Cost-Utility Analysis of Direct-Acting Antivirals for Treatment of Chronic Hepatitis C Genotype 1 and 6 in Vietnam

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ABSTRACT

Objective: Very few cost-utility analyses have either evaluated direct-acting antivirals (DAAs) on hepatitis C virus (HCV) genotype 6 patients or undertaken societal perspective. Recently, DAAs have been introduced into the Vietnamese health insurance drug list for chronic hepatitis C (CHC) treatment without empirical cost-effectiveness evidence. This study was conducted to generate these data on DAAs among CHC patients with genotypes 1 and 6 in Vietnam.

Methods: A hybrid decision-tree and Markov model was employed to compare costs and quality-adjusted life-years (QALYs) of available DAAs, including (1) sofosbuvir/ledipasvir, (2) sofosbuvir/velpatasvir, and (3) sofosbuvir plus daclatasvir, with pegylated-interferon plus ribavirin (PR). Primary data collection was conducted in Vietnam to identify costs and utility values. Incremental cost-effectiveness ratios were estimated from societal and payer perspectives. Uncertainty and scenario analyses and value of information analyses were performed.

Results: All DAAs were cost-saving as compared with PR in CHC patients with genotypes 1 and 6 in Vietnam, and sofosbuvir/velpatasvir was the most cost-saving regimen, from both societal and payer perspectives. From the societal perspective, DAAs were associated with the increment of quality-adjusted life-years by 1.33 to 1.35 and decrement of costs by $6519 to $7246. Uncertainty and scenario analyses confirmed the robustness of base-case results, whereas the value of information analyses suggested the need for further research on relative treatment efficacies among DAA regimens.

Conclusions: Allocating resources for DAA treatment for HCV genotype 1 and 6 is surely a rewarding public health investment in Vietnam. It is recommended that the government rapidly scale up treatment and enable financial accessibility for HCV patients.

Keywords: chronic hepatitis C, direct-acting antivirals, economic evaluation, genotype 6, Vietnam

Introduction

In Vietnam, an estimated 1%-2% of the total population is infected with hepatitis C virus (HCV)1-5 and there are 6 new HCV infections per 100 000 persons annually.6 In addition, Vietnam is also found to have the unique HCV genotype 6 as the most prevalent genotype, followed by HCV genotype 1, which together account for more than 85% of HCV infections.7-11 It should be noted that genotype 6, which is mainly found in Southeast Asia, and only accounts for 2% of HCV infections in the world, is relatively restricted in geographical extent.12,13

Since 2019, the Ministry of Health has implemented a new health insurance drug list, where direct-acting antiviral (DAA) regimens have been introduced for the first time. Three regimens were included: (1) sofosbuvir/ledipasvir (SOF/LDV), (2) sofosbuvir/velpatasvir (SOF/VEL), and (3) sofosbuvir plus daclatasvir (SOF+DCV), while also retaining the old standard of HCV treatment, pegylated-interferon plus ribavirin (PR).14 Nevertheless, there has been no empirical evidence on the cost-effectiveness of the newly included DAA regimens in the Vietnamese population. Although there have already been several cost-utility analyses (CUAs) of DAA regimens conducted, very few have evaluated DAA...
regimens on HCV genotype 6, been conducted in low- and middle-income countries (LMICs), or undertook a societal perspective, according to the results of recently published systematic reviews on CUAs of DAA regimens. This has posed a significant gap in knowledge on the adaptability of the new DAs. Therefore, this CUA was conducted on an HCV population genotype 1 and 6 in Vietnam, from both societal and payer perspectives. The cost-effective evidence generated by this study may inform policy makers in revising the drug list in the coming years and revising the HCV treatment guidelines. Moreover, this study may contribute to the global knowledge on the cost-effectiveness of DAA regimens, as being among the first CUAs of DAA regimens that considered HCV genotype 6 patients in an LMIC using a societal perspective.

Methods

Target Population

The model simulated cohorts of patients infected with HCV genotype 1 and 6 in Vietnam because these 2 genotypes are the most prevalent. The mean age of the HCV patients was assumed to be 50 years old, based on the results from recent surveys in Vietnam. The patients had no comorbidity and were at either non-cirrhotic chronic hepatitis C (CHC) or compensated cirrhosis (CC) health states—the 2 health states that are eligible for HCV antiviral treatment in Vietnam.

Model Structure

A hybrid of decision-tree and Markov models adapted from Kapol et al was applied, which was validated by clinical experts in Vietnam’s National Hospital of Tropical Diseases. Patients entered a decision tree at the initiation of treatment and were chosen to receive either DAA regimens or PR. Upon completion of each regimen, patients could move to 1 of corresponding 4 health states based on their status of sustained virologic response (SVR)—the indication of successful treatment. CHC and CC patients who achieved SVR were assumed to be cured, but CC patients could still progress to hepatocellular carcinoma (HCC), although at a slower rate, and patients who failed to achieve SVR would continue to progress over time. Therefore, all patients, except those who achieved SVR from CHC, moved to a discrete-time state-transition Markov model for natural disease progression (Fig. 1).

