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Cost-effectiveness analysis of sofosbuvir plus peginterferon/ribavirin in the treatment of chronic hepatitis C virus genotype 1 infection

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SUMMARY

Background
Sofosbuvir, an oral NS5B nucleotide polymerase inhibitor, is indicated for the treatment of patients infected with hepatitis C virus (HCV).

Aim
To evaluate the long-term health economic outcomes of sofosbuvir + pegylated interferon alfa/ribavirin (pegIFN/RBV) compared with current treatments in patients infected with HCV genotype 1 in the US.

Methods
A decision-analytic Markov model was developed to estimate health outcomes, number needed to treat and short-term and long-term economic outcomes, including incremental cost-effectiveness ratios and cost per sustained virological response (SVR), for several sofosbuvir–comparator regimen pairings for a cohort of 10 000 patients. It considered three patient cohorts: treatment-naïve, treatment-experienced and treatment-naïve human immunodeficiency virus (HIV) co-infected. Subgroup analyses were conducted for treatment-naïve patients with and without cirrhosis.

Results
Reductions in the incidence of new cases of liver-disease complications with sofosbuvir + pegIFN/RBV compared with pegIFN/RBV, boceprevir + pegIFN/RBV, telaprevir + pegIFN/RBV and simeprevir + pegIFN/RBV were 64–82%, 50–68%, 43–58% and 33–56%, respectively. Sofosbuvir + pegIFN/RBV was typically associated with the lowest 1-year cost per SVR. When considering the lifetime incremental cost per quality-adjusted life-year gained, sofosbuvir + pegIFN/RBV was the most cost-effective treatment option assessed. Sofosbuvir + pegIFN/RBV generally dominated (less costly and more effective than) boceprevir + pegIFN/RBV, telaprevir + pegIFN/RBV and simeprevir + pegIFN/RBV.

Conclusion
Sofosbuvir + pegIFN/RBV yields more favourable future health and economic outcomes than current treatment regimens for patients across all levels of treatment experience and cirrhosis stage, as well as for individuals with or without HIV co-infection.

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INTRODUCTION

Hepatitis C virus (HCV) infection imposes a substantial economic burden on the United States (US) healthcare resources each year.[1–3] An evidence-based review found that numerous studies indicate associations of HCV with clinical, quality of life and economic burden, with chronic HCV being independently and significantly associated with increased healthcare costs.[3] Early intervention with HCV therapy has been shown to be associated with lower downstream direct medical costs.[4] The treatment of HCV infection has evolved rapidly in recent years and the introduction of novel, all-oral, interferon-free regimens is expected to increase treatment uptake and cure rates.[5] It is therefore becoming increasingly important to evaluate the cost-effectiveness of emerging treatments across the general HCV infected population and across various subpopulations, including those that are difficult to treat such as patients co-infected with human immunodeficiency virus (HIV).

The prevalence of HCV in patients infected with HIV is approximately 30%.[6] Patients co-infected with HIV/HCV have a worse prognosis and lower responsiveness to current standard therapies than those with HCV mono-infection.[7, 8] Other subpopulations of individuals with HCV that are particularly difficult to treat include patients with cirrhosis, especially those with clinically decompensated liver disease, because the current standard treatment is complicated by the occurrence of haematological adverse events.[9] Reducing the rate of liver-disease progression in treatment-experienced patients using currently available therapies has also been shown to be difficult.[10]

Hepatitis C virus genotype 1 accounts for 79% of all chronic cases, making it the most common type of HCV infection in the US.[11] Until recently, the standard of care for patients infected with this genotype was an oral protease inhibitor (boceprevir or telaprevir) combined with pegylated interferon alfa (pegIFN) plus ribavirin (RBV).[12] Although 60–80% of previously untreated patients who received boceprevir or telaprevir + pegIFN/RBV showed sustained virological response (SVR) in clinical trials,[13–16] and had a shorter overall duration of treatment than patients receiving pegIFN/RBV alone,[17] these regimens were associated with many adverse events and high discontinuation rates,[18] particularly in the HCV cirrhotic patient population.[19] The proportion of patients progressing to cirrhosis in the US has been projected to increase rapidly over the course of this decade because of the longer-term persistence of HCV infection.[20] Real-world effectiveness studies of these regimens in the general HCV patient population have shown SVR rates of 45–49% and resultant costs of $183 428[21] and $195 000 per SVR.[22]

Simeprevir is a second-generation protease inhibitor that was approved at the end of 2013 for the treatment of patients infected with HCV genotype 1 and/or 4, in combination with pegIFN/RBV.[23] Clinical trials have shown that it is associated with higher SVR rates than pegIFN/RBV alone, is well tolerated and is associated with mild and reversible adverse events.[24–26] Sofosbuvir is a nucleotide analogue HCV NS5B polymerase inhibitor shown to be effective in an interferon-limiting regimen in patients infected with HCV genotype 1, 4, 5 or 6[27, 28] and in an interferon-free regimen for those infected with HCV genotype 2 or 3[27–29] in phase III clinical trials. In patients infected with HCV genotype 1, the addition of sofosbuvir to pegIFN/RBV regimens yielded SVR rates of approximately 90% 12 weeks after completion of treatment.[27] Sofosbuvir-based oral regimens have an acceptable safety profile and are generally well tolerated, with no reported premature discontinuations of therapy due to adverse events.[28, 30] The American Association for the Study of Liver Diseases and the Infectious Diseases Society of America (AASLD/IDSA) guidelines were recently updated with simeprevir- and sofosbuvir-based regimens.[31]

Earlier studies have demonstrated that protease inhibitors in combination with pegIFN/RBV are more cost-effective than pegIFN/RBV alone in patients previously treated for chronic HCV genotype 1 infection.[32, 33] More recent cost analyses have indicated that all-oral, interferon-free regimens are cost-effective compared with the standard of care for patients infected with genotype 1.[34, 35] However, no studies to date have evaluated the cost-effectiveness of sofosbuvir in combination with pegIFN/RBV against currently available HCV treatment regimens. The aim of this study was to develop a model to assess the health outcomes and cost-effectiveness of sofosbuvir + pegIFN/RBV compared with the currently available therapies (pegIFN/RBV, boceprevir + pegIFN/RBV, telaprevir + pegIFN/RBV and simeprevir + pegIFN/RBV)[31] for the treatment of patients infected with HCV genotype 1 from a third-party payer perspective in the US. The model included patients with different levels of treatment experience and cirrhosis stages, as well as individuals with and without HIV co-infection.

MATERIALS AND METHODS

Model overview and assumptions

A decision-analytic Markov model was developed in Microsoft Excel 2010 to estimate health and economic outcomes for sofosbuvir and comparators in patients with HCV genotype 1. The model consisted of an initial decision tree, in which patients were eligible to receive treatment, and a state-transition model to project patients' outcomes. Figure 1 shows the health-state transitions included in the model following the treatment phase. In the decision tree, patients received sofosbuvir + pegIFN/RBV or one of four comparator treatments: pegIFN/RBV, boceprevir + pegIFN2b/RBV, telaprevir + pegIFN2a/RBV or simeprevir + pegIFN2a/RBV. A comparison was also made with receiving no treatment. The decision tree divided a hypothetical cohort of 10 000 patients into two health states at the end of each treatment period on the basis of response to the therapy: SVR or chronic HCV infection. The Markov state-transition model included the health-state transitions following the decision-analytic phase. For each 1-year model cycle, patients remained in or transitioned between the following health states: SVR without cirrhosis; SVR with compensated cirrhosis; without cirrhosis; compensated cirrhosis; decompensated cirrhosis; hepatocellular carcinoma (HCC); liver transplant and death. Those patients who did not receive treatment continued to progress to other health states. Decompensated cirrhosis encompassed a variety of serious symptomatic manifestations including ascites, variceal bleeding and hepatic encephalopathy. Patients who achieved SVR were assumed to maintain SVR and experience no further disease progression until their death. It was assumed that individuals who did not achieve SVR were at risk of progressive liver disease. Patients were assumed to complete only one course of treatment before achieving SVR; retreatment was not evaluated. In a sensitivity analysis, it was assumed that there was progression of liver disease in patients who achieved SVR but at a slower rate of deterioration than those who did not achieve SVR, or that they could be re-infected or have recurrence. The model structure, inputs and assumptions were validated by a panel of clinical hepatologists and an infectious disease specialist (Sammy Saab, Stuart Gordon, Aijaz Ahmed, Mark Sulkowski and Zobair Younossi).

Patient population

We considered three representative patient cohorts with HCV genotype 1 infection: (i) patients with HCV genotype 1 infection who have never been treated (treatment-naïve) and are not HIV co-infected, (ii) patients with HCV genotype 1 infection who have been previously treated (treatment-experienced) and are not HIV

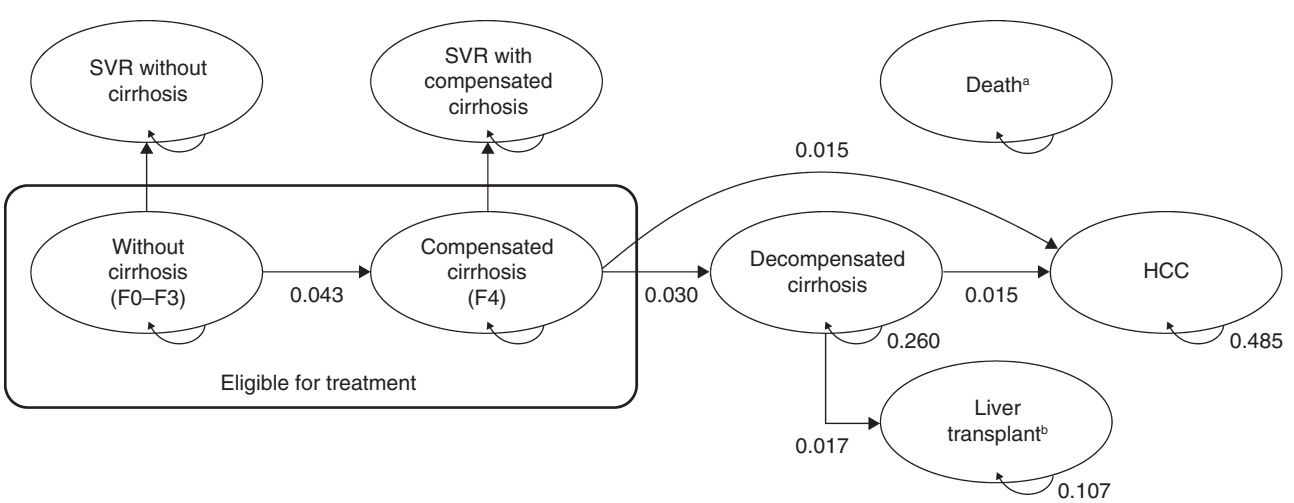

Figure 1 | Health-state transitions in the cost-effectiveness and budget-efficiency model. SVR, sustained virological response; F0–F3, METAVIR fibrosis score F0–F3; F4, METAVIR fibrosis score F4; HCC, hepatocellular carcinoma. [a]Patients were at risk of death in any health state. Patients in the decompensated cirrhosis, HCC and liver transplant health states were additionally at risk of disease-specific death. [b]Following the year of liver transplant, patients were assumed to remain in the post-transplant health state until their death. Values represent annual transition probabilities; data sources presented in Table 1.

