











RESEARCH ARTICLE

REVISED **The direct-medical costs associated with interferon-based treatment for Hepatitis C in Vietnam [version 2; peer review: 2 approved]**

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Abstract

Background: Injectable interferon-based therapies have been used to treat hepatitis C virus (HCV) infection since 1991. International guidelines have now moved away from interferon-based therapy towards direct-acting antiviral (DAA) tablet regimens, because of their superior efficacy, excellent side-effect profiles, and ease of administration. Initially DAA drugs were prohibitively expensive for most healthcare systems. Access is now improving through the procurement of low-cost, generic DAAs acquired through voluntary licenses. However, HCV treatment costs vary widely, and many countries are struggling with DAA treatment scale-up. This is not helped by the limited cost data and economic evaluations from low- and middle-income countries to support HCV policy decisions. We conducted a detailed analysis of the costs of treating chronic HCV infection with interferon-based therapy in Vietnam. Understanding these costs is important for performing necessary economic evaluations of novel treatment strategies.

Methods: We conducted an analysis of the direct medical costs of treating HCV infection with interferon alpha (IFN) and pegylated-interferon alpha (Peg-IFN), in combination with ribavirin, from the health sector perspective at the Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam, in 2017.

Results: The total cost of the IFN treatment regimen was estimated to range between US\$1,120 and US\$1,962. The total cost of the Peg-IFN treatment regimen was between US\$2,156 and US\$5,887. Drug

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1

2

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version 1


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report



report

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expenses were the biggest contributor to the total treatment cost (54-89%) and were much higher for the Peg-IFN regimen.

Conclusions: We found that treating HCV with IFN or Peg-IFN resulted in significant direct medical costs. Of concern, we found that all patients incurred substantial out-of-pocket costs, including those receiving the maximum level of support from the national health insurance programme. This cost data highlights the potential savings and importance of increased access to generic DAAs in low- and middle-income countries and will be useful within future economic evaluations.

Keywords

interferon-based therapy, direct medical costs, cost analysis, hepatitis C, Vietnam



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REVISED Amendments from Version 1

Based on the comments from two reviewers, we have updated the manuscript with some additional information and clarifications.

The most significant update is in the section "Payment from the national health insurance programme" with the explanation of how the patient's co-payment is calculated. Figure 2 has changed from the co-payment mechanism to the payment mechanism from Vietnam's national health insurance programme.

Other updates include:

- Adding the "average per week" for the drug costs in Table 3
- Clarifying that the cost estimates are based on a standard treatment following the Vietnam's Ministry of Health guidelines.
- Adding that a potential advantage of DAAs is that they may allow the decentralising of treatment to primary health care facilities in some settings
- Updating some references for the cost of DAAs, and the argument of few costing studies and economic evaluations of HCV treatment in low- and middle-income countries.

Any further responses from the reviewers can be found at the end of the article

Introduction

The World Health Organization (WHO) estimates that there are 71 million people living with chronic hepatitis C infection globally¹. Hepatitis C virus (HCV) is typically transmitted through intravenous drug use, unsafe injection practice and the transfusion of unscreened blood/blood products¹. There are six major HCV strains, genotypes 1–6, and the prevalence of each genotype varies significantly between regions¹. Currently, most data relate to the treatment of genotypes 1–4; few data exist regarding the treatment outcomes and costs of genotype 6 infection, which accounts for over 50% of HCV infections in Vietnam².