The Markov model was based on the natural history of hepatitis C, and the classification of health states was in line with the current treatment guidelines in Vietnam. There were 6 mutually exclusive health states, including an SVR state achieved after successful treatment of CC, 4 disease states (ie, CHC, CC, decompensated cirrhosis [DC], and HCC), and a dead state, which was liver-related death (LRD). The age-specific probabilities of all-cause mortality were applied to all health states, whereas only patients with DC and HCC would die from liver-related mortality. The model simulation ended when all patients in the cohort died (ie, reached 100 years old according to the latest life table of Vietnam). We assumed that patients who failed treatment were not re-treated, and all patients completely complied with the treatment.

Costs and health outcomes were estimated in a lifetime period with 1-year cycle length. A within-cycle correction method, the Simpson’s one-third rule correction method, was applied, as suggested by Elbash and Chhatwal. An annual discount rate of 3% was used for both costs and outcomes, as suggested by the World Health Organization. Costs were converted to Vietnamese Dong in the year 2019 using Vietnam’s consumer price index, then converted to US dollars using the exchange rate of $1.00 = 23143 Vietnamese Dong. The cost-effectiveness threshold of 1 gross domestic product (GDP) per capita of Vietnam ($2389) was used.

The model was designed and run in Microsoft Office Excel.

The CUA from a societal perspective estimated cost components such as direct medical and direct non-medical costs, including time cost associated with the treatment of patients and their caregivers (ie, informal care). The indirect costs (ie, morbidity cost and mortality cost) were excluded to avoid a double-counting issue in the CUA. Meanwhile, the analysis from a payer perspective only estimated direct medical cost covered by the payer in Vietnam—the Vietnam Social Security.

Interventions and Comparator

All DAA regimens in the current Vietnamese health insurance drug list, including SOF/LDV, SOF+DCV, and SOF/VEL, were...
compared with the old standard of HCV treatment (ie, PR). Recommendations of treatment regimens and durations were based on Vietnam’s current treatment guidelines.21,22

**Model Parameters**

The model considered the following input parameters, classified into 4 major groups: transition probabilities, treatment efficacy, costs, and utilities (Table 1).

**Transition probabilities**

The disease-related transition probabilities were obtained from Japan owing to the unavailability of data in Vietnam. Among Asian countries, Japan was found to have the most comprehensive set of transition probabilities estimated from their own population.26,27,37,38 To test the validity of these transition probabilities, cross-model validations were performed to compare the long-term disease progression predicted by this model against other published models. The age-specific probabilities of all-causes mortality were derived from the latest life table of Vietnam published by the Vietnam General Statistics Office in 2016.28

**Treatment efficacy**

Treatment efficacy of HCV antivirals was measured by the rate of SVR at the 12th week after stopping antivirals (SVR12). For HCV genotype 1, a systematic search of existing meta-analyses on the efficacy of DAA regimens in genotype 1 was performed, which identified 7 relevant meta-analyses.39-45 Individual trials were extracted from these meta-analyses by DAA regimens. For regimens that had only 1 meta-analysis (such as SOF/VEL), we used the result of that meta-analysis; meanwhile, for regimens that had more than 1 meta-analysis (such as SOF/LDV and SOF+DCV), we performed a new pooling and used our pooled result. Regarding HCV genotype 6, we conducted a meta-analysis to pool SVR12 from existing trials on DAA regimens in genotype 6.46 The treatment efficacy of PR was obtained from a published meta-analysis.47

**Costs**

Direct medical, direct non-medical, and time costs associated with treatment were obtained from primary data collection in Vietnam’s 2 central-level hospitals, Bach Mai Hospital and the National Hospital of Tropical Diseases, in 2019. Ethics approval for the study was granted by the Institutional Review Board of the Hanoi University of Public Health.50 Each patient participated in 1 interview, conducted when the patient was at the hospital for either outpatient or inpatient care due to their HCV-related complications.

**Utilities**

The health outcome of choice was quality-adjusted life-years (QALYs), which is the multiplication of life-years (LYs) by utility score. The utility of each health state was obtained from primary data collection using the EQ-5D-5L questionnaire29,30 in the aforementioned hospitals in 2019, and the EQ-5D-5L value set of Vietnam was applied.54 Permission from the EuroQOL group was granted for using the Vietnamese version of the questionnaire. Ethics approval for the study was granted by the Institutional Review Board of the Hanoi University of Public Health.50 Each patient participated in 1 interview, conducted when the patient was at the hospital for either outpatient or inpatient care due to their HCV-related complications.

**Result Presentation**

Total costs, LYs, and QALYs for each treatment were estimated in a lifetime period. In addition, lifetime cumulative incidence of HCV-related complications was calculated by cumulatively adding up the number of HCV-related complications from the first cycle to the last cycle in the model.

To estimate the cost-effectiveness of each regimen compared with PR, an incremental cost-effectiveness ratio, calculated by an incremental cost divided by an incremental LY or QALY, was estimated and compared with the cost-effectiveness threshold of 1 GDP per capita of Vietnam per QALY gained. Furthermore, the corresponding net monetary benefit (NMB) of all 3 DAA regimens was compared in order to rank their cost-effectiveness.

