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Economic evaluation of pan-genotypic generic direct-acting antiviral regimens for treatment of chronic hepatitis C in Iran: a cost-effectiveness study

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ABSTRACT

Introduction Low-cost generic direct-acting antiviral (DAA) regimens for treatment of hepatitis C virus (HCV) are available in several low-income/middle-income countries, important for treatment scale-up. This study evaluated the cost-effectiveness of genotype-dependent and pan-genotypic DAA regimens in Iran as an example of a resource-limited setting.

Methods A Markov model was developed to simulate HCV natural history. A decision tree was developed for HCV treatment, assuming four scenarios, including scenario 1: genotyping, sofosbuvir/ledipasvir (SOF/LDV) for genotype 1, and sofosbuvir/daclatasvir (SOF/DCV) for genotype 3; scenario 2: genotyping, SOF/LDV for genotype 1, and sofosbuvir/velpatasvir (SOF/VEL) for genotype 3; scenario 3: no genotyping and SOF/DCV for all; and scenario 4: no genotyping and SOF/VEL for all. A 1-year cycle length was used to calculate the cumulative cost and effectiveness over a lifetime time horizon. We calculated quality-adjusted life years (QALYs), and incremental cost-effectiveness ratio (ICER) using a health system perspective. Costs were converted to US dollars using purchasing power parity exchange rate ($PPP). All costs and outcomes were discounted at an annual rate of 3%.

Results Among people with no cirrhosis, scenario 3 had the minimum cost, compared with which scenario 4 was cost-effective with an ICER of 4583 $PPP per QALY (willingness-to-pay threshold: 9,311 $PPP per QALY). Among both people with compensated or decompensated cirrhosis, scenario 4 was cost saving. In sensitivity analysis, scenario 4 would be also cost-saving among people with no cirrhosis provided a 39% reduction in the cost of 12 weeks SOF/VEL.

Conclusion Initiating all patients on pan-genotypic generic DAA regimens with no pretreatment genotyping was cost-effective compared with scenarios requiring pretreatment HCV genotype tests. Among generic pan-genotypic DAA regimens, SOF/VEL was cost-effective, for people with no cirrhosis and cost-saving for those with cirrhosis.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ To simulate the long-term costs and outcomes of treating individuals with hepatitis C with direct-acting antiviral regimens, a decision tree and a Markov model were combined.
⇒ A cost-effectiveness analysis was conducted in three subgroups based on liver disease stages, including no cirrhosis, compensated cirrhosis and decompensated cirrhosis.
⇒ The analysis was from the health system perspective and did not consider indirect costs (eg, productivity losses) from a societal perspective.
⇒ Transition probabilities and utility values were derived from studies conducted in other countries, given unavailable Iranian-specific data.

INTRODUCTION

Hepatitis C virus (HCV) infection is a major public health issue in many countries. In 2015, an estimated 71 million people were living with HCV infection worldwide.[1] Among 30 countries, accounting for 80% of the total number of people living with HCV infection globally, the large majority are low-income or middle-income countries, indicating a high disease burden of HCV in countries with limited resources.[1]

In the previous two decades, the only approved HCV treatments were interferon-containing regimens, with suboptimal efficacy (40%–60% cure) and major side-effects.[2 3] The advent of interferon-free direct-acting antiviral (DAA) therapies with high cure rates and minimal side-effects have changed the paradigm of HCV treatment, with the potential to reduce HCV disease burden.[3 4] However, high drug pricing is a major barrier for access to DAA treatment, particularly in low-income/middle-income countries.[5] The median price of a standard course of originator DAA treatment in 50 countries has been between US$27 000 and US$47 000 for different DAA regimens.[6] A generic formulation of DAAs has substantially reduced the drug costs. Generic price in some cases is approximately one-hundredth

to one-thousandth of the brand price.[6] HCV diagnostics and other pretreatment laboratory tests are also expensive while in many low/middle-income countries access to qualified facilities is limited, another barrier for initiating treatment in these settings.[7] Some DAA regimens have higher efficacy against specific genotypes of HCV, necessitating the determination of HCV genotype before treatment initiation.[8] The introduction of pan-genotypic DAA regimens with high efficacy across all HCV genotypes has facilitated HCV treatment by exempting patients from pretreatment HCV genotyping tests.[9] Although some pan-genotypic DAA regimens are more expensive than genotype-dependent regimens, using pan-genotypic DAA regimens may reduce the overall cost of treatment given removing genotyping cost and shortening treatment in some patients.

In Iran, an estimated 186 500 individuals were living with HCV infection in 2014, with 420 individuals experiencing HCV-related advanced liver diseases or death each year.[10] Locally manufactured generic DAAs are available in Iran at a much cheaper price than originator DAA.[11] However, the cost of HCV diagnostics and other pretreatment laboratory tests (eg, HCV genotyping) is still a barrier for HCV treatment scale-up. A previous study compared the cost-effectiveness of interferon-based treatment and DAA treatment among individuals with HCV genotype 1.[12] This study demonstrated that treatment with a combination of sofosbuvir and ledipasvir or sofosbuvir and pegylated interferon and ribavirin were cost-effective compared with treatment with pegylated interferon and ribavirin. However, an expanded economic evaluation is required to compare cost-effectiveness across DAA regimens, and also between pan-genotypic and genotype-dependent regimens. This current study evaluated the cost-effectiveness of available DAA regimens, and assessed various treatment scenarios to determine the most cost-effective strategy for HCV treatment in Iran, as an example of a resource-limited setting.

MATERIALS AND METHODS

Model structure and assumptions

A decision tree was developed for various HCV treatment scenarios (figure 1A), and a Markov state transition model was used to simulate the natural history of HCV infection and progression of liver disease in people living with HCV (figure 1B). Similar to model structures used in the previous studies,[13–15] the Markov model states included various stages of liver fibrosis based on METAVIR score,[16] decompensated cirrhosis,