Interferon-based therapies have been used to treat HCV since 1991³. The original interferon (IFN) intramuscular injections had to be administered daily and were associated with poor cure rates and unpleasant side effects⁴. Pegylated IFN (Peg-IFN) was first licensed in 2001⁵ and has improved pharmacokinetics, requiring only weekly injections. Additionally, Peg-IFN is more effective than IFN and is associated with fewer adverse effects⁶. When used for 24–48 weeks with the anti-viral tablet ribavirin, Peg-IFN is associated with cure rates of 54–63% (depending on the infecting viral genotype)⁷. In recent years, new oral direct-acting antivirals (DAAs) have been developed. DAA therapy requires a shorter duration of treatment (typically 12 weeks) and has superior cure rates to interferon-based therapy (>95%)⁸. The tablets have almost no side effects and forgo the need for weekly injections⁹. When they first emerged, DAA drugs were prohibitively expensive for many healthcare systems, making them unavailable in most low- and lower-middle-income countries. Whilst prices still restrict access in many settings, the situation is improving, with steep price reductions for DAAs, driven largely by increased competition from generic manufacturers and the issuing of voluntary

licenses¹⁰. In 2016, 86% of people starting HCV therapy worldwide received DAA drugs rather than interferon-based therapy¹¹. Recently, the WHO recommended that interferon-based therapy should no longer be used where DAA drugs are available⁸.

In 2016, the WHO released the first Global Health Sector Strategy on viral hepatitis with a goal of eliminating viral hepatitis as a public health threat by 2030¹². The specific goals set for hepatitis C were that 80% of patients are treated, along with a 90% reduction in the incidence and a 65% reduction in HCV related mortality¹². In 2015, only 7% of the 71 million people living with chronic HCV infection were treated¹². Therefore, access to treatment needs to expand if the elimination goals are to be achieved.

Although improving, the global scale-up of DAA treatment has been markedly uneven, with a handful of countries (e.g. Egypt, China) accounting for the majority of the increase in uptake¹¹. A WHO analysis of country experiences of DAA scale-up shows that, while access to affordable treatment is important, countries also need a strong government response, including national plans for preventing, diagnosing and treating HCV, and adequate financing to roll out and sustain HCV services^{11,13}. For this to occur, it is vital to have a detailed understanding of the cost and cost-effectiveness of the different treatment options available in low- and middle-income countries^{14,15}.

We conducted a detailed analysis of the costs of treating chronic HCV with the pre-existing standard of care in Vietnam, IFN and Peg-IFN therapy. Since 2016, Vietnam has started to move away from interferon-based therapy towards DAA treatment regimens (in keeping with WHO guidelines). In June 2019, DAAs started to be covered by the national health insurance programme (NHI)¹⁶. Consequently, due to its side effect profile and the increasing availability of DAAs, interferon-based therapy is becoming more infrequently used in Vietnam. However, data on the costs of interferon-based therapy are still essential for conducting accurate economic evaluations of DAA treatment, as interferon-based treatment will likely be the comparator (Box 1) within the analysis.

Box 1. Glossary**Catastrophic health expenditure**

When the medical expenditure of a household exceeds a certain level of capacity such that the household has to cut down on necessities (such as food, clothing, and their children's education).

Comparator

Within an economic evaluation, the new intervention being investigated is compared to a comparator. The comparator generally reflects the current clinical practice.

Direct costs	The costs related to the goods, services and resources consumed to implement and access healthcare.
Direct medical costs	The costs directly related to the use of medical services/ resources (such as physician services, diagnostic tests and drugs).
Direct non-medical costs	The costs related to the consumption of non-medical resources (such as transportation to the health facility, food expenses and accommodation).
Health sector perspective	A perspective that only includes the costs associated with the health sector, such as the costs covered by the national health insurance programme and the patient's copayment for the medical services.
National health insurance programme (NHI)	An insurance programme managed by the government that helps patients pay for medical services.
Out-of-pocket payment	The medical expenses incurred by patients that do not get reimbursed by insurance programmes. The out-of-pocket payment is usually equal to the price of the medical services/ drugs in question multiplied by the patient's co-payment rate.
Patients co-payment rate	The proportion of the total billed healthcare costs that insured patients pay. For example, if the insurers pay 80%, the remaining 20% will be paid by the patient.
Perspective	The viewpoint adopted for deciding which types of costs and health benefits are to be included within an economic evaluation.
Productivity costs (indirect costs)	Represent the value of the productivity losses that result from illness, treatment, or premature death.
Societal perspective	A perspective that includes all the costs associated with an intervention/healthcare, regardless of whom they are incurred by, i.e. this includes the health systems and patient's direct medical costs, direct non-medical costs and indirect costs.
Universal health coverage	All individuals have access to good quality healthcare services without facing financial hardship.

