In the Veterans Affairs population with genotype 1, 1119 died out of 12 166 (9%) during follow-up. Compared with our analysis, we assumed that SVR would eliminate further disease progression and, thus, avoid liver-related death associated with cirrhosis and HCC later in life, but patients would still be at increased risk for non–liver-related death after SVR. To directly compare results with those found by Backus and colleagues, we adjusted our model inputs to reflect their population in terms of sex (96% male), severity of fibrosis (13% cirrhosis), and follow-up (4 years). We ran our model for a cohort aged 50 to 54 years separately for patients both with and without SVR. At the end of 4 years, our model indicated that 6.3% of the patients who achieved SVR were dead and 8.2% of those who did not achieve SVR were dead—a ratio of 0.77, compared with Backus and colleagues' 0.7. Given the differences in age distributions (the mean age of Backus and colleagues' cohort was 52 years), the uncertain differences in the fibrosis distributions (F0 to F3 distribution is not reported in Backus and colleagues' study), and baseline population characteristics (in general, veterans have higher background mortality than the general U.S. population, such as populations sampled in NHANES III), we believe that our model outputs are reasonably similar to the mortality estimates of Backus and colleagues.

Treatment Effectiveness

Standard Therapy

Complete virologic response profiles for the duration of treatment stratified for race and IL-28B genotype are not available from the clinical trials. For standard therapy effectiveness, we used data from the intention-to-treat IL-28B analysis of the IDEAL study cohorts after a genomewide association study (4, 8, 12). We inferred missing subgroup estimates stratified by race and IL-28B genotype, consistent with the SVRs reported (**Appendix Tables 1** and **2**).

Triple Therapy

For the effectiveness of treatments including the new protease inhibitors, we used data reported from the response-guided therapy groups of the telaprevir and boceprevir phase 3 clinical trials (5, 6, 13, 14, 29) and inferred missing subgroup estimates stratified by race and IL-28B genotype, consistent with the SVRs reported using the formula and constraints in **Appendix Table 2**.

From **Appendix Tables 1** and **2**, we assumed that the SVRs for patients with F0 to F2 fibrosis are 68% for white patients and 42% for black patients from triple therapy, compared with 46% for white patients and 19% for black patients from standard therapy. Patients with more advanced fibrosis have proportionately lower SVRs with standard therapy (4). Similar trends were observed in the protease inhibitor trials (13, 14). On the basis of the ratio of efficacy observed in the telaprevir ADVANCE trial (6), we estimated that final SVR rates would be 20% lower in patients with advanced fibrosis (F3 and F4).

Effectiveness of Retreatment

We used scenario analyses to explore the role of triple therapy for retreatment, in which we considered a total of 5 strategies (**Appendix Figure 6**): standard therapy, universal triple therapy, IL-28B–guided triple therapy, standard therapy with retreatment, and IL-28B–guided triple therapy with retreatment. Prior studies have shown that retreatment with standard therapy after failure of initial standard therapy has low effectiveness (56). Scarce but growing data support the effectiveness of triple therapy for patients whose 2-drug therapy fails (31, 57). No published evidence exists on retreatment with triple therapy for patients whose triple therapy fails. Therefore, we considered 2 additional strategies for which evidence was available: standard therapy with triple therapy retreatment of those whose initial therapy fails; and the IL-28B–guided triple therapy used in the base-case analysis extended so that patients with CC type whose standard therapy fails are then retreated with triple therapy. For these strategies, we assumed that 80% of patients whose initial standard therapy failed would complete retreatment in the following year, and we varied this percentage in sensitivity analysis. The effectiveness of retreatment using triple therapy was derived from the protease inhibitors trial data (14), with treatment response stratified by prior failure status (that is, those who experienced no response, those who experienced partial response, and those who experienced relapse). Due to similar treatment response rates among the IL-28B genotypes within each failure status and little information on racial differences, we stratified SVR probabilities only by prior treatment failure status and assumed that the SVR for black patients is 73% of the SVR for white patients, consistent with racial difference in SVRs for treatment-naive patients (13, 14).

Utility Estimates

Chronic HCV negatively affects patients' quality of life. Variability among the HCV health-state utility research is substantial and, therefore, systematic review and combination of results is important. **Appendix Table 11** presents results from 1 systematic review (37), 3 papers with utilities elicited from patients (34–36), and 1 report using a panel of experts (15).

In the last column of **Appendix Table 11**, we report estimates for utilities for all fibrosis stages, HCC, liver transplant, and post-SVR health states, which were extracted from several sources (15, 34–37). We assumed that patients with fibrosis F0 to F1 would have very little decrement in utility, consistent with the findings of Salomon and colleagues (15). The utilities for moderate chronic HCV (F2 and F3), F4, and decompensated cirrhosis came directly from the time-tradeoff results in Sherman and colleagues' study (35). The utility for the state after liver transplant came from McLernon and colleagues' study (37). The

utility for SVR after moderate HCV came from the standard gamble results in Chong and colleagues' study (36), and then converted to time-tradeoff by using the formula in McLernon and colleagues' study (37). The utility of HCC came from Chong and colleagues' study (36) and is assumed to be similar to the utility of decompensated cirrhosis. In summary, patients' utilities for chronic HCV states, recovery states, and states after liver transplant are assumed to have a preference ranking order. The utility of:

Mild chronic HCV ≥ moderate chronic HCV ≥ F4 ≥ decompensated cirrhosis, HCC

SVR after mild HCV ≥ mild chronic HCV

SVR after moderate HCV ≥ moderate chronic HCV

SVR after cirrhosis ≥ F4

After liver transplant ≥ decompensated cirrhosis, HCC

SVR after mild HCV ≥ SVR after moderate HCV ≥ SVR after cirrhosis

We maintained these ranking orders in all deterministic and probabilistic sensitivity analyses.

Probabilistic Sensitivity Analyses

In probabilistic sensitivity analyses, all model parameters were sampled simultaneously from their respective uncertainty distributions (**Appendix Table 12**). We used a normal gamma or beta distribution to capture the mean and range of each model variable reported in literature. For patients with initial mild and advanced fibrosis, we conducted separate Monte Carlo simulations (5000 samples each). For each strategy in each simulation, we then calculated the net monetary benefit [(total QALYs × willingness-to-pay) − total cost] (58). We then constructed acceptability curves showing the probability that a given strategy yields the highest net monetary benefit at various willingness-to-pay thresholds.

Appendix 2: Supplemental Results

Scenario Analysis on Fibrosis Stage

Chronic hepatitis C virus (HCV) is a slowly progressing disorder that can take 30 years to cause end-stage liver disease. Meanwhile, patients may die of non–liver-related causes. Therefore, a patient's initial fibrosis stage can strongly affect the cost-effectiveness of treatment strategies. We considered clinical scenarios in which a patient's fibrosis stage is known (**Appendix Figure 3**). In general, universal triple therapy provides relatively more benefit per dollar spent for patients with more advanced liver fibrosis than those with less advanced fibrosis (ICERs below $50 000 per QALY for those with F4 fibrosis increasing to >$150 000 per QALY for those with no fibrosis).

Scenario Analysis on the Comparison Between Boceprevir and Telaprevir

The difference in price between the 2 new protease inhibitors available is large, and data from head-to-head clinical trials on which drug offers superior effectiveness are lacking. This may prompt benefits managers to ask whether they should include 1 or both of the new protease inhibitors in their formularies.

If a benefits provider were offering any protease inhibitor whose effectiveness was generally equal to both new drugs and whose price was similar to boceprevir, then universal triple therapy costs close to or less than $100 000 per QALY, even for patients with mild fibrosis compared with IL-28B–guided triple therapy. If the price of the protease inhibitor were equal to telaprevir and the effectiveness was that of telaprevir reported in the ADVANCE trial, then the ICERs of universal triple therapy to IL-28B–guided triple therapy are $102 400 per QALY for patients with mild fibrosis and $54 100 per QALY for patients with advanced fibrosis—very similar to the results for a protease inhibitor like boceprevir.

Comparing the drugs, for patients with advanced fibrosis the effectiveness of telaprevir needs to be greater than boceprevir and greater than that observed in the ADVANCE trial to yield an ICER less than $50 000 per QALY. For example, if its effectiveness yielded 86% SVRs for white patients and 61% SVRs for black patients, universal triple therapy with telaprevir would cost $205 402 and deliver 10.01 discounted QALYs and an ICER of $39 300 per QALY compared with universal triple therapy with boceprevir. For patients with mild fibrosis, the results are more extreme: Telaprevir needs to achieve a much higher SVR than that of boceprevir to achieve ICERs less than $50 000 per QALY. For example, if telaprevir yielded an SVR of 94% for white patients and 73% for black patients, it would cost $201 126 and gain 11.70 discounted QALYs and an ICER of $44 200 per QALY compared with boceprevir. Notably, these scenario analyses assume that, aside from price and effectiveness, the 2 drugs do not differ in the overall severity and costs of adverse effects or adherence (**Appendix Figure 4**).

Scenario Analysis on Costs

Prices for brand-name drugs vary substantially between purchasing institutions. For example, the Veterans Health Administration may purchase drugs at the Federal Supply Schedule price. In that case, the ICERs for universal triple therapy compared with IL-28B–guided triple therapy are $41 100 per QALY gained for advanced fibrosis and $81 300 per QALY gained for mild fibrosis, although specific estimates depend on the price levels and relative prices of standard therapy and new protease inhibitors (**Appendix Table 3**).

In **Appendix Table 3**, we report the ICERs from different treatment cost scenarios. The ICERs from universal triple therapy to IL-28B–guided triple therapy range from $60 100 to $102 600 per QALY gained for mild fibrosis, and $31 000 to $51 500 per QALY gained for advanced fibrosis.

Scenario Analysis on Adverse Effects of Triple Therapy

Adverse effects from triple therapy are more frequent and potentially more severe than those from standard therapy, which include anemia, depression, rash, and flu-like symptoms. Higher rates and severity of adverse effects may undermine the cost-effectiveness of universal triple therapy. We performed a threshold analysis to determine how severe the adverse effect profile would need to be for the ICER to exceed $100 000 per QALY for patients with advanced fibrosis (**Appendix Table 4**). We found that it did not exceed this threshold, even when the costs of adverse effects were tripled ($7500) and the disutility of ad-

verse effects was doubled (equal to a disutility of −0.36 QALYs per year with triple therapy).

Scenario Analysis on Adherence

In our base-case analysis, we assumed equal adherence for standard therapy and triple therapy (70% of patients taking ≥80% of their HCV medications). In a threshold analysis, we identified that if adherence for standard therapy remained at 70% but was as low as 50% for triple therapy, then universal triple therapy is more costly but achieves no additional benefit compared with IL-28B–guided triple therapy and was consequently not cost-effective for patients with either mild or advanced fibrosis (**Appendix Table 5**). However, even with 50% of patients adherent to triple therapy, universal triple therapy for those with advanced fibrosis costs $73 200 per QALY compared with standard therapy with 70% adherence. For mild fibrosis, universal triple therapy for this scenario costs greater than $150 000 per QALY compared with standard therapy.