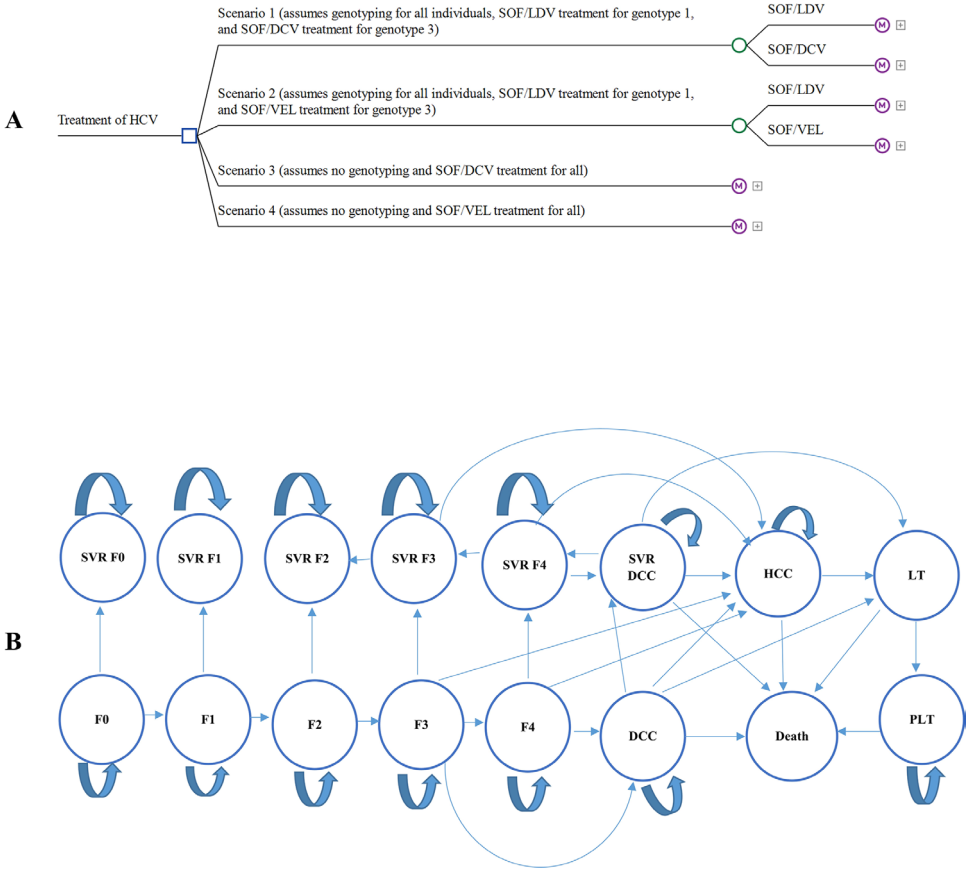

Figure 1 The decision tree and Markov model, used in this study. SOF/LDV, sofosbuvir/ledipasvir; SOF/DCV, sofosbuvir/daclatasvir; SOF/VEL, sofosbuvir/velpatasvir; F0-F4, METAVIR fibrosis states; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplantation; PLT; post-liver transplantation; SVR, sustained virologic response; SVR F0-F4, patient in F0-F4 states following SVR; SVR DCC, patient in DCC state following SVR.

hepatocellular carcinoma, liver transplantation, post-liver transplantation and death. METAVIR score defines four stages of liver fibrosis, including F0 (no fibrosis), F1 (mild fibrosis), F2 (moderate fibrosis), F3 (advanced fibrosis without cirrhosis) and F4 (compensated cirrhosis). The model also included the liver disease states following HCV cure (also known as sustained virological response, SVR).

Each individual underwent one of the DAA treatment scenarios, followed by a state-transition model to predict clinical outcomes. The time horizon of the study was a lifetime, and the length of the cycle was considered 1 year. Both costs and outcomes were discounted at a rate of 3%.[17] The structure of the model as well as all assumptions and inputs were validated by clinical experts, including an experienced hepatologist, two clinical epidemiologists, experienced in HCV epidemiology and natural history, and a health economist.

Study population characteristics

Our baseline population consisted of treatment-naive people living with HCV. An estimated 186 500 people were living with HCV in Iran in 2014 with a median age of 30 years.[10] Thus, we assumed that people entered the model at the age of 30. The initial distribution of liver fibrosis stages among people with HCV was assumed as 52% F0, 31% F1, 9% F2, 5% F3, 2% F4, and 1% decompensated cirrhosis, hepatocellular carcinoma, or liver transplantation.[10] The study population was restricted to people with HCV genotype 1 or 3 as the dominant genotypes in a large majority of countries,[1] including among >95% of people with HCV in Iran.[10]

Treatment regimens and scenarios

Treatment scenarios were considered based on available generic DAA regimens in Iran, which is also applicable to several other low-income/middle-income countries.[18–20] A combination of sofosbuvir and velpatasvir (SOF/VEL) is a pan-genotypic DAA regimen, recommended for all HCV genotypes by Iranian and international HCV clinical guidelines.[9 21] Sofosbuvir and daclatasvir (SOF/DCV) has been recommended as another pan-genotypic DAA regimen in Iranian guideline,[21] while international guidelines have also recommended this regimen in the settings where other pan-genotypic regimens are not available or not affordable.[9] Sofosbuvir and ledipasvir (SOF/LDV) is recommended for genotype 1[21 22] while its generic formulation is used in several low-income/middle-income countries.[18–20]

Four treatment scenarios were developed using these three regimens:

- Scenario 1: pretreatment HCV genotype test is performed for all individuals. Based on HCV genotyping results, people with genotype 1 receive SOF/LDV and those with genotype 3 receive SOF/DCV.
- Scenario 2: similar to the first scenario, a pretreatment HCV genotype test is performed for all individuals, and people with genotype 1 receive SOF/LDV. However, in this scenario, those with genotype 3 receive SOF/VEL.
- Scenario 3: no pretreatment HCV genotype test is performed, and all individuals receive pan-genotypic SOF/DCV.
- Scenario 4: similar to the third scenario, no pretreatment HCV genotype test is performed, but all individuals receive pan-genotypic SOF/VEL.

In the first and the second scenarios, the proportion of individuals with HCV genotype 1 was considered as 54%.[23] In all scenarios, routine pretreatment liver disease assessments (listed in online supplemental table 1) are assumed to be conducted for all individuals to identify people with cirrhosis, including those with decompensated cirrhosis. Duration of treatment is considered based on cirrhosis status for each regimen (table 1). Ribavirin was not considered in any regimen given its side-effects and recommendation of the clinical guidelines for prioritising ribavirin-free regimens.[9]

Clinical inputs

The data of effectiveness of DAA regimens (ie, SVR) were derived from published literature (table 1). For SOF/DCV, the data of a large Iranian study, using generic SOF/DCV were used.[24] For SOF/LDV and SOF/VEL, given unavailable represetative Iranian studies, SVR estimates were derived from large international observational real-world studies.[25–27] The SVR of SOF/VEL in decompensated cirrhosis was obtained from a clinical trial.[28]

We extracted transition probabilities from studies conducted in other countries given unavailable data of large cohort studies evaluating HCV natural history in Iran (table 1). Following treatment completion, individuals with fibrosis score F0–F2 who achieved SVR were presumed to maintain SVR and did not progress to more advanced liver disease. Individuals with F3, F4 and decompensated cirrhosis could progress to more advanced liver disease status after achieving SVR, but with a lower rate in comparison with those who did not achieve SVR. Individuals who did not achieve SVR experienced disease progression based on HCV natural history while those with F3 and F4 were at risk of developing decompensated cirrhosis and hepatocellular carcinoma. Individuals with decompensated cirrhosis (with SVR or without SVR) or hepatocellular carcinoma could be candidates for liver transplantation.

Cost inputs

The health system perspective was used in this study, and only direct medical costs were considered in the analysis. All costs were converted to US dollar using purchasing power parity (PPP) exchange rate[29] (one PPP dollar=146 681 Iranian Rials). Direct medical costs consisted of the costs of medications and other outpatient and inpatient services for HCV and liver diseases clinical care (online supplemental table 1 and 2). DAA treatment costs were estimated, considering the indicated duration of treatment and unit drug costs. The price of DAA drugs

Table 1 The estimates of treatment effectiveness, health utilities, transition probabilities, and costs, used as input parameters