Methods

Study location

Vietnam is a lower-middle-income country in Southeast Asia with a population of over 95 million people¹⁷, and a 2017 GDP per capita of US\$2365¹⁸. The seroprevalence of HCV in the general population has been estimated to be between 1 and 4.7%^{19,20}, which is high relative to other countries in the region. In Vietnam, genotypes 1 and 6 predominate^{19,21}. These genotypes are considered hardest to treat with interferon-based therapies and both genotypes 1 and 6 require prolonged treatment courses (48 weeks as opposed to 24 weeks)²².

The Hospital for Tropical Diseases (HTD) in Ho Chi Minh City is the major referral hospital for infectious diseases in the south of Vietnam. Our cost estimation was performed in the context of the HTD in 2017.

The resources and services required for HCV treatment

The Ministry of Health (MoH) approved four interferon-based treatments within their first HCV treatment guidelines in 2013: IFN α -2a, IFN α -2b, Peg-IFN α -2a and Peg-IFN α -2b²³. To enhance treatment efficacy, each of these injection-based treatments is combined with the antiviral tablet ribavirin (Table 1). In late 2016, the MoH published an updated treatment guideline for Hepatitis C, in which the recommended treatments were Peg-IFN and DAAs. Although standard IFN was no longer included as a recommended treatment, it remained on the list of medicines covered by the national health insurance programme (Box 1). From the end of 2016, IFN was no longer used at HTD. However, as it was still used in other hospitals in Vietnam, we have included cost analysis related to IFN treatment within this paper.

We estimated the quantity of the drugs required for an average treatment based on the recommended dosages within the 2013

Table 1. The Vietnam MoH treatment guidelines for HCV drugs.

Name of drugs	Dose
IFN α -2a	3 million IU three times per week
IFN α -2b	3 million IU three times per week
Peg-IFN α -2a	180 μ g once per week
Peg-IFN α -2b	1.5 μ g/kg once per week
Ribavirin	Genotype 1/4/6: 1000mg per day
	Genotype 2/3: 800mg per day

Based on the HCV guidelines from the MoH in 2013²³. IU, international unit.

HCV treatment guidelines from the MoH (Table 1)²³. The dosage of Peg-IFN α -2b was calculated assuming an average body weight of 58 kilograms for men and 50 kilograms for women²⁴.

The utilisation of the other resources and services (such as the medical tests) required to provide HCV treatment were based on the MoH 2013 treatment guidelines²³. These recommend that a patient should visit the outpatient clinic once prior to treatment, every four weeks during treatment and once after ending treatment. A summary of the required medical tests at these different stages of treatment is shown in

Table 2. Following the hospital's classification, the tests were grouped into seven different classes. The duration of treatment depends on the genotype of HCV: 24 weeks for genotypes 2/3 and 48 weeks for genotypes 1/4/6²³. Both of these regimens were considered in our analysis.

Cost estimation and outputs

Our cost analysis estimated the direct medical cost of HCV treatment from the health sector perspective (Box 1). The direct non-medical costs and indirect costs (Box 1) were not quantified.

Table 2. A summary of the recommended medical tests within the Vietnam Ministry of Health (MoH) hepatitis C virus (HCV) treatment guidelines.