Sensitivity Analysis on Risk for HCC

Limited evidence suggests that there is the risk for HCC from more advanced fibrosis stages, even after achieving SVR. To explore this, we conducted a sensitivity analysis in which we assumed that patients with F4 fibrosis who were successfully treated had an annual rate of developing hepatocellular carcinoma that was 20% of that for F4 before treatment. The results did not alter the main conclusions (**Appendix Table 6**).

Sensitivity Analysis on Non–Liver-Related Death

In NHANES III mortality analyses, we analyzed non–liver-related death similar to the methods described by El-Kamary and colleagues (54) to generate Cox models to estimate the mortality rate ratio for non–liver-related death in persons with chronic HCV compared with those with no HCV antibodies, described in **Appendix 1**. Risky behaviors are poorly reported in NHANES III, but many persons who would be excluded from HCV treatment are not well-captured by NHANES III (for example, active drug users, those who drink heavily, persons with unstable housing, persons who are homeless). Exclusions from treatment are often poorly justified and not supported by evidence. We conducted an additional sensitivity analysis on reducing the non–liver-related mortality hazard ratio by 30% from our base case (now 1.3 to 1.9, depending on race and sex). We found that this change reduced our base-case ICERs by 11% (advanced fibrosis) and 19% (mild fibrosis). Our main conclusion remained the same, but with reduced background mortality, treatment looks more favorable for patients with mild fibrosis (**Appendix Table 7**).

Retreatment

In addition to the use of new protease inhibitors in first-line therapy, the question of their use for retreatment of patients whose initial therapy fails has important clinical implications. We considered 2 additional strategies that used triple therapy for patients whose initial standard 2-drug therapy fails (**Appendix Figure 6**).

Assuming boceprevir cost, we find that offering first-line therapy with standard 2-drug treatment to all patients with mild fibrosis and offering triple therapy as retreatment costs more and is less effective than universal triple therapy (**Appendix Tables 8** and **9**). For patients with advanced fibrosis, such a strategy costs nearly $226 000 per QALY compared with universal triple therapy. A strategy in which patients with IL-28B CC type with mild fibrosis whose initial 2-drug therapy fails are retreated with triple therapy costs more than $116 500 per QALY compared with universal triple therapy. For advanced fibrosis, the ICER is nearly $50 000 per QALY. However, we do not consider triple therapy as retreatment for patients whose initial triple therapy fails because of lack of effectiveness data, and therefore, IL-28B–guided triple therapy with retreatment may, in fact, be less attractive than the present analysis suggests.

In the race-stratified results, IL-28B–guided triple therapy without retreatment is reasonably cost-effective (ICERs, $28 800 to $82 500 per QALY) compared with standard therapy for all cases. Using IL-28B–guided triple therapy with retreatment further increases QALYs gained compared with strategies without retreatment but also increases costs. Compared with universal triple therapy, IL-28B–guided triple therapy with retreatment costs $34 600 to $82 400 per QALY gained in white patients and $92 500 to $353,800 per QALY gained in black patients. Given the IL-28B genotype distribution among black patients (small percentage of CC type), using IL-28B–guided triple therapy with second-line triple therapy for those whose standard initial treatment fails is not cost-effective for black patients with mild fibrosis.

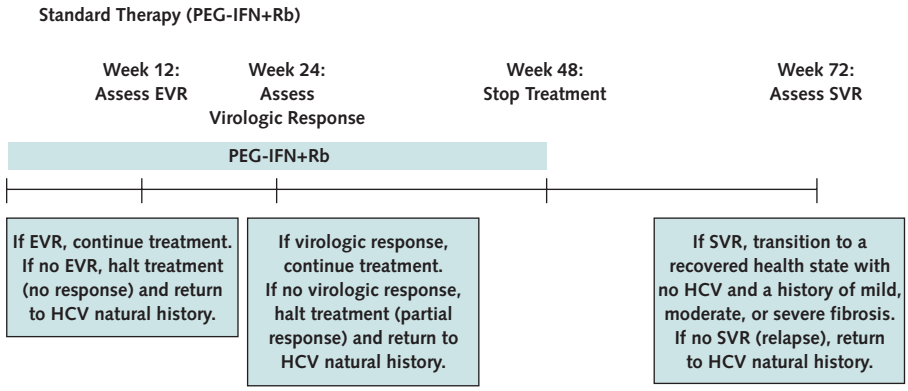
Subgroup Analyses by Race, Sex, Age, IL-28B Genotype, and Fibrosis

Although universal triple therapy for treatment-naive patients with chronic, genotype 1 HCV monoinfection seems to be effective for all patients, it achieves differentially greater health benefits per dollar spent in some groups of patients. We examined the ICERs between universal triple therapy to standard therapy for subgroups of patients defined in terms of race, sex, age, IL-28B genotype, and fibrosis (**Appendix Table 10**). In general, we find that subgroups of patients who are younger, those with more advanced fibrosis, and those with non-CC IL-28B genotypes derive differentially larger benefits and are more cost-effective to treat using universal triple therapy.

Probabilistic Sensitivity Analyses

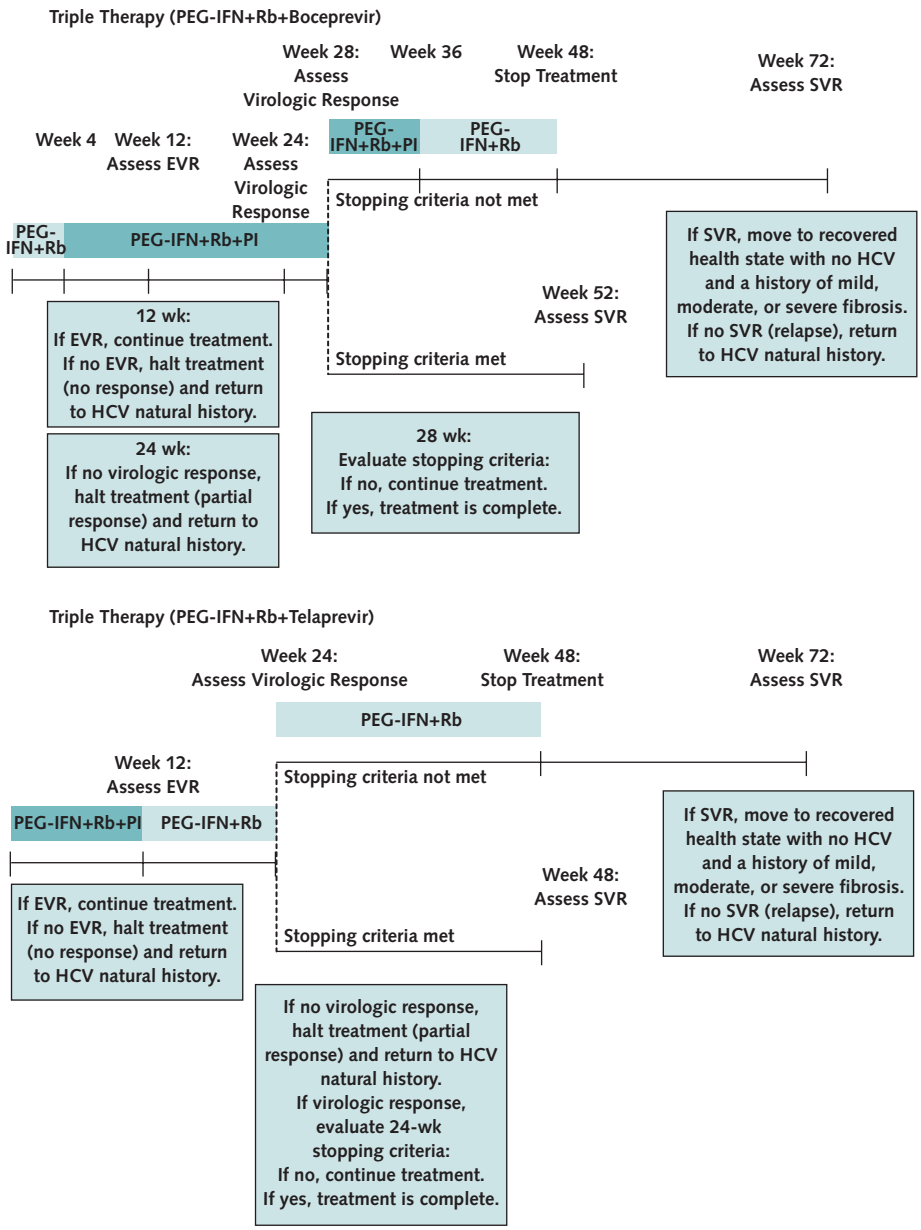
In probabilistic sensitivity analyses, we used the boceprevir cost (**Appendix Figure 5**). For patients with advanced fibrosis, willingness-to-pay thresholds of $50 000 and $100 000 per QALY, using either universal triple therapy or IL-28B–guided triple therapy was optimal 98% or 100% of the time, respectively. For patients with mild fibrosis, using either universal triple therapy or IL-28B–guided triple therapy was optimal 18% or 95% of the time at $50 000 or $100 000 per QALY, respectively. Conversely, at a threshold of $50 000 per QALY, standard therapy was optimal 82% of the time for mild fibrosis but only 2% of the time for advanced fibrosis.

Appendix Figure 1. **Schematic of first-line response-guided therapy for standard 2-drug therapy.**



Sustained virologic response is the goal of treatment, and it is measured 24 wk after treatment is stopped. Early virologic response is defined as a reduction of $\geq$2 $\log_{10}$/mL or complete absence of serum HCV RNA at week 12 of treatment compared with the baseline level. EVR = early virologic response; HCV = hepatitis C virus; PEG-IFN = pegylated interferon; Rb = ribavirin; SVR = sustained virologic response.

Appendix Figure 2. **Schematic of first-line response-guided therapy for triple therapy strategies.**



EVR = early virologic response; HCV = hepatitis C virus; PEG-IFN = pegylated interferon; PI = protease inhibitor; Rb = ribavirin; SVR = sustained virologic response.

Appendix Table 1. **Effectiveness of Standard Therapy (Pegylated Interferon With Ribavirin), by Race***

Variable	Genotype		Overall Calculated (Model)†	Overall Reported (Target) (12)
	CC	Non-CC		
White race				
Initial IL-28B distribution (12)	37	63	–	–
Probability of EVR at 12 wk	90	66	75	75
Probability of terminating treatment at 12 wk because of no EVR	10	34	25	–
After 12 wk, IL-28B distribution	45	55	–	–
Overall probability of virologic response at 24 wk				62
Probability of virologic response at 24 wk, conditional on EVR	92‡	75‡	83	82§
Probability of terminating treatment at 24 wk because of no virologic response at week 24, conditional on EVR	8	25	17	–
After 24 wk, IL-28B distribution	50	50	–	–
Probability of SVR, conditional on completing 48 wk of treatment	83‡	64‡	73.4	74
Final SVR calculated on the basis of model inputs‖	69	32	46¶	46
Final SVR reported (target) (12)	69	32	46	46
Black race				
Initial IL-28B distribution (12)	14	86	–	–
Probability of EVR at 12 wk	76	45	49	49
Probability of terminating treatment at 12 wk because of no EVR	24	55	51	–
After 12 wk, IL-28B distribution	22	78	–	–
Overall probability of virologic response at 24 wk				41
Probability of viral response at 24 wk, conditional on EVR	95‡	78‡	82	82
Probability of terminating treatment at 24 wk because of no virologic response at week 24, conditional on EVR	5	22	18	–
After 24 wk, IL-28B distribution	25	75	–	–
Probability of SVR, conditional on completing 48 wk of treatment	67‡	40‡	47	47
Final SVR calculated on the basis of model inputs‖	48	14	19¶	19
Final SVR reported (target) (12)	48	14	19	19

EVR = early virologic response; IL-28B = interleukin-28B; SVR = sustained virologic response.