co-infected and (iii) patients co-infected with HIV and HCV genotype 1 infection who have never been treated (treatment-naïve HIV co-infected). Characteristics of the modelled patient population were based on baseline characteristics of participants in sofosbuvir clinical trials.[27, 36] Eighty-three per cent of the population had no cirrhosis (METAVIR fibrosis score F0–F3) and 17% had cirrhosis (METAVIR fibrosis score F4). This is in alignment with estimates for the US: the proportion of patients infected with HCV who have cirrhosis was projected to be 25% in 2010.[37] The mean age was 52 years and mean body weight was 79 kg. For the treatment-naïve cohort, subgroup analysis was conducted for patients with cirrhosis and without cirrhosis at the initiation of treatment.

Clinical inputs

The model incorporated clinical inputs for treatment efficacy, duration and adverse events for the sofosbuvir-based and comparator regimens. These were derived from three key sofosbuvir clinical trials[27, 38, 39] and published literature on the four comparator regimens.[13, 14, 24, 25, 27, 38–55] To date, there have been no clinical trials conducted on treatment-experienced patients infected with HCV genotype 1 and treated with sofosbuvir + pegIFN/RBV. Therefore, the related clinical inputs were based on US Food and Drug Administration modelling, which correlated SVR rates in treatment-experienced patients with those in treatment-naïve patients, adjusting for multiple negative predictors of SVR, including high viral load, cirrhosis status and *IL28B* genotype (*CT* and *TT*).[56]

The primary efficacy measure used in the model was the SVR, 12 weeks after the conclusion of treatment in the case of the sofosbuvir regimen and 24 weeks after the conclusion of treatment in the case of each of the comparators (Table 1). The measurement of SVR rates at 12 weeks and at 24 weeks has been demonstrated to be concordant for a large population of patients with HCV infection across different treatment regimens and durations.[57, 58] SVR rates were stratified according to whether patients did or did not have cirrhosis at the initiation of treatment, because SVR rates are different at various stages of cirrhosis. SVR rates for patients with and

Table 1 | Model clinical inputs (SVR rates and mean duration of treatment)

	SOF + pegIFN/RBV		pegIFN/RBV*		BOC + pegIFN/RBV		TVR + pegIFN/RBV		SMV + pegIFN/RBV	
	Without cirrhosis	With cirrhosis	Without cirrhosis	With cirrhosis	Without cirrhosis	With cirrhosis	Without cirrhosis	With cirrhosis	Without cirrhosis	With cirrhosis
SVR rates at baseline (%)†,‡										
Treatment-naïve	91	79	58	33	64	55	74	61	77	57
Treatment- naïve HIV co-infected	90	78	30	17	62	53	72	59	79	58
Treatment-experienced§	72	62	17	5	39	34	54	25	57	46
Mean duration of treatment (weeks)¶										
Treatment-naïve	12		43		31		26		22	
Treatment-naïve HIV co-infected	12		42		38		33		26	
Treatment-experienced	12		45		35		30		39	

SVR, sustained virological response; SOF, sofosbuvir; RBV, ribavirin; pegIFN, pegylated interferon alfa; BOC, boceprevir; TVR, telaprevir; SMV, simeprevir; HIV, human immunodeficiency virus; FDA, Food and Drug Administration.

* Mean SVR rate and mean duration of treatment were assumed to be the same for pegIFN2a and pegIFN2b.[61]

† Compensated cirrhosis is defined as METAVIR fibrosis score F4; without compensated cirrhosis is defined as METAVIR fibrosis score F0–F3.

‡ Data derived from clinical trials and published literature.[13, 14, 27, 29, 38–48, 54, 86]

§ Additional FDA modelling work estimated SVR rates for treatment-experienced patients infected with HCV genotype 1 treated with SOF + pegIFN2a/RBV. The distribution of treatment-experienced patients was assumed to be 50% prior partial responders and 50% prior null responders.

¶ Data derived from clinical trials and published literature.[13, 14, 27, 29, 38–51, 53, 54, 86]

without cirrhosis at the initiation of treatment were calculated for each regimen using relative risk and weighted distribution based on clinical trials. SVR rates for genotypes 1a and 1b were derived separately and the relative risks for noncirrhotic vs. cirrhotic SVR rates were applied. The relative prevalences of genotypes 1a and 1b in the US were derived from published literature[59] and the proportion of patients with genotype 1a and Q80K polymorphism was assumed to be 48%.[60] Mean treatment duration for each regimen was taken from clinical trials (Table 1); it was determined using the percentage of the cohort that discontinued early for various reasons, such as adverse events, stopping rules, response-guided therapy and the time points at which these discontinuations occurred. The SVR rates and treatment duration for pegIFN2a and 2b were assumed to be the same.[61]

The model accounted for clinically relevant grade 3/4 adverse events using data from clinical trials; reported events included nausea, vomiting, diarrhoea, pruritus, rash, thrombocytopenia, neutropenia, depression and central nervous system events. Grades 2–4 were considered for anaemia because management with epoetin-alfa and blood transfusion begins at grade 2 for some patients.[52] For each comparator, the proportion of patients experiencing each adverse event was stratified by level of treatment experience.

Transition probabilities

The annual transition probabilities for the Markov model are presented in Figure 1 and Table 2. Transition probabilities for patients without SVR were derived from recently published literature.[37, 62–64] The transition probability for patients without cirrhosis (F0–F3) going to compensated cirrhosis (0.043) was based on a weighted average of transition rates/probabilities for a representative population. Patients (both cirrhotic and noncirrhotic) who did not achieve SVR (either treatment failures or those who did not receive treatment) were at risk of death related to liver disease once decompensation occurred. In every health state, patients were at risk of death not related to liver disease. Probabilities of HCV-related death were taken from published literature on liver-related mortality.[63, 64] For causes of death not related to HCV, inputs were based on US general population probabilities by age.[65] For the HIV/HCV co-infected population, the transition probabilities for the compensated cirrhosis health state were estimated to be twice the values used for the mono-infected population.[66–68] Patients with HIV/HCV co-infection were not considered eligible for liver transplant.[67] Liver transplantation for patients co-infected with HIV and HCV is not performed routinely because the 5-year survival rate is less than 50%, which is substantially below that of the acceptable threshold.[69–71]

Cost inputs

The model accounted for four types of HCV-related cost: drug regimen, treatment monitoring, adverse events and health state (downstream liver-disease complications). All costs were in US dollars and were inflated to 2013 values using the medical care component of the consumer price index.[72] Calculated drug regimen costs were based on indicated drug dosing, mean clinical trial therapy duration and unit drug costs (Table 2). Monitoring costs varied by treatment regimen, level of treatment experience, and cirrhosis status. Weekly costs were calculated according to specified monitoring resource use, and unit costs using the Resource-Based Relative Values Scale.[73] Total monitoring costs over the treatment period were then aggregated from the weekly totals.

Adverse event costs were estimated based on the incidence of each event and pharmacy costs associated with their management. Pharmacy costs for the management of each adverse event in the model were based on drug-treatment algorithms and unit wholesale acquisition costs from Red Book Online.[74] Anaemia was assumed to be treated via blood transfusion and/or erythropoietin.[52] Table 2 presents the aggregate costs for each health state. For each health state, in-patient, out-patient, emergency department, ambulatory and pharmacy costs were accounted for. For the treatment-naïve HIV co-infected patient cohort, additional HIV-related health state costs ($18 715) were included, assuming that patients remained in the 351–500 CD4 cell count range and were on highly active anti-retroviral therapy.[75]

Utility values

The utility values assigned in the model are presented in Table 2. Each health state in the model was assigned a utility score between 0 (death) and 1 (perfect health) to quantify patient utilities for residing in that state. These were estimated from published studies reporting 36-item Short-Form Health Survey (SF-36) health-related quality of life (HRQoL) scores, which were converted to 6-dimension Short-Form Health Survey (SF-6D) utility scores.[76, 77] Utility decrements, which were specific to each treatment regimen, were assigned during treatment to account for reduced HRQoL associated with treatment-related adverse events. A utility increment of 0.05 was assigned to patients who achieved SVR.

