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Budget impact and cost-effectiveness analyses of direct-acting antivirals for chronic hepatitis C virus infection in Hong Kong

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Abstract

The purpose of this investigation was to evaluate the budget impact and cost-effectiveness of direct-acting antivirals (DAAs) for the treatment of hepatitis C virus (HCV) infection in Hong Kong. A decision analytic model was developed to compare short-term costs and health outcomes of patients with chronic HCV genotype 1 infection in Hong Kong who were treated with an interferon (INF)-based treatment (dual therapy of pegylated interferon and ribavirin) or DAA-based treatments (sofosbuvir or ledipasvir/sofosbuvir or ombitasvir/paritaprevir/ritonavir ~~and~~ plus dasabuvir). Compared to INF-based

treatment, DAA-based treatments yielded an incremental cost of $24,677–$31,171 per course while improving the rate of sustained virologic response (SVR) from 59–66% to 82.3–99.8%. The incremental cost-effective ratios of DAA-based treatments ranged from $9724 to $29,189 per treatment success, which were all below the cost-effectiveness threshold of local GDP per capita ($42,423 in 2015). Introducing DAAs resulted in a 126.1% ($383.7 million) budget increase on HCV infection management over 5 years. A 50% change in DAA medication costs reflected a change in the incremental budget from $55.2 to $712.3 million. DAA-based treatments are cost-effective alternatives to INF-based treatment in Hong Kong. Introducing DAAs to the public hospital formulary yields a considerable budget increase but is still economically favorable to the local government.

Electronic supplementary material

The online version of this article (doi: 10.1007/s10096-017-2995-7) contains supplementary material, which is available to authorized users.

Introduction

Globally, 2–3% of the population is infected with hepatitis C virus (HCV) and 55–85% become chronic infections with increased morbidity and mortality [1]. Approximately 700,000 deaths were attributed to chronic HCV infection each year in 1990–2010 [2], most of which were caused by persistent HCV infection resulting in liver cirrhosis and hepatocellular carcinoma [3, 4]. Chronic HCV infection-related economic burden is also considerable. In the USA, the average lifetime cost of an individual with chronic HCV infection was estimated at $64,490 in 2011, which was 130% of the GDP per capita; the associated total healthcare costs were estimated to be $6.5 billion during the same year and expected to peak at $9.1 billion in 2024 [5].

As no vaccine is currently available for HCV infection, the infection control is largely dependent on antiviral medications. The standard treatment for HCV infection has undergone a remarkable transformation in recent years from parenteral indirect-acting therapy with ~50% treatment success along with frequent adverse events to oral direct-acting antivirals (DAAs) with greatly improved efficacy, safety, and tolerability profiles and shortened treatment

durations [6, 7, 8].

In Hong Kong, several DAAs have been approved by the Drug Office as alternatives to interferon (INF)-based treatment, but only a few DAAs were listed in the public hospital formulary. In addition to safety and efficacy, pharmacoeconomic evaluations including cost-effectiveness and budget impact are among the three principle considerations for drug listing and subsidization by the government [9, 10]. Despite the cost-effectiveness of DAAs having been well established in overseas studies [11, 12, 13, 14, 15, 16, 17, 18], the conclusions were largely subject to patient profiles and local economic factors. The demonstration of their potential cost and health benefits to the local Hong Kong population remains limited. The primary objective of this study is to evaluate the 5-year budget impact of introducing DAAs for HCV treatments to the public hospital formulary to assess the government affordability. A short-term cost-effectiveness evaluation of DAA-based treatments compared to INF-based treatment was also conducted to assist shared decision-making from ~~pervasive~~key stakeholders.