* All values are percentages.

† Overall calculated = percentage (CC type) × virologic response (CC type) + percentage (non-CC type) × virologic response (non-CC type), at 12, 24, and 48 wk. We calculated the virologic response for CC type and non-CC type using the percentage of each type and by matching the overall calculated value to the overall value reported by Thompson and colleagues (12).

‡ Model inputs.

§ The conditional probability of virologic response at 24 wk conditional on EVR was calculated = [overall probability of virologic response at 24 wk]/[probability (EVR)]. Using white race for a numeric example: 62/75 = 82.

‖ Final SVR calculated on the basis of model inputs = probability (EVR) × probability (virologic response at 24 wk, conditional on EVR) × probability (SVR, conditional on completing 48 wk of treatment). Using white CC-types for a numeric example: 0.90 × 0.92 × 0.83 = 0.69. We identified model inputs to match the "final SVR calculated on the basis of model inputs" to the "final SVR reported (target)" in the last row of each section, and to match the "overall calculated (model)" to the "overall reported (target)" columns. Additionally, we imposed the constraint that the virologic response for CC type must be greater than or equal to the virologic response for non-CC type at 24 and 48 wk.

¶ The final SVRs calculated using model inputs matched targeted SVRs reported by Thompson and colleagues (12).

Appendix Table 2. Effectiveness of Protease Inhibitor Therapy, by Race*

Variable	Genotype		Overall Calculated (Model)†	Overall Reported (Target)	Source
	CC	Non-CC			
White race					
Initial IL-28B distribution‡	37	63	–	–	12
Probability of EVR at 12 wk	98§	90§	93	92	SPRINT-2, ADVANCE
Probability of terminating treatment at 12 wk because of no EVR	2	10	7	–	Calculated
After 12 wk, IL-28B distribution	39	61	–	–	Calculated
Probability of treatment completion at 24 wk (telaprevir) or 28 wk (boceprevir)	–	–	–	46	SPRINT-2
Probability of continuing treatment until 48 wk	–	–	–	34	ADVANCE
Conditional on EVR					
Probability of terminating treatment at 24 wk because of no virologic response at 24 wk	10	15	13	14	
Probability of treatment completion at 24 wk (telaprevir) or 28 wk (boceprevir)	62§	43§	50	50	
Probability of continuing treatment until 48 wk	28§	42§	37	37	
After 24 wk, IL-28B distribution	30	70	–	–	Calculated
SVR					
Probability of SVR, conditional on completing 24–28 wk of treatment	98§	95§	96	95	SPRINT-2, ADVANCE
Probability of SVR, conditional on completing 48 wk of treatment	75§	65§	68	68	SPRINT-2
Final SVR calculated on the basis of model inputs‖	80	61	68¶	67	
Final SVR reported (target)**	79	60	68	67	Estimated
Final SVR reported, IL-28B–stratified, boceprevir	82	63	70	67	SPRINT-2
Final SVR reported, IL-28B–stratified, telaprevir	90	71	78	75	ADVANCE
Black race					
Initial IL-28B distribution	14	86	–	–	12
Probability of EVR at 12 wk	80§	60§	63	61††	SPRINT-2, ADVANCE
Probability of terminating treatment at 12 wk because of no EVR	20	40	37	–	
After 12 wk, IL-28B distribution	18	82	–	–	Calculated
Probability of treatment completion at 24–28 wk	–	–	–	29	SPRINT-2
Probability of continuing treatment until 48 wk	–	–	–	23	SPRINT-2
Conditional on EVR					
Probability of terminating treatment at 24 wk because of no virologic response at 24 wk	14	14	14	18	
Probability of treatment completion at 24–28 wk	48§	48§	48	48	
Probability of continuing treatment until 48 wk	38§	38§	38	38	
After 24 wk, IL-28B distribution	18	82	–	–	Calculated
SVR					
Probability of SVR, conditional on completing 24–28 wk of treatment	95§	89§	90	88	SPRINT-2, ADVANCE
Probability of SVR, conditional on completing 48 wk of treatment	70§	60§	62	59	SPRINT-2
Final SVR calculated on the basis of model inputs¶	58	39	42**	39	
Final SVR reported (target)‡‡	58	44	42	44	SPRINT-2, Estimated

ADVANCE = A New Direction in HCV Care: A Study of Treatment-Naive Hepatitis C Patients with Telaprevir (telaprevir phase 3 clinical trial [NCT00627926] T12PR group data [6, 14, 28]); EVR = early virologic response; IL-28B = interleukin-28B; SPRINT-2 = Serine Protease Inhibitor Therapy 2 (boceprevir phase 3 clinical trial [NCT00705432], group 2 data [5, 13, 30]); SVR = sustained virologic response.

* All values are percentages.

† Overall calculated = percentage (CC type) × virologic response (CC type) + percentage (non-CC type) × virologic response (non-CC type), at 12, 24, and 48 wk.

‡ The genotyping information from the protease inhibitor trials are very similar to the ones reported in Thompson and colleagues (12), in which CC type was 37% among white participants and 14% among black participants. In the telaprevir ADVANCE trial, CC type was 36% among white patients (T12PR group). In the boceprevir SPRINT-2 trial, CC type was 35% among white patients in the response-guided therapy group.

§ Model inputs.

‖ Final probability of SVR calculated on the basis of model inputs = probability (EVR) × [probability (treatment completion at 24 wk, conditional on EVR) × probability (SVR, conditional on treatment completion at 24 wk) + probability (treatment completion at 48 wk, conditional on EVR) × probability (SVR, conditional on treatment completion at 48 wk)]. We identified model inputs to match the "final SVR calculated on the basis of model inputs" to the "final SVR reported (target)" in the last row of each section, and to match the "overall calculated (model)" to the "overall reported (target)" columns. Additionally, we imposed the constraint that the virologic response for CC type must be greater than or equal to the virologic response for non-CC type at 12, 24, and 48 wk.

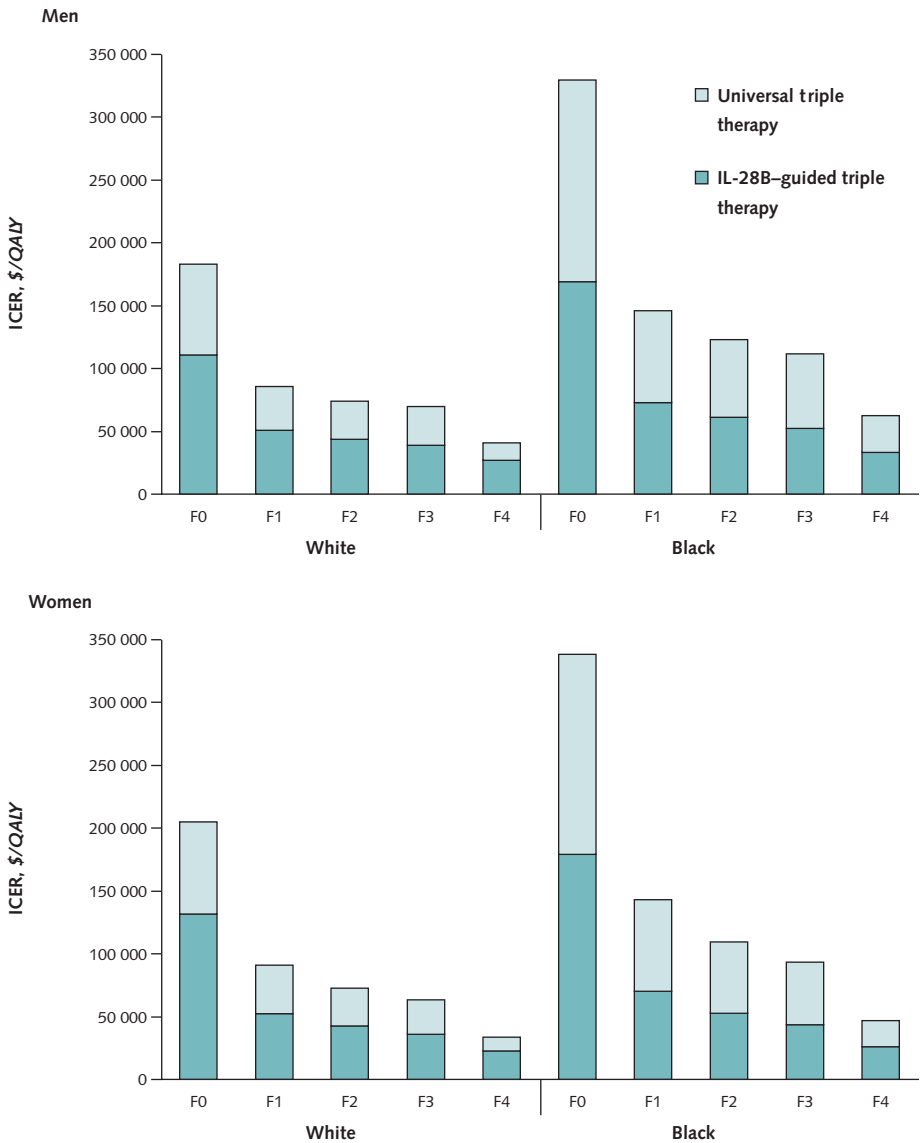
¶ The final SVRs calculated on the basis of model inputs matched targeted overall SVRs reported in literature.

** The SVRs reported for the subpopulations in which IL-28B genotype was known are higher than those reported in the whole trial population. For both the SPRINT-2 and ADVANCE trials, the overall SVR for the trial was 4% lower than the overall SVR rate that would be implied by the weighted average of the genotype stratified results (SPRINT-2: [Overall trial SVR]/[Overall SVR implied by genotype stratified results] = 0.67/0.70 = 0.96; ADVANCE: 0.75/0.78 = 0.96). Therefore, to estimate the target genotype stratified final SVR rates, we multiplied the genotype stratified SVR rates reported in the SPRINT-2 trial by a factor of 0.96 to correct this potential sampling bias.

†† To estimate the target EVR for black patients treated with triple therapy, we assumed that the EVR rate ratio observed between white and black patients with standard therapy would be the maintained with triple therapy. For standard therapy, 75% of white patients and 49% of black patients achieved EVR at 12 wk (12), resulting in an EVR rate ratio of 0.49/0.75 = 0.66. We calculated the probability of EVR at 12 wk for black patients as 0.66 times the probability of EVR at 12 wk for white patients: 0.66 × 0.92 = 0.61.