Table 2 | Model transition probabilities, cost inputs and utilities

Transition probabilities for patients without SVR		
From – to	**Annual transition probabilities**	**Source**
Without cirrhosis* to compensated cirrhosis; nongenotype 3, ≥50 years	0.043	Thein *et al.*[62], Probst *et al.*[87]
Compensated cirrhosis		
To decompensated cirrhosis	0.030	Davis *et al.*[37]
To HCC	0.015	Razavi *et al.*[63]
Decompensated cirrhosis		
To HCC	0.015	Razavi *et al.*[63]
To liver transplant	0.017	Razavi *et al.*[63]
To death	0.260	Liu *et al.*[64]
HCC to death	0.485	Liu *et al.*[64]
Liver transplant† to death, year 1	0.107	Razavi *et al.*[63]
Post liver transplant to death, year 2	0.049	Razavi *et al.*[63]
Cost inputs		
Treatment	**Cost per pack (WAC) ($)‡**	**Source**
SOF	28 000	Red Book Online[74]; 28 × 400 mg tablets
RBV	138	Red Book Online[74]; 84 × 200 mg tablets/capsules
pegIFN2a	771	Red Book Online[74]; 180 μg/mL kit
pegIFN2b	705	Red Book Online[74]; 120 μg/mL kit
BOC	6683	Red Book Online[74]; 336 × 200 mg tablets
TVR	22 052	Red Book Online[74]; 168 × 375 mg tablets
SMV	22 120	Red Book Online[74]; 28 × 150 mg capsules
Health state	**Annual cost ($ in 2013 US Dollars)**	**Source§**
Without cirrhosis	4872	Mean of McAdam-Marx *et al.*[88], Gordon *et al.*[1]
Compensated cirrhosis	5604	Mean of McAdam-Marx *et al.*[88], Gordon *et al.*[1]
Decompensated cirrhosis	39 111	Mean of McAdam-Marx *et al.* 2011[88] and Gordon *et al.* 2012[1]
HCC	86 116	Mean of McAdam-Marx *et al.*[88], Gordon *et al.*[1]
Liver transplant	174 486	Mean of McAdam-Marx *et al.*[88] and Gordon *et al.*[1] including the cost of transplant and medical costs in the year of the transplant
Post liver transplant	42 943	McAdam-Marx *et al.*[88]; annual medical costs each year after transplant
Utilities		
	Utility value	**Source**
Health state: mono-infected		
Without cirrhosis	0.79	Thein *et al.*[76], Chong *et al.*[89]
Compensated cirrhosis	0.75	McLernon *et al.*[90]
Decompensated cirrhosis	0.67	McLernon *et al.*[90]
HCC	0.61	Hsu *et al.*[91]
Liver transplant	0.65	Hsu *et al.*[91]
Post liver transplant	0.71	McLernon *et al.*[90]
Health state: HIV/HCV co-infected		
Without cirrhosis	0.72	Hartwell *et al.*[36]
Compensated cirrhosis	0.55	Hartwell *et al.*[36]
Decompensated cirrhosis	0.45	Hartwell *et al.*[36]
HCC	0.45	Hartwell *et al.*[36]
Decrements for treatment¶	**Utility value (%)**	**Source**
SOF + pegIFN/RBV	−14.50	NEUTRINO[27]
pegIFN/RBV	−12.43	Wright *et al.*[92]; FISSION[27]

Table 2 | (Continued)

BOC + pegIFN/RBV**	−16.50	Liu *et al.*[64]
TVR + pegIFN/RBV**	−16.50	Liu *et al.*[64]
SMV + pegIFN/RBV	−14.50	Assumed to be the same as SOF
Increment for SVR	**Value**	**Source**
Increment for achieving SVR	+0.05	Wright *et al.*[92]

SVR, sustained virological response; HCC, hepatocellular carcinoma; WAC, wholesale acquisition cost; SOF, sofosbuvir; RBV, ribavirin; pegIFN, pegylated interferon alfa; BOC, boceprevir; TVR, telaprevir; SMV, simeprevir; HIV, human immunodeficiency virus; HCV, hepatitis C virus.

* For the HIV/HCV co-infected population, the transition probabilities to the compensated cirrhosis health state were estimated to be twice the values used for the mono-infected population.[66–68]

† Patients with HIV/HCV co-infection were not eligible for liver transplant.[67]

‡ As of December 12, 2013.

§ The mean value from McAdam-Marx *et al.*[88] and Gordon *et al.*[1] was obtained by inflating the values from each source to 2013 values and then calculating the average 2013 cost.

¶ Decrements for treatment were assumed to be the same for mono-infected and HIV/HCV co-infected cohorts.

** Relevant treatment regimen only for treatment-naïve patients infected with HCV genotype 1.

Time horizon and discounting

Short-term (1-year) and long-term (lifetime) time horizons were modelled. Both costs and outcomes were discounted at 3.0% per year.[78] The Markov model was terminated when the cohort reached 100 years of age.

Model analysis

Comparisons of health and economic outcomes were made across treatment regimens for all three cohorts. The following long-term health outcomes were estimated: new cases of compensated cirrhosis; cases of decompensated liver disease, HCC and liver transplant; and number of HCV-related deaths. The number needed to treat (NNT) was also calculated, which indicates the number of patients who would need to be treated with a specified regimen, rather than remain untreated, to avoid one negative outcome (e.g. one case of liver-disease sequelae).

The short-term health economic outcome of the model was 1-year costs per SVR. This was calculated by dividing the total per-patient costs accrued in year 1 by the SVR rate outcome to provide costs per successfully treated patient. The long-term health economic outcomes comprised: life-years (life expectancy); quality-adjusted life-years (QALYs); total lifetime costs (including costs associated with drug regimen, monitoring, adverse events and health state); and incremental lifetime cost per QALY gained [which is an incremental cost-effectiveness ratio (ICER); it indicates the cost-effectiveness of one treatment regimen over another (sofosbuvir + pegIFN/RBV vs. its five comparators)]. The incremental lifetime cost per QALY gained for sofosbuvir + pegIFN/RBV were compared against the conventional willingness-to-pay threshold of $50 000 per QALY.

For treatment-naïve cohorts, a subgroup analysis was conducted for patients with and without cirrhosis at the initiation of treatment to evaluate the impact of early treatment for HCV genotype 1 infection on health economic outcomes.

Sensitivity analyses

To test the robustness of the base-case results, a comprehensive deterministic sensitivity analysis was conducted for the lifetime incremental cost per QALY gained for sofosbuvir + pegIFN/RBV compared with simeprevir + pegIFN/RBV. This one-way sensitivity analysis assessed the impact of individual changes to model inputs and assumptions on the model results. Key parameters varied included SVR rates (±10% to maximum of 99%), transition probabilities (95% confidence intervals), costs for adverse event management and health states (±20%), incidence of adverse events (±50%), and utility estimates (±20%). The deterministic sensitivity analysis which compared sofosbuvir + pegIFN/RBV with simeprevir + pegIFN/RBV was also manipulated to investigate the effect of lower cirrhosis prevalence (10%), lower fibrosis progression rates (0.034 for mono-infected patients and 0.068 for HIV co-infected patients) and a range of transition probabilities for recurrence in patients who achieve SVR, with and without cirrhosis (0.01, 0.02 and 0.03). For patients with cirrhosis who achieve SVR, the costs of HCC screening (e.g. alpha-fetoprotein and liver

ultrasonography) were included. A probabilistic sensitivity analysis was also conducted varying each parameter by the same ranges as used in the deterministic sensitivity analysis by the appropriate distributions: costs by gamma distribution and transition probabilities, SVR rate, and utilities by beta distribution. Drug costs in the probabilistic sensitivity analysis were varied by ±10% and SVR rates for patients with cirrhosis by ±20%. In addition, deterministic and probabilistic sensitivity analyses were performed for sofosbuvir + pegIFN/RBV compared with no treatment.

RESULTS

Long-term health outcomes

The projected number of cases of advanced liver-disease complications (decompensated cirrhosis, HCC, liver transplant, and HCV-related death) per treated cohort of 10 000 patients is presented in Table 3. Of all the treatment regimens assessed, sofosbuvir + pegIFN/RBV was associated with the lowest number of all types of advanced liver-disease complications, even in difficult-to-treat patients. For example, in the treatment-experienced patient subgroup, the incidence of HCC was 469 per 10 000 patients in the cohort treated with sofosbuvir + pegIFN/RBV, but ranged from 700 to 1299 across the four treatment comparators. Table 3 also presents the percentage reduction in advanced liver-disease complications for patients receiving sofosbuvir + pegIFN/RBV compared with the other regimens. Reductions in the incidence of liver-disease complications with sofosbuvir + pegIFN/RBV ranged from 64% to 82%, 50% to 68%, 43% to 58% and 33% to 56% compared with pegIFN/RBV, boceprevir + pegIFN/RBV, telaprevir + pegIFN/RBV and simeprevir + pegIFN/RBV, respectively. In difficult-to-treat patients, reductions in liver-disease complications with sofosbuvir + pegIFN/RBV compared with current treatment were substantial: 33–64% in

Table 3 | Long-term health outcomes

	Number of cases per treated cohort of 10 000 patients				% reduction in ALD cases with SOF*
	DLC	HCC	Liver transplants	HCV-related deaths	
Treatment-naïve					
SOF + pegIFN/RBV	352	192	17	462	–
PegIFN/RBV†	1366	745	68	1800	−74
BOC + pegIFN/RBV	1080	589	53	1419	−67
TVR + pegIFN/RBV	822	448	41	1079	−57
SMV + pegIFN/RBV	802	437	40	1055	−56
No treatment	2742	1496	137	3641	−87
Treatment-naïve HIV co-infected					
SOF + pegIFN/RBV	459	251	N/A	617	–
pegIFN/RBV†	2569	1410	N/A	3501	−82
BOC + pegIFN/RBV	1424	781	N/A	1925	−68
TVR + pegIFN/RBV	1098	602	N/A	1481	−58
SMV + pegIFN/RBV	913	501	N/A	1231	−50
No treatment	3482	1913	N/A	4793	−87
Treatment-experienced					
SOF + pegIFN/RBV	860	469	42	1129	–
pegIFN/RBV†	2380	1299	118	3152	−64
BOC + pegIFN/RBV	1718	937	85	2264	−50
TVR + pegIFN/RBV	1504	820	75	1983	−43
SMV + pegIFN/RBV	1283	700	63	1687	−33
No treatment	2742	1496	137	3641	−69

DLC, decompensated liver cirrhosis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ALD, advanced liver disease; SOF, sofosbuvir; pegIFN, pegylated interferon alfa; RBV, ribavirin; BOC, boceprevir; TVR, telaprevir; SMV, simeprevir.

* Compared with sofosbuvir + pegIFN2b/RBV. ALD includes cases of DLC, HCC, liver transplant and HCV-related death.

† Mean SVR rate was assumed to be the same for pegIFN2a and pegIFN2b,[61] therefore these two treatments were also assumed to have the same long-term health outcomes.

treatment-experienced patients and 50–82% in patients co-infected with HIV. Compared with no treatment, the reductions in advanced liver-disease complications ranged from 69% to 87% when treating with sofosbuvir + pegIFN/RBV.

The NNT outcomes can be found in Table S1. The NNT to avoid a liver transplant in treatment-naïve and treatment-experienced patients was 84 and 106, respectively, for the sofosbuvir + pegIFN/RBV regimen, but ranged from 145 to 547, 120 to 194, 105 to 162 and 104 to 137 for pegIFN/RBV, boceprevir + pegIFN/RBV, telaprevir + pegIFN/RBV and simeprevir + pegIFN/RBV, respectively.