**Uncertainty Analysis**

**Parameter uncertainty**

To test the robustness of the base-case results, a deterministic 1-way sensitivity analysis was performed by stochastically varying 1 parameter at a time between its lower and upper limits, and the corresponding change of NMB was captured and shown graphically as a tornado diagram. Key parameters varied including discount rates (±3%), transition probabilities (±20%), treatment efficacies (because the SVR12s of DAAs were relatively high, their range for variation was purposely set between –20% and 100%), costs (±20%), utilities (95% confidence interval [CI]), and epidermolysis parameters (±20%).

In addition, to assess the impact of parameter uncertainty on the results, probabilistic sensitivity analyses were conducted by stochastically varying all key parameters simultaneously within their probability distribution. The Monte Carlo simulation was run in 1000 iterations, then shown graphically as a cost-effectiveness plane and a cost-effectiveness acceptability curve.

**Scenario analysis**

In the base-case CUA, the government’s co-payment rate for DAA regimens was set at 50%, according to current regulation.14 To examine the generalizability of the model, scenarios of different government’s copayment rates for DAA regimens (50%, 70%, 90%, and 100%) were also explored.

**Value of Information Analysis**

The study performed the value of information analysis in terms of total expected value of perfect information (EVPPI) and expected value of partial perfect information (EVPI) in order to estimate the expected value of further information to resolve the current uncertainty and to identify which type of information would be the most worthwhile.

The time horizon for estimating EVPI for population was set at 5 years, which was assumed to be the lifespan of these DAA regimens. The annual affected population was calculated by...
Table 1. Input parameters used in the model.

| Input parameters                | Mean    | Standard error | Distribution | Source   |
|--------------------------------|---------|----------------|--------------|----------|
| Transition probabilities       |         |                |              |          |
| From                           | To      |                |              |          |
| CHC                            | CC      | 0.019          | 0.005        | Beta     |
| CC                             | DC      | 0.056          | 0.014        | Beta     |
| HCC                            | DC      | 0.056          | 0.014        | Beta     |
| DC                             | HCC     | 0.056          | 0.014        | Beta     |
| LRD                            | HCC     | 0.056          | 0.014        | Beta     |
| HCC                            | LRD (year 1) | 0.118      | 0.030        | Beta     |
| LRD (from year 2)              |         | 0.222          | 0.056        | Beta     |
| SVR (CC)                       | HCC     | 0.018          | 0.005        | Beta     |
| Treatment efficacy (SVR12)     |         |                |              |          |
| Genotype 1                     |         |                |              |          |
| SOF/LDV                        | 0.980   | 0.008          | Beta         | Meta-analysis |
| SOF/VEL                        | 0.980   | 0.005          | Beta         | Meta-analysis |
| SOF+DCV                        | 0.990   | 0.020          | Beta         | Meta-analysis |
| PegIFN+RBV                     | 0.625   | 0.096          | Beta         |           |
| Genotype 6                     |         |                |              |          |
| SOF/LDV                        | 0.992   | 0.008          | Beta         |          |
| SOF/VEL                        | 1.000   |                | Beta         |          |
| SOF+DCV                        | 0.990   | 0.020          | Beta         |          |
| PegIFN+RBV                     | 0.802   | 0.027          | Beta         |          |
| Direct medical cost            |         |                |              |          |
| Drug cost                      |         |                |              |          |
| SOF/LDV (12-week)              | 1,384.4 | 276.9          | gamma        | Primary data |
| SOF/VEL (12-week)              | 1,739.7 | 347.9          | gamma        | Primary data |
| SOF+DCV (12-week)              | 1,733.0 | 346.6          | gamma        | Primary data |
| PegIFN (per week)              | 114.5   | 22.9           | gamma        | Primary data |
| RBV (per day)                  | 1.2     | 0.2            | gamma        | Primary data |
| Monitoring cost                |         |                |              |          |
| DAAs (12-week)                 | 355.6   | 71.1           | gamma        | Primary data |
| DAAs (24-week)                 | 360.4   | 72.1           | gamma        | Primary data |
| PegIFN+RBV (48-week)           | 525.3   | 105.1          | gamma        | Primary data |
| Cost of palliative care (per year) |      |                |              |          |
| CHC                            | 108.5   | 21.7           | gamma        | Primary data |
| CC                             | 598.7   | 119.7          | gamma        | Primary data |
| DC                             | 964.1   | 192.8          | gamma        | Primary data |
| HCC                            | 3,676.0 | 735.2          | gamma        | Primary data |
| Direct non-medical cost (per year) |      |                |              |          |
| For antiviral treatment        |         |                |              |          |
| CHC treated with DAAs          | 87.6    | 17.5           | gamma        | Primary data |
| CC treated with DAAs           | 268.1   | 53.6           | gamma        | Primary data |
| CHC/CC treated with PegIFN+RBV | 235.7   | 47.1           | gamma        | Primary data |
| For palliative care            |         |                |              |          |
| CHC                            | 174.1   | 34.8           | gamma        | Primary data |
| CC                             | 212.2   | 42.4           | gamma        | Primary data |
| DC                             | 364.5   | 72.9           | gamma        | Primary data |
| HCC                            | 334.2   | 66.8           | gamma        | Primary data |
| Time cost (per year)           |         |                |              |          |
| For antiviral treatment        |         |                |              |          |
| CHC treated with DAAs          | 129.2   | 25.8           | gamma        | Primary data |
| CC treated with DAAs           | 165.1   | 33.0           | gamma        | Primary data |
| CHC treated with PegIFN+RBV    | 129.2   | 25.8           | gamma        | Assumed   |
| CC treated with PegIFN+RBV     | 165.1   | 33.0           | gamma        | Assumed   |
| For palliative care            |         |                |              |          |
| CHC                            | 189.8   | 38.0           | gamma        | Primary data |
| CC                             | 201.6   | 40.3           | gamma        | Primary data |
| DC                             | 369.9   | 74.0           | gamma        | Primary data |