Input parameter	Base case value (range)	References
SVR estimates		
SOF/LDV		
No cirrhosis (12 week)	0.961 (0.945–0.972)	25
Compensated cirrhosis (24 week)	0.918 (0.877–0.948)	26
Decompensated cirrhosis (24 week)	0.877 (0.818–0.922)	26
SOF/DCV		
No cirrhosis (12 week)	0.965 (0.950–0.976)	24
Compensated cirrhosis (24 week)	0.939 (0.913–0.959)	24
Decompensated cirrhosis (24 week)	0.797 (0.688–0.882)	24
SOF/VEL		
No cirrhosis (12 week)	0.980 (0.960–0.990)	27
Compensated cirrhosis (12 week)	0.963 (0.929–0.984)	27
Decompensated cirrhosis (24 week)	0.895 (0.811–0.951)	28
Utility values		
F0	0.790 (0.632–0.948)	13 15 45 46
F1	0.790 (0.632–0.948)	13 15 45 46
F2	0.790 (0.632–0.948)	13 15 45 46
F3	0.790 (0.632–0.948)	13 15 45 46
F4	0.748 (0.598–0.898)	13 15 45 46
F0 SVR	0.840 (0.672–1.00)	13 15 47
F1 SVR	0.840 (0.672–1.00)	13 15 47
F2 SVR	0.840 (0.672–1.00)	13 15 47
F3 SVR	0.840 (0.672–1.00)	13 15 47
F4 SVR	0.799 (0.639–0.959)	13 15 47
DCC SVR	0.722 (0.578–0.866)	15
DCC	0.672 (0.538–0.806)	13 15 45 46
HCC	0.610 (0.488–0.732)	13 15 45 46
LT	0.650 (0.520–0.780)	13 15 46 47
Post-LT	0.709 (0.567–0.851)	13 15 45–47
Transition probabilities		
F0 – F1	0.117 (0.104–0.130)	48
F1 – F2	0.085 (0.075–0.096)	48
F2 – F3	0.121 (0.109–0.133)	48
F3 – F4	0.115 (0.104–0.129)	48
F3 – DCC	0.012 (0.009–0.015)	49
F3 – HCC	0.011 (0.008–0.014)	49
F4 – DCC	0.039 (0.029–0.049)	49
F4 – HCC	0.033 (0.025–0.041)	50
DCC – HCC	0.014 (0.011–0.018)	51
DCC – LT	0.031 (0.023–0.039)	52
DCC – Death	0.129 (0.097–0.161)	51
HCC – LT	0.040 (0.000–0.140)	53
HCC – Death	0.485 (0.364–0.606)	54
LT – Death	0.107 (0.080–0.134)	55
Post-LT – Death	0.049 (0.037–0.061)	55

Continued

Table 1 Continued

Input parameter	Base case value (range)	References
F3 SVR – F2 SVR	0.267 (0.200–0.334)	56
F4 SVR – F3 SVR	0.076 (0.057–0.095)	57
F3 SVR – HCC	0.003 (0.002–0.004)	58
F4 SVR – HCC	(RR=0.24) * 0.033 = 0.007 (0.005–0.009)	58 59
F4 SVR – DCC SVR	0.003 (0.002–0.004)	49 50
DCC SVR – HCC	0.009 (0.007–0.011)	50 51
DCC SVR – LT	0.009 (0.007–0.011)	Assume RR of 0.296 for DCC to LT (RR from [60])
DCC SVR – F4 SVR	0.076 (0.057–0.095)	Assume same probability as F4 SVR to F3 SVR
DCC SVR – Death	0.049 (0.039–0.059)	Assume RR of 0.381 for DCC to death (RR from [60])
Health state costs per annum (PPP dollar)		
F0–F3	139	
F4	195	
DCC	377	
HCC	3949	
LT	1407	
Post-LT	206	
Treatment costs per week (PPP dollar)		
SOF/LDV	7.4	
SOF/DCV	5.8	
SOF/VEL	11.9	

DCC, decompensated cirrhosis; F0-F4, METAVIR fibrosis states; HCC, hepatocellular carcinoma; LT, liver transplantation; Post-LT, post-liver transplantation; PPP, purchasing power parity; RR, risk ratio; SOF/DCV, sofosbuvir/daclatasvir; SOF/LDV, sofosbuvir/ledipasvir; SOF/VEL, sofosbuvir/velpatasvir; SVR, sustained virologic response; SVR DCC, patient in DCC state achieving SVR; SVR F0-F4, patient in F0-F4 states achieving SVR.

was extracted from the Iranian Food and Drug Administration website (http://www.fda.gov.ir/en/). In cases where there was more than one product of a DAA, the lowest price was used in the analyses, while the change in drugs cost was evaluated in the sensitivity analysis. The frequency of physician's visits, laboratory tests, and diagnostic services was based on expert opinion. For estimation of annual costs for HCV and liver disease management (eg, hospitalisation, physician's visits, diagnostic and laboratory costs), the cost items and associated costs were collected from one of the major public hospitals in the southeast region of Iran (Afzalipour Hospital, Kerman)[30] in 2020, and the cost of each case was then multiplied by its average frequency (online supplemental table 1 to 3). The large majority of clinical care services in Iran are delivered through the public health system with almost similar service fees across the country.

Utility inputs

The intended outcomes for HCV treatment scenarios in this study were life-years (LY) and quality-adjusted life-years (QALY). Given unavailable health state utility data from Iran, utility values were extracted from international studies (table 1). The increased utility for SVR was considered as 0.05.[31] Given that all the studied regimens were interferon-free, no disutility was considered.

Model analysis

The model was developed using TreeAge Pro 2020. According to a recent study,[32] the willingness to pay threshold for Iran was estimated as 9311 PPP dollars per QALY. Cost-effectiveness analysis was conducted in three subgroups based on liver diseases stages, including no cirrhosis, compensated cirrhosis and decompensated cirrhosis.

To evaluate the uncertainty of the model parameters, both deterministic sensitivity analysis, and probabilistic sensitivity analysis were performed. In deterministic sensitivity analysis, the most important parameters affecting the model were initially identified by the tornado diagram. We used an incremental net monetary benefit (INMB) tornado diagram instead of an ICER tornado diagram because the ICER tornado is sometimes difficult to interpret (when the incremental effectiveness passes through zero). A positive INBM indicates that the first strategy is cost-effective compared with the other strategies. Input parameters included costs, utility values, transition probabilities, SVR estimates and discount rates. The range

Table 2 The cost-effectiveness of various scenarios considered for treatment of people with hepatitis C

	Strategy	QALY	LY	Cost (PPP $)	ICER (PPP $/QALY)	
No cirrhosis	Scenario 3 (reference)	21.555	25.741	245	–	
	Scenario 1	21.553	25.741	280	−17 500	Dominated
	Scenario 4	21.567	25.747	300	4583	Cost-effective
	Scenario 2	21.559	25.744	305	15 000	
Compensated cirrhosis	Scenario 4 (reference)	16.296	20.982	3847	–	
	Scenario 3	16.169	20.838	3904	−449	Dominated
	Scenario 2	16.179	20.850	3957	−940	Dominated
	Scenario 1	16.121	20.784	3985	−789	Dominated
Decompensated cirrhosis	Scenario 4 (reference)	10.975	14.674	4023	–	
	Scenario 3	10.308	14.593	4076	−79	Dominated
	Scenario 2	10.909	14.219	4033	−151	Dominated
	Scenario 1	10.602	13.861	4064	−110	Dominated
All patients	Scenario 3 (reference)	21.448	25.646	321	–	
	Scenario 1	21.445	25.644	358	−12 333	Dominated
	Scenario 4	21.462	25.653	374	3786	Cost-effective
	Scenario 2	21.451	25.647	381	20 000	

Scenario 1 assumes genotyping for all individuals, SOF/LDV treatment for genotype 1, and SOF/DCV treatment for genotype 3. Scenario 2 assumes genotyping for all individuals, SOF/LDV treatment for genotype 1, and SOF/VEL treatment for genotype 3. Scenario 3 assumes no genotyping and SOF/DCV treatment for all. Scenario 4 assumes no genotyping and SOF/VEL treatment for all.
LY, life-year; QALY, quality-adjusted life-year.

of cost change was considered ±25%, and the range of change of other parameters was based on a 95% CI. For probabilistic sensitivity analysis, a Monte Carlo simulation with 10 000 replications was performed to investigate the effect of uncertainty of all variables on ICER per QALY. Gamma distribution was assumed for costs, and beta distribution was assumed for utility values, SVR estimates, and transition probabilities.[33] Finally, the results of probabilistic sensitivity analysis were shown in the cost-effectiveness acceptability curve.