Short-term health economic outcomes

The 1-year cost per SVR was lower for sofosbuvir + pegIFN/RBV than telaprevir-based, boceprevir-based, or simeprevir-based regimens in all the patient subpopulations, including difficult-to-treat patients (Figure 2). The cost per SVR for sofosbuvir + pegIFN/RBV was 8–15% ($9882–$20 576) lower in treatment-naïve patients, 13–30% ($20 038–$57 266) lower in patients co-infected with HIV, and 26–38% ($50 734–$88 964) lower in treatment-experienced patients than the cost per SVR for boceprevir + pegIFN/RB, telaprevir + pegIFN/RBV, and simeprevir + pegIFN/RBV, respectively. When compared with pegIFN/RBV alone, sofosbuvir + pegIFN/RBV was associated with lower 1-year SVR costs in treatment-experienced patients (55% lower than pegIFN2a/RBV and 52% lower than pegIFN2b/RBV), treatment-experienced patients co-infected with HIV (43% lower than pegIFN2a/RBV and 40% lower than pegIFN2b/RBV) and patients with cirrhosis (14% lower than pegIFN2a/RBV and 9% lower than pegIFN2b/RBV). However, the 1-year costs per SVR were lower with pegIFN/RBV compared with sofosbuvir in treatment-naïve patients (22% lower with pegIFN2a/RBV and 27% lower with PegIFN2b/RBV) and in patients without cirrhosis (27% lower with pegIFN2a/RBV and 32% lower with pegIFN2b/RBV).

In the subgroup analysis of outcomes in patients with and without cirrhosis, 1-year cost per SVR, across all treatments analysed in the model, was 15–47% ($19 444–$72 313) lower in patients who initiated treatment at the noncirrhotic stage compared with those whose treatment was initiated at the cirrhotic stage.

Long-term health economic outcomes

Table 4 presents the lifetime health economic outcomes for patients infected with HCV genotype 1 by patient population. In the model, treatment-naïve patients treated with sofosbuvir + pegIFN/RBV lived 0.92, 0.63, 0.41 and 0.41 years longer than those treated with pegIFN/RBV alone, boceprevir + pegIFN/RBV, telaprevir + pegIFN/RBV and simeprevir + pegIFN/RBV, respectively. Treatment-experienced patients receiving sofosbuvir + pegIFN/RBV lived 1.35, 0.74, 0.61 and 0.37 years longer than patients receiving pegIFN/RBV alone, boceprevir + pegIFN/RBV, telaprevir + pegIFN/RBV and simeprevir + pegIFN/RBV, respectively.

Sofosbuvir + pegIFN/RBV treatment also provided patients with the most QALYs compared with the other regimens in all patient populations analysed (Table 4). Treatment-naïve patients treated with sofosbuvir + pegIFN/RBV gained 1.10, 0.82, 0.53 and 0.50 more QALYs than patients treated with pegIFN/RBV alone, boceprevir + pegIFN/RBV, telaprevir + pegIFN/RBV, and simeprevir + pegIFN/RBV, respectively. Treatment-experienced patients treated with sofosbuvir + pegIFN/RBV gained 1.67, 0.96, 0.73 and 0.47 more QALYs than patients treated with pegIFN/RBV alone, boceprevir + pegIFN/RBV, telaprevir + pegIFN/RBV and simeprevir + pegIFN/RBV, respectively.

For treatment-naïve patients, the total lifetime healthcare costs of patients treated with the sofosbuvir + pegIFN/RBV regimen ($132 560) were lower than those of patients treated with the boceprevir + pegIFN/RBV ($136 973), telaprevir + pegIFN/RBV ($143 009), and simeprevir + pegIFN/RBV ($135 183) regimens. The lowest total costs, however, were associated with the pegIFN/RBV regimens ($105 299–$108 504). In treatment-experienced patients, the total costs of the sofosbuvir + pegIFN/RBV regimen ($148 812) were also lower than those of the boceprevir + pegIFN/RBV ($165 983), telaprevir + pegIFN/RBV ($165 428) and simeprevir + pegIFN/RBV ($168 251) regimens. In treatment-experienced patients, the lowest total costs were associated with the pegIFN/RBV regimens ($141 647–$145 009; Table 4).

Sofosbuvir + pegIFN/RBV dominated (i.e. was less costly and more effective than) the boceprevir + pegIFN/RBV, telaprevir + pegIFN/RBV and simeprevir + pegIFN/RBV regimens in most of the cases analysed. Compared with pegIFN/RBV, sofosbuvir + pegIFN/RBV had incremental costs per QALY gained ranging from $2277 to $4290 in treatment-experienced patients, and from $21 869 to $24 783 in treatment-naïve patients, which compare favourably to the conventional $50 000 per QALY willingness-to-pay threshold. Treatment with sofosbuvir was also cost-effective compared with no

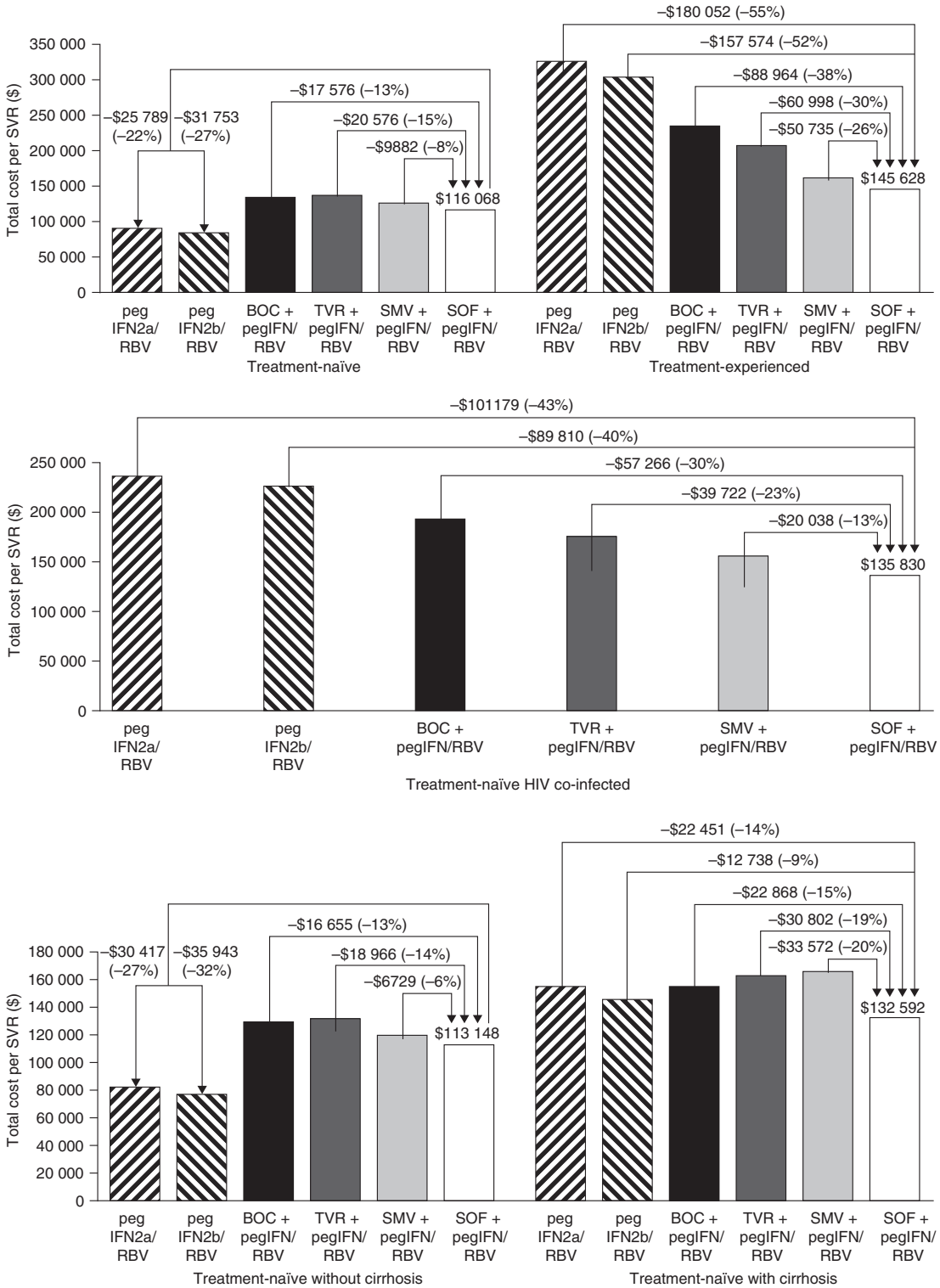

Figure 2 | Short-term 1-year total cost per SVR by patient population. SVR, sustained virological response; BOC, boceprevir; pegIFN, pegylated interferon alfa; RBV, ribavirin; TVR, telaprevir; SMV, simeprevir; SOF, sofosbuvir; HIV, human immunodeficiency virus.

Table 4 | Lifetime health economic outcomes by patient population

	Life-years	QALY	Total costs ($)	Incremental life-years	Incremental QALY	Incremental cost per QALY gained* ($)
Treatment-naïve						
All patients						
SOF + pegIFN/RBV	19.18	15.71	132 560	–	–	–
pegIFN/RBV†	18.26	14.61	105 299–108 504	−0.92	−1.10	21 869–24 783
BOC + pegIFN/RBV	18.55	14.89	136 973	−0.63	−0.82	SOF dominates
TVR + pegIFN/RBV	18.77	15.18	143 009	−0.41	−0.53	SOF dominates
SMV + pegIFN/RBV	18.77	15.21	135 183	−0.41	−0.50	SOF dominates
No treatment	17.10	13.17	116 872	−2.08	−2.54	6176
Without cirrhosis						
SOF + pegIFN/RBV	19.36	16.00	116 715	–	–	–
pegIFN/RBV†	18.78	15.16	92 127–95 333	−0.58	−0.84	25 455–29 271
BOC + pegIFN/RBV	18.88	15.28	124 229	−0.48	−0.72	SOF dominates
TVR + pegIFN/RBV	19.06	15.55	128 879	−0.30	−0.45	SOF dominates
SMV + pegIFN/RBV	19.11	15.64	120 318	−0.25	−0.36	SOF dominates
No treatment	17.76	13.77	112 093	−1.60	−2.23	2071
With cirrhosis						
SOF + pegIFN/RBV	18.30	14.28	209 923	–	–	–
PegIFN/RBV†	15.74	11.90	169 609–172 814	−2.56	−2.38	15 592–16 939
BOC + pegIFN/RBV	16.96	13.01	199 192	−1.34	−1.27	8450
TVR + pegIFN/RBV	17.33	13.36	211 996	−0.97	−0.92	SOF dominates
SMV + pegIFN/RBV	17.08	13.14	207 758	−1.22	−1.14	1899
No treatment	13.87	10.25	140 210	−4.43	−4.03	17 299
Treatment-naive HIV co-infected						
SOF + pegIFN/RBV	19.06	13.72	237 897	–	–	–
PegIFN/RBV†	17.08	11.20	355 842–358 992	−1.98	−2.52	SOF dominates
BOC + pegIFN/RBV	18.17	12.55	317 441	−0.89	−1.17	SOF dominates
TVR + pegIFN/RBV	18.47	12.95	293 523	−0.59	−0.77	SOF dominates
SMV + pegIFN/RBV	18.62	13.20	266 860	−0.44	−0.52	SOF dominates
No treatment	16.22	10.11	406 021	−2.84	−3.61	SOF dominates
Treatment-experienced						
All patients						
SOF + pegIFN/RBV	18.74	15.15	148 812	–	–	–
PegIFN/RBV†	17.39	13.48	141 647–145 009	−1.35	−1.67	2277–4290
BOC + pegIFN/RBV	18.00	14.19	165 983	−0.74	−0.96	SOF dominates
TVR + pegIFN/RBV	18.13	14.42	165 428	−0.61	−0.73	SOF dominates
SMV + pegIFN/RBV	18.37	14.68	168 251	−0.37	−0.47	SOF dominates
No treatment	17.10	13.17	115 911	−1.64	−1.98	16 617