Methods

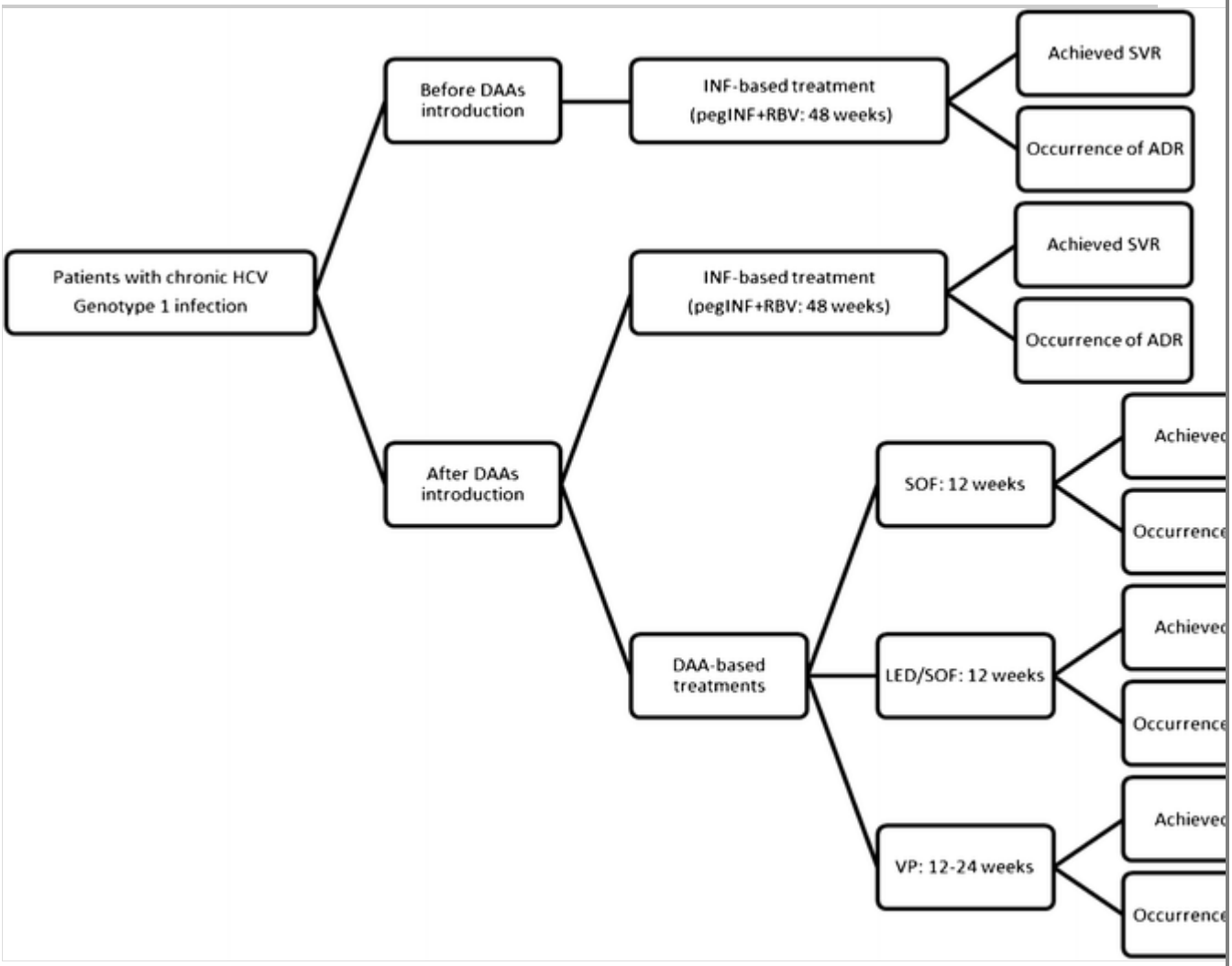
Model overview

A decision analytic model was developed using Microsoft Excel (2010) with the model framework recommended by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guideline for cost-effectiveness and budget impact analyses (Fig. 1) [19]. The model was applied to simulate short-term health outcomes of chronic HCV infection during the treatment period and estimate the cost incurred from medication, clinical management, and adverse drug reactions (ADRs). Target patients were assigned to receive INF- or DAA-based treatments according to the market share of each treatment option. The total cost per treatment success and government healthcare expenditure over 5 years were estimated to assess the cost-effectiveness of DAA-based treatments and the budget impact of introducing DAAs to the formulary. Key elements and assumptions of the model are detailed in Supplemental Table 1.

Fig. 1

Decision analytical model structure. *ADR* Adverse drug reaction; *DAAs* direct-

acting antivirals; *INF* interferon; *LED/SOF* ledipasvir/sofosbuvir; *pegINF* pegylated interferon; *SOF* sofosbuvir; *SVR* sustained virologic response; *RBV* ribavirin; *VP* ombitasvir/paritaprevir/ritonavir ~~and~~plus dasabuvir



Competing alternatives

Competing alternatives were INF-based treatment versus available DAA-based treatments in Hong Kong for patients with HCV genotype 1 (including genotypes 1a and 1b) infection (Table 1). The INF-based treatment was dual therapy of pegylated interferon (pegIFN, PEGasys®) and ribavirin (RBV, Copegus®). DAA-based treatments included three options from the second-generation DAAs: sofosbuvir (SOF, Sovaldi®), ledipasvir/sofosbuvir (LED/SOF, Harvoni®), and ombitasvir/paritaprevir/ritonavir ~~and~~plus dasabuvir (VP, Viekira Pak®). All DAAs may be prescribed as a single drug or in combination with pegIFN and RBV, depending on the patient treatment history and cirrhotic conditions.

Treatment regimens settings in the model (Supplemental Table 2) were based on the recommendations for testing, managing, and treating hepatitis C from the American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) [20].

Table 1

Treatments for hepatitis C virus (HCV) infection (genotypes 1a and 1b)

	Dosage	Route	Dosage regimen	Treatment duration (weeks)
INF-based treatment				
Pegylated interferon (pegIFN)	180 μg	Subcutaneous injection	Once a week	48
+ Ribavirin (RBV)	800–1200 mg	Oral	Twice daily	
DAA-based treatments				
Sofosbuvir (SOF)	400 mg	Oral	Once daily	12
Ledipasvir/sofosbuvir (LED/SOF)	90/400 mg	Oral	Once daily	12
Ombitasvir/paritaprevir /ritonavir ~~and~~ plus dasabuvir (VP, Viekira Pak®)	25/150/100 mg 250 mg	Oral Oral	Once daily Twice daily	12–24

DAA Direct-acting antivirals; *INF* interferon

Analytical perspective, time horizon, and discounting

The analysis was conducted from a public institutional perspective of Hong Kong with relevant direct medical costs considered. The analytical time horizon was 5 years and all costs were discounted at 4% per year given the typical range of 3–5% in the health economic literature [21]. Costs are presented as the value in US dollars in 2015 (1 US dollar to 7.76 HK dollars).