Name of required tests		Before treatment	During treatment	After treatment	
Group 1: Electrocardiogram	Electrocardiogram	Yes	No	No	
Group 2: Ultrasound	Abdominal ultrasound		Every 12 weeks		
	Fibro-scan		No		
Group 3: X-ray	Chest X-ray		No		
Group 4: Blood tests	Full blood count		Every 4 weeks		
	The international normalized ratio		No		
	Prothrombin		Every 12 weeks		
Group 5: Immunoassay	Alpha-fetoprotein				
	Free thyroxine				
	Thyroid-Stimulating Hormone				No
	Hepatitis B surface antigen				
Human immunodeficiency virus					
Group 6: Biochemical tests	Electrolytes		No		
	Albumin				
	Bilirubin				
	Creatinine (urine and blood)	Every 4 weeks			
	Urea	No			
	Alanine transaminase	Every 4 weeks			
	Aspartate aminotransferase	No			
	Gamma-glutamyl transferase	No			
Group 7: Molecular biology tests	HCV-RNA viral load test	Every 8 weeks	Yes		
	HCV genotype real-time PCR	No	No		

Before treatment, certain tests are required to assess disease severity and to ensure that treatment can be safely tolerated. During treatment, monitoring tests are required every 4, 8 or 12 weeks to assess treatment response and drug side effects. After treatment, the HCV-RNA viral load test is repeated to assess treatment response. This is based on the 2013 HCV treatment guidelines from the MoH²³.

The identified resources and services (Table 1 and Table 2) were costed based on the services and drug unit price list of HTD in 2017 relating to those covered by the national health insurance programme²⁵. One exception to this was the costs relating to the IFN drugs which were obtained from a 2017 report from the Drug Administration of Vietnam²⁶.

The main output was the total cost of the different treatments, stratified by the three main cost components: the cost of the drugs, the cost of the medical tests and the costs related to the clinical consultation fees.

All costs were converted to US dollars (US\$) following the average 2017 exchange rate where 22,370 Vietnamese dong (VND) equal 1 US\$²⁷.

Results

The total cost of the IFN treatment regimen was estimated to range between US\$1,120 and US\$1,962 and the total cost of the Peg-IFN treatment regimen between US\$2,156 and US\$5,887 (Table 3). The cost of treating genotypes 1/4/6 (which require a 48-week treatment regimen) was substantially higher than the cost of treating genotypes 2/3 (which require a 24-week regimen). The cost was not exactly double, due to the different dosages of ribavirin used for the different genotypes (Table 1 and Table 3) and the fact that the pre- and post-treatment tests are identical.

We estimated the costs of the three main components of HCV treatment: the drugs, medical tests and clinical consultation fees. The costs of the drugs contributed between 54–89% to the total treatment cost and were much higher for the Peg-IFN regimen. These were shown as a range because the exact price varies depending on which brand is used (Table 4). This variation was most significant for Peg-IFN α -2a. The cost of the ribavirin only represented 2–8% of the costs relating to the drugs.

The costs of the medical tests were also notable (US\$498 for treating genotypes 2/3 and US\$613 for treating genotypes 1/4/6) (Figure 1). The HCV-RNA viral load tests accounted for the majority of this (approximately 70%). The costs relating to the tests used pre- and post-treatment were the same for both genotype groups (Figure 1). However, the costs of the tests used during the treatment were double for the 48-week treatment regimen compared to the 24-week regimen (genotypes 1/4/6 vs genotypes 2/3) (Table 2 and Figure 1).

Discussion

Treating HCV in Vietnam with IFN or Peg-IFN results in significant direct medical costs. These costs are particularly high because the genotypes that are most prevalent (1 and 6) require a prolonged (48 weeks) duration of therapy²⁸. The drug-related costs contributed the most (54–89%) to the total treatment cost (Table 3). The drug-related costs for treating HCV genotypes 1/6 were approximately US\$25 per week for IFN plus

Table 3. The estimated cost of the different regimens.