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multiplying the prevalent number of CHC and CC patients with genotypes 1 and 6, with the current diagnosis rate, treatment coverage, and proportion of eligible-to-treat population (Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.03.018). Consequently, the 5-year affected population, given the annual discount rate of 3%, was 3711 persons.

Both pairwise EVPI (each DAA compared with PR) and general EVPI (all DAAs and PR compared with each other) were estimated. The EVPI was estimated by different ceiling ratios, whereas the EVPPi used the ceiling ratios of 1 GDP per capita of Vietnam and was run by 100 outer loops and 100 inner loops.

### Results

#### Model Validation

In addition to face validation performed by clinical experts, our model’s predictions of HCV natural history were cross-validated with other published modeling studies (Fig. S1B in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.03.018). Regarding the cumulative incidence of CC (Fig. S1A), our study predicted a 20-year cumulative incidence of 29.018%. In addition to face validation performed by clinical experts, our predictions of HCV natural history were cross-validated with other published modeling studies (Fig. S1B in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.03.018).

The base-case cost-effectiveness analysis indicated that all DAA regimens dominated PR (ie, were less costly and more effective), based on both societal and payer perspectives (Table 2). From a societal perspective, compared with PR, treatments with DAA regimens in Vietnam’s HCV population genotypes 1 and 6 were associated with the increase of overall life expectancy by 0.65 to 0.66 years and the increment of discounted QALYs by 1.33 to 1.35 QALYs, whereas costs were significantly decreased by $6519 to $7246. In addition, the lifetime costs of DAA regimens and PR were further classified into intervention cost (ie, costs of drugs and treatment monitoring) and non-intervention cost (ie, costs of palliative care) and shown graphically, which demonstrated the lower values of both intervention and non-intervention costs of DAA regimens compared with PR (Fig. S2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.03.018).

Among 3 DAA regimens, SOF/VEL was associated with the lowest lifetime cost at $4055 per patient and was found to be the most efficacious at 15.09 QALYs. Furthermore, in order to directly compare the cost-effectiveness among the 3 DAA regimens, the corresponding NMB of all 3 DAA regimens was calculated, which showed that SOF/VEL was the most cost-effective regimen, followed by SOF/LDV as the second, and SOF+DCV as the third, from both perspectives (Table 2).

Different scenarios of government’s co-payment rates (50%-100%) were explored. In all scenarios, 3 DAAs remained cost-saving in comparison to PR, and SOF/VEL remained the most cost-effective regimen, regardless of the copayment rates, from both perspectives (Appendix Table 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.03.018).
Parameter Uncertainty

One-way deterministic sensitivity analysis was shown graphically as a tornado diagram (Fig. 2), which illustrated the parameters that most heavily influenced the incremental NMB (at the cost-effectiveness threshold of 1 GDP per capita of Vietnam) of the most cost-saving regimen (ie, SOF/VEL) compared to PR, from a societal perspective. The incremental NMB was always positive, which indicated that SOF/VEL always remained cost-effective at the threshold of 1 GDP per capita of Vietnam. In addition, the incremental NMB was most sensitive to the treatment efficacy of PR and SOF/VEL, the discount rates for outcome and cost, the distribution of HCV genotype 1 and 6 in Vietnam, and the utility values. Furthermore, discount rates for costs at 3%, QALY at 1.5%, and 1.5% for both QALY and costs were tested, which confirmed the base-case results (Appendix Table 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.03.018).

The probabilistic sensitivity analysis, performed from a societal perspective, confirmed the robustness of the base-case cost-effectiveness result, of which all DAA regimens dominated PR, and SOF/VEL was the most cost-saving regimen. Specifically, the cost-effectiveness plane showed the cost-saving result of DAA regimens in 100% of the 1000 simulations, whereas the cost-effectiveness acceptability curve indicated that at all willingness-to-pay thresholds, SOF/VEL always remained the most cost-effective regimen (Fig. 3).

Value of Information Analysis

The pairwise EVPI for population (each DAA regimen compared to PR) was zero at all willingness-to-pay values (Fig. 4), suggesting that the cost-saving results of any DAA regimen compared to PR were robust and not likely to change even under perfect information; therefore, further information might not be necessary in this case.