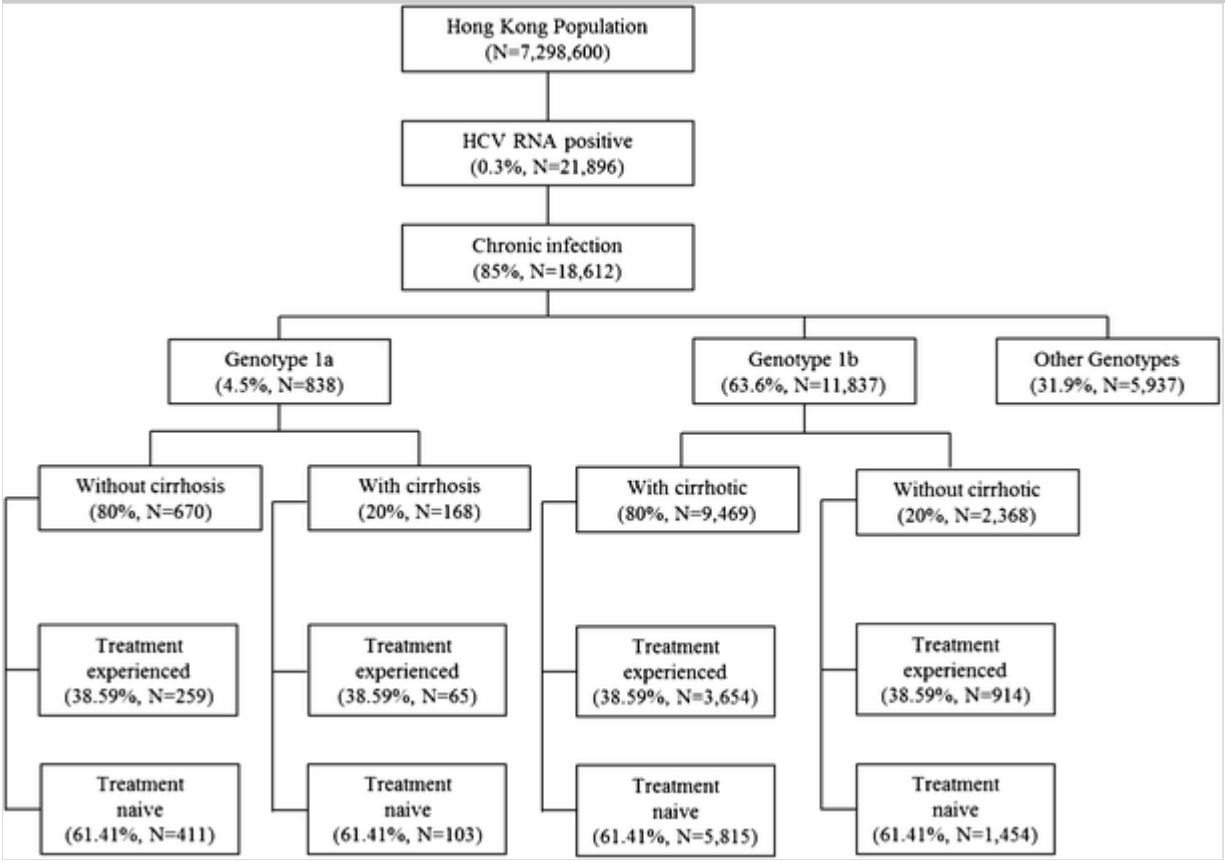
Target population

This study focused on patients with chronic HCV genotype 1 infection, which

accounted for approximately 70% of the overall HCV chronic infections in Hong Kong [22]. It was assumed all HCV-positive individuals were treated and that treatment was only required once. Therefore, all prevalent cases in year one of the study were treated and then all incident cases were treated in each subsequent year for the remainder of the study period. Target population identification is illustrated in Fig. 2. Treatment regimens depended on HCV genotype (1a or 1b), cirrhosis condition (with or without cirrhosis), and treatment history (treatment-naïve or treatment-experienced), resulting in patients being categorized into eight groups and analyzed separately.

Fig. 2

Flow and sources for target population identification



Epidemiological and clinical inputs

Epidemiological and clinical inputs of the decision analytical model are summarized in Supplemental Table 3. Approximately 0.3% (n = 21,869) of the population in Hong Kong was HCV-positive, with an average of 563 new cases diagnosed annually from 2004 to 2014 [23].Correspondingly, the number of

patients treated in year 1 and the subsequent 4 years were set to be 12,675 and 330 in the model according to the proportion of chronic genotype 1 infections in Hong Kong [22]. Treatment-naïve (TN) was defined as patients who had never received any treatment for HCV infection. Treatment-experienced (TE) was defined as patients who had received IFN-based therapy but failed to achieve sustained virologic response (SVR) after completion of the treatment [24]. The proportion of TE patients was adopted from two local hospital-based longitudinal studies, while the rates of SVR and incidences of ADR for each treatment were based on relevant international landmark trials (data sources detailed in Supplemental Table 3 and Supplemental References).

Economic inputs

Key economic inputs of the model are summarized in Supplemental Table 4. Medication cost was calculated by multiplying the wholesale acquisition cost of drugs by the corresponding treatment duration. In the absence of local drug price information, wholesale acquisition costs were estimated by multiplying HCV drug prices in the UK with the drug price ratio between HK and the UK. It was estimated that the UK:HK price ratio of oral anticoagulants was 0.89 in the previous study of our research group (data not published), which was used for the estimation of HCV treatment costs in this study.

Clinical management cost was calculated by multiplying outpatient charges for specialist clinic (SOPC) attendance by the clinical visit frequency for treatment and the control of ADRs. Only common ADRs managed in the SOPC were considered. Serious ADRs that needed inpatient treatment were not included given the rare incidence observed in clinical trials. Under the public healthcare system of Hong Kong, the charge for medical attendance in the SOPC covers the costs of prescriptions, pathology investigations, radiology, and other examinations; therefore, it was considered as the overall estimation of clinical management cost [25]. The frequency of clinical visits required for receiving the treatment and managing the ADRs was based on the AASLD/IDSA guideline and a previous budget impact study~~, respectively~~ [20, 26].

Before the introduction of DAAs, INF-based treatment accounted for 100% of the market share. After the introduction, the market shares for each DAA in years 1 and 2 of the study were referenced from US prescription volume data,

considering similar timing and drug approval policy as that in Hong Kong. However, the market shares in the 3rd to 5th years were assumed in this study, as market data were not available at the time of the study.

Outcomes

In the cost-effectiveness analysis (CEA), outcomes included total treatment costs, incremental rate of SVR, and incremental cost-effectiveness ratio (ICER), defined as the incremental cost per treatment success for each individual. Treatment with ICER less than one local GDP per capita ($42,423 in 2015) was considered cost-effective. In the budget impact analysis (BIA), changes of government healthcare expenditure on HCV infection management before and after the introduction of DAAs were assessed.