QALY, quality-adjusted life-year; SOF, sofosbuvir; pegIFN, pegylated interferon alfa; RBV, ribavirin; BOC, boceprevir; TVR, telaprevir; SMV, simeprevir; HIV, human immunodeficiency virus.

* SOF + pegIFN/RBV vs. the comparator. 'SOF dominates' indicates that the SOF + pegIFN/RBV regimen dominated (was less costly and more effective than) the comparator regimen.

† Range of costs owing to difference in pricing for pegIFN2a and pegIFN2b.

treatment, with ICERs ranging from dominance to $16 617 per QALY (also below the $50 000 per QALY willingness-to-pay threshold), depending on the patient subgroup (Table 4).

In the subgroup analysis, which compared patients by disease severity at the initiation of treatment, total costs were 38–46% ($74 963–$93 208) lower among patients initiating treatment before the development of cirrhosis than among those with compensated cirrhosis. This result stems from higher SVR rates among patients without cirrhosis and the resulting costs avoided via averted cases of liver-disease complications (Table 4).

Sensitivity analyses

Figure 3 presents results of the deterministic sensitivity analysis for sofosbuvir + pegIFN/RBV compared with

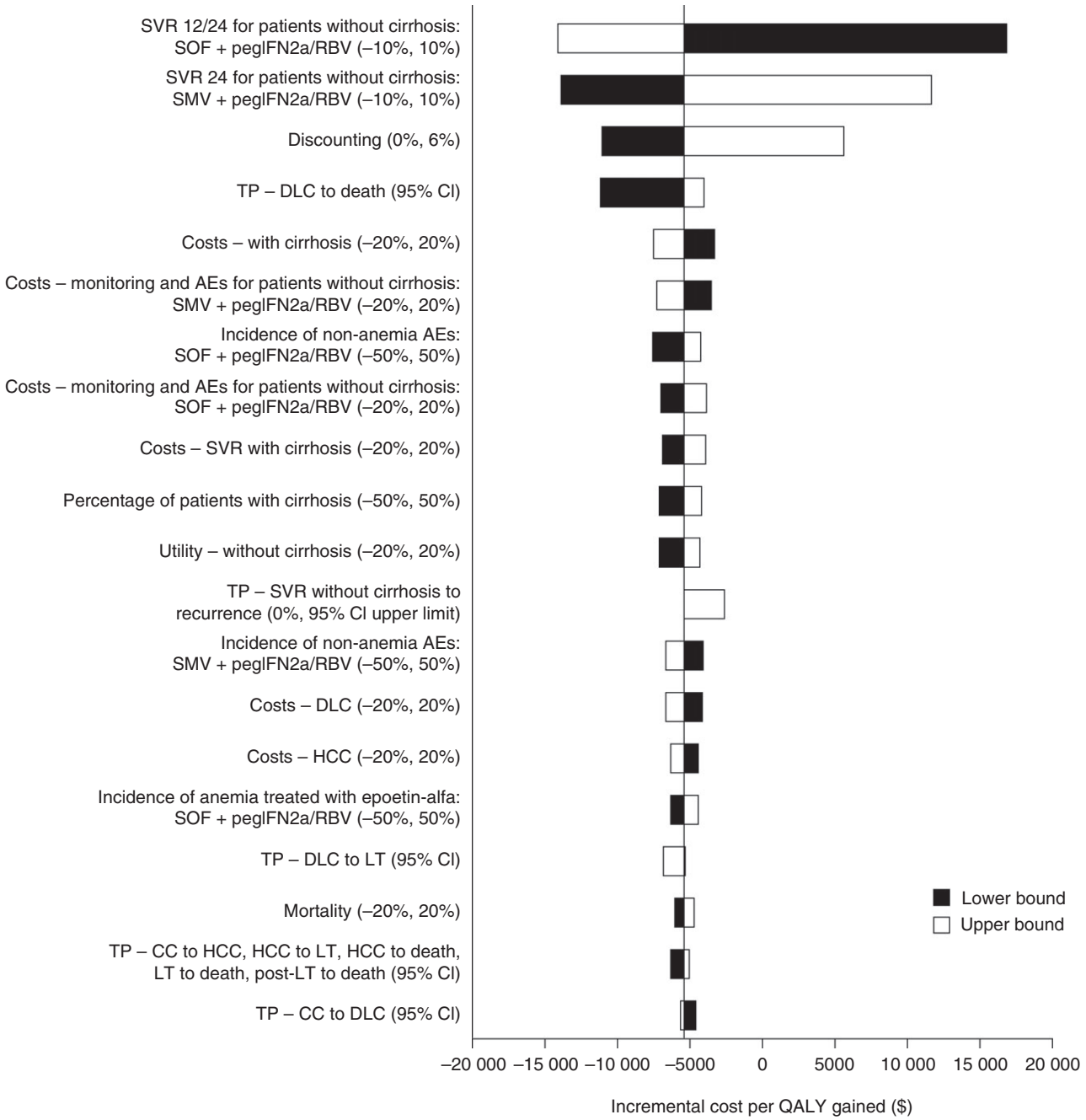

Figure 3 | Deterministic sensitivity analysis for treatment-naïve patients: lifetime incremental cost per QALY for SOF + pegIFN/RBV compared with SMV + pegIFN/RBV. QALY, quality-adjusted life-year; SOF, sofosbuvir; pegIFN2a, pegylated interferon alfa; RBV, ribavirin; SMV, simeprevir; SVR, sustained viral response; TP, transition probability; DLC, decompensated liver cirrhosis; CI, confidence interval; AE, adverse event; HCC, hepatocellular carcinoma; LT, liver transplant; CC, compensated cirrhosis.

simeprevir + pegIFN/RBV among treatment-naïve patients. It displays the 20 factors that most heavily influenced the ICER. The ICERs ranged from −$13 093 to $16 970. The ICERs were negative for all values of key parameters that were varied for sofosbuvir compared with simeprevir (i.e. sofosbuvir + pegIFN/RBV dominated simeprevir + pegIFN/RBV). In general, reductions in cirrhosis prevalence and fibrosis rates, and varying transition probabilities to recurrence in patients who achieve SVR, with and without cirrhosis (0.01, 0.02 and

0.03), increased the incremental cost per QALY gained (Table S2). However, these outcomes still supported sofosbuvir being the most cost-effective option overall. The probabilistic sensitivity analysis results (Figure 4) show that the probability of sofosbuvir + pegIFN/RBV being cost-effective vs. simeprevir + pegIFN/RBV was 96.8% at the $50 000 willingness-to-pay level.

Deterministic and probabilistic sensitivity analyses for sofosbuvir + pegIFN/RBV compared with no treatment are presented in Figures S1 and S2, respectively. The outcomes from these analyses also support sofosbuvir + pegIFN/RBV being the most cost-effective option. The probability of sofosbuvir + pegIFN/RBV being cost-effective vs. no treatment was 100% at the $50 000 willingness-to-pay level (Figure S2).

DISCUSSION

This study comprises a health economic analysis of sofosbuvir + pegIFN/RBV for the treatment of patients with HCV genotype 1. Outcomes from the cost-effectiveness model show that sofosbuvir + pegIFN/RBV yields the most favourable future health economic outcomes compared with other currently available regimens across a broad spectrum of patients, including those with different treatment experiences and severity of fibrosis as well as individuals with and without HIV co-infection.