The general EVPI for population (3 DAA regimens and PR compared to each other) was $8.4 million at the willingness to pay of 1 GDP per capita of Vietnam (Fig. 4), corresponding to an individual EVPI of $480. The difference between pairwise EVPI and general EVPI implied that there were uncertainties among DAA regimens (but not between any DAA regimen versus PR), which were worthwhile to eliminate. As the willingness to pay increased, the EVPI become higher owing to the increment of NMB; however, no peak of EVPI curve could be observed, suggesting that the current cost-effectiveness ranking among DAA regimens was robust and not likely to change, even under the perfect information.

The 5-year general EVPPI at the willingness to pay of 1 GDP per capita of Vietnam was estimated on all major parameter groups, including DAAs’ treatment efficacy, direct medical cost, direct non-medical and time cost, transition probabilities, utilities, and epidemiology (Fig. 4). The uncertainties were observed in DAA efficacy and cost parameter groups, which suggested that if...

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Table 2. Cost-effectiveness of direct-acting antivirals compared with pegylated-interferon plus ribavirin for treatment of chronic hepatitis C virus genotypes 1 and 6 in Vietnam (US dollars, 2019).

| Parameter       | Societal perspective | Payer perspective |
|-----------------|----------------------|-------------------|
|                 | PR                   | SOF/LDV           | SOF/VEL           | SOF + DCV          |
| Discounted cost | 11 301               | 4430              | 4055              | 4782               |
| Discounted LYs  | 14.69                | 15.34             | 15.36             | 15.35              |
| Discounted QALYs| 13.74                | 15.06             | 15.09             | 15.08              |
| Incremental cost| –6870                | –7246             | –6519             |                   |
| Incremental LYs | 0.65                 | 0.66              | 0.66              |                   |
| Incremental QALYs| 1.33                 | 1.35              | 1.34              |                   |
| ICER per LY     | Dominant             | Dominant          | Dominant          |                   |
| ICER per QALY   | Dominant             | Dominant          | Dominant          |                   |
| NMB*            | 21 519               | 31 555            | 31 993            | 31 234             |
| Discounted cost | 4611                 | 2317              | 2101              | 2461               |
| Discounted LYs  | 14.69                | 15.34             | 15.36             | 15.35              |
| Discounted QALYs| 13.74                | 15.06             | 15.09             | 15.08              |
| Incremental cost| –2294                | –2509             | –2149             |                   |
| Incremental LYs | 0.65                 | 0.66              | 0.66              |                   |
| Incremental QALYs| 1.33                 | 1.35              | 1.34              |                   |
| ICER per LY     | Dominant             | Dominant          | Dominant          |                   |
| ICER per QALY   | Dominant             | Dominant          | Dominant          |                   |
| NMB*            | 28 209               | 33 669            | 33 947            | 33 555             |

DAA indicates direct-acting antiviral; DCV, daclatasvir; GDP, gross domestic product; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; LY, life-year; NMB, net monetary benefit; PR, pegylated-interferon plus ribavirin; SOF, sofosbuvir; VEL, velpatasvir; QALY, quality-adjusted life-year

*At cost-effectiveness threshold of 1 GDP per capita in Vietnam: $2389 per QALY gained

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further research is conducted, researchers should aim to obtain better data on relative treatment efficacy between DAA regimens or better cost estimation.

Discussion

In this study, the cost-effectiveness of all available DAA regimens in the Vietnamese health insurance drug list for HCV patients with genotypes 1 and 6 was assessed. All DAA regimens were associated with lower cost and higher effectiveness, thereby being cost-saving compared with PR, from both societal and payer perspectives. Our results may be particularly useful for countries with a high prevalence of HCV genotype 6, such as Laos (95.6%), Cambodia (56.0%), Myanmar (49.0%), and Thailand (21.8%).

The robustness of these findings was tested by performing extensive deterministic and probabilistic sensitivity analyses, which found that DAA prices in Vietnam were likely to change even under perfect information. Nevertheless, if policy makers demand more certain recommendation in terms of cost-effectiveness ranking among DAA regimens, further research to obtain better data on relative treatment efficacies among DAA regimens or better cost estimation might be worthwhile.

The cost-saving results of DAA regimens in Vietnam were mainly attributed to the significantly lower DAA prices in Vietnam compared with their original prices. The reduced prices were due to the result of voluntary license agreements signed by the originator companies, which allowed HCV patients to access generic DAA regimens. Currently, more than 100 countries around the world have benefited from the license agreements, including a majority of LMICs. Our study findings are in accordance with several studies conducted in Asian countries, including a study of Rattanavippong in Thailand, where SOF/LDV and SOF/DCV regimens were cost-saving compared with PR, and another study of Igarashi in Japan, where SOF/LDV was also found to be cost-saving compared with PR. Some other studies that compared DAA regimens to no treatment also reported the cost-saving result of DAA regimens, including a study of Aggarwal on SOF/LDV and SOF/VEL, and another study of Goel in India on SOF/VEL.