Analyses

The analyses were performed under the best scenario assuming that all target patients received one of the treatments and no occurrence of premature treatment discontinuation or switch. The effect of uncertainties on the base-case results was evaluated by one-way sensitivity analysis (SA). The clinical parameter [proportion of TE patients (20–60%)] and economic parameters [medication cost of DAAs (±50%) and market share of all treatments (±5%)] were tested under the predefined ranges to evaluate the robustness of results. All tested parameters were ranked according to the descending order of variation in base-case results and presented in tornado diagrams. Model inputs were entered, cross-checked, and analyzed independently by two authors (XL and NSC).

Results

Cost-effectiveness analysis

The cost-effectiveness of DAA-based treatments against INF-based treatment is shown in Table 2. As the major cost component, medication costs accounted for over 60% and 95% of the total treatment costs for INF and DAA-based treatments, respectively. In general , DAA-based treatments cost 2.1–2.4 times as much as INF-based treatment, regardless of patient cirrhosis condition or treatment history. Among the three DAA-based treatments, the incremental cost by descending order was LED/SOF ($29,734–$31,171), SOF ($29,380), and VP ($24,677–$27,794).

Table 2

Cost-effectiveness analysis (CEA) of INF-based versus DAA-based treatments by treatment

Patient type	Treatments	Medication cost ($)	Management cost ($)	Total cost ($)	Incremental cost ($)	
Treatment-naïve without cirrhosis	pegIFN and RBV	13,477	8215	21,692	Reference	
	SOF	48,656	2416	51,072	29,380	
	LED/SOF	50,460	966	51,426	29,734	
	VP	45,403	966	46,369	24,677	
Treatment-naïve with cirrhosis	pegIFN and RBV	13,477	8215	21,692	Reference	
	SOF	48,656	2416	51,072	29,380	
	LED/SOF	50,460	966	51,426	29,734	
	VP	48,488	998	49,486	27,794	
Treatment-experienced without cirrhosis	pegIFN and RBV	13,477	8215	21,692	Reference	
	SOF	48,656	2416	51,072	29,380	
	LED/SOF	50,460	966	51,426	29,734	
	VP	45,403	966	46,369	24,677	
Treatment-experienced with cirrhosis	pegIFN and RBV	13,477	8215	21,692	Reference	
	SOF	48,656	2416	51,072	29,380	
	LED/SOF	51,897	966	52,863	31,171	
	VP	48,488	998	49,486	27,794	

ICER Incremental cost-effectiveness ratio, defined as incremental cost per treatment succ

[a]Cost per treatment success = total treatment cost/SVR

Compared to INF-based treatment, all DAA-based treatments yielded improved treatment success with an incremental rate of SVR between 16.3 and 40.7%. The cost per treatment success for INF-based treatment ranged from $32,867 to

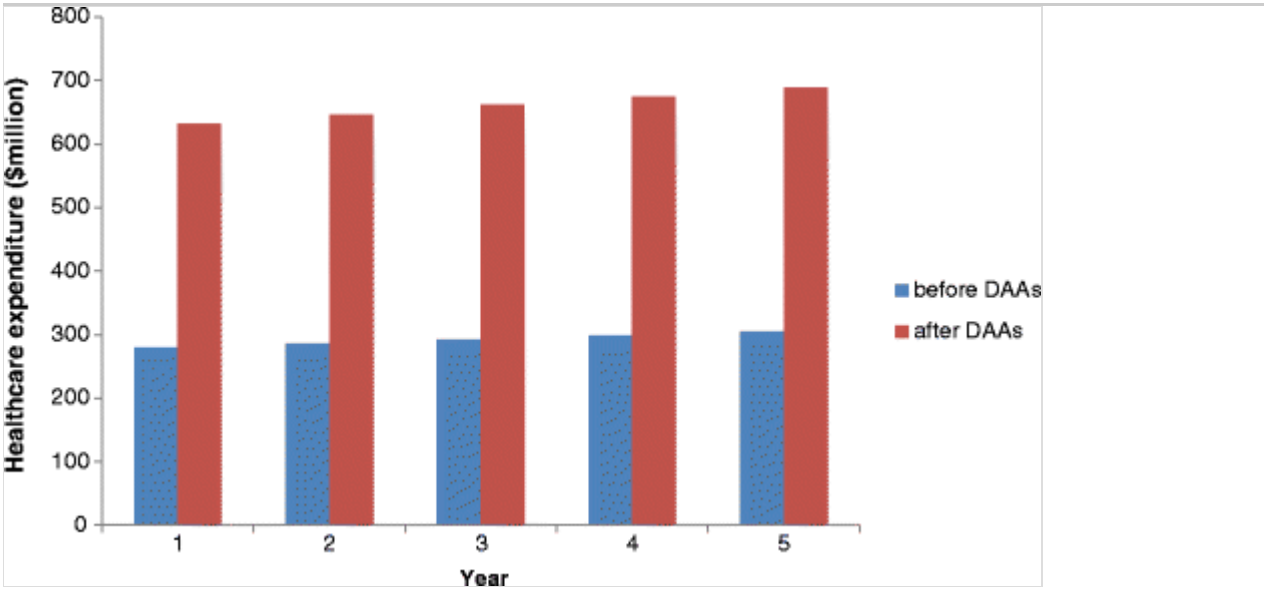
$36,767, with corresponding costs for DAA-based treatments increasing by 1.5–1.9-fold. Using INF-based treatment as the reference group, the ICERs of DAA-based treatments ranged from $9742 to $29,189 per treatment success, which were all below the predefined cost-effectiveness threshold.