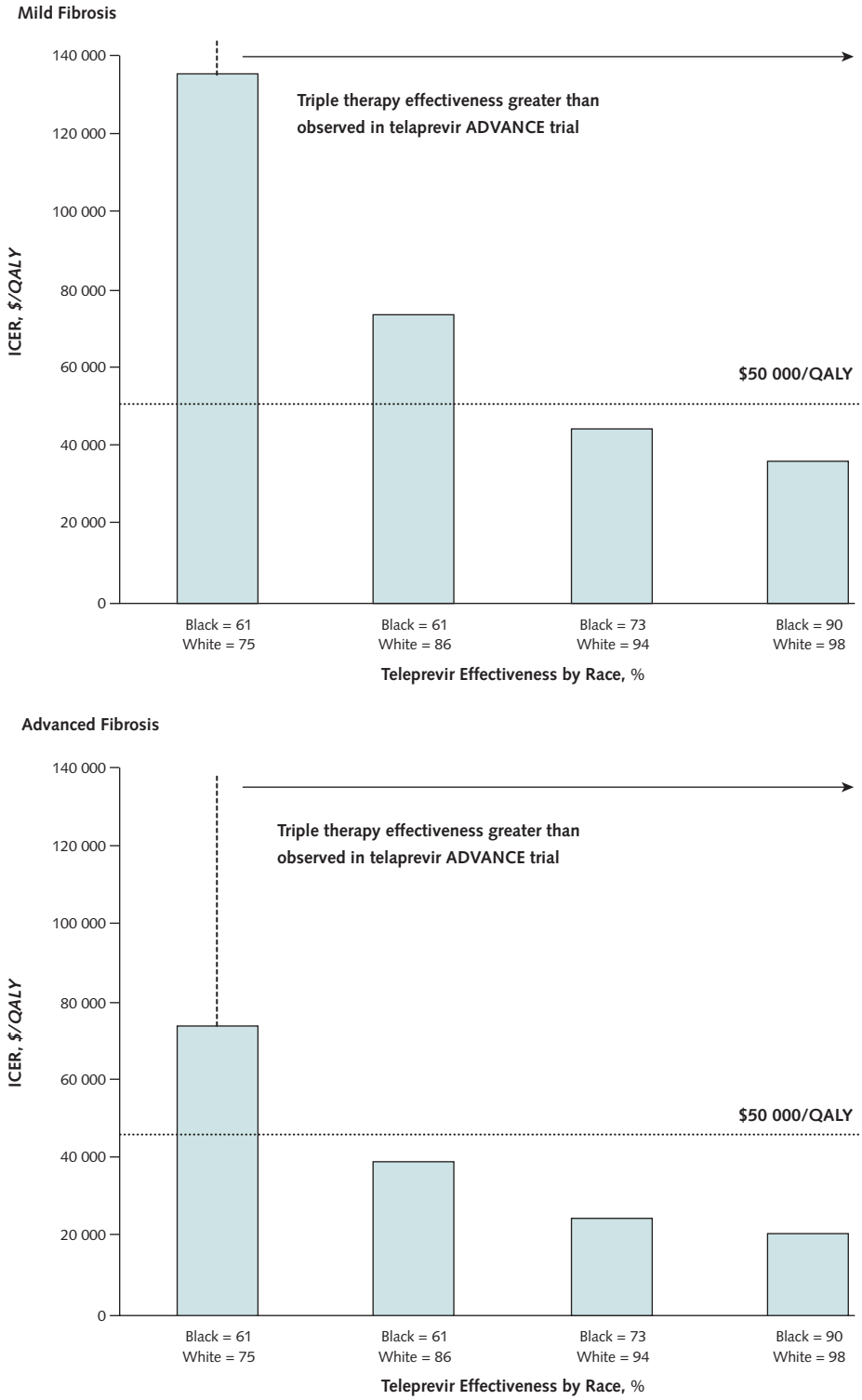
‡‡ To estimate the target final genotype specific SVR for black patients treated with triple therapy, we assumed that the overall SVR rate ratio observed between white and black patients in the SPRINT-2 trial would be maintained across IL-28B genotypes. In the SPRINT-2 trial, the final SVR was 67% for white patients and 42% for black patients, resulting in an SVR rate ratio of 0.42/0.67 = 0.73. We calculated the genotype stratified SVR for black patients as 0.73 times the final target SVR for white patients. Using CC type as a numeric example: 0.73 × 0.79 = 0.58.

Appendix Figure 3. **Cost-effectiveness results, depending on the fibrosis stage of the cohort.**



The ICER of strategies on the efficient frontier compared with the next best strategy on the frontier, assuming protease inhibitor costs $1100 per week. ICER = incremental cost-effectiveness ratio; IL-28B = interleukin-28B; QALY = quality-adjusted life-year.

Appendix Figure 4. **Protease inhibitor scenario analysis: ICERs between universal triple therapy using telaprevir to universal triple therapy using boceprevir (base case).**



ADVANCE = A New Direction in HCV Care: A Study of Treatment-Naive Hepatitis C Patients with Telaprevir; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Appendix Table 3. **ICERs of Treatment Strategies, by Severity of Fibrosis Stage, Assuming Base-Case Boceprevir in Different Treatment Cost Scenarios***

Fibrosis Severity	ICER, *$/QALY*		
	IL-28B to Standard Therapy	**Triple Therapy to IL-28B**	**Triple Therapy to Standard Therapy**
Mild fibrosis			
Best price for PEG-IFN+Rb (base case)	62 857	102 563	70 127
Best price for PEG-IFN+Rb, SPRINT-2 trial schedule†	55 057	88 945	61 287
AMP for PEG-IFN+Rb	63 315	94 901	69 098
AWP for PEG-IFN+Rb	63 887	85 324	67 812
FSS price for all drugs	41 610	81 341	48 885
FSS price for protease inhibitor only, and best price for PEG-IFN+Rb	42 881	60 070	46 028
	IL-28B Stratification to Standard Therapy	**Triple Therapy to IL-28B Stratification**	**Triple Therapy to Standard Therapy**
Advanced fibrosis			
Best price for PEG-IFN+Rb (base case)	32 786	51 459	36 251
Best price for PEG-IFN+Rb, SPRINT-2 trial†	29 079	45 188	32 073
AMP for PEG-IFN+Rb	33 014	47 832	35 763
AWP for PEG-IFN+Rb	33 299	43 298	35 154
FSS price for all drugs	22 398	41 114	25 871
FSS price for protease inhibitor only, and best price for PEG-IFN+Rb	23 031	31 045	24 518

AMP = average manufacturing price; AWP = average wholesale price; FSS = Federal Supply Schedule; ICER = incremental cost-effectiveness ratio; IL-28B = interleukin-28B; PEG-IFN= = pegylated interferon; QALY = quality-adjusted life-year; Rb = ribavirin; SPRINT-2 = Serine Protease Inhibitor Therapy 2 (boceprevir phase 3 clinical trial for treatment-naive patients [5]).
* The best price is at 64% of AWP. AMP is at 80% of AWP. The FSS prices for PEG-IFN+Rb and boceprevir are $190/wk and $781/wk, respectively.
† In the SPRINT-2 trial, boceprevir was used for a total of 24 wk.

Appendix Table 4. **ICERs Comparing Universal Triple Therapy to IL-28B–Guided Triple Therapy for Various Adverse Effect Scenarios: Costs of Adverse Effects Versus Additional Disutility of Adverse Effects on Triple Therapy, by Severity of Fibrosis***

	Disutility	ICER, by Total Cost of Adverse Effects of Triple Therapy, *$/QALY*			
		(1 × Base Case) $2586	**$4167**	**$5833**	**$7500**
Mild fibrosis					
(1 × base case)	−0.055	102 563	110 803	119 484	128 170
	−0.12	123 052	132 938	143 353	153 775
	−0.185	153 771	166 124	179 140	192 163
	−0.25	204 929	221 393	238 739	256 095
Advanced fibrosis					
(1 × base case)	−0.055	51 459	55 430	59 614	63 801
	−0.12	55 934	60 250	64 798	69 348
	−0.185	61 261	65 988	70 968	75 952
	−0.25	67 708	72 933	78 438	83 946

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.
* In all scenarios, we assumed that the protease inhibitor used in triple therapy costs $1100/wk. Results are weighted averages over race and sex based on relative prevalence of these groups for patients with chronic hepatitis C virus from NHANES III (Third National Health and Nutrition Examination Survey) data (white male, 51%; white female, 23%; black male, 17%; and black female, 9%).

Appendix Table 5. **Scenario Analysis on Adherence to Triple Therapy: Lifetime Discounted Costs, QALYs, and ICERs of Treatment Strategies, by Severity of Fibrosis Stage***

Strategy	Mild Fibrosis				Advanced Fibrosis			
	Cost, $	QALYs	ICER, $/QALY	ICER Excluding IL-28B, $/QALY†	Cost, $	QALYs	ICER, $/QALY	ICER Excluding IL-28B, $/QALY†
65% adherence								
Standard therapy	160 456	10.97	–	–	161 312	8.84	–	–
IL-28B–guided triple therapy	176 897	11.20	71 754	–	178 680	9.31	36 963	–
Universal triple therapy	182 935	11.24	164 621	84 600	184 863	9.39	78 600	42 900
55% adherence								
Standard therapy	160 456	10.97	–	–	161 312	8.84	–	–
IL-28B–guided triple therapy	176 611	11.16	84 239	–	178 234	9.24	42 769	–
Universal triple therapy	182 567	11.18	455 997	107 900	184 228	9.27	185 636	53 500
50% adherence								
Standard therapy	160 456	10.97	–	–	161 312	8.84	–	–
IL-28B–guided triple therapy	176 285	11.12	103 200	–	177 745	9.16	51 500	–
Universal triple therapy	182 145	11.11	Dominated‡	152 800	183 528	9.14	Dominated‡	73 200

ICER = incremental cost-effectiveness ratio; IL-28B = interleukin-28B; QALY = quality-adjusted life-year.
* Results are weighted averages over race and sex based on relative prevalence of these groups for patients with chronic hepatitis C virus from NHANES III (Third National Health and Nutrition Examination Survey) data (white male, 51%; white female, 23%; black male, 17%; and black female, 9%). In all scenarios, we assumed that the protease inhibitor used in triple therapy costs $1100/wk.
† If IL-28B genotyping is unavailable, ICER is between universal triple therapy and standard therapy.
‡The strategy costs more and provides fewer benefits than another strategy or a combination of 2 strategies.

Appendix Table 6. **Scenario Analysis of Increased Risk for Hepatocellular Carcinoma After Sustained Virologic Response From F4: Lifetime Discounted Costs, QALYs, and ICERs of Treatment Strategies, by Severity of Fibrosis Stage***

Strategy	Mild Fibrosis			Advanced Fibrosis		
	Cost, $	QALYs	ICER, $/QALY	Cost, $	QALYs	ICER, $/QALY
Standard therapy	160 456	10.97	–	161 032	8.78	–
IL-28B–guided triple therapy	177 152	11.24	62 900	178 679	9.29	34 400
Universal triple therapy	183 257	11.30	102 500	185 004	9.41	54 100

ICER = incremental cost-effectiveness ratio; IL-28B = interleukin-28B; QALY = quality-adjusted life-year.
* We assumed that the protease inhibitor used in triple therapy costs $1100/wk.