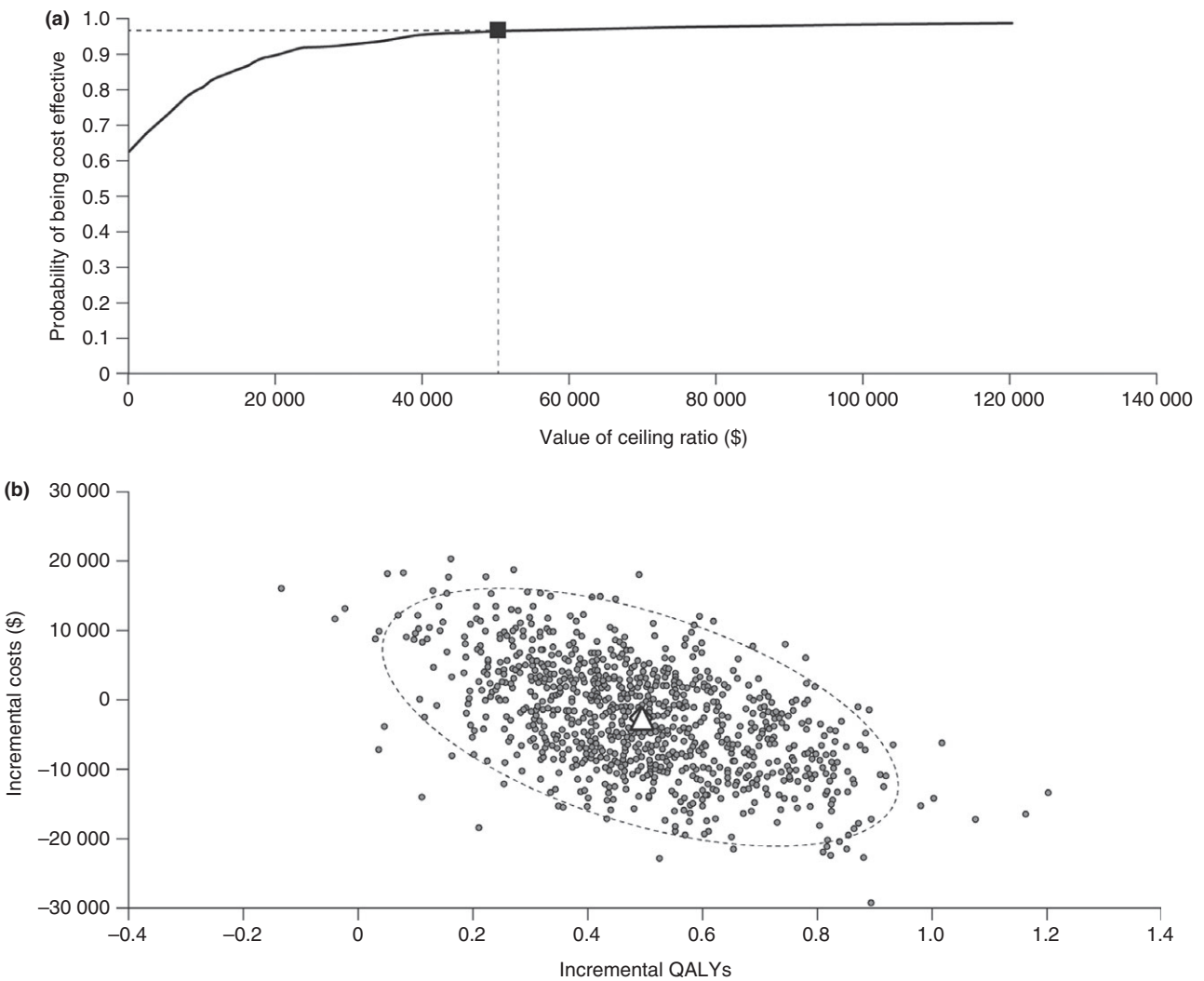

Figure 4 | Probabilistic sensitivity analysis for treatment-naïve patients: lifetime incremental cost per QALY for SOF + pegIFN/RBV compared with SMV + pegIFN/RBV: (a) cost-effectiveness acceptability curve[a] and (b) incremental cost-effectiveness plane. QALY, quality-adjusted life-year; SOF, sofosbuvir; pegIFN, pegylated interferon alfa; RBV, ribavirin; SMV, simeprevir. [a]Probability of being cost-effective at willingness-to-pay ratio of $50 000/QALY is 96.8%.

Compared with other current treatment regimens, sofosbuvir + pegIFN/RBV was associated with the lowest incidence of liver-disease complications such as decompensated cirrhosis, HCC, liver transplant and HCV-related deaths. In all patient subgroups, the estimated percentage reduction in these sequelae was greater than 43% for sofosbuvir vs. the comparator regimens, except for simeprevir + pegIFN/RBV in the treatment-experienced patient subgroup (a reduction of 33%). The lower 1-year cost per SVR associated with sofosbuvir + pegIFN/RBV indicated that more patients can be successfully treated under a fixed budget with this regimen than with boceprevir + pegIFN/RBV, telaprevir + pegIFN/RBV and simeprevir + pegIFN/RBV. The greater increase in SVR rate and the shorter treatment duration with sofosbuvir than with other regimens resulted in significant risk reductions in morbidity (i.e. liver-disease complications), death and costs. The 1-year SVR costs associated with sofosbuvir + pegIFN/RBV were higher than those associated with pegIFN/RBV alone in treatment-naïve patients and those without cirrhosis. However, it should be noted that pegIFN/RBV alone or with boceprevir or telaprevir is not recommended for treatment of HCV genotype 1 in either of these patient populations.[31]

Previous cost analyses have revealed that HCV treatment regimens including protease inhibitors (boceprevir and telaprevir) are cost-effective.[32, 33, 79] The findings from the present analysis, relating to the lifetime incremental cost per QALY gained for patients infected with HCV genotype 1, indicate that sofosbuvir + pegIFN/RBV is currently the most cost-effective option available, even including treatment-experienced patients and those with cirrhosis. Sofosbuvir + pegIFN/RBV was both less costly and more effective than boceprevir + pegIFN/RBV, telaprevir + pegIFN/RBV and simeprevir + pegIFN/RBV regimens. Results from the sensitivity analysis indicated that sofosbuvir + pegIFN/RBV continued to be a cost-effective strategy (compared with both simeprevir + pegIFN/RBV and no treatment) even when key clinical and cost parameters (such as SVR rates, adverse event incidence, costs for treatment monitoring and management of adverse events and transition probability estimates) were adjusted across wide, yet plausible, ranges. The outcomes from this model were also robust when sensitivity analyses were performed to account for lower cirrhosis prevalence and fibrosis rates, various transition probabilities to recurrence in patients who achieve SVR (with and without cirrhosis), and the rate of HCC and decompensation in patients with cirrhosis. These findings support those from other recently published cost-effectiveness models, which indicated that oral antiviral regimens are cost-effective compared with the current standard of care for HCV genotype 1.[34, 35]

The outcomes from the model revealed that, for all treatment regimens analysed, the 1-year costs per SVR were lower for treatment-naïve patients than for treatment-experienced patients; similarly, they were also lower for patients without cirrhosis than cirrhotic patients. These findings are comparable to those reported in a recent cost analysis of protease inhibitor-based therapy.[80] Cases of liver-disease complications are lower when therapy is initiated early, because of higher SVR rates among patients without cirrhosis than among patients with cirrhosis, and the resulting costs avoided via averted cases of liver-disease complications.

Another important finding from this study is that the benefits of treating HCV are considerable, with over a 69% reduction in advanced liver disease cases when treating with an efficacious regimen such as sofosbuvir + pegIFN/RBV compared with no treatment. Gordon *et al.* demonstrated that the annual costs of end-stage liver disease in patients with untreated HCV were five times higher than the annual costs of non-cirrhotic disease in treated patients.[4] Hagan *et al.* found that the ICER for receiving HCV treatment vs. no treatment was $10 920/QALY.[34] Our cost-effectiveness model found similar ICERs. The ICER for the treatment of HCV genotype 1 treatment-naïve patients with sofosbuvir was around $6000/QALY compared with no treatment. This ICER is well below the commonly accepted willingness-to-pay threshold of $50 000/QALY and less than the ICERs for Papanicolaou test and biennial mammography screening ($17 000/QALY and $27 000/QALY, respectively, in 2013 US dollars).[81, 82]

There are a few potential limitations of this model. First, it is predominantly populated with clinical trial data, which represents a controlled rather than a real-world environment. Numerous studies have suggested that real-world therapy completion rates and SVR rates associated with existing treatment regimens are substantially lower, and adverse event incidence is higher, than previously reported in clinical trial settings.[21, 42, 52, 83, 84] The cost per SVR achieved may be substantially higher than those reported in this analysis when real-world adverse event incidence, discontinuation and virological failures are considered. Sufficient real-world data to populate the model fully are not available; therefore, issues related to differences between clinical trial and real-world efficacy and safety could not be accounted for in this

analysis. In addition, the SVR rates for each comparator were obtained from separate clinical trial arms, as no head-to-head clinical trials or meta-analyses including sofosbuvir and its comparators were available at the time of this analysis. Furthermore, some of the SVR rates for the treatment options in the cirrhosis patient subgroup were based on clinical trials with small sample sizes; as a result, F3 and F4 data were combined in some instances. Patient demographical and clinical characteristics may be different across clinical trials, which can affect patients' SVR rates. However, we took stage of cirrhosis at baseline into consideration, which is the most significant predictor of SVR rate in patients with HCV. In addition, the deterministic sensitivity analysis demonstrates that the findings from this study are robust over a range of SVR rates. Overall, adverse event management accounted for less than 3% of costs for all comparators. When the relevant data become available, additional analyses will be necessary to determine the potential impact of the greater expected real-world differences between the sofosbuvir-based regimens and the other available therapies.

Another potential limitation to consider is that in order to estimate the long-term impact of health and economic outcomes in a clinical trial setting, the model predicted the course of liver disease for each individual over their remaining lifetime and mortality based on literature estimates of natural disease progression data. It is possible that disease progression may vary depending on a patient's gender, race, other comorbidities (e.g. co-infection with hepatitis B virus) or alcohol consumption, which were not accounted for in this model. However, to estimate transition probabilities, we used nationally representative, recent data that controlled for covariates or previously used data for HCV models. The model is also limited with regard to the fact that it does not account for the potential risk of HCC to develop in patients who achieve SVR (specifically if treated at F4 cirrhosis stage).[85] An additional limitation is that this study only included US data; costs of HCV treatments may vary considerably across other countries which may influence cost-effectiveness analysis outcomes. In the future, it would therefore be beneficial for this analysis to be repeated for other countries. Furthermore, other benefits of efficacious and tolerable regimens, such as lower indirect costs, reduction in the incidence of extrahepatic manifestations, impact on viral transmission and improved work productivity were not considered in this model. The model does, however, reflect the best available evidence consistent with the opinions of a panel of experts in hepatology and serves as a valuable tool for evaluating the health economic outcomes associated with HCV infection therapies.

Clinical trials have demonstrated that sofosbuvir-based regimens for patients infected with HCV genotypes 1–6 resulted in high SVR rates and a favourable safety profile and tolerability as substantiated by the recommended status on the AASLD/IDSA guidelines.[27, 29, 31] In combination with the outcomes from this evaluation, the clinical attributes of sofosbuvir and its broad utility across patient populations can be projected to result in advantageous real-world economic outcomes. Further analyses need to incorporate real-world data, additional genotypes and future comparators.

In summary, these findings demonstrate that long-term sofosbuvir + pegIFN/RBV is the most cost-effective treatment option for patients infected with HCV genotype 1 because of averted liver-disease costs. Earlier initiation of the more effective sofosbuvir-based regimen yields improved health economic outcomes than later initiation, reducing advanced liver-disease complications and the downstream costs associated with advancing disease.

AUTHORSHIP

Guarantor of the article: Sammy Saab.