Budget impact analysis

Government healthcare expenditure on HCV infection management was estimated to increase steadily from $280.0 to $304.4 million in 5 years if INF-based treatment was the only option. Introducing DAAs to the formulary was associated with a 126.1% ($383.7 million) increase in budget, with a maximum healthcare expenditure of $688.1 million at year 5 (Fig. 3).

Fig. 3

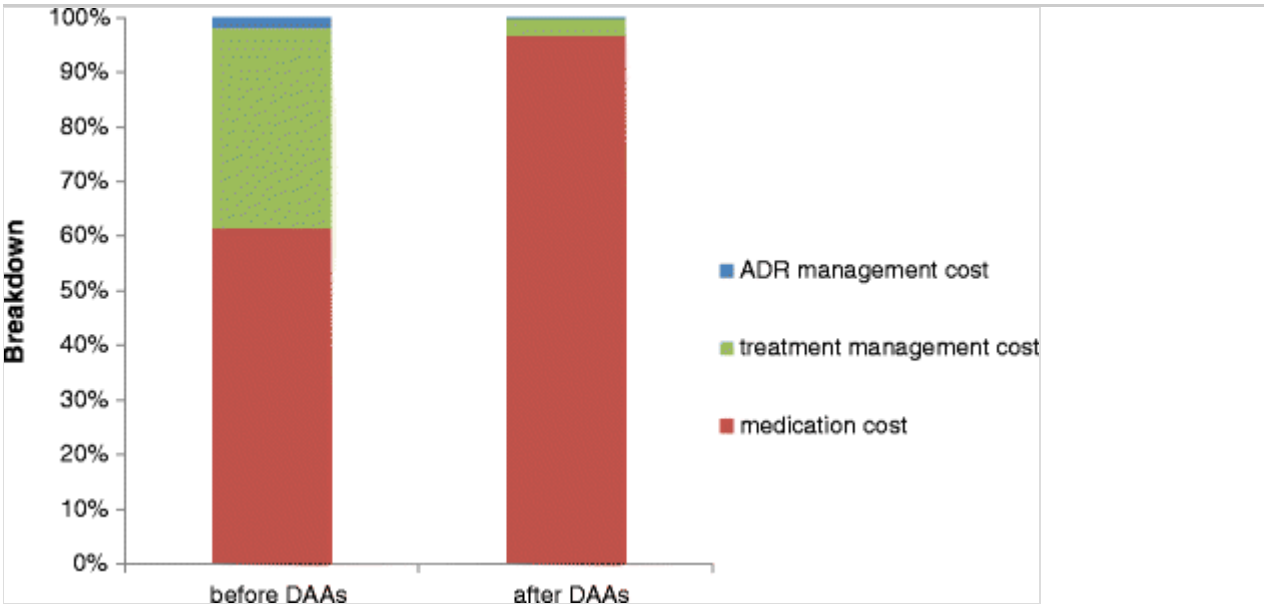
Healthcare expenditure before and after the introduction of DAAs



Breakdowns of the total healthcare expenditure before and after the introduction of DAAs are illustrated in Fig. 4. Upon the introduction of DAAs, the share of medication cost increased from 61.5% to 96.7%, with a simultaneously decreased share of treatment management cost from 36.7% to 3.1%. The clinical management cost for ADRs decreased 4.2-fold after the introduction ~~of DAAs~~, although it consistently accounted for less than 2% of the total healthcare expenditure before (1.8%) and after (0.2%) the introduction.

Fig. 4

Breakdown of 5-year healthcare expenditure before and after the introduction of DAAs