Appendix Table 7. **Lifetime Discounted Costs and QALYs of Treatment Strategies by Severity of Fibrosis State: Reducing the Non–Liver-Related Mortality Hazard Ratio by 30% From Base Case***

Strategy	Mild Fibrosis			Advanced Fibrosis		
	Cost, $	QALYs	ICER, $/QALY	Cost, $	QALYs	ICER, $/QALY
Standard therapy	181 429	11.99	–	178 550	9.58	–
IL-28B–guided triple therapy	198 209	12.32	50 700	197 298	10.22	29 200
Universal triple therapy	204 345	12.39	85 400	203 868	10.36	46 000

ICER = incremental cost-effectiveness ratio; IL-28B = interleukin-28B; QALY = quality-adjusted life-year.
* We assumed that the protease inhibitor used in triple therapy costs $1100/wk.

Appendix Table 8. Lifetime Discounted Costs and QALYs of Treatment Strategies, by Severity of Fibrosis Stage*

Strategy	Mild Fibrosis†			Advanced Fibrosis‡		
	Cost, $	QALYs	ICER, $/QALY§	Cost, $	QALYs	ICER, $/QALY§
Standard therapy	160 456	10.97	–	161 312	8.84	–
IL-28B–guided triple therapy	177 152	11.24	62 900	179 090	9.38	32 800
Universal triple therapy	183 257	11.30	102 600	185 447	9.51	Dominated‖
Standard therapy with retreatment	196 042	11.26	Dominated‖	201 260	9.58	Dominated‖
IL-28B–guided triple therapy with retreatment	200 340	11.44	116 500	205 991	9.93	49 200

ICER = incremental cost-effectiveness ratio; IL-28B = interleukin-28B; QALY = quality-adjusted life-year.
* We assumed that the protease inhibitor used in triple therapy costs $1100/wk.
† F0, 30%; F1, 41%; and F2, 29%.
‡ F2, 29%; F3, 23%; and F4, 48%.
§ Results are weighted averages over race and sex based on relative prevalence of these groups for patients with chronic hepatitis C virus from NHANES III (Third National Health and Nutrition Examination Survey) data (white male, 51%; white female, 23%; black male, 17%; and black female, 9%).
‖ The strategy costs more and provides fewer benefits than another strategy or a combination of 2 strategies.

Appendix Table 9. Lifetime Discounted Costs and QALYs of Treatment Strategies, by Race, Sex, and Severity of Fibrosis Stage*

	White			Black		
	Cost, $	QALYs	ICER, $/QALY	Cost, $	QALYs	ICER, $/QALY
Mild fibrosis†						
Men						
Standard therapy	156 422	10.77	–	120 661	8.48	–
IL-28B–guided triple therapy	172 747	11.06	57 400	138 483	8.69	82 500
Universal triple therapy	180 113	11.13	Dominated§	140 988	8.71	166 000
IL-28B–guided triple therapy with retreatment	192 120	11.30	79 600	172 513	8.80	353 800
Women						
Standard therapy	199 441	13.27	–	158 861	10.95	–
IL-28B–guided triple therapy	215 758	13.54	59 200	176 494	11.18	77 200
Universal triple therapy	223 141	13.61	Dominated§	178 992	11.20	157 500
IL-28B–guided triple therapy with retreatment	235 150	13.78	82 400	210 524	11.29	324 700
Advanced fibrosis‡						
Men						
Standard therapy	158 448	8.82	–	126 403	6.75	–
IL-28B–guided triple therapy	175 602	9.34	32 600	144 030	7.18	41 600
Universal triple therapy	183 163	9.49	Dominated§	146 515	7.21	81 900
IL-28B–guided triple therapy with retreatment	198 808	9.92	40 300	179 197	7.46	128 800
Women						
Standard therapy	194 483	10.60	–	158 703	8.42	–
IL-28B–guided triple therapy	213 370	11.25	28 800	177 476	9.00	32 800
Universal triple therapy	221 399	11.43	Dominated§	180 046	9.04	64 000
IL-28B–guided triple therapy with retreatment	238 691	11.98	34 600	213 746	9.40	92 500

ICER = incremental cost-effectiveness ratio; IL-28B = interleukin-28B; QALY = quality-adjusted life-year.
* We assumed that the protease inhibitor used in triple therapy costs $1100/wk.
† F0, 30%; F1, 41%; and F2, 29%.
‡ F2, 29%; F3, 23%; and F4, 48%.
§ The strategy costs more and provides fewer benefits than another strategy or a combination of 2 strategies.

Appendix Table 10. **Lifetime Discounted Costs and QALYs of Treatment Strategies, by Race, Sex, Age, IL-28B Genotype, and Fibrosis***

Race	Sex	Age, *y*	IL-28B Genotype	Fibrosis	Standard Therapy		IL-28B–Guided Triple Therapy		Universal Triple Therapy		ICER, *$/QALY*†	Cost-Effective at $50 000/QALY?
					Cost, *$*	QALYs	Cost, *$*	QALYs	Cost, *$*	QALYs		
W	M	40	CC	0	156 491	15.06	156 862	15.06	177 385	15.17	180 574	
W	M	40	CC	1	157 602	14.70	157 973	14.70	178 122	14.95	83 879	
W	M	40	CC	2	157 645	13.48	158 016	13.48	178 146	13.79	66 801	
W	M	40	CC	3	159 907	12.61	160 278	12.61	180 931	12.96	59 713	
W	M	40	CC	4	162 724	10.96	163 095	10.96	184 737	11.70	29 996	Yes
W	M	40	Non-CC	0	155 494	14.75	181 025	15.00	180 654	15.00	103 255	
W	M	40	Non-CC	1	157 698	14.02	182 350	14.57	181 979	14.57	43 614	Yes
W	M	40	Non-CC	2	157 634	12.61	182 339	13.32	181 968	13.32	34 515	Yes
W	M	40	Non-CC	3	158 218	11.55	184 271	12.40	183 900	12.40	30 197	Yes
W	M	40	Non-CC	4	158 213	9.16	186 511	10.70	186 140	10.70	18 094	Yes
W	M	50	CC	0	156 545	11.62	156 916	11.62	177 680	11.73	191 981	
W	M	50	CC	1	157 408	11.28	157 779	11.28	178 258	11.51	89 702	
W	M	50	CC	2	157 636	10.37	158 007	10.37	178 396	10.63	77 800	
W	M	50	CC	3	159 782	9.70	160 153	9.70	180 952	9.99	73 432	
W	M	50	CC	4	162 152	8.76	162 523	8.76	184 124	9.27	42 642	Yes
W	M	50	Non-CC	0	154 745	11.32	180 900	11.55	180 529	11.55	108 383	
W	M	50	Non-CC	1	156 415	10.66	181 920	11.17	181 549	11.17	49 207	Yes
W	M	50	Non-CC	2	156 598	9.64	182 075	10.24	181 704	10.24	42 375	Yes
W	M	50	Non-CC	3	157 396	8.85	183 949	9.54	183 578	9.54	38 190	Yes
W	M	50	Non-CC	4	157 810	7.54	185 965	8.59	185 594	8.59	26 472	Yes
W	M	60	CC	0	150 339	8.26	150 710	8.26	171 789	8.35	262 119	
W	M	60	CC	1	151 130	8.00	151 501	8.00	172 318	8.18	119 810	
W	M	60	CC	2	151 652	7.38	152 023	7.38	172 644	7.57	110 909	
W	M	60	CC	3	153 853	6.98	154 224	6.98	175 126	7.17	110 501	
W	M	60	CC	4	155 991	6.46	156 362	6.46	177 790	6.78	68 029	
W	M	60	Non-CC	0	147 486	8.04	174 450	8.22	174 079	8.22	155 452	
W	M	60	Non-CC	1	149 000	7.57	175 379	7.93	175 008	7.93	72 174	
W	M	60	Non-CC	2	149 664	6.91	175 835	7.30	175 464	7.30	65 606	
W	M	60	Non-CC	3	150 999	6.44	177 873	6.87	177 502	6.87	60 591	
W	M	60	Non-CC	4	152 053	5.75	179 825	6.37	179 454	6.37	44 382	Yes
W	M	70	CC	0	135 475	5.10	135 846	5.10	157 331	5.14	531 719	
W	M	70	CC	1	136 170	4.95	136 541	4.95	157 798	5.05	222 283	
W	M	70	CC	2	136 930	4.57	137 301	4.57	158 279	4.67	213 209	
W	M	70	CC	3	139 146	4.38	139 517	4.38	160 609	4.48	216 896	
W	M	70	CC	4	141 507	4.11	141 878	4.11	163 092	4.28	130 533	
W	M	70	Non-CC	0	131 299	5.00	159 251	5.08	158 880	5.08	378 927	
W	M	70	Non-CC	1	132 610	4.75	160 063	4.92	159 692	4.92	158 013	
W	M	70	Non-CC	2	133 756	4.35	160 801	4.54	160 430	4.54	146 350	
W	M	70	Non-CC	3	135 753	4.13	163 002	4.33	162 631	4.33	133 945	
W	M	70	Non-CC	4	137 868	3.79	165 255	4.08	164 884	4.08	94 567	
W	F	40	CC	0	192 648	17.47	193 019	17.47	213 480	17.57	206 777	
W	F	40	CC	1	193 692	17.14	194 063	17.14	214 175	17.36	92 425	
W	F	40	CC	2	192 967	15.69	193 338	15.69	213 709	16.00	67 349	
W	F	40	CC	3	192 669	14.72	193 040	14.72	214 363	15.09	58 200	
W	F	40	CC	4	189 687	12.39	190 058	12.39	213 900	13.29	26 871	Yes
W	F	40	Non-CC	0	192 024	17.23	217 292	17.43	216 921	17.43	126 362	
W	F	40	Non-CC	1	194 070	16.52	218 529	17.02	218 158	17.02	48 123	Yes
W	F	40	Non-CC	2	192 419	14.82	217 604	15.53	217 233	15.53	34 921	Yes
W	F	40	Non-CC	3	189 001	13.60	216 680	14.50	216 309	14.50	30 281	Yes
W	F	40	Non-CC	4	179 333	10.12	212 562	12.05	212 191	12.05	17 044	Yes
W	F	50	CC	0	199 880	14.17	200 251	14.17	220 927	14.26	215 722	
W	F	50	CC	1	200 571	13.84	200 942	13.84	221 396	14.05	95 735	
W	F	50	CC	2	199 923	12.69	200 294	12.69	220 977	12.96	76 073	
W	F	50	CC	3	199 454	11.86	199 825	11.86	221 346	12.18	67 038	
W	F	50	CC	4	196 882	10.36	197 253	10.36	220 963	11.03	35 687	Yes
W	F	50	Non-CC	0	198 558	13.92	224 378	14.12	224 007	14.12	128 484	
W	F	50	Non-CC	1	199 843	13.24	225 182	13.73	224 811	13.73	51 657	
W	F	50	Non-CC	2	198 315	11.92	224 334	12.54	223 963	12.54	40 948	Yes
W	F	50	Non-CC	3	195 023	10.88	223 283	11.67	222 912	11.67	35 528	Yes
W	F	50	Non-CC	4	187 202	8.71	219 931	10.12	219 560	10.12	22 940	Yes
W	F	60	CC	0	198 012	10.62	198 383	10.62	219 350	10.70	277 960	
W	F	60	CC	1	198 637	10.36	199 008	10.36	219 776	10.53	121 214	
W	F	60	CC	2	198 417	9.51	198 788	9.51	219 631	9.72	101 583	
W	F	60	CC	3	198 699	8.95	199 070	8.95	220 523	9.18	92 539	
W	F	60	CC	4	197 129	8.05	197 500	8.05	220 607	8.50	52 142	
W	F	60	Non-CC	0	195 710	10.43	222 294	10.58	221 923	10.58	171 695	