Author contributions: SS, SG, HP, MS, AA and ZY contributed to the concept and design, analysis and interpretation of data, and critical revision of the manuscript. HP and ZY contributed to acquisition of data. SS and HP contributed to the writing of the manuscript. All authors approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Deterministic sensitivity analysis for treatment-naïve patients: lifetime incremental cost per QALY for SOF + pegIFN/RBV compared with no treatment.

Figure S2. Probabilistic sensitivity analysis for treatment-naïve patients: lifetime incremental cost per QALY for SOF + pegIFN/RBV compared with no treatment.

Table S1. Number needed to treat to avoid a negative outcome by treatment regimen.

Table S2. Lifetime health economic outcomes by patient population (Table 4 in the manuscript presents the base-case results): updated following re-runs of the deterministic sensitivity analysis.

REFERENCES

1. Gordon SC, Pockros PJ, Terrault NA, *et al.* Impact of disease severity on healthcare costs in patients with chronic hepatitis C (CHC) virus infection. *Hepatology* 2012; **56**: 1651–60.
2. McCombs JS, Yuan Y, Shin J, *et al.* Economic burden associated with patients diagnosed with hepatitis C. *Clin Ther* 2011; **33**: 1268–80.
3. Younossi ZM, Kanwal F, Saab S, *et al.* The impact of hepatitis C burden: an evidence-based approach. *Aliment Pharmacol Ther* 2014; **39**: 518–31.
4. Gordon SC, Hamzeh FM, Pockros PJ, *et al.* Hepatitis C virus therapy is associated with lower health care costs not only in noncirrhotic patients but also in patients with end-stage liver disease. *Aliment Pharmacol Ther* 2013; **38**: 784–93.
5. Hagan LM, Schinazi RF. Best strategies for global HCV eradication. *Liver Int* 2013; **33**(Suppl. 1): 68–79.
6. Soriano V, Sulkowski M, Bergin C, *et al.* Care of patients with chronic hepatitis C and HIV co-infection: recommendations from the HIV-HCV International Panel. *AIDS* 2002; **16**: 813–28.
7. Kim AY, Chung RT. Coinfection with HIV-1 and HCV- one-two punch. *Gastroenterology* 2009; **137**: 795–814.
8. Hadigan C, Kottilil S. Hepatitis C virus infection and coinfection with human immunodeficiency virus: challenges and advancements in management. *JAMA* 2011; **306**: 294–301.
9. Ghany MG, Strader DB, Thomas DL, *et al.* Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology* 2009; **49**: 1335–74.
10. Haque M, Yoshida EM. Hepatitis C antiviral long-term treatment against cirrhosis (HALT-C) trial. *Ann Hepatol* 2009; **8**: 78–9.
11. Nainan OV, Alter MJ, Kruszon-Moran D, *et al.* Hepatitis C virus genotypes and viral concentrations in participants of a general population survey in the United States. *Gastroenterology* 2006; **131**: 478–84.
12. Ghany MG, Nelson DR, Strader DB, *et al.* An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology* 2011; **54**: 1433–44.
13. Poordad F, McCone J Jr, Bacon BR, *et al.* Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med* 2011; **364**: 1195–206.
14. Jacobson IM, McHutchison JG, Dusheiko G, *et al.* Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med* 2011; **364**: 2405–16.
15. Shiffman ML, Suter F, Bacon BR, *et al.* Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. *N Engl J Med* 2007; **357**: 124–34.
16. Fried MW, Shiffman ML, Reddy KR, *et al.* Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002; **347**: 975–82.
17. Nelson DR. The role of triple therapy with protease inhibitors in hepatitis C virus genotype 1 naive patients. *Liver Int* 2011; **31**(Suppl. 1): 53–7.
18. Falck-Ytter Y, Kale H, Mullen KD, *et al.* Surprisingly small effect of antiviral treatment in patients with hepatitis C. *Ann Intern Med* 2002; **136**: 288–92.
19. Hezode C, Fontaine H, Dorival C, *et al.* Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme (ANRS CO20-CUPIC) – NCT01514890. *J Hepatol* 2013; **59**: 434–41.
20. Davis GL, Albright JE, Cook SF, *et al.* Projecting future complications of chronic hepatitis C in the United States. *Liver Transpl* 2003; **9**: 331–8.
21. Sethi N, Vong A, Firdoos S, *et al.* Analysis of direct and indirect costs of HCV care with PEG-Interferon triple therapy. Oral presentation at the Liver Meeting: the 64th Annual Meeting of the American Association for the Study of Liver Diseases; November 1–5, 2013. Washington, DC. Presentation no. 1847.
22. Bichoupan K, Martel-Laferriere V, Ng M, *et al.* Real world costs of telaprevir-based triple therapy, including costs of managing adverse events, at the Mount Sinai Medical Center, NY: $195,000 per SVR12. *Heptology* 2013; **558**(Suppl.): 329A–30A.
23. Vaidya A, Perry CM. Simeprevir: first global approval. *Drugs* 2013; **73**: 2093–106.
24. Dieterich D, Rockstroh J, Orkin C, *et al.* Simeprevir (TMC435) in combination with peginterferon/

ribavirin in patients co-infected with HCV genotype and HIV-1: primary analysis of the C212 study. 14th European AIDS Conference 2013, 16–19 October, 2013. Brussels, Belgium.
25. Janssen. Briefing Document. Simeprevir (TMC435) treatment of patients with chronic hepatitis C, 2013. Available at: http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/antiviraldrugsadvisorycommittee/ucm371624.pdf. Accessed March 2014.
26. Fried MW, Buti M, Dore GJ, *et al.* Once-daily simeprevir (TMC435) with pegylated interferon and ribavirin in treatment-naive genotype 1 hepatitis C: the randomized PILLAR study. *Hepatology* 2013; **58**: 1918–29.
27. Lawitz E, Mangia A, Wyles D, *et al.* Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med* 2013; **368**: 1879–87.
28. Koff RS. Review article: the efficacy and safety of sofosbuvir, a novel, oral nucleotide NS5B polymerase inhibitor, in the treatment of chronic hepatitis C virus infection. *Aliment Pharmacol Ther* 2014; **39**: 478–87.
29. Jacobson IM, Gordon SC, Kowdley KV, *et al.* Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med* 2013; **368**: 1867–77.
30. Gane EJ, Stedman CA, Hyland RH, *et al.* Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *N Engl J Med* 2013; **368**: 34–44.
31. American Association for the Study of Liver Diseases (AASLD) & Infectious Disease Society of America (IDSA). Recommendations for testing, managing, and treating hepatitis C, 2014. Available at: http://www.hcvguidelines.org/full-report-view. Accessed March 2014.
32. Chhatwal J, Ferrante SA, Brass C, *et al.* Cost-effectiveness of boceprevir in patients previously treated for chronic hepatitis C genotype 1 infection in the United States. *Value Health* 2013; **16**: 973–86.
33. Cure S, Bianic F, Gavart S, *et al.* Cost-effectiveness of telaprevir in combination with pegylated interferon alpha and ribavirin in previously untreated chronic hepatitis C genotype 1 patients. *J Med Econ* 2014; **17**: 65–76.
34. Hagan LM, Yang Z, Ehteshami M, *et al.* All-oral, interferon-free treatment for chronic hepatitis C: cost-effectiveness analyses. *J Viral Hepat* 2013; **20**: 847–57.
35. Younossi ZM, Singer ME, Mir HM, *et al.* Impact of interferon free regimens on clinical and cost outcomes for chronic hepatitis C genotype 1 patients. *J Hepatol* 2014; **60**: 530–5.
36. Hartwell D, Jones J, Baxter L, *et al.* Peginterferon alfa and ribavirin for chronic hepatitis C in patients eligible for shortened treatment, re-treatment or in HCV/HIV co-infection: a systematic review and economic evaluation. *Health Technol Assess* 2011; **15**: 1–210.
37. Davis GL, Alter MJ, El-Serag H, *et al.* Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. *Gastroenterology* 2010; **138**: 513–21.
38. Sulkowski MS, Rodriguez-Torres M, Lalezari JP, *et al.* All-oral therapy with sofosbuvir plus ribavirin for the treatment of HCV genotype 1, 2, and 3 infection in patients co-infected with HIV (PHOTON-1). Oral presentation at the Liver Meeting: the 64th Annual Meeting of the American Association for the Study of Liver Diseases; November 1–5, 2013. Washington, DC. Presentation no. 212.
39. Rodriguez-Torres M, Rodriguez-Orengo J, Gagger A, *et al.* Sofosbuvir and peginterferon alfa-2a/ribavirin for treatment-naïve genotype 1-4 HCV-infected patients who are coinfected with HIV. Poster presented at IDWeek 2013; October 2–6, 2013. San Francisco, CA. Poster no. 714.
40. Bacon BR, Khalid O. New therapies for hepatitis C virus infection. *Mol Med* 2011; **108**: 255–9.
41. Bruno S, Shiffman ML, Roberts SK, *et al.* Efficacy and safety of peginterferon alfa-2a (40KD) plus ribavirin in hepatitis C patients with advanced fibrosis and cirrhosis. *Hepatology* 2010; **51**: 388–97.
42. Dieterich D, Soriano V, Sherman K, *et al.* Telaprevir in combination with peginterferon alfa-2a/ribavirin in hepatitis C/HIV co-infected patients: a 24-week treatment interim analysis. 19th Conference on Retroviruses and Opportunistic Infections. March 5–8, 2012. Seattle, WA. Abstract no. 46.
43. Poynard T, Colombo M, Bruix J, *et al.* Peginterferon alfa-2b and ribavirin: effective in patients with hepatitis C who failed interferon alfa/ribavirin therapy. *Gastroenterology* 2009; **136**: 1618–28.
44. Sulkowski MS, Pol S, Cooper C, *et al.* Boceprevir plus peginterferon/ribavirin for the treatment of hepatitis C/HIV co-infected patients. 19th Annual Conference on Retroviruses and Opportunistic Infections, March 5–8, 2012. Seattle, WA. Abstract no. 47.
45. Sulkowski MS, Sherman KE, Dieterich DT, *et al.* Combination therapy with telaprevir for chronic hepatitis C virus genotype 1 infection in patients with HIV: a randomized trial. *Ann Intern Med* 2013; **159**: 86–96.
46. Sulkowski MS, Pol S, Mallolas J, *et al.* Boceprevir versus placebo with pegylated interferon alfa-2b and ribavirin for treatment of hepatitis C virus genotype 1 in patients with HIV: a randomised, double-blind, controlled phase 2 trial. *Lancet Infect Dis* 2013; **13**: 597–605.
47. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, *et al.* Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N Engl J Med* 2004; **351**: 438–50.
48. Zeuzem S, Andreone P, Pol S, *et al.* Telaprevir for retreatment of HCV infection. *N Engl J Med* 2011; **364**: 2417–28.
49. Krawitt EL, Ashikaga T, Gordon SR, *et al.* Peginterferon alfa-2b and ribavirin for treatment-refractory chronic hepatitis C. *J Hepatol* 2005; **43**: 243–9.
50. Jacobson IM, Marcellin P, Zeuzem S, *et al.* Refinement of stopping rules during treatment of hepatitis C genotype 1 infection with boceprevir and peginterferon/ribavirin. *Hepatology* 2012; **56**: 567–75.
51. Roberts SK, Weltman MD, Crawford DH, *et al.* Impact of high-dose peginterferon alfa-2A on virological response rates in patients with hepatitis C genotype 1: a randomized controlled trial. *Hepatology* 2009; **50**: 1045–55.
52. Gordon SC, Muir AJ, Lim JK. The frequency and management of adverse events in chronic hepatitis C (HCV) treated with boceprevir or telaprevir: real world experience from HCV-TARGET longitudinal observational study. *Hepatology* 2013; **58**(Suppl. 1): 1104A.
53. Sherman KE, Flamm SL, Afdhal NH, *et al.* Response-guided telaprevir combination treatment for hepatitis C virus infection. *N Engl J Med* 2011; **365**: 1014–24.
54. Lawitz E, Gane E, Stedman C, *et al.* GS-7977 phase II trials: concordance of SVR4 with SVR12 and SVR24 in HCV genotypes 1-3. *J Hepatol* 2012; **56** (Suppl. 2): S4.
55. Gilead Sciences Inc. Briefing document: sofosbuvir for treatment of chronic hepatitis C infection. Submitted to the FDA Antiviral Drugs Advisory Committee. 25 October 2013. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/