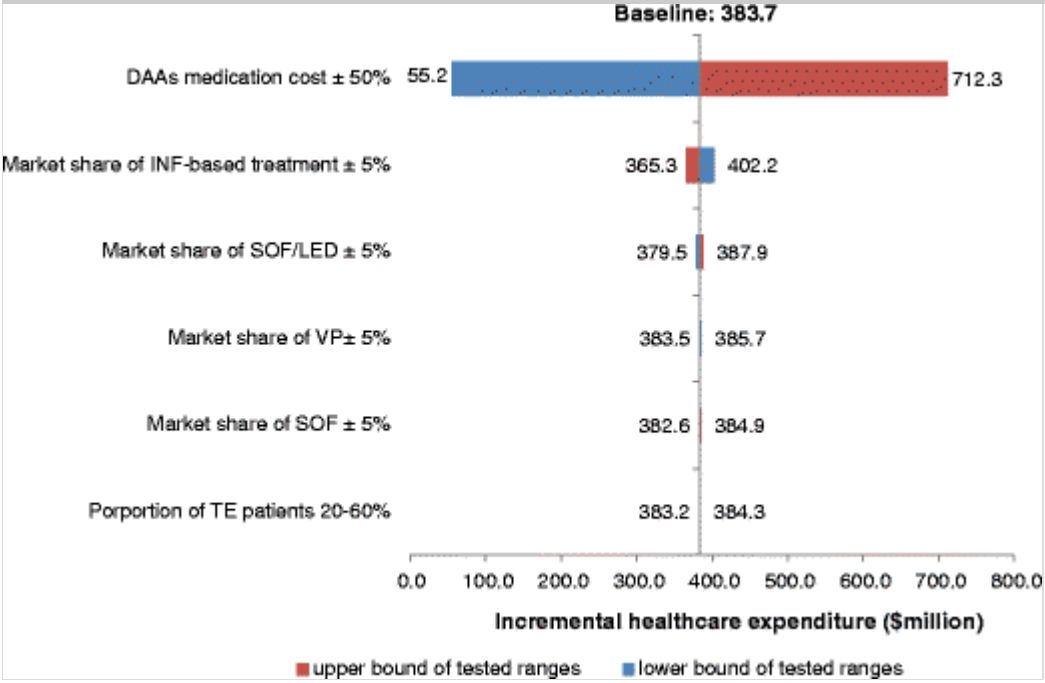


Sensitivity analysis

Variations of incremental healthcare expenditure caused by parameter uncertainties are illustrated in Fig. 5. Fifty percent of the fluctuation in the medication costs of DAAs caused the greatest variation of the increased budget. When all DAAs were introduced with halved drug acquisition costs, the incremental healthcare expenditure was estimated to be reduced from $383.7 million at base case to $55.2 million. In the meanwhile, if the medication costs increased to 150% of our base-case estimation, the budget is expected to increase by $712.3 million. Among all the uncertainties in market shares, a 5% fluctuation in the market share of INF-based treatment had the greatest impact on expenditure ($365.3 to $402.2 million). The market share of DAAs had limited impact on the base-case analysis, as there were only marginal changes in incremental healthcare. The incremental healthcare expenditure ($383.2 to 384.3 million) was positively associated with the proportion of TE patients; however, the impact was minimal among all tested parameters.

Fig. 5

Tornado diagram for one-way sensitivity analysis. *DAA* Direct-acting antivirals; *INF* interferon; *LED/SOF* ledipasvir/sofosbuvir; *SOF* sofosbuvir; *TE* treatment-experienced; *VP* ombitasvir/paritaprevir/ritonavir ~~and~~plus dasabuvir



Discussion

Despite the relatively low prevalence of HCV infection in the general population of Hong Kong (0.3% in 2001), the infection was commonly found in injecting drug users (66.8%), patients with hemophilia (56%), and hemodialysis (4.6%) and other patients requiring frequent ~~blood/~~blood product transfusions [23]. The control of HCV infection remains an important public health issue. The landscape of HCV treatment is undergoing a revolutionary change from parenteral IFN-based to all-oral DAA-based treatment regimens in recent years. Second-generation DAAs not only provide IFN-free treatments with > 95% SVR and lower incidence of ADRs, but also decrease treatment duration by 50% to 12–24 weeks [27, 28]. These new treatments are rapidly growing in the market but are costly for patients [29]. Hence, drug listing and subsidization are important factors impacting potential accessibility and uptake. Cost-effectiveness studies of DAA-based treatments have been conducted broadly in Europe, USA, Australia, and Asian countries, with the majority estimating the ICERs of new

treatments to be within the accepted range of medical practices and willingness-to-pay [5, 11, 12, 13, 14, 15, 16, 17, 18, 30, 31, 32]. However, there are derived assumptions on population profile, disease progression, and economic factors across various models, which limited their generalizability. It is also well recognized that each healthcare jurisdiction has its own unique system and no international studies and recommendations are fully applicable to local drug policies [10]. To the best of our knowledge, this is the first population-based health economic evaluation of DAA-based treatments in Hong Kong to explore their potential to be listed in the public hospital formulary.

Unlike traditional CEA studies using quality-adjusted life years as the long-term measurement of health outcomes [11, 12, 18, 30, 31, 32], a simplified decision analytic model was used to assess the cost-effectiveness of different treatments during the treatment course (12–48 weeks) to provide timely costs data relevant to stakeholders, including clinicians, patients, and policymakers. This study indicated that the medication cost of DAA-based treatments was more than twice that of the INF-based treatment; however, the total cost per treatment success was partially paid off by the greatly shortened treatment duration and improved rate of SVR. Consistent with the current literature, it was not surprising to find that the three DAA-based treatments were cost-effective in all of the scenarios, regardless of patient treatment history or cirrhosis condition, given that the ICERs were all less than the GDP per capita~~, which is~~ - the commonly accepted willingness-to-pay threshold for cost-effectiveness evaluations [33]. In addition, although this study was not designed to compare the three options within the DAA-based treatment group, it is interesting to find that VP is the most cost-effective DAA-based treatment, with lowest ICER for all groups of patients.

Financing the overall healthcare costs for all patients with HCV infection remains a global challenge given the excluded cases that were undiagnosed, untreated, discontinued treatment, or failed to respond to treatments [34, 35, 36, 37]. The present BIA was intended to maximize the required healthcare expenditure by setting all of the target patients treated and assuming no discontinuation occurred over the analytical time horizon. From this perspective, introducing DAAs to the formulary was estimated to increase the government budget of HCV management by 126.1% ($383.7million) over 5 years. Apparently, the introduction required considerable investment from end-payers in the short term. However, with the greatly improved rate of SVR of up to 99%,

DAA-based treatments are offering promising cure therapies for HCV infection. More importantly, patients with chronic HCV infection are at risk for progressive liver fibrosis, cirrhosis, portal hypertension, hepatocellular carcinoma, and decompensated liver disease [38, 39, 40]. Since more patients are expected to be successfully treated by DAA-based treatments, the introduction of DAAs has greater potential for saving healthcare resources and expenditures for the management of hepatitis C-related comorbidities in the long term.

The average total healthcare expenditure as a percentage of GDP was approximately 5% in Hong Kong in the past 10 years [41], which is equivalent to $15.50 billion in 2015 [42]. Based on these estimates, the increased budget on HCV infection management accounted for 2.5% of the overall healthcare expenditure in 2015. It might indicate that introducing DAA-based treatments to the formulary is affordable to the government. It is noted that clinical management costs for receiving the treatment and managing ADRs were largely decreased after introducing DAAs. It is meaningful for saving clinical healthcare resources in public hospitals, which is known to be always demanding and insufficient. Last but not least, despite the foreseeable health and economic benefits of DAA-based treatments, medication costs were found to be the major economic burden at both the individual and population levels. Strategically reducing medication costs will be the key determinant to further lowering the healthcare cost for individuals and society ~~as a whole~~.