Patient and public involvement statement

Study participants or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Base-case results

The outputs of the base-case analysis have been summarised in table 2. In each subgroup, we considered the scenario with the lowest cost as the reference. We have also presented the results of the probabilistic cost-effectiveness analysis in online supplemental table 4.

Among people with chronic HCV, but with no cirrhosis, scenario 3 (no genotyping, and SOF/DCV for all) had the minimum cost; thus, it was chosen as the reference. Scenario 4 (no genotyping, and SOF/VEL for all) provided the highest LYs and QALYs but with higher costs than scenario 3. Compared with scenario 3, scenario 4 was cost-effective with an ICER of 4583 PPP dollars per QALY (table 2).

Among people with compensated cirrhosis and those with decompensated cirrhosis, scenario 4 (no genotyping, and SOF/VEL for all) resulted in gaining the most LYs and QALYs, and also had the lowest costs and was identified as cost-saving. Compared with other scenarios, scenario 4 saved between 449 and 940 PPP dollars per QALY among people with compensated cirrhosis, and saved between 79 and 151 PPP dollars per QALY among people with decompensated cirrhosis (table 2).

In total population, scenario 3 (no genotyping, and SOF/DCV for all) had the minimum cost. Compared with this scenario, scenario 4 (no genotyping, and SOF/VEL for all) had an ICER of 3786 PPP dollars per QALY and was identified as cost effective.

Among medical services required for individuals with HCV (other than HCV medications), the highest cost was associated with the laboratory tests (excluding HCV genotype), followed by imaging assessment (including elastography (Fibroscan) for liver fibrosis assessment). The lowest cost was the physician's consultation fees (online supplemental table 1 and 2).

Sensitivity analysis

A summary of one-way deterministic sensitivity analysis under scenario 3 has been presented as tornado diagrams (figure 2). At a willingness to pay threshold of 9311 PPP dollars per QALY, INMBs were sensitive to SVR of SOF/

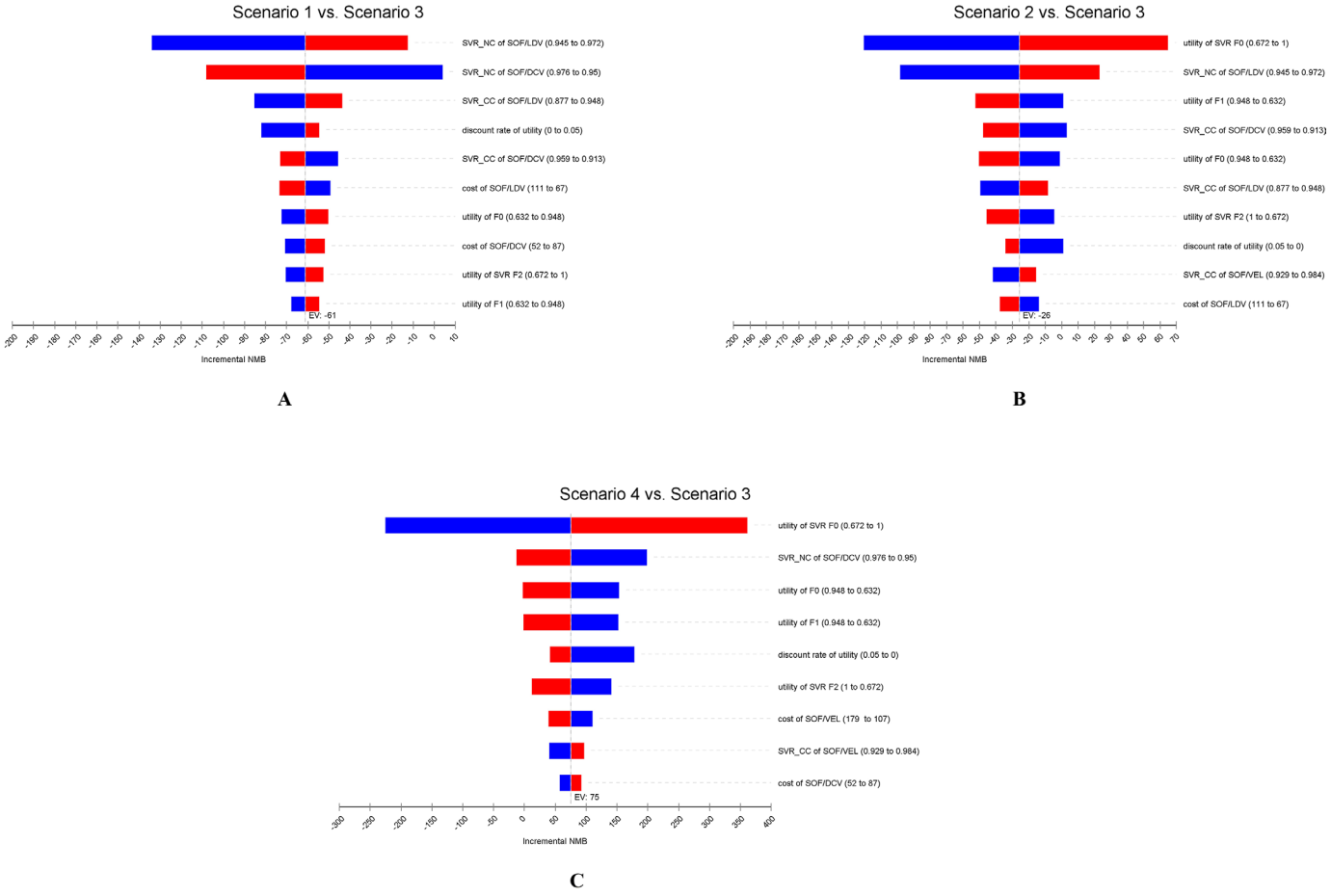

Figure 2 Tornado diagrams demonstrating the effects of the lower and upper values of each parameter on the incremental net monetary benefit of scenario 3 to other scenarios in total population: (A) scenario 1 versus scenario 3; (B) scenario 2 versus scenario 3; (C) scenario 4 versus scenario 3. Each bar shows the variation in INMB (blue colour: low value; red colour: high value). SOF/LDV, sofosbuvir/ledipasvir; SOF/DCV, sofosbuvir/daclatasvir; SOF/VEL, sofosbuvir/velpatasvir; NC, non-cirrhosis; CC, compensated cirrhosis; DCC, decompensated cirrhosis; SVR, sustained virological response; F0–F4, METAVIR fibrosis states; NBM, net monetary benefit.

LDV in people with no cirrhosis, SVR of SOF/DCV in people with no cirrhosis, SVR of SOF/DCV in people with compensated cirrhosis, and utility of people in F0 state after achieving SVR. In addition, when the cost of 12 weeks SOF/DCV increased to >122 PPP dollars (or the cost of 12 weeks SOF/VEL decreased to <89 PPP dollars), scenario 4 would become cost-saving.

Similar results were observed for the subgroup of people with no cirrhosis (online supplemental figure S1), among whom when the cost of 12 weeks SOF/DCV increased to >125 PPP dollars (or the cost of 12 weeks SOF/VEL decreased to <87 PPP dollars (39% reduction)), scenario 4 would become cost-saving. Among people with compensated cirrhosis, changing the parameters had no effects on the base-case results (online supplemental figure S2). However, in people with decompensated cirrhosis, INMBs were sensitive to the SVRs of SOF/LDV and SOF/VEL in people with compensated cirrhosis (at a willingness to pay threshold of 9,311 PPP dollars per QALY) (online supplemental figure S3).