To meet the World Health Organization's goal of eliminating HCV as a public health threat by 2030, a rapid scale-up of DAA regimens is needed.
treatment is required. Nevertheless, despite demonstrating the cost-saving benefits for the society and payer in Vietnam, scale-up of DAA treatment in reality might depend on other factors, such as enabling financial accessibility for the HCV population, which is among the most important factors. In a study by Thu Nguyen et al\textsuperscript{68} that measured the willingness to pay of HCV patients for diagnosis tests and 12-week antiviral treatment, 54.6% of patients were not willing to pay more than $440. Meanwhile, our model

\textbf{Figure 3.} Probabilistic sensitivity analysis of DAA\textsuperscript{S} compared with pegylated-interferon plus ribavirin for treatment of chronic hepatitis C virus genotype 1 and 6 in Vietnam, under societal perspective (US dollars, 2019).

DAA indicates direct-acting antiviral; DCV, daclatasvir; GDP, gross domestic product; LDV, ledipasvir; PR, pegylated-interferon plus ribavirin; QALY, quality-adjusted life-year; SOF, sofosbuvir; VEL, velpatasvir.
estimated that the total cost for diagnosis tests and the 12-week DAA treatment was at least $980; in this case the DAA regimen used was the cheapest one (ie, SOF/LDV), the patient had health insurance (ie, the patient only needed to pay for 50% of DAA cost and an average of 20% of testing cost), and the health state was non-cirrhotic. Hence, the government should consider strategies to reduce patients’ out-of-pocket payments for DAA treatment. Several strategies might be considered, such as: (1) implementing further price-reduction strategies; (2) increasing the government’s copayment rate for DAA regimens, which currently is 50% (it should be noted that, DAA regimens are still cost-saving at 100% the government’s copayment rate, as demonstrated in the scenario analysis); or (3) seeking donor support.

**Limitations**

This study has several limitations. First, our model assumed that all patients complied with the treatment, although dropouts were likely to occur in reality, which may overestimate the benefits of DAA regimens. Second, we assumed that patients had no comorbidities, but in reality, comorbidities may be common at 50 years old; therefore, we may underestimate the benefits of DAA regimens. Third, we did not consider the benefits of HCV treatments in preventing transmissions in society; however, it is expected that the cost-effectiveness results of DAA regimens would be more favorable if this public health benefit were taken into account. Fourth, our model did not include liver transplantation as a health state because it was neither included in the health insurance package nor currently widely accessible in Vietnam. Lastly, owing to the unavailability of some epidemiological data in Vietnam, such as annual age-specific incidence and prevalence of HCV and its complications, in addition to the lack of longitudinal studies on HCV patients, we cannot perform the model calibration to fit actual data in the Vietnamese context. However, the results of all uncertainty analyses have confirmed the robustness of our cost-effectiveness results.

**Conclusions**

In conclusion, this study has demonstrated that all 3 DAA regimens in the Vietnamese health insurance drug list (ie, SOF/LDV, SOF+DCV, SOF/VEL) are cost-saving in HCV patients with genotypes 1 and 6 from both societal and payer perspectives; thus,
allocating resources for DAA treatment is surely a rewarding public health investment. Our results may be particularly useful for countries with a high prevalence of HCV genotype 6. Furthermore, because more current evidence suggesting that DAs might be effective for advanced-stage HCV patients, future studies in LMICs should investigate the cost-utility of DAs among patients at all disease stages.

In the DAs era, the elimination of HCV as a public health threat would be feasible, as illustrated by the evidence that we have presented, yet this could not be accomplished without seamless political commitments, a responsive health system, and strong public support.

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Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.vjal.2020.03.018.