Treatment	Drugs (US\$)		Tests (US\$)	Consultation fees (US\$)	Total treatment cost (US\$)
	Total	Average per week			
Genotype 2/3: 24-week treatment regimen					
IFN α -2a + ribavirin	619.17 – 655.17	25.79 - 27.30	498.18	13.95	1,155.29 – 1,167.31
IFN α -2b + ribavirin	607.75 – 619.77	25.32 - 25.82	498.18	13.95	1,119.88 – 1,131.90
Peg-IFN α -2a + ribavirin	1,644.14 – 2,617.89	68.50 - 109.07	498.18	13.95	2,156.27 – 3,130.02
Peg-IFN α -2b + ribavirin	1,680.07 – 1,967.78	70.00 - 81.99	498.18	13.95	2,192.20 – 2,470.91
Genotype 1/4/6: 48-week treatment regimen					
IFN α -2a + ribavirin	1,325.52 – 1,333.78	27.61 - 27.79	613.24	24.41	1,953.84 – 1,961.90
IFN α -2b + ribavirin	1,254.71 – 1,262.97	26.14 - 26.31	613.24	24.41	1,882.83 – 1,892.09
Peg-IFN α -2a + ribavirin	3,327.48 – 5,259.20	69.32 - 109.57	613.24	24.41	3,955.60 – 5,887.32
Peg-IFN α -2b + ribavirin	3,375.89 – 3,950.73	70.33 - 82.30	613.24	24.41	4,003.43 – 4,578.85

The range in the costs for a given regimen is due to the variation in the costs of the different brands of the drugs and the different dosages (minimum and maximum values are shown in Table 4). Costs are in 2017 prices.

Table 4. The assumed input and unit cost for the direct medical cost of interferon-based treatment for Hepatitis C in Vietnam.

Item		Total Quantity		Unit cost (VND)	Unit cost (US\$)
		Genotype 2/3	Genotype 1/4/6		
Drug					
IFN α-2a	Feronsure (3×10 ⁶ IU)	216×10 ⁶	432×10 ⁶	189000	8.32
IFN α-2b	Superferon (3×10 ⁶ IU)	216×10 ⁶	432×10 ⁶	178000	7.84
Peg-IFN α-2a	Pegasys (135 µg)	4320	8640	1797313	79.14
	Pegasys (135 µg) new version	4320	8640	2327195	102.48
	Pegasys (180 µg) old version	4320	8640	1400000	61.65
	Pegasys (180 µg) new version	4320	8640	1950000	85.87
	Pegnano (180 µg) old version	4320	8640	1750000	77.06
	Pegnano (180 µg) new version	4320	8640	1500000	66.05
Peg-IFN α-2b	Peg-intron (50 µg) ^a	Man: 2088 Woman:1800	Man: 4176 Woman: 3600	1014860	44.69
	Peg-intron (80 µg) ^a	Man: 2088 Woman:1800	Man: 4176 Woman: 3600	1639400	72.19
	Peg-intron redipen (100 µg) ^a	Man: 2088 Woman:1800	Man: 4176 Woman: 3600	2058000	90.62
Ribavirin	Barivir (400 mg)	403200	336000	2900	0.13
	Barivir (500 mg)	403200	336000	3900	0.17
Medical tests					
Group 1: Electrocardiogram					
	Electrocardiogram	1	1	45900	2.02
Group 2: Ultrasound					
	Abdominal ultrasound	3	5	49000	2.16
	Fibro-scan	1	1	79500	3.50
Group 3: X-ray					
	Chest X-ray	1	1	69000	3.04
Group 4: Blood tests					
	Full blood count	1	1	44800	1.97
	The international normalized ratio	1	1	12300	0.54
	Prothrombin	3	5	61600	2.71
Group 5: Immunoassay					
	Alpha-fetoprotein	3	5	90100	3.97
	Free thyroxine	3	5	63600	2.80
	Thyroid-stimulating Hormone	3	5	58300	2.57
	Hepatitis B surface antigen	1	1	712000	31.35
	Human immunodeficiency virus	1	1	319700	14.08