The results of the probabilistic sensitivity analysis revealed that scenario 4 has the highest probability of being cost-effective when compared with the other scenarios (figure 3). Compared with other scenarios, scenario 4 was cost-effective in 47% of iterations in total population (figure 3A), 46% of iterations among people with no cirrhosis (figure 3B), 91% of iterations among people with compensated cirrhosis (figure 3C), and 69% of iterations among people with decompensated cirrhosis (figure 3D). This analysis also revealed that in total population and at a willingness to pay threshold of 9311 PPP dollars per QALY, the probability of scenarios 4, 2, 1, and 3 being cost-effective was 47%, 15%, 29% and 9%, respectively (figure 3A).

DISCUSSION

This study provided the cost-effectiveness data of various DAA treatment scenarios for people living with HCV, based on using available generic DAAs in Iran, as an example of a country with limited resources. The findings of this study demonstrated that among people with no cirrhosis, a scenario including no pretreatment genotyping and treating all patients with pan-genotypic

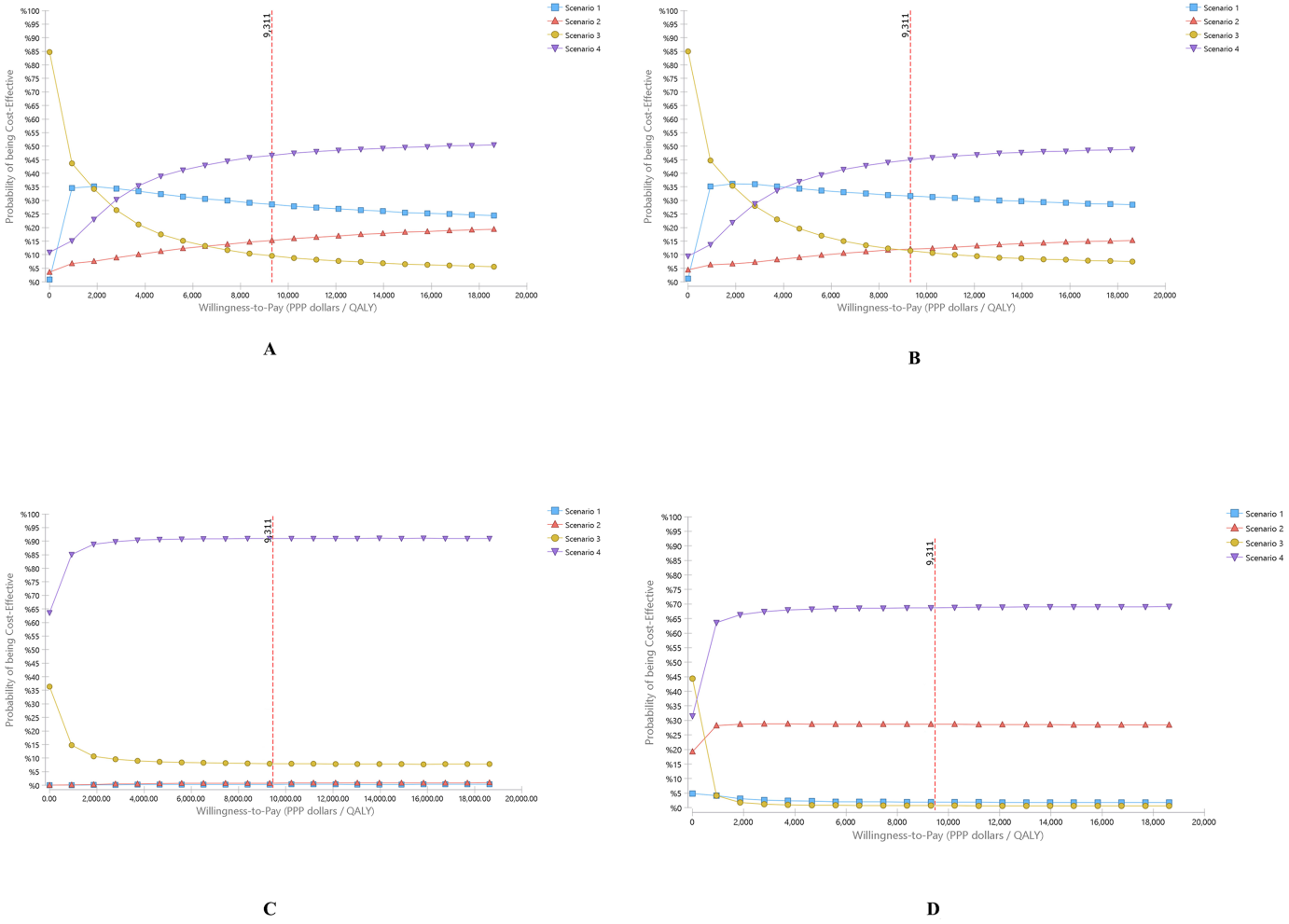

Figure 3 Acceptability curves comparing the cost-effectiveness of different scenarios. Each curve presents the relative cost-effectiveness of one scenario compared with other three scenarios as a function of the willingness to pay (WTP) threshold. For each WTP threshold, the curves use net benefits to determine the percentage of simulation iterations that favours each scenario, (A) in total population; (B) in subpopulation with no cirrhosis subgroup; (C) in subpopulation with compensated cirrhosis; (D) in subpopulation with decompensated cirrhosis. Scenario 1 assumes genotyping for all individuals, SOF/LDV treatment for genotype 1, and SOF/DCV treatment for genotype 3; scenario 2 assumes genotyping for all individuals, SOF/LDV treatment for genotype 1, and SOF/VEL treatment for genotype 3; scenario 3 assumes no genotyping and SOF/DCV treatment for all; scenario 4 assumes no genotyping and SOF/VEL treatment for all; QALY, quality-adjusted life-years; PPP, purchasing power parity; WTP, willingness to pay.

SOF/DCV had the minimum cost, while changing pan-genotypic DAA regimen to SOF/VEL was more costly but still cost-effective. Among people with cirrhosis, a scenario including no genotyping and treating all patients with SOF/VEL was cost-saving. These data can inform health policy for resource allocation for HCV treatment in Iran and other resource-limited settings.

Our findings demonstrated that treatment scenarios suggesting initiating all patients on pan-genotypic DAA regimens with no pretreatment HCV genotype tests were cost-effective (and even cost-saving in most scenarios and/or subpopulations) compared with scenarios requiring pretreatment HCV genotype tests. Other economical evaluations from low-income/middle-income countries have also demonstrated cost-effectiveness or cost-savings associated with using pan-genotypic DAA regimens and removing pretreatment genotyping among all individuals with HCV or those with cirrhosis.[34–36] A study by Goel *et al* in India identified that treatment of patients with pan-genotypic SOF/VEL compared with using genotype-dependent regimens (SOF/LDV for genotypes 1 and 4 and SOF/DCV for genotype 3) was cost-effective while it increased QALY by 0.44 and increased costs by $US 107.[35] In our study, using SOF/VEL compared with same comparison regimen in the Goel's study (scenario 1) was also cost-effective although it was associated with a QALY gain of 0.017 and a 16 PPP dollar increase in costs. The study by Goel *et al* also indicated a reduction in pretreatment clinical assessment costs from US$119 for genotype-dependent treatment scenario to US$44 for pan-genotypic treatment scenario.[35] This cost reduction of US$75 is basically the cost of HCV genotyping. In our study, the cost of genotyping test was 17 PPP dollars (~US$59), slightly cheaper than that in the Goel's study.

In another Indian study, compared with a scenario using SOF/DCV for patients with no cirrhosis and SOF/LDV and SOF/DCV (based on genotype) for those with cirrhosis, a scenario in which treatment regimen in patients with cirrhosis changed to SOF/VEL was cost saving.[36] Given the treatment scenarios in this study were different from those in our study, it would be difficult to compare the cost-effectiveness findings. However, the cost of 12-week SOF/VEL regimen in our study was 143 PPP dollars (~US$499), whereas it was US$187 in that study. It indicated that although the generic DAA was much cheaper than the originator products, the price was still different across countries which should be considered in comparative economic evaluation studies.