Several limitations were acknowledged in this study. Firstly, in line with the majority of landmark trials for DAA-based treatments [43, 44, 45, 46, 47, 48], we restricted the regiments to genotype 1 infection only. Although it is the most common genotype of HCV in Hong Kong, the real healthcare expenditure on HCV management is expected to be greater than our estimation. Secondly, key clinical parameters including SVR and incidences of ADRs were extracted from phase III clinical trials of predominately Caucasian patients. It may not completely reflect the real treatment efficacy and safety in Asian patients. Local epidemiological and clinical studies are required to provide data inputs for more realistic estimation in Hong Kong Chinese patients. Thirdly, this study was restricted to providing short-term health economic insights on DAA-based treatments in Hong Kong. Long-term health outcomes of hepatitis C-related ~~morbidities~~sequelae such as cirrhosis, hepatocellular carcinoma and liver failure, and mortality and the relevant costs were not measured. The ~~important~~ impact of

preventingon of further transmission of HCV infection upon successful eradication by DAAs was also not assessed.

In conclusion, DAA-based treatments are cost-effective alternatives to INF-based treatment for patients with chronic genotype 1 HCV infection in Hong Kong. Introducing DAAs to the public hospital formulary yields a considerable budget increase but is still economically favorable to the local government. Comprehensive analysis considering other HCV genotypes, long-term health and economic outcomes, and advanced sensitivity analyses are warranted for future studies.

Compliance with ethical standards

Funding This work received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest EWC has received financial support from Janssen, a division of Johnson & Johnson, Bristol Myers Squibb, Pfizer, and Eisai; The Pharmaceutical Society of Hong Kong; The University of Hong Kong; Early Career Scheme and the General Research Fund, Research Grants Council, Hong Kong, all unrelated to the current work. The other co-authors declare no conflict of interest.

Ethical approval and informed consent The requirements for Institutional Review Board (IRB) approval and informed consent were waived as this was a pharmacoeconomic modeling study without patient contact.

Authorship contribution statement Conception and design of the work: XL, NSC, IFNH, and EWC; data collection, analysis, and interpretation: XL and NSC; drafting the article: XL; critical revision of the article: XL, NSC, AWT, IFNH, and EWC; final approval of the version to be published: XL, NSC, AWT, IFNH, and EWC.

Electronic supplementary material

Below is the link to the electronic supplementary material.

ESM 1

(DOCX 105 kb)

References

1. World Health Organization (WHO) (2016) Hepatitis C fact sheet. Available online at: http://www.who.int/mediacentre/factsheets/fs164/en/ . Accessed 13 Sep 2016

2. Lozano R, Naghavi M, Foreman K et al (2012) Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380:2095–2128

3. Averhoff FM, Glass N, Holtzman D (2012) Global burden of hepatitis C: considerations for healthcare providers in the United States. Clin Infect Dis 55(Suppl 1):S10–S15

4. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H (2014) Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol 61:S45–S57

5. Razavi H, Elkhoury AC, Elbasha E et al (2013) Chronic hepatitis C virus (HCV) disease burden and cost in the United States. Hepatology 57:2164–2170

6. Thiagarajan P, Ryder SD (2015) The hepatitis C revolution part 1: antiviral treatment options. Curr Opin Infect Dis 28:563–571

7. Kohli A, Shaffer A, Sherman A, Kottilil S (2014) Treatment of hepatitis C: a systematic review. JAMA 312:631–640

8. Suwanthawornkul T, Anothaisintawee T, Sobhonslidsuk A, Thakkinstian A, Teerawattananon Y (2015) Efficacy of second generation direct-acting antiviral agents for treatment naïve hepatitis C genotype 1: a systematic

review and network meta-analysis. PLoS One 10:e0145953

9. World Health Organization (WHO). An overview of the rationale, activities and goals of WHO-CHOICE: why is cost-effectiveness analysis important? Available online at: http://www.who.int/choice/description/importance/en/ . Accessed 18 Nov 2016

10. Hospital Authority of Hong Kong. Drug formulary management manual. Available online at: http://www.ha.org.hk/hadf/Portals/0/Docs/HADF_manual_Eng.pdf . Accessed 18 Nov 2016

11. Kuwabara H, Westerhout K, Treur M, Cerri K, Mahlich J, Yatsuhashi H (2015) Cost-effectiveness analysis of simeprevir in combination with peginterferon and ribavirin for treatment-naïve chronic hepatitis C genotype 1 patients in Japan. J Med Econ 18:502–511

12. Pfeil AM, Reich O, Guerra IM et al (2015) Cost-effectiveness analysis of sofosbuvir compared to current standard treatment in Swiss patients with chronic hepatitis C. PLoS One 10:e0126984

13. Saab S, Gordon SC, Park H, Sulkowski M, Ahmed A, Younossi Z (2014) Cost-effectiveness analysis of sofosbuvir plus peginterferon/ribavirin in the treatment of chronic hepatitis C virus genotype 1 infection. Aliment Pharmacol Ther 40:657–675

14. San Miguel R, Gimeno-Ballester V, Blázquez A, Mar J (2015) Cost-effectiveness analysis of sofosbuvir-based regimens for chronic hepatitis C. Gut 64:1277–1288

15. Younossi ZM, Park H, Saab S, Ahmed A, Dieterich D, Gordon SC (2015) Cost-effectiveness of all-oral ledipasvir/sofosbuvir regimens in patients with chronic hepatitis C virus genotype 1 infection. Aliment Pharmacol Ther 41:544–563

16. Bickerstaff C (2015) The cost-effectiveness of novel direct acting antiviral agent therapies for the treatment of chronic hepatitis C. Expert Rev Pharmacoecon Outcomes Res 15:787–800

17. Cure S, Guerra I, Cammà C, Craxì A, Carosi G (2015) Cost-effectiveness of sofosbuvir plus ribavirin with or without pegylated interferon for the treatment of chronic hepatitis C in Italy. J Med Econ 18:678–690