REFERENCES

1. Nguyen TVT, Tran DQ, Nguyen TA, et al. Estimate and projection of disease burden and investment case for hepatitis C in Vietnam. J Viral Hepat. 2018;25(52):P2-065.
2. Gish RG, Bui TD, Nguyen CT, et al. Liver disease in Vietnam: screening, surveillance, management and education: a 5-year plan and call to action. J Gastroenterol Hepatol. 2012;27(2):238–247.
3. Kakumku S, Sato K, Morishita T, et al. Prevalence of hepatitis B, hepatitis C, and GB virus C/Hepatitis G virus infections in liver disease patients and inhabitants in Ho Chi Minh. Vietnam. J Med Virol. 1998;54:243–248.
4. Huy TTT, Hiroshi Quang XV, et al. Prevalence of hepatitis virus types B through E and genotypic distribution of HBV and HCV in Ho Chi Minh City, Vietnam. Hepatol Res. 2003;26:275–280.
5. Nguyen TVT, McLaws ML, Dore G. Prevalence and risk factors for hepatitis C infection in rural North Vietnam. Hepatol Int. 2007;1:387–393.
6. World Health Organization. Global Hepatitis Report 2017. Geneva, Switzerland: World Health Organization; 2017.
7. Pham DA, Leuangwutiwong P, Jittmittraphap A, et al. High prevalence of hepatitis C virus genotype 6 in Vietnam. Asian Pac J Allergy Immunol. 2011;29:153–160.
8. Van NP, Huyen DPN, Phat TH, et al. Very high prevalence of hepatitis C virus genotype 6 variants in southern Vietnam: Large-scale survey based on sequence determination. Jpn J Infect Dis. 2011;64(6):537–539.
9. Thy Th, Dat HT, Toan NB. The different incidences of HCV genotypes using two different regions of classification: 5’NC and NS5B in Vietnamese patients chronically infected with hepatitis C genotype 1b. Value Health Reg Issues. 2014;3:136–145.
10. Van NP, Dinh NT, Tuan GD, et al. Prevalence of hepatitis C virus genotypes in Vietnam. Asian Pac J Allergy Immunol. 2009;27:153–160.
11. Van NP, Huyen DPN, Phat TH, et al. Very high prevalence of hepatitis C virus genotype 6 variants in southern Vietnam: Large-scale survey based on sequence determination. Jpn J Infect Dis. 2011;64(6):537–539.
12. Dat HT, Thy Th, Tong NT, et al. Prevalence of HCV genotypes in Vietnam. Ho Chi Minh City J of Medicine. 2006;10(1):28–34.
13. Quang VM, Phong ND, Khiem DT. Epidemiological, clinical and paraclinical characteristics of viral hepatitis C patients treated at Ho Chi Minh City Hospital of Tropical Diseases in 2006–2007. Ho Chi Minh City J of Medicine. 2009;13(11):268–273.
14. Gower E, Estes C, Blach S, Razavi-Sharerv K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol. 2004;41(suppl 1):S4–S57.
15. Thrift AP, El-Serag HB, Kamal F. Global epidemiology and burden of HCV and HCV-related disease. Nat Rev Gastroenterol Hepatol. 2017;14:122–132.
16. Vietnam Ministry of Health. Promulgating the List of modern medicines, biologicals, radiopharmaceuticals and tracers covered by health insurance, insurance coverage ratio and payment conditions thereof. Circular No. 30/2018/TT-BYT. https://thuvienphapluat.vn/van-ban/Bao-hiem-Thong-tu-30-2018-TT-BYT.thanh-toan-thuoc-hoa-duoc-sinh-pham-cua-nguoi-tham-gia-bao-hiem-y-te-400126.aspx. Accessed July 10, 2020.
17. He T, Lopez-Olivo MA, Hur C, Chhatwal J. Systematic review: cost-effectiveness of direct-acting antivirals for treatment of hepatitis C genotypes 1 and 7. Aliment Pharmacol Ther. 2017;46(6):713–723.
18. Chhatwal J, He T, Lopez-Olivo MA. Systematic review of modelling approaches for the cost-effectiveness of hepatitis C treatment with direct-acting antivirals. Pharmacoeconomics. 2016;34(6):551–567.
19. Chhatwal J, He T, Hur C, Lopez-Olivo MA. Direct-acting antiviral agents for patients with hepatitis C virus genotype 1 infection are cost-saving. Clin Gastroenterol Hepatol. 2017;15(6):827–837, e828.
20. Puig-Junoy J, Pascual-Arregui N, Puig-Codina L, Planellas L, Solizobal M. Cost-utility analysis of second-generation direct-acting antivirals for hepatitis C: a systematic review. Expert Rev Gastroenterol Hepatol. 2018;12(12):1251–1263.
21. Do SH, Yamada H, Fujimoto M, et al. High prevalences of hepatitis B and C virus infections among adults living in Binh Thu An Province. Vietnam. Hepatol Res. 2015;45(3):259–268.
22. Ngoc CL, Thanh TT, Tan PTT, et al. Differential prevalence and geographic distribution of hepatitis C virus genotypes in acute and chronic hepatitis C patients in Vietnam. PLoS One. 2019;14(5):e0212734.
23. Van NP, Dinh NT, Tuan GD, et al. Prevalence of hepatitis C virus genotypes in Vietnam. Asian Pac J Allergy Immunol. 2011;29:153–160.
24. World Health Organization. The Treatment Guideline in Diagnosis and Treatment of Hepatitis C Decision No 4817/QĐ-BYT. https://thuvienphapluat.vn/van-ban/thanh-toan-thuoc-hoa-duoc-sinh-pham-cua-nguoi-tham-gia-bao-hiem-y-te-400126.aspx. Accessed July 10, 2020.
25. Vietnam Ministry of Health. The Treatment Guideline in Diagnosis and Treatment of Hepatitis C Decision No 5012/QĐ-BYT. https://thuvienphapluat.vn/van-ban/thanh-toan-thuoc-hoa-duoc-sinh-pham-cua-nguoi-tham-gia-bao-hiem-y-te-400126.aspx. Accessed July 10, 2020.
26. Vietnam Ministry of Health, Labour and Welfare, Japan. The Treatment Guideline in Diagnosis and Treatment of Hepatitis C Decision No 4817/QĐ-BYT. https://mhlw-grants.niph.go.jp/nih/index/NIDDD0007?reschNum=201333004A. Accessed July 10, 2020.
27. US Government. National Health Accounts, State Budget and Insurance. Statistical Yearbook of Vietnam. Hanoi, Vietnam: US Government. 2014;136–145.
28. Davis PJ, Rabinowitz P. Methods of Numerical Integration. 2nd ed. New York, NY: Academic Press; 1967.
29. Elbasha EH, Chhatwal J. Myths and misconceptions of within-cycle correction: a guide for modelers and decision makers. Pharmacoeconomics. 2016;34:13–22.
30. World Health Organization, Making Choices in Health: WHO Guide to Cost-Effectiveness Analysis. Geneva, Switzerland: World Health Organization; 2003.
31. Tống Duyen and Thọ. Vietnam: The Treatment Guideline in Diagnosis and Treatment of Hepatitis C. Decision No 5012/QĐ-BYT. https://thuvienphapluat.vn/van-ban/thanh-toan-thuoc-hoa-duoc-sinh-pham-cua-nguoi-tham-gia-bao-hiem-y-te-400126.aspx. Accessed July 10, 2020.
32. Davis PJ, Rabinowitz P. Methods of Numerical Integration. 2nd ed. New York, NY: Academic Press; 1967.
33. Elbasha EH, Chhatwal J. Myths and misconceptions of within-cycle correction: a guide for modelers and decision makers. Pharmacoeconomics. 2016;34:13–22.
34. World Health Organization, Making Choices in Health: WHO Guide to Cost-Effectiveness Analysis. Geneva, Switzerland: World Health Organization; 2003.
35. Tống Duyen and Thọ. Vietnam: The Treatment Guideline in Diagnosis and Treatment of Hepatitis C. Decision No 5012/QĐ-BYT. https://thuvienphapluat.vn/van-ban/thanh-toan-thuoc-hoa-duoc-sinh-pham-cua-nguoi-tham-gia-bao-hiem-y-te-400126.aspx. Accessed July 10, 2020.
Ahmed H, Abushouk AI, Menshawy A, et al. Meta-analysis of grazoprevir plus elbasvir for treatment of hepatitis C virus genotype 1 infection. *Ann Hepatol*. 2018;17(1):18–32.