Apart from the additional cost associated with genotype testing, limited access to required testing facilities in several low-income/middle-income countries poses a further challenge for using genotype-specific treatments in these settings.[7] The WHO recommended using pan-genotypic DAA regimens to simplify the care pathway by removing pre-treatment genotyping.[37] Further simplifications of the care pathway have been also suggested to improve HCV treatment uptake, such as point-of-care HCV testing, serological tests for liver fibrosis assessment, and delivery of HCV treatment in primary care.[7 38]

Among two pan-genotypic regimens evaluated in this current study (ie, SOF/DCV and SOF/VEL), our findings indicated that SOF/DCV was associated with lower costs. The HCV clinical guideline developed by the European Association for the Study of the Liver (EASL) recommended SOF/VEL and glecaprevir and pibrentasvir (GLE/PIB) as the first-line treatment of choice.[9] However, they have also recommended SOF/DCV in the settings where other pan-genotypic regimens are not available or not affordable given high effectiveness and safety profile.[9] The findings of our study identified the economic benefits of this regimen as well, underpinning the EASL clinical recommendation for resource-limited countries.

Our study demonstrated that treatment of people with cirrhosis using SOF/VEL could provide higher QALYs and also save 449 to 79 PPP dollars per QALY compared with SOF/DCV treatment. Among individuals with no cirrhosis, SOF/DCV treatment had the lower cost although SOF/VEL treatment was still cost-effective. Further, our sensitivity analysis indicated that in individuals with no cirrhosis, treatment with SOF/VEL would become cost-saving if the cost of 12 weeks SOF/VEL decreased to less than 87 PPP dollars (39% reduction) or the cost of 12 weeks SOF/DCV increased to more than 125 PPP dollars. The latter is important to inform policy-making regarding resource allocation for HCV treatment in countries like Iran where several companies are manufacturing generic SOF/DCV with their products costing between 70 (used in our estimation) to 191 PPP dollars for a 12-week treatment course. It means that in the case of considering the SOF/DCV product cost at 191 PPP dollars (ie, 27 972 000 Iranian Rials and US$666), as the standard of care, the treatment scenario which includes SOF/VEL treatment for all would be cost-saving for all subpopulations regardless of cirrhosis status. These data can also inform the public health sector's and health insurance organisations' policies in Iran in selecting the most cost-effective treatment strategies for HCV.

In this study, the estimated costs of HCV treatment for people with no cirrhosis (as the subpopulation with the lowest treatment costs) was 70 PPP dollars for generic SOF/DCV and 143 PPP dollars for generic SOF/VEL. Although these costs are much lower than the originator products, it may not be still affordable for many patients given the purchasing power of the people who inject drugs as the main population at risk of HCV in Iran.[10] Government health insurance is available for a large majority of Iranian people, which reduces the out-of-pocket cost of HCV treatment by about 30%. However, most people who inject drugs are highly marginalised and in the lowest socioeconomic status levels and may not still afford the subsidised treatment cost. Pilot projects, using simplified HCV testing and treatment strategies, including free tests and medications, among marginalised people who inject drugs identified high treatment initiations of 70% to over 90%.[39–41] These data suggested that affordability of HCV testing and treatment, as a crucial factor in the HCV treatment uptake, should be re-evaluated considering the economic status and willingness to pay of the target population.

Our data identified that among medical services, other than HCV medications and HCV genotype, required for HCV clinical care, the laboratory tests, and medical imaging had the highest cost. For individuals with no cirrhosis, HCV RNA testing (26 PPP dollars) and liver elastography for liver fibrosis assessment (Fibroscan, 44 PPP dollars) were the most costly items among laboratory tests, and medical imaging services, respectively. Other methods such as HCV core antigen test and serological tests for liver fibrosis assessment have been demonstrated as reliable, and inexpensive alternative methods,[7 42 43] and can decrease the overall cost of HCV treatment. Our data can inform HCV public health management policies through identifying the areas where using cheaper quality services can make HCV clinical care more affordable, crucial for treatment scale-up and controlling HCV burden in Iran.

This study has some limitations. We used SVR estimates of Iranian generic SOF/DCV. However, given no available Iranian large studies evaluating the effectiveness of other DAA regimens, those SVR estimates were derived from international multicentre studies. For some regimens, small Iranian studies were available, indicating effectiveness consistent with originator regimens.[44] GLE/PIB, another pan-genotypic DAA regimen recommended by the HCV clinical guidelines,[9] and salvage DAA regimens used for individuals failing to achieve SVR with first-line DAA regimens (eg, sofosbuvir, velpatasvir, and voxilaprevir) were not included in this analysis given that generic products are not currently available

globally. Transition probabilities and utility values have been derived from studies conducted in other countries, due to the unavailability of Iranian-specific data. Among treatment scenarios, 'no treatment' was not considered as the status quo, given that all people living with HCV have been strongly recommended to be treated by DAA in HCV clinical guidelines.[9 21] Change in QALY and LY among four treatment strategies were small given the high efficacy of DAA treatment in general. Then, the cost of different scenarios was the main factors influencing the cost-effectiveness. We conducted a sensitivity analysis, considering a range of ±25% for cost change, to evaluate how it may have impacted the results.

In conclusion, our data demonstrated that initiating patients on generic pan-genotypic DAA regimens with no pre-treatment HCV genotype tests was cost-effective compared with scenarios requiring pretreatment HCV genotype tests while it was even cost-saving in most subgroup comparisons. Our data also demonstrated that among generic pan-genotypic DAA regimens, SOF/VEL was cost-effective, for people with no cirrhosis and cost-saving for those with cirrhosis although it would be cost-saving for all subpopulations if the price of SOF/VEL could be reduced by 39%. These results support the use of pan-genotypic regimens to simplify the care pathway and save resources, particularly important in resource-limited countries. These data can inform health policy-making, including in resources allocation.

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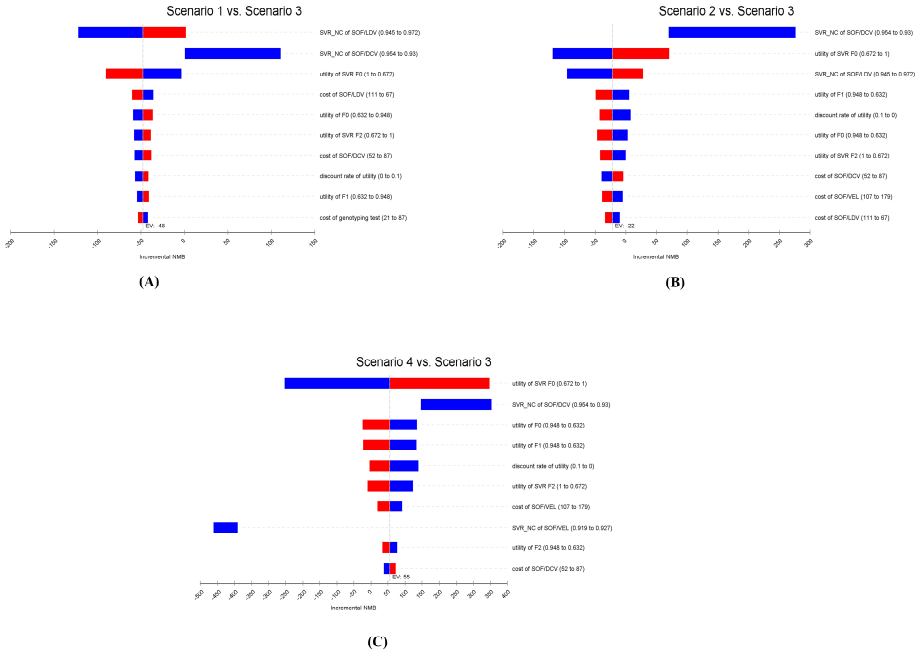
Supplementary Materials



Figures S1. Tornado diagrams demonstrating the effects of the lower and upper values of each parameter on the incremental net monetary benefit of scenario 3 to other scenarios in no cirrhosis subgroup: (A) scenario 1 vs. scenario 3; (B) scenario 2 vs. scenario 3; (C) scenario 4 vs. scenario 3. Each bar shows the variation in INMB (blue color: low value; red color: high value).