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Appendix Table 10—**Continued**

Race	Sex	Age, *y*	IL-28B Genotype	Fibrosis	Standard Therapy		IL-28B–Guided Triple Therapy		Universal Triple Therapy		ICER, *$/QALY*†	Cost-Effective at $50 000/ QALY?
					Cost, *$*	QALYs	Cost, *$*	QALYs	Cost, *$*	QALYs		
W	F	60	Non-CC	1	196 863	9.91	223 021	10.27	222 650	10.27	69 966	
W	F	60	Non-CC	2	196 199	8.96	222 674	9.42	222 303	9.42	57 825	
W	F	60	Non-CC	3	194 420	8.26	222 531	8.81	222 160	8.81	50 350	
W	F	60	Non-CC	4	189 336	7.00	220 525	7.90	220 154	7.90	34 079	Yes
W	F	70	CC	0	182 313	7.00	182 684	7.00	204 028	7.05	493 590	
W	F	70	CC	1	182 946	6.84	183 317	6.84	204 460	6.94	204 710	
W	F	70	CC	2	183 346	6.29	183 717	6.29	204 710	6.42	174 125	
W	F	70	CC	3	184 936	6.00	185 307	6.00	206 579	6.13	162 956	
W	F	70	CC	4	185 281	5.50	185 652	5.50	207 772	5.75	88 867	
W	F	70	Non-CC	0	178 717	6.90	206 288	6.98	205 917	6.98	355 830	
W	F	70	Non-CC	1	179 902	6.59	207 031	6.79	206 660	6.79	133 366	
W	F	70	Non-CC	2	180 508	6.00	207 418	6.24	207 047	6.24	109 881	
W	F	70	Non-CC	3	181 275	5.64	208 860	5.93	208 489	5.93	94 501	
W	F	70	Non-CC	4	180 082	4.96	209 042	5.43	208 671	5.43	$60 571	
B	M	40	CC	0	127 843	12.72	128 214	12.72	148 374	12.78	332 412	
B	M	40	CC	1	129 646	12.31	130 017	12.31	149 862	12.45	147 639	
B	M	40	CC	2	130 491	11.19	130 862	11.19	150 547	11.37	112 121	
B	M	40	CC	3	133 950	10.46	134 321	10.46	154 173	10.67	96 174	
B	M	40	CC	4	139 809	8.74	140 180	8.74	160 040	9.19	45 386	Yes
B	M	40	Non-CC	0	124 563	12.54	145 117	12.68	144 746	12.68	146 901	
B	M	40	Non-CC	1	127 431	11.89	147 182	12.21	146 811	12.21	59 300	
B	M	40	Non-CC	2	128 740	10.63	148 126	11.06	147 755	11.06	44 076	Yes
B	M	40	Non-CC	3	131 670	9.76	151 462	10.29	151 091	10.29	36 687	Yes
B	M	40	Non-CC	4	137 101	7.46	157 136	8.47	156 765	8.47	19 502	Yes
B	M	50	CC	0	122 380	9.23	122 751	9.23	143 147	9.28	379 238	
B	M	50	CC	1	123 784	8.87	124 155	8.87	144 308	8.99	168 099	
B	M	50	CC	2	124 769	8.09	125 140	8.09	145 100	8.24	141 435	
B	M	50	CC	3	127 886	7.57	128 257	7.57	148 323	7.74	127 441	
B	M	50	CC	4	132 458	6.68	132 829	6.68	152 881	6.96	71 070	
B	M	50	Non-CC	0	118 224	9.07	139 423	9.19	139 052	9.19	165 512	
B	M	50	Non-CC	1	120 432	8.50	141 020	8.79	140 649	8.79	71 213	
B	M	50	Non-CC	2	121 882	7.66	142 082	8.00	141 711	8.00	58 737	
B	M	50	Non-CC	3	124 684	7.05	145 130	7.45	144 759	7.45	50 347	
B	M	50	Non-CC	4	129 010	5.89	149 585	6.52	149 214	6.52	32 007	Yes
B	M	60	CC	0	117 228	6.44	117 599	6.44	138 232	6.48	531 590	
B	M	60	CC	1	118 364	6.17	118 735	6.17	139 172	6.27	229 178	
B	M	60	CC	2	119 395	5.66	119 766	5.66	139 998	5.76	207 908	
B	M	60	CC	3	122 041	5.35	122 412	5.35	142 708	5.46	198 328	
B	M	60	CC	4	125 582	4.89	125 953	4.89	146 208	5.06	119 807	
B	M	60	Non-CC	0	112 216	6.32	134 051	6.41	133 680	6.41	237 965	
B	M	60	Non-CC	1	113 979	5.92	135 334	6.12	134 963	6.12	105 002	
B	M	60	Non-CC	2	115 438	5.38	136 415	5.60	136 044	5.60	92 948	
B	M	60	Non-CC	3	117 931	5.03	139 037	5.28	138 666	5.28	82 668	
B	M	60	Non-CC	4	121 395	4.44	142 518	4.80	142 147	4.80	57 410	
B	M	70	CC	0	110 039	4.08	110 410	4.08	131 287	4.09	1 146 603	
B	M	70	CC	1	110 858	3.92	111 229	3.92	131 967	3.97	426 475	
B	M	70	CC	2	111 790	3.60	112 161	3.60	132 715	3.65	398 088	
B	M	70	CC	3	113 977	3.45	114 348	3.45	134 906	3.50	392 199	
B	M	70	CC	4	117 080	3.21	117 451	3.21	137 872	3.30	234 522	
B	M	70	Non-CC	0	104 183	4.03	126 656	4.06	126 285	4.06	563 404	
B	M	70	Non-CC	1	105 422	3.80	127 567	3.90	127 196	3.90	220 232	
B	M	70	Non-CC	2	106 731	3.47	128 541	3.58	128 170	3.58	199 474	
B	M	70	Non-CC	3	108 982	3.30	130 761	3.42	130 390	3.42	179 251	
B	M	70	Non-CC	4	112 263	3.00	133 853	3.17	133 482	3.17	123 465	
B	F	40	CC	0	158 916	15.12	159 287	15.12	179 363	15.17	354 492	
B	F	40	CC	1	160 672	14.72	161 043	14.72	180 812	14.85	153 936	
B	F	40	CC	2	160 614	13.34	160 985	13.34	180 761	13.53	105 826	
B	F	40	CC	3	161 710	12.49	162 081	12.49	182 293	12.72	88 501	
B	F	40	CC	4	162 178	9.97	162 549	9.97	183 631	10.54	37 529	Yes
B	F	40	Non-CC	0	156 076	14.97	176 334	15.09	175 963	15.09	164 237	
B	F	40	Non-CC	1	158 860	14.31	178 342	14.62	177 971	14.62	61 458	
B	F	40	Non-CC	2	158 720	12.74	178 250	13.20	177 879	13.20	41 494	Yes
B	F	40	Non-CC	3	158 278	11.71	178 952	12.30	178 581	12.30	34 602	Yes
B	F	40	Non-CC	4	155 793	8.29	178 691	9.61	178 320	9.61	17 137	Yes
B	F	50	CC	0	160 656	11.81	161 027	11.81	181 306	11.86	388 642	
B	F	50	CC	1	161 898	11.43	162 269	11.43	182 335	11.55	165 199	

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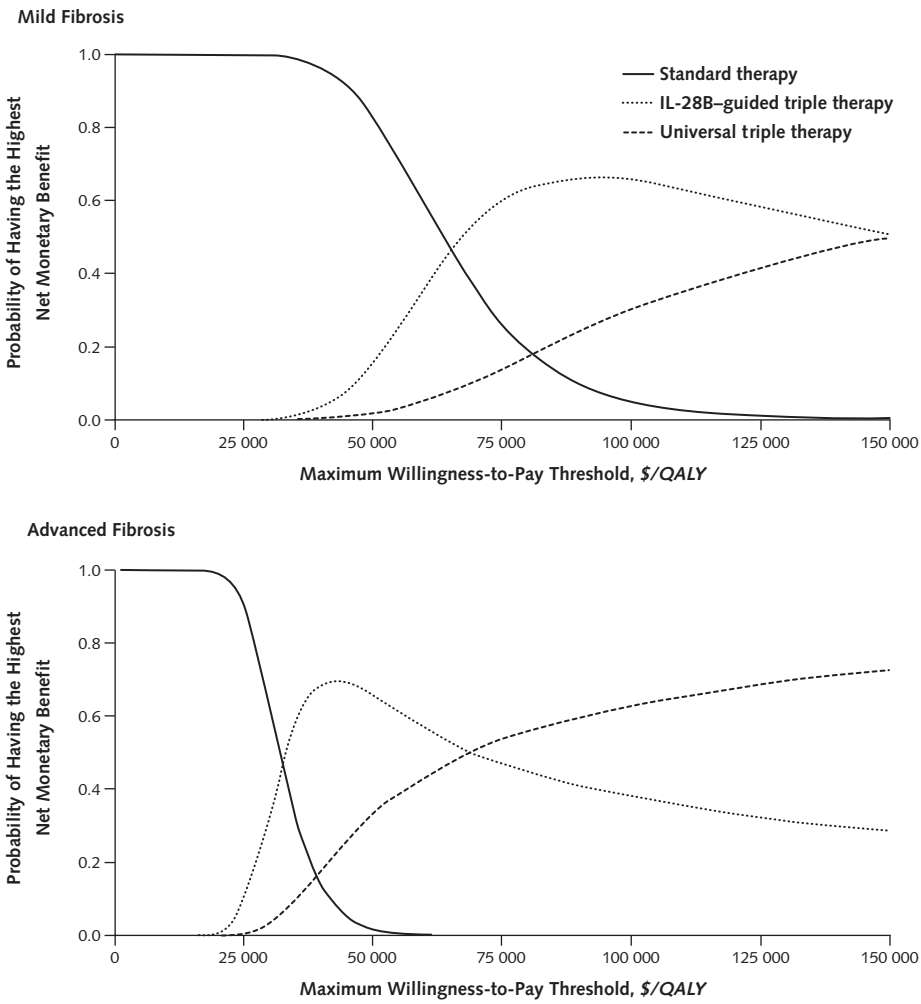
Appendix Table 10—**Continued**