18. Rein DB, Wittenborn JS, Smith BD, Liffmann DK, Ward JW (2015) The cost-effectiveness, health benefits, and financial costs of new antiviral treatments for hepatitis C virus. Clin Infect Dis 61:157–168

19. Sullivan SD, Mauskopf JA, Augustovski F et al (2014) Budget impact analysis—principles of good practice: report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. Value Health 17:5–14

20. American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) (2016) Recommendations for testing, managing, and treating hepatitis C. Available online at: http://hcvguidelines.org/sites/default/files /HCV-Guidance_July_2016_b.pdf . Accessed 6 Sep 2016

21. O'Mahony JF, Newall AT, van Rosmalen J (2015) Dealing with time in health economic evaluation: methodological issues and recommendations for practice. Pharmacoeconomics 33:1255–1268

22. Zhou DX, Tang JW, Chu IM et al (2006) Hepatitis C virus genotype distribution among intravenous drug user and the general population in Hong Kong. J Med Virol 78:574–581

23. Centre for Health Protection, Department of Health, The Government of the Hong Kong Special Administrative Region (2014) Surveillance of viral hepatitis in Hong Kong: 2014 update report. Available online at: http://www.chp.gov.hk/en/epidemiology/29/135/622/133.html . Accessed 8 Nov 2016

24. Hassanein T, Shiffman ML, Zein NN (2007) The practical management of treatment failure in chronic hepatitis C: a summary of current research and management options for refractory patients. Gastroenterol Hepatol 3:4–32

25. The Hospital Authority (2013) Hospital authority ordinance (Chapter

113). Revisions to list of charges. Available online at: http://www.ha.org.hk /haho/ho/cs/207298en_txt.pdf . Accessed 8 Nov 2015

26. Thorlund K, Druyts E, El Khoury AC, Mills EJ (2012) Budget impact analysis of boceprevir and telaprevir for the treatment of hepatitis C genotype 1 infection. Clinicoecon Outcomes Res 4:349–359

27. Lewis H, Cunningham M, Foster G (2012) Second generation direct antivirals and the way to interferon-free regimens in chronic HCV. Best Pract Res Clin Gastroenterol 26:471–485

28. Borba HH, Wiens A, Steimbach LM et al (2017) Network meta-analysis of first- and second-generation protease inhibitors for chronic hepatitis C genotype 1: efficacy based on RVR and SVR 24. Eur J Clin Pharmacol 73:1–14

29. Gohil K (2014) Huge growth seen in hepatitis C market. Pharm Ther 39:517

30. Westerhout K, Treur M, Mehnert A, Pascoe K, Ladha I, Belsey J (2015) A cost utility analysis of simeprevir used with peginterferon + ribavirin in the management of genotype 1 hepatitis C virus infection, from the perspective of the UK National Health Service. J Med Econ 18:838–849

31. Gimeno-Ballester V, Mar J, San Miguel R (2016) Cost-effectiveness analysis of simeprevir with daclatasvir for non-cirrhotic genotype-1b-naïve patients plus chronic hepatitis C. Expert Rev Pharmacoecon Outcomes Res 16:285–294

32. Najafzadeh M, Andersson K, Shrank WH et al (2015) Cost-effectiveness of novel regimens for the treatment of hepatitis C virus. Ann Intern Med 162:407–419

33. World Health Organization (WHO) (2016) Making choices in health: WHO guide to cost-effectiveness analysis. Available online at: http://www.who.int/choice/publications/p_2003_generalised_cea.pdf?ua=1 . Accessed 11 Nov 2016

34. Lyons MS, Kunnathur VA, Rouster SD et al (2016) Prevalence of diagnosed and undiagnosed hepatitis C in a midwestern urban emergency department. Clin Infect Dis 62:1066–1071

35. Taylor LE, Foont JA, DeLong AK et al (2014) The spectrum of undiagnosed hepatitis C virus infection in a US HIV clinic. AIDS Patient Care STDs 28:4–9

36. Scott JA (2014) The dangers of untreated hepatitis C. Available online at: http://www.everydayhealth.com/hs/hepatitis-c-living-well/dangers-untreated-hepatitis-c/ . Accessed 22 Nov 2016

37. LaFleur J, Hoop R, Morgan T et al (2014) High rates of early treatment discontinuation in hepatitis C-infected US veterans. BMC Res Notes 7:266

38. Chen SL, Morgan TR (2006) The natural history of hepatitis C virus (HCV) infection. Int J Med Sci 3:47–52

39. Marinho RT, Barreira DP (2013) Hepatitis C, stigma and cure. World J Gastroenterol 19:6703–6709

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

41. Food and Health Bureau, The Government of the Hong Kong Special Administrative Region (2016) Health expenditure. Available online at: http://www.fhb.gov.hk/statistics/en/statistics/health_expenditure.htm . Accessed 18 Nov 2016

42. The World Bank (2016) GDP (current US$). Available online at: http://data.worldbank.org/indicator/NY.GDP.MKTP.CD?locations=HK . Accessed Nov 18 2016

43. Andreone P, Colombo MG, Enejosa JV et al (2014) ABT-450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with

HCV genotype 1b infection. Gastroenterology 147:359–365.e1

44. Poordad F, Hezode C, Trinh R et al (2014) ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. N Engl J Med 370:1973–1982

45. Bacon BR, Gordon SC, Lawitz E et al (2011) Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med 364:1207–1217

46. Poordad F, McCone J Jr, Bacon BR et al (2011) Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med 364:1195–1206

47. Afdhal N, Zeuzem S, Kwo P et al (2014) Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med 370:1889–1898

48. Feld JJ, Moreno C, Trinh R et al (2016) Sustained virologic response of 100% in HCV genotype 1b patients with cirrhosis receiving ombitasvir/paritaprevir/r and dasabuvir for 12 weeks. J Hepatol 64:301–307