SOF/LDV, sofosbuvir/ledipasvir; SOF/DCV, sofosbuvir/daclatasvir; SOF/VEL, sofosbuvir/velpatasvir; NC, non-cirrhosis; CC, compensated cirrhosis; DCC, decompensated cirrhosis; SVR, sustained virologic response; F0–F4, METAVIR fibrosis states; NBM, net monetary benefit

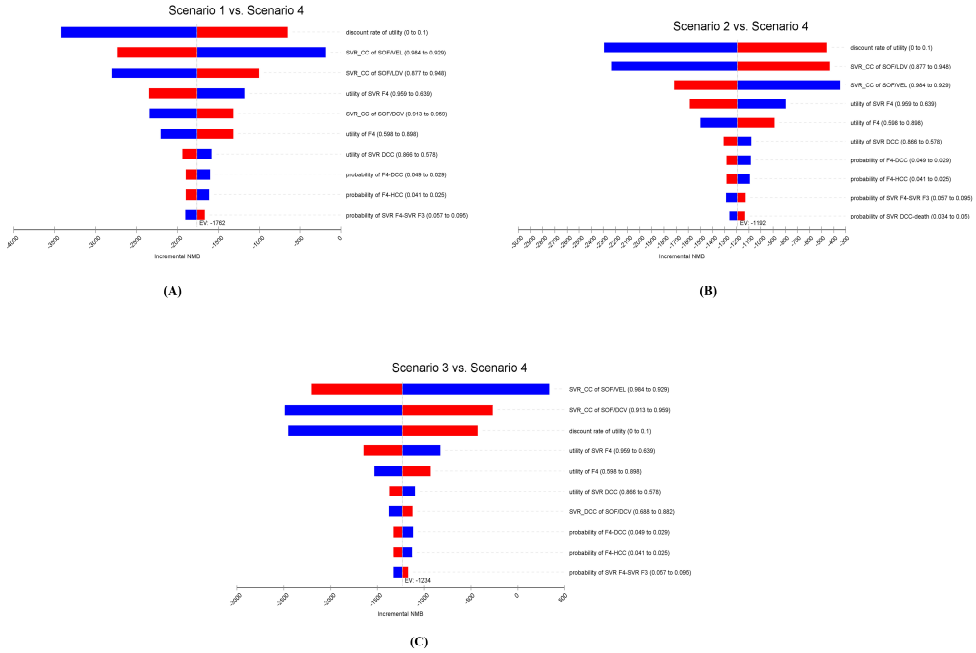


Figure S2. Tornado diagrams demonstrating the effects of the lower and upper values of each parameter on the incremental net monetary benefit of scenario 4 to other scenarios in cirrhosis subgroup: (A) scenario 1 vs. scenario 4; (B) scenario 2 vs. scenario 4; (C) scenario 3 vs. scenario 4. Each bar shows the variation in INMB (blue color: low value; red color: high value).

SOF/LDV, sofosbuvir/ledipasvir; SOF/DCV, sofosbuvir/daclatasvir; SOF/VEL, sofosbuvir/velpatasvir; NC, non-cirrhosis; CC, compensated cirrhosis; DCC, decompensated cirrhosis; SVR, sustained virologic response; F0–F4, METAVIR fibrosis states; NBM, net monetary benefit.

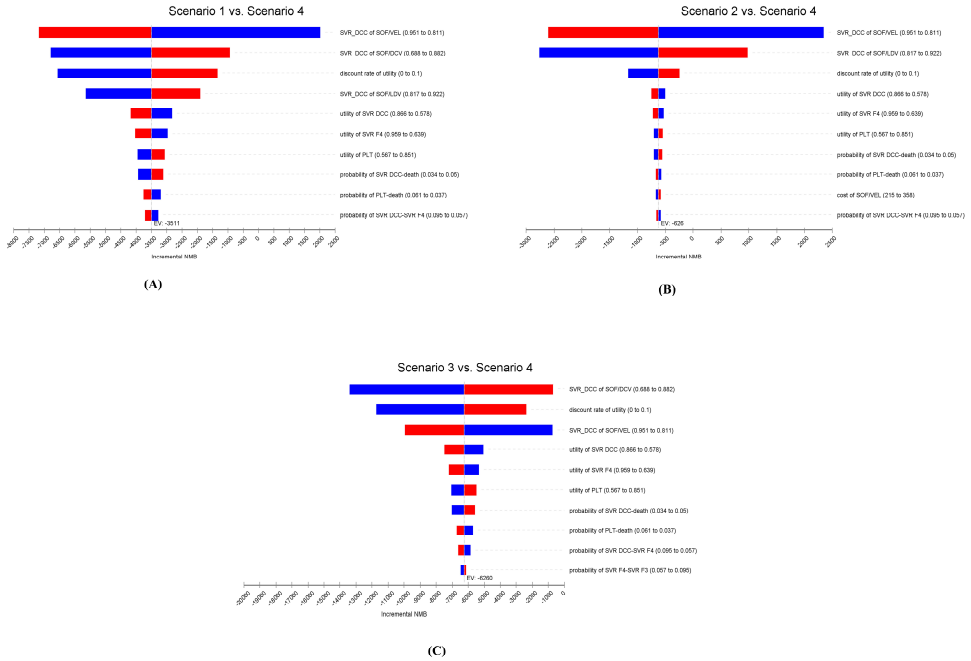


Figure S3. Tornado diagrams demonstrating the effects of the lower and upper values of each parameter on the incremental net monetary benefit of scenario 4 to other scenarios in decompensated cirrhosis subgroup: (A) scenario 1 vs. scenario 4; (B) scenario 2 vs. scenario 4; (C) scenario 3 vs. scenario 4. Each bar shows the variation in INMB (blue color: low value; red color: high value).

SOF/LDV, sofosbuvir/ledipasvir; SOF/DCV, sofosbuvir/daclatasvir; SOF/VEL, sofosbuvir/velpatasvir; NC, non-cirrhosis; CC, compensated cirrhosis; DCC, decompensated cirrhosis; SVR, sustained virologic response; F0–F4, METAVIR fibrosis states; NBM, net monetary benefit.