Race	Sex	Age, *y*	IL-28B Genotype	Fibrosis	Standard Therapy		IL-28B–Guided Triple Therapy		Universal Triple Therapy		ICER, *$/QALY*†	Cost-Effective at $50 000/ QALY?
					Cost, *$*	QALYs	Cost, *$*	QALYs	Cost, *$*	QALYs		
B	F	50	CC	2	161 970	10.39	162 341	10.39	182 387	10.55	125 705	
B	F	50	CC	3	162 978	9.69	163 349	9.69	183 746	9.88	106 363	
B	F	50	CC	4	163 441	8.16	163 812	8.16	184 920	8.57	52 986	
B	F	50	Non-CC	0	157 070	11.66	177 879	11.78	177 508	11.78	176 131	
B	F	50	Non-CC	1	159 005	11.05	179 285	11.34	178 914	11.34	68 373	
B	F	50	Non-CC	2	159 040	9.88	179 326	10.27	178 955	10.27	51 285	
B	F	50	Non-CC	3	158 790	9.04	180 008	9.53	179 637	9.53	42 495	Yes
B	F	50	Non-CC	4	157 041	7.00	179 966	7.92	179 595	7.92	24 697	Yes
B	F	60	CC	0	157 773	8.64	158 144	8.64	178 668	8.68	524 533	
B	F	60	CC	1	158 744	8.34	159 115	8.34	179 474	8.44	216 327	
B	F	60	CC	2	159 107	7.61	159 478	7.61	179 761	7.73	175 170	
B	F	60	CC	3	160 406	7.15	160 777	7.15	181 294	7.28	153 616	
B	F	60	CC	4	161 277	6.28	161 648	6.28	182 648	6.53	82 645	
B	F	60	Non-CC	0	153 286	8.53	174 759	8.62	174 388	8.62	243 112	
B	F	60	Non-CC	1	154 775	8.07	175 848	8.28	175 477	8.28	95 111	
B	F	60	Non-CC	2	155 255	7.26	176 211	7.53	175 840	7.53	75 539	
B	F	60	Non-CC	3	155 735	6.71	177 302	7.04	176 931	7.04	63 343	
B	F	60	Non-CC	4	155 250	5.57	177 898	6.14	177 527	6.14	39 544	Yes
B	F	70	CC	0	147 445	5.64	147 816	5.64	168 609	5.66	1 029 150	
B	F	70	CC	1	148 202	5.46	148 573	5.46	169 241	5.51	383 009	
B	F	70	CC	2	148 873	4.99	149 244	4.99	169 780	5.06	312 139	
B	F	70	CC	3	150 731	4.75	151 102	4.75	171 715	4.83	285 083	
B	F	70	CC	4	152 744	4.29	153 115	4.29	173 872	4.43	151 283	
B	F	70	Non-CC	0	141 962	5.58	164 170	5.63	163 799	5.63	525 926	
B	F	70	Non-CC	1	143 101	5.31	165 011	5.43	164 640	5.43	185 098	
B	F	70	Non-CC	2	144 078	4.81	165 729	4.95	165 358	4.95	147 065	
B	F	70	Non-CC	3	145 728	4.53	167 546	4.70	167 175	4.70	124 744	
B	F	70	Non-CC	4	147 381	3.94	169 500	4.23	169 129	4.23	75 840	

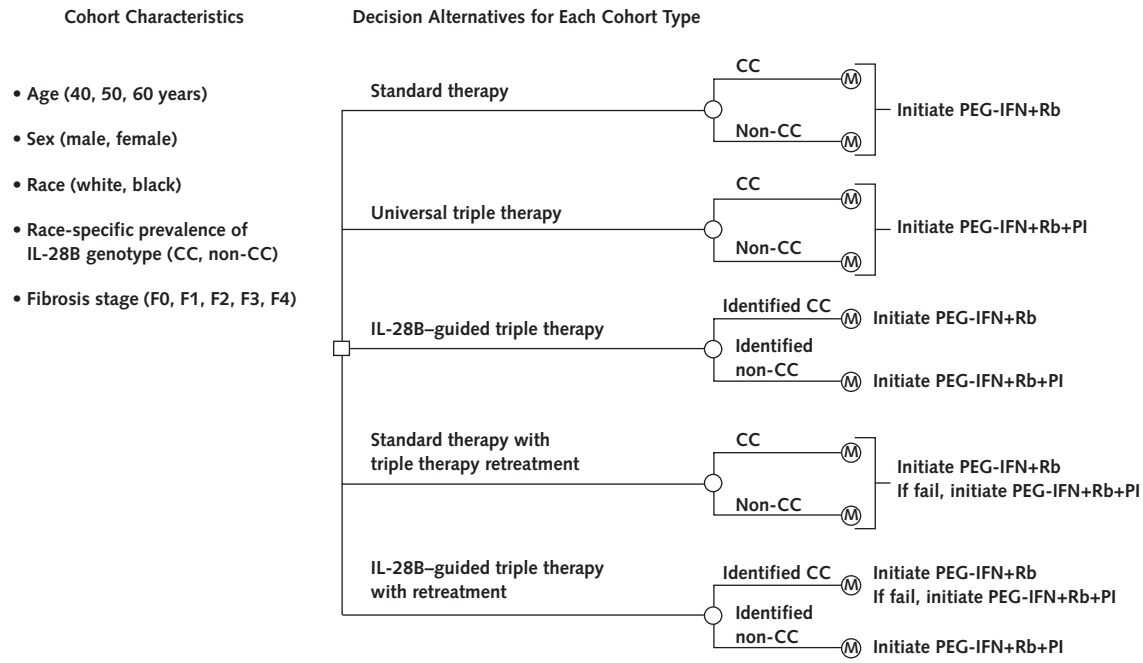
B = black; F = female; ICER = incremental cost-effectiveness ratio; IL-28B = interleukin-28B; M = male; QALY = quality-adjusted life-year; W = white.
* ICERs are shown between universal triple therapy and standard therapy.
† We assumed that the protease inhibitor used in triple therapy costs $1100/wk.

Appendix Figure 5. **Cost-effectiveness acceptability curve, assuming protease inhibitor costs $1100 per week.**



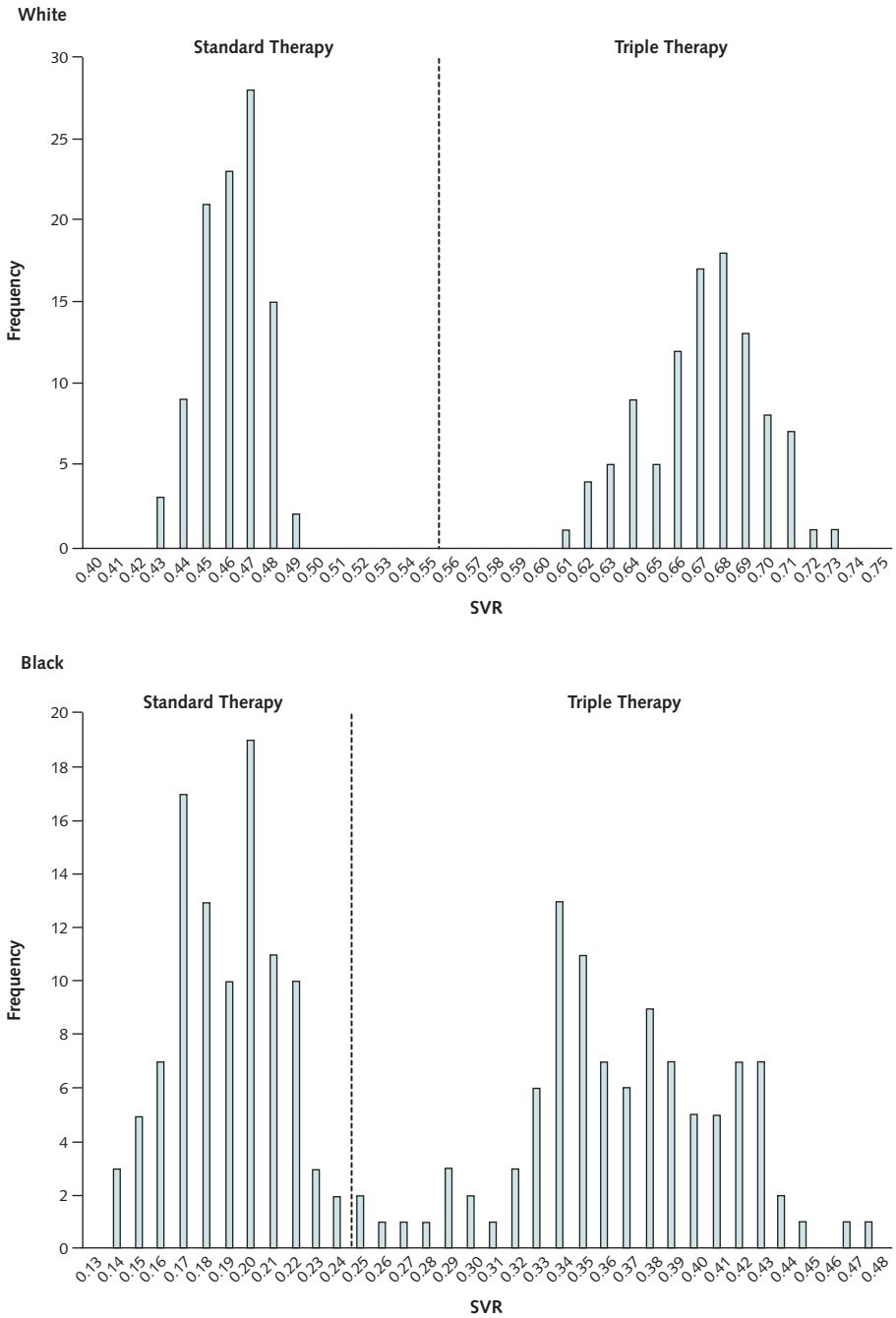
The figure shows the probability of each strategy providing the maximum net monetary benefits at various willingness-to-pay thresholds. IL-28B = interleukin-28B; QALY = quality-adjusted life-year.

Appendix Figure 6. **Model schematics: 5 strategies.**



The small square represents the decision to implement a policy of therapy. The small circle with inset "M" indicates the Markov model. IL-28B = interleukin-28B; PEG-IFN = pegylated interferon; PI = protease inhibitor; Rb = ribavirin.

Appendix Figure 7. **Overall probability of SVR; by race: 100 treatment effectiveness profiles.**



SVR = sustained virologic response.