Ahmed H, Elgebaly A, Abushouk AI, Hammad AM, Attia A, Negida A. Safety and efficacy of sofosbuvir plus ledipasvir with and without ribavirin for chronic HCV genotype-1 infection: a systematic review and meta-analysis. *Antivir Ther*. 2017;22(5):369–379.

Ji F, Wei B, Yeo YH, et al. Systematic review with meta-analysis: effectiveness and tolerability of interferon-free direct-acting antiviral regimens for chronic hepatitis C genotype 1 in routine clinical practice in Asia. *Aliment Pharmacol Ther*. 2018;47(5):550–562.

Kowdley KV, Sundaram V, Jeon CY, et al. Eight weeks of ledipasvir/sofosbuvir for treatment of hepatitis C virus genotype 1 chronic hepatitis C in routine clinical practice in Asia. *Aliment Pharmacol Ther*. 2018;47(5):550–562.

Mai VQ, Minh HV, Sun S, et al. An EQ-5D-5L value set for Vietnam. *Qual Life Res*. 2017;26(7):1881–1886.

van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA*. 2012;308(24):2584–2593.

Bennett W, Inoue Y, Beck J, Wong J, Pauker S, Davis G. Estimates of the cost-effectiveness of a single course of interferon-α 2b in patients with histologically mild chronic hepatitis C. *Ann Intern Med*. 1997;127(10):855–865.

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(6):973–986.

Chhatwal J, Kanwal F, Roberts MS, Dunn MA. Cost-effectiveness and budget impact of hepatitis C virus treatment with sofosbuvir and ledipasvir in the United States. *Ann Intern Med*. 2015;162(6):457–466.

Petta S, Cabibbo G, Enea M, et al. Cost-effectiveness of sofosbuvir-based triple therapy for untreated patients with genotype 1 chronic hepatitis C. *Hepatology* (Baltimore, Md). 2014;59(5):1695–1705.

Siebert U, Sroczyński G, Rossol S, et al. Cost-effectiveness of peginterferon α-2b plus ribavirin versus interferon α-2b plus ribavirin for initial treatment of chronic hepatitis C. *Gut*. 2003;52(3):425–432.

World Health Organization. *Progress Report on Access to Hepatitis C Treatment: Focus on Overcoming Barriers in Low- and Middle-Income Countries*. Geneva, Switzerland: World Health Organization; 2018.

Rattanavipapong W, Anothaisintawee T, Teerawattananon Y. Revisiting policy on chronic HCV treatment under the Thai Universal Health Coverage: An economic evaluation and benefit impact analysis. *PLoS One*. 2018;13(2):e0193112. https://doi.org/10.1371/journal.pone.0193112.

Igarashi A, Tang W, Guerra I, Marié L, Cure S, Lopresti M. Cost–utility analysis of ledipasvir/sofosbuvir for the treatment of genotype 1 chronic hepatitis C in Japan. *Curr Med Res Opin*. 2017;33(1):11–21.

Aggarwal R, Chen Q, Goel A, et al. Cost-effectiveness of hepatitis C treatment using generic direct-acting antivirals available in India. *PLoS One*. 2017;(5):12. e0176503.

Aggarwal R, Chen Q, Chhatwal J, Aggarwal R. Cost-effectiveness of generic pan-genotypic sofosbuvir/velpatasvir versus genotype-dependent direct-acting antivirals for hepatitis C treatment. *J Clin Exp Hepatol*. 2018;33:2029–2036.

Kamp WM, Sellers CM, Stein S, Lim JK, Kim HS. Impact of direct acting antivirals on survival in patients with chronic hepatitis C and hepatocellular carcinoma. *Sci Rep*. 2019;9(1):17081.