Supplementary Table 1. Costs of medical services, and frequency of use in each year required for hepatitis C clinical care, by liver disease stage

Visits	Cost per item (PPP dollars)	Frequency							
		No cirrhosis	CC	DCC	HCC	LT	Post-LT	CC SVR	DCC SVR
Physician's visit	1.53	3	3	6	6	-	3	3	6
Surgeon's visit	1.53	-	-	-	1	2	-	-	-
Hematologist	1.53	-	-	-	6	-	-	-	-
Psychiatrist	1.61	-	-	-	2	-	-	-	-
Radiologist	1.27	-	-	-	2	2	2	-	-
Tests									
HCV Genotyping	17.06	1	1	1	1	-	1	-	-
HCV RNA PCR	25.92	2	2	2	2	-	2	-	-
Blood Urea Nitrogen (BUN)	0.14	2	3	6	6	6	6	2	2
Creatinine (Cr)	0.17	2	3	6	6	6	6	2	2
Prothrombin Time (PT)	0.27	2	3	6	6	6	6	2	2
Total Bilirubin (Bili-T)	0.25	2	3	6	6	6	6	2	2
Direct Bilirubin (Bili-D)	0.25	2	3	6	6	6	6	2	2
Aspartate Aminotransferase (AST)	0.21	2	3	6	6	6	6	2	2
Alanine Aminotransferase (ALT)	0.21	2	3	6	6	6	6	2	2
Fasting Blood Sugar (FBS)	0.16	2	3	6	6	6	6	2	2
Triglycerides (TG)	0.20	2	3	6	6	6	6	2	2
Albumin	0.14	2	3	6	6	6	6	2	2
Alpha-Fetoprotein (αFP)	1.04	2	3	6	6	6	6	2	2
Uric Acid (U.A)	0.16	2	3	6	6	6	6	2	2
Cholesterol	0.17	2	3	6	6	6	6	2	2
low-density lipoprotein (LDL)	0.24	2	3	6	6	6	6	2	2
Calcium (Ca)	0.21	1	1	1	1	1	1	1	1
Potassium (P)	0.19	1	1	1	1	1	1	1	1
Thyroxine (T4)	0.53	2	3	3	3	3	3	2	2
White Blood Cell (WBC)	0.16	2	3	6	6	6	6	2	2
Thyroid stimulating hormone (TSH)	0.69	2	3	6	6	6	6	2	2
International normalized ratio (INR)	0.62	2	3	6	6	6	6	2	2
Alkaline Phosphatase (ALKp)	0.21	2	3	6	6	6	6	2	2
Hemoglobin (Hb)	0.07	2	3	6	6	6	6	2	2
Complete blood count (CBC)	0.28	2	3	6	6	6	6	2	2
Triiodothyronine (T3)	0.53	2	3	3	3	3	3	-	-
HCVAB	1.51	1	1	1	1	1	1	-	-
HIVAB	1.51	1	1	1	1	1	1	-	-
HBsAg	1.51	1	1	1	1	1	1	-	-
Radiology									
Abdominal ultrasound	3.70	1	2	2	4	4	4	2	2
Bone density	11.16	-	1	1	2	2	-	-	-
Endoscopy	11.84	-	-	-	2	2	2	-	-
Fibroscan	43.76	1	1	1	1	1	1	-	-
Angiography	48.83	-	-	-	4	4	-	-	-
Chest CT scan	6.22	-	-	-	1	1	1	-	-
Abdominal CT scan	10.37	-	-	-	3	3	-	-	-

CC, compensated cirrhosis; DCC, decompensated cirrhosis; SVR, sustained virologic response; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplantation; Post-LT; post-liver transplantation; SVR, sustained virologic response; SVR F4, patient in F4 states achieving SVR; SVR DCC, patient in DCC state achieving SVR; SOF/LDV, sofosbuvir/ledipasvir; SOF/DCV, sofosbuvir/daclatasvir; SOF/VEL, sofosbuvir/velpatasvir.

Supplementary Table 2. Annual cost (PPP dollars) of clinical care services and cost of each DAA treatment course (PPP dollars) for hepatitis C, by liver disease stage

Cost items	No cirrhosis	CC	DCC	HCC	LT	Post-LT	CC SVR	DCC SVR
Physician's visit	4.6	4.6	9.2	25.7	5.6	7.1	4.6	9.2
Tests	70.1	76.8	93.7	93.7	41.9	93.7	13.3	13.3
Radiology	47.5	62.3	62.3	337.2	337.2	88.5	7.4	7.4
Hospitalization	-	34.1	34.1	340.7	1363.5	-	-	136.4
HCV Genotyping test	17.1	17.1	17.1	17.1	-	17.1	-	-
Non-antiviral treatment	-	-	-	-	-	-	104.5	118.3
Treatment regimens								
SOF/LDV	88.8	177.5	177.5	177.5	-	177.5	-	-
SOF/DCV	69.9	139.7	139.7	139.7	-	139.7	-	-
SOF/VEL	143.2	143.2	286.3	143.2	-	143.2	-	-

Supplementary Table 3. Clinical management costs of hepatocellular carcinoma

Items	Approximate proportion of patients receiving this treatment	Cost (PPP dollars)	Cost per item (PPP dollars)
Radiofrequency ablation (RFA)	15%	920	138
Liver transplantation (LT)	5%	1363	68
Transcatheter arterial chemoembolization (TACE)	20%	2045	409
Medical	60%	4197	2518
Total	100%		3133

Supplementary Table 4. The cost-effectiveness of various scenarios considered for treatment of people with hepatitis C (ranges represent 95% confidence intervals (CIs) from the Monte Carlo simulation)

	Strategy	QALY (95%CI)	LY	Cost (PPP $) (95%CI)	ICER (PPP $/QALY) (95%CI)	
No cirrhosis	Scenario 3 (reference)	21.559 (21.483 to 21.636)	25.741	248 (245 to 252)	-	
	Scenario 1	21.542 (21.489 to 21.595)	25.741	282 (280 to 284)	-132 (-317 to 52)	Dominated
	Scenario 4	21.602 (21.522 to 21.683)	25.747	301 (300 to 302)	9,022 (2,434 to 15,610)	Cost-effective
	Scenario 2	21.571 (21.494 to 21.648)	25.744	305 (304 to 306)	-105 (-1,446 to 1,236)	Dominated
Compensated cirrhosis	Scenario 4 (reference)	15.932 (15.862 to 16.001)	20.982	3,718 (3,712 to 3,723)	-	
	Scenario 3	15.810 (15.742 to 15.878)	20.838	3,766 (3,757 to 3,774)	-59 (-1,305 to 1187)	Dominated
	Scenario 2	15.822 (15.755 to 15.890)	20.850	3,822 (3,816 to 3,827)	-1,148 (-1,401 to -895)	Dominated
	Scenario 1	15.767 (15.699 to 15.834)	20.784	3,846 (3,839 to 3,852)	-1,024 (-1,240 to -808)	Dominated
Decompensated cirrhosis	Scenario 4 (reference)	10.508 (10.455 to 10.561)	14.674	3,831 (3,822 to 3,840)	-	
	Scenario 3	9.913 (9.864 to 9.963)	14.593	3,856 (3,841 to 3,871)	-180 (-749 to 389)	Dominated
	Scenario 2	10.451 (10.399 to 10.502)	14.219	3,839 (3,830 to 3,847)	-250 (-362 to -139)	Dominated
	Scenario 1	10.177 (10.128 to 10.226)	13.861	3,856 (3,846 to 3,866)	-15 (-467 to 437)	Dominated
All patients	Scenario 3 (reference)	21.465 (21.387 to 21.544)	25.646	316 (313 to 320)	-	
	Scenario 1	21.460 (21.405 to 21.514)	25.644	354 (352 to 355)	-62 (-250 to 126)	Dominated
	Scenario 4	21.480 (21.400 to 21.559)	25.653	370 (360 to 371)	2,184 (-2,657 to 7,025)	Cost-effective
	Scenario 2	21.466 (21.412 to 21.521)	25.647	377 (376 to 378)	-522 (-1,578 to 535)	Dominated

Scenario 1 assumes genotyping for all individuals, SOF/LDV treatment for genotype 1, and SOF/DCV treatment for genotype 3; Scenario 2 assumes genotyping for all individuals, SOF/LDV treatment for genotype 1, and SOF/VEL treatment for genotype 3; Scenario 3 assumes no genotyping and SOF/DCV treatment for all; Scenario 4 assumes no genotyping and SOF/VEL treatment for all; QALY, quality-adjusted life-year; LY, life-year; CI, confidence interval.