UCM252562.pdf. Accessed December 6, 2013.
56. Sovaldi Prescribing Information. Clinical trials in subjects with genotype 1 or 4 CHC (14.2). Available at: http://www.gilead.com/~/media/Files/pdfs/medicines/liverdisease/sovaldi/sovaldi_pi.pdf. Accessed March 25, 2014.
57. Chen J, Florian J, Carter W, *et al.* Earlier sustained virologic response end points for regulatory approval and dose selection of hepatitis C therapies. *Gastroenterology* 2013; **144**: 1450–5.
58. Lawitz E, Gane EJ, Lalezari J, *et al.* High concordance of SVR4, SVR12, and SVR24 in patients with HCV infection who have received treatment with sofosbuvir. EASL 48th Annual Meeting, April 24–28, 2013, Amsterdam, the Netherlands.
59. Zein NN. Clinical significance of hepatitis C virus genotypes. *Clin Microbiol Rev* 2000; **13**: 223–35.
60. Lenz O, Fevery B, Verbinnen T, *et al.* Resistance analyses of HCV isolates from patients treated with simeprevir in Phase IIB/III studies. 64th Annual Meeting of the America Association for the Study of Liver Diseases, November 1–5, 2013, Washington, DC, USA.
61. Toyoda H, Kumada T. Pharmacotherapy of chronic hepatitis C virus infection – the IDEAL trial: '2b or not 2b (= 2a), that is the question'. *Expert Opin Pharmacother* 2009; **10**: 2845–57.
62. Thein HH, Yi Q, Dore GJ, *et al.* Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. *Hepatology* 2008; **48**: 418–31.
63. Razavi H, Elkhoury AC, Elbasha E, *et al.* Chronic hepatitis C virus (HCV) disease burden and cost in the United States. *Hepatology* 2013; **57**: 2164–70.
64. Liu S, Cipriano LE, Holodniy M, *et al.* New protease inhibitors for the treatment of chronic hepatitis C: a cost-effectiveness analysis. *Ann Intern Med* 2012; **156**: 279–90.
65. Murphy SL, Xu JQ, Kochanek KD. Division of Vital Statistics. Deaths: final data for 2010. Table 3. Number of deaths and death rates, by age, race, and sex: United States, 2010. National Vital Statistics Reports, vol. 61, no. 4, May 2013. Available at: http://www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_04.pdf. Accessed July 16, 2013.
66. Graham CS, Baden LR, Yu E, *et al.* Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. *Clin Infect Dis* 2001; **33**: 562–9.
67. Kuehne FC, Bethe U, Freedberg K, *et al.* Treatment for hepatitis C virus in human immunodeficiency virus-infected patients: clinical benefits and cost-effectiveness. *Arch Intern Med* 2002; **162**: 2545–56.
68. Hornberger J, Torriani FJ, Dieterich DT, *et al.* Cost-effectiveness of peginterferon alfa-2a (40 kDa) plus ribavirin in patients with HIV and hepatitis C virus co-infection. *J Clin Virol* 2006; **36**: 283–91.
69. Terrault NA, Roland ME, Schiano T, *et al.* Outcomes of liver transplant recipients with hepatitis C and human immunodeficiency virus coinfection. *Liver Transpl* 2012; **18**: 716–26.
70. de Vera ME, Dvorchik I, Tom K, *et al.* Survival of liver transplant patients coinfected with HIV and HCV is adversely impacted by recurrent hepatitis C. *Am J Transplant* 2006; **6**: 2983–93.
71. Ragni MV, Belle SH, Im K, *et al.* Survival of human immunodeficiency virus-infected liver transplant recipients. *J Infect Dis* 2003; **188**: 1412–20.
72. Bureau of Labor Statistics. US Department of Labor. Consumer Price Index - all urban consumers (current series), July 2013. Available at: http://data.bls.gov/cgi-bin/surveymost?cu. Accessed July 16, 2013.
73. Resource-Based Relative Values Scale (R-BRVS). *The Essential RBRVS: A Comprehensive Listing of RBRVS Values for CPT and HCPCS Codes*. Salt Lake City, UT, USA: Optum Insight Inc, 2013.
74. Red Book Online. Micromedex 2.0. Available at: http://www.micromedexsolutions.com/home/dispatch. Accessed December 12, 2013.
75. Campos NG, Salomon JA, Servoss JC, *et al.* Cost-effectiveness of treatment for hepatitis C in an urban cohort co-infected with HIV. *Am J Med* 2007; **120**: 272–9.
76. Thein HH, Krahn M, Kaldor JM, *et al.* Estimation of utilities for chronic hepatitis C from SF-36 scores. *Am J Gastroenterol* 2005; **100**: 643–51.
77. Younossi ZM, Stepanova M, Nader F, *et al.* Health utilities in patients with chronic hepatitis C treated with sofosbuvir (SOF) containing regimens: results from POSITRON, FISSION, FUSION and NEUTRINO studies. *Hepatology* 2013; **58**(Suppl.): 385.
78. Gold MR, Siegel JE, Russell LB, *et al. Cost-Effectiveness in Health and Medicine*. New York: Oxford University Press, 1996.
79. Blazquez-Perez A, San Miguel R, Mar J. Cost-effectiveness analysis of triple therapy with protease inhibitors in treatment-naive hepatitis C patients. *Pharmacoeconomics* 2013; **31**: 919–31.
80. Bichoupan K, Martel-Laferriere V, Sachs D, *et al.* Costs of telaprevir-based triple therapy including adverse event management at the Mount Sinai Medical Center, NY $189,000 per SVR. Oral presentation at the Liver Meeting: the 64th Annual Meeting of the American Association for the Study of Liver Diseases; November 1–5, 2013. Washington, DC. Presentation no. 244.
81. Mandelblatt JS, Lawrence WF, Womack SM, *et al.* Benefits and costs of using HPV testing to screen for cervical cancer. *JAMA* 2002; **287**: 2372–81.
82. Lindfors KK, Rosenquist CJ. The cost-effectiveness of mammographic screening strategies. *JAMA* 1995; **274**: 881–4.
83. Ngygen MH, Brooks L, Livornese RC. Suboptimal treatment rates and treatment completion rates of chronic hepatitis C virus therapy in patients with comorbidities: analysis of a large real-world US cohort. Poster presented at the Liver Meeting: the 64th Annual Meeting of the American Association for the Study of Liver Diseases; November 1–5, 2013. Washington, DC. Poster no. 2040.
84. Backus LI, Belperio PS, Shahoumian TA, *et al.* Comparative effectiveness of the hepatitis C virus protease inhibitors boceprevir and telaprevir in a large U.S. cohort. *Aliment Pharmacol Ther* 2014; **39**: 93–103.
85. Poynard T, Moussalli J, Munteanu M, *et al.* Slow regression of liver fibrosis presumed by repeated biomarkers after virological cure in patients with chronic hepatitis C. *J Hepatol* 2013; **59**: 675–83.
86. Zeuzem S, Dusheiko GM, Salupere R, *et al.* Sofosbuvir + ribavirin for 12 or 24 weeks for patients with HCV genotype 2 or 3: the VALENCE Trial. Poster presented at the Liver Meeting: the 64th Annual Meeting of the American Association for the Study of Liver Diseases; November 1–5, 2013. Washington, DC. Poster no. 1085.
87. Probst A, Dang T, Bochud M, *et al.* Role of hepatitis C virus genotype 3 in liver fibrosis progression–a systematic review and meta-analysis. *J Viral Hepat* 2011; **18**: 745–59.
88. McAdam-Marx C, McGarry LJ, Hane CA, *et al.* All-cause and incremental per patient per year cost associated with chronic hepatitis C virus and associated liver complications in the United States: a managed care perspective. *J Manag Care Pharm* 2011; **17**: 531–46.

89. Chong CA, Gulamhussein A, Heathcote EJ, *et al.* Health-state utilities and quality of life in hepatitis C patients. *Am J Gastroenterol* 2003; **98**: 630–8.
90. McLernon DJ, Dillon J, Donnan PT. Health-state utilities in liver disease: a systematic review. *Med Decis Making* 2008; **28**: 582–92.
91. Hsu PC, Federico CA, Krajden M, *et al.* Health utilities and psychometric quality of life in patients with early- and late-stage hepatitis C virus infection. *J Gastroenterol Hepatol* 2012; **27**: 149–57.
92. Wright M, Grieve R, Roberts J, *et al.* Health benefits of antiviral therapy for mild chronic hepatitis C: randomized controlled trial and economic evaluation. *Health Technol Assess* 2006; **10**: 1–113.