Item	Total Quantity		Unit cost (VND)	Unit cost (US\$)
	Genotype 2/3	Genotype 1/4/6		
Group 6: Biochemical tests				
Electrolytes	1	1	28600	1.26
Albumin	1	1	21200	0.93
Bilirubin	1	1	21200	0.93
Creatinine (urine)	6	12	15900	
Creatinine (blood)	7	13	21200	0.93
Urea	1	1	21200	0.93
Alanine transaminase	1	1	21200	0.93
Aspartate aminotransferase	7	13	21200	0.93
Gamma-glutamyl transferase	1	1	19000	0.84
Group 7: Molecular biology tests				
HCV-RNA viral load test	5	8	1310000	57.69
HCV genotype: Real time PCR	1	1	1550000	68.25
Consultation				
Clinical consultation fees	8	14	39000	1.72

^aThe dosage is prescribed following average body weight for men is 58 kg and for women is 50 kg²⁹. Costs are in 2017 prices. IU, international unit

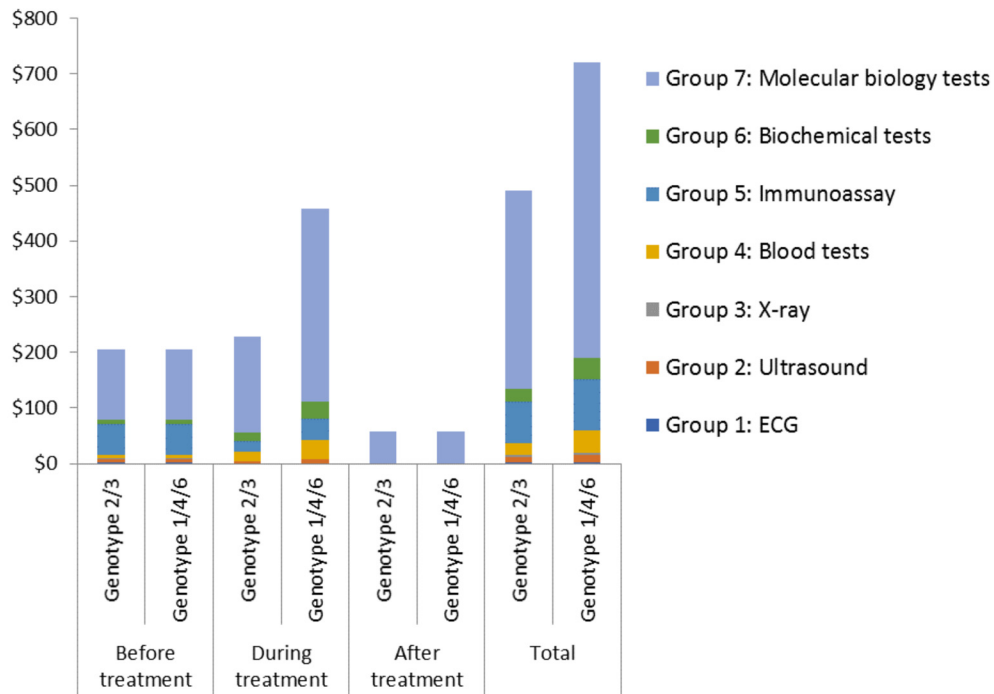


Figure 1. The cost of the medical tests associated with treating genotypes 2/3 (24-week treatment regimen) and genotypes 1/4/6 (48-week treatment regimen). A summary of the recommended medical tests at different stages of hepatitis C virus treatment is shown in Table 2. The unit costs of the different types of tests are shown in Table 3. Costs are in 2017 prices.

ribavirin and between US\$68-109 per week for Peg-IFN plus ribavirin. The costs of the medical tests and monitoring also contributed notably to the total treatment cost (10–44%) and were related to the duration of the treatment.

The results relate to the cost of a treatment regimen and not the cost per patient cured. Although the cost of treatment with IFN is cheaper, it is less likely to cure the patient successfully and the costs associated with treatment failure can be significant. Consequently, IFN treatment is rarely used in Vietnam.

Studies in neighboring countries have reported the cost of Peg-IFN using the same doses. One study from Thailand reported that the Peg IFN-2a/2b and ribavirin for treating HCV genotypes 1/6 cost US\$90 per week (2013 prices)³⁰, which is similar to our finding. Another study reported that in China³¹, the Peg IFN-2a and ribavirin for treating HCV genotype 1, cost US\$174 per week (2016 prices), almost double our estimate.

These cost estimates relate to a standard treatment (based on MoH guidelines). It should be noted that in practice there will be variations in these treatment costs and resources utilized, such as for those not finishing the treatment regimen, experiencing treatment failure or those with co-infections such as HIV.

Payment from the national health insurance programme

In Vietnam, the proportion of the population covered by the NHI as of December 2016 is estimated to be 81.7%³². However, even the patients covered by the NHI can incur significant out-of-pocket payments (Box 1) for HCV treatment.

For the drug costs relating to HCV treatment, the patient's out-of-pocket payment will be based on the price of the drug and the patient's co-payment rate (the proportion of the billed costs that insured patients pay) (Equation 1).

Equation 1: Out-of-pocket payment for the drugs = Price of the drug × Patient's co-payment rate

The patient's co-payment rate is what is remaining after subtracting the proportion covered by the NHI (Equation 2). In the case of these drug costs, the proportion covered by the NHI (Equation 3) is given by three components (the drug related rate, group related rate and referral related rate). These are outlined in Figure 2.

Equation 2: Patients co-payment rate = 1 – proportion covered by the NHI

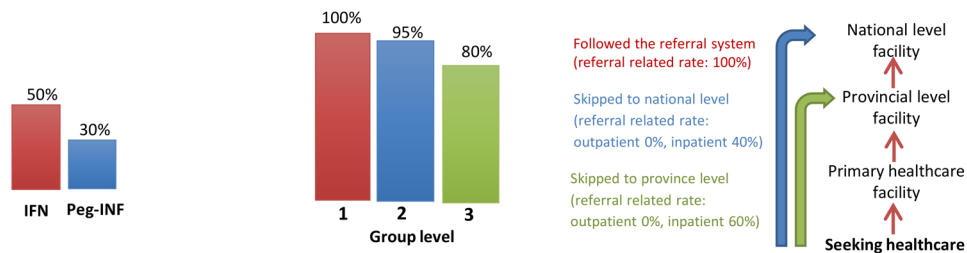
Equation 3: Proportion covered by the NHI = Drug related rate × Group related rate × Referral related rate

Based on these rates, even with the maximum level of insurance cover, patients still have to pay 50% of the cost of the IFN drugs and 70% of the cost of the Peg-IFN drugs (See Drug related rate within Figure 2)¹⁶. Furthermore, if patients attend the HTD without a formal referral from their primary health care facility, they have to pay for the full cost of the treatment (as though uninsured) (See Referral related rate within Figure 2 and Figure 3)³³. The payment mechanism within the NHI is

Payment mechanism from Vietnam's national health insurance programme

The proportion of the drug costs relating to interferon-based treatment that is covered by the national health insurance programme is given by three components, which are multiplied together.

Drug related rate × Group related rate × Referral related rate



The NHI has different payment rates for specific drugs. IFN and Peg-IFN are on the programme's expensive medicine list. The health insurance programme therefore pays a maximum rate of 50% of the cost of the IFN drugs and 30% of the Peg-IFN drugs.

The NHI has different group specific payment rates. This grouping is based on the individual's financial capacity (with poorer individuals getting a higher level of support). The three different group related rates are 100%, 95%, and 80%.

The payment rate from the NHI is also influenced by how the patient is referred. Patients who follow the referral system have a referral related rate of 100%. However, patients who self-refer receive a much lower level of support.

Figure 2. Summary of the payment mechanism for the drug costs relating to interferon-based treatment from the national health insurance programme. Information adapted from 16, 33. NHI: National health insurance programme.