Appendix Table 11. **Summary of HCV Health State Utility in the Literature**

Variable	McLernon and colleagues (37)*	Sherman and colleagues (35)	Chong and colleagues (36)	Grieve and colleagues (34)	Salomon and colleagues (15)	Current Analysis†
Estimation method‡	TTO	TTO	SG	EQ-5D	SG	
HCV health states						
HCV mild fibrosis (F0, F1)§	NA	0.85	0.79	0.77	0.98	0.98
During standard therapy	NA	NA	NA	0.66‖	NA	0.87
SVR after mild fibrosis	NA	NA	0.86	0.82	NA	1.00
HCV moderate fibrosis (F2, F3)	0.863	0.85	0.79	0.66	0.92	0.85
During standard therapy	NA	NA	NA	NA	NA	0.74
SVR after moderate fibrosis	NA	NA	0.86	NA	NA	0.933¶
Compensated cirrhosis (F4)	0.864	0.79	0.8	0.55	0.82	0.79
During standard therapy	NA	0.86	NA	NA	NA	0.68
SVR after cirrhosis	NA	NA	0.86	NA	NA	0.933¶
Decompensated cirrhosis	0.788	0.72	0.6	0.45	0.58	0.72
HCC	NA	NA	0.72	0.45	0.55	0.72
After liver transplant	0.825	0.81	0.73	0.45	0.86	0.825

EQ-5D = EuroQol-5D; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; NA = not available; SG = standard gamble; SVR = sustained virologic response; TTO = time tradeoff.

* Numbers were estimated using formula and conversion factors provided for TTO in Table 4 of McLernon and colleagues (37).

† The quality-of-life weight for a given age and HCV disease state is computed as the product of the mean age-specific quality weight obtained from published data (32, 33) and the utility associated with the HCV disease state in the model.

‡ Health state utilities can be measured directly by using such methods as TTO and the SG, measured indirectly by using health state classification systems, such as EQ-5D, or estimated from health care experts.

§ In both Sherman and colleagues (35) and Chong and colleagues (36), mild HCV and moderate HCV health states were combined in the same category.

‖ In Grieve and colleagues (34), they assumed a disutility of 0.11 during HCV treatment.

¶ Converting 0.86 from SG in Chong and colleagues (36) to TTO equivalent measure using formula from McLernon and colleagues (37): 0.86 + (0.116 – 0.043) = 0.933.

Appendix Table 12. Distributions Used in Probabilistic Sensitivity Analyses

Variable	Distribution*	Parameters
Proportion with IL-28B genotype, CC-type polymorphism (vs. non-CC type)		
White	Beta	a = 618; b = 1053
Black	Beta	a = 234; b = 1437
HCV natural history		
Proportion of patients with no fibrosis (F0) who do not progress	Normal	mean, 0.24 (SD, 0.02)
Annual probability of spontaneous remission from no fibrosis (F0) health state	Normal	mean, 1.19% (SD, 0.25%)
Fibrosis progression (annual probability)		
Males		
Age 40–49 y	Normal	mean, 5.26% (SD, 1.34%)
Age 50–59 y	Normal	mean, 11.75% (SD, 2.57%)
Age 60–69 y	Normal	mean, 19.83% (SD, 4.69%)
Age ≥70 y	Normal	mean, 25.99% (SD, 7.18%)
Females		
Age 40–49 y	Normal	mean, 2.76% (SD, 0.75%
Age 50–59 y	Normal	mean, 6.29% (SD, 1.83%)
Age 60–69 y	Normal	mean, 10.77% (SD, 3.54%)
Age 70–79 y	Normal	mean, 14.27% (SD, 3.92%)
Age ≥80 y	Normal	mean, 18.94% (SD, 6.29%)
Cirrhosis to decompensated cirrhosis	Normal	mean, 3.92% (SD, 0.40%)
Cirrhosis (both F4 and decompensated cirrhosis) to HCC	Normal	mean, 2.08% (SD, 0.20%)
Liver transplant (annual probability)		
Decompensated cirrhosis to liver transplant	Gamma	α = 0.10; λ = 1/54232
HCC to liver transplant	Gamma	α = 1.47; λ = 1/11031
Hazard ratio for sex-, race-, and age-specific mortality from nonliver causes in patients with chronic HCV infection	Normal	mean, 2.5 (SD, 0.25)
Liver-related mortality (annual probability)		
Liver transplant	Normal	mean, 14.10% (SD, 0.40%)
After liver transplant	Normal	mean, 4.99% (SD, 0.06%)
Decompensated cirrhosis	Normal	mean, 26.36% (SD, 4.40%)
HCC		
First year	Normal	mean, 72.00% (SD, 15.63%)
Subsequent year	Normal	mean, 25.31% (SD, 3.34%)
Treatment-related mortality	Normal	mean, 0.45% (SD, 0.20%)
Effectiveness of treatment in treatment-naive patients		Table of correlated effectiveness†
Standard therapy (PEG-INF+Rb)		
Mild fibrosis (F0/F1/F2), white		
Probability of EVR (assessed at 12 wk)	Beta	Overall: a = 878; b = 293 Non-CC: a = 487; b = 251
Overall probability of SVR	Beta	Overall: a = 534; b = 637 Non-CC: a = 235; b = 503
Mild fibrosis (F0/F1/F2), black		
Probability of EVR (assessed at 12 wk)	Beta	Overall: a = 148; b = 152 Non-CC: a = 116; b = 142
Overall probability of SVR	Beta	Overall: a = 39; b = 167 Non-CC: a = 25; b = 152
Triple therapy (PEG-INF+Rb+PI)		Table of correlated effectiveness†
Mild fibrosis (F0/F1/F2), white		
Probability of EVR (assessed at 12 wk)	Beta	Overall: a = 291; b = 25 Non-CC: a = 179; b = 20
Probability of treatment completion at either 24 or 28 wk	Beta	Overall: a = 145; b = 171 Non-CC: a = 86; b = 113
Probability of continuing treatment until 48 wk	Beta	Overall: a = 123; b = 240 Non-CC: a = 96; b = 113
Probability of SVR, conditional on completed treatment (24 or 28 wk)	Beta	Overall: a = 139; b = 7 Non-CC: a = 87; b = 5
Overall probability of SVR	Beta	Overall: a = 212; b = 104 Non-CC: a = 120; b = 79
Mild fibrosis (F0/F1/F2), black		
Probability of EVR (assessed at 12 wk)	Beta	Overall: a = 31; b = 21 Non-CC: a = 27; b = 18
Probability of treatment completion at either 24 or 28 wk	Beta	Overall: a = 15; b = 37 Non-CC: a = 21; b = 23
Probability of continuing treatment until 48 wk	Beta	Overall: a = 12; b = 40 Non-CC: a = 17; b = 28
Probability of SVR, conditional on completed treatment (24 or 28 wk)	Beta	Overall: a = 13; b = 2 Non-CC: a = 11; b = 1
Overall probability of SVR	Beta	Overall: a = 23; b = 29 Non-CC: a = 20; b = 25

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Appendix Table 12—Continued

Variable	Distribution*	Parameters
Reduction in SVR for advanced (F3 and F4) fibrosis stage	Normal	mean, 0.8 (SD, 0.05)
Effectiveness of retreatment		
Proportion of patients who do not achieve SVR and seek retreatment	Normal	mean, 0.8 (SD, 0.05)
Overall SVR after retreatment with triple therapy		
White		
No response	Beta	a = 47; b = 87
Partial response	Beta	a = 51; b = 28
Relapse	Beta	a = 180; b = 29
Black	White × 0.73	
Quality of life		
HCV-specific QALY weights‡		
HCV mild fibrosis (F0, F1)	Beta	a = 5.88; b = 0.12
SVR after mild fibrosis	Beta	a = 5.88; b = 0.12
HCV moderate fibrosis (F2, F3)	Beta	a = 38; b = 7
SVR after moderate fibrosis	Beta	a = 34; b = 2
Compensated cirrhosis (F4)	Beta	a = 40; b = 11
SVR after cirrhosis	Beta	a = 34; b = 2
Decompensated cirrhosis	Beta	a = 36; b = 14
HCC	Beta	a = 36; b = 14
Liver transplant (after)	Beta	a = 8; b = 2
Standard therapy decrement	Normal	mean, –0.11 (SD, 0.045)
PI treatment decrement§	Normal	mean, –0.05 (SD, 0.03)
Liver transplant decrement	Normal	mean, –0.2 (SD, 0.08)
Cost (2010 U.S. dollars), $		
IL-28B testing	Normal	mean, 371 (SD, 93)
Treatment (drug and medical care)		
PEG-INF+Rb (48 wk)	Normal	mean, 35 416 (SD, 3500)
PIs (per wk)	Normal	mean, 1100 (SD, 56)
AEs, standard therapy	Normal	mean, 1920 (SD, 288)
AEs, standard therapy, PI	Normal	mean, 2586 (SD, 388)
Retreatment (48 wk)	Normal	mean, 83 677 (SD, 4180)
Annual care		
HCV mild fibrosis (F0, F1)	Normal	mean, 1410 (SD, 141)
HCV portal fibrosis (F2)	Normal	mean, 1410 (SD, 141)
HCV bridging fibrosis (F3)	Normal	mean, 1410 (SD, 141)
Compensated cirrhosis (F4)	Normal	mean, 4194 (SD, 210)
Decompensated cirrhosis	Normal	mean, 11 109 (SD, 2780)
HCC	Normal	mean, 44 224 (SD, 11 054)
Liver transplant, first year	Normal	mean, 145 640 (SD, 36 410)
Liver transplant, subsequent	Normal	mean, 25 430 (SD, 6358)
Costs in the recovered F0 to F3 (reduction factor from cost prior to treatment)	Normal	mean, 0.29 (SD, 0.029)
Costs in the recovered F4 (reduction factor from cost prior to treatment)	Normal	mean, 0.19 (SD, 0.02)

AE = adverse event; EVR = early virologic response; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; IL-28B = interleukin-28B; PEG-INF = pegylated interferon; PI = protease inhibitor; Rb = ribavirin; SD = standard deviation; SVR = sustained virologic response.

* We used Beta, Gamma, and Normal distributions to describe the uncertainty around model parameters. Distributions are parameterized as follows: Beta (a, b) where the mean of the distribution is $a/[a + b]$ and the variance is $[a \times b]/[(a + b + 1) \times (a + b)^2]$; Gamma ($\alpha$, λ) where the mean of the distribution is α/λ and the variance is $\alpha/[\lambda^2]$; and Normal which is directly parameterized using its mean and standard deviation.

† The table of correlated effectiveness contains 100 rows; each row contains a complete set of virologic response profile for the entire duration of treatment stratified by race and IL-28B genotype, which is consistent with the rules for inferring missing data in Appendix Tables 1 and 2. At each simulation, a random row is selected to be used as the treatment effectiveness profile for that simulation. Histograms displaying the overall probability of SVR on both standard and triple therapy by race in the table are displayed in **Appendix Figure** 7.

‡ Patients' utilities for chronic HCV states and recovery states have a preference ranking order in the model. The utility of: mild chronic HCV ≥ moderate chronic HCV ≥ F4 ≥ decompensated cirrhosis, HCC; SVR after mild HCV ≥ mild chronic HCV; SVR after moderate HCV ≥ moderate chronic HCV; SVR after cirrhosis ≥ F4; after liver transplant ≥ decompensated cirrhosis, HCC; SVR after mild HCV ≥ SVR after moderate HCV ≥ SVR after cirrhosis. We maintained these preference orders in probabilistic sensitivity analyses.

§ This disutility is added to the disutility of standard therapy while receiving triple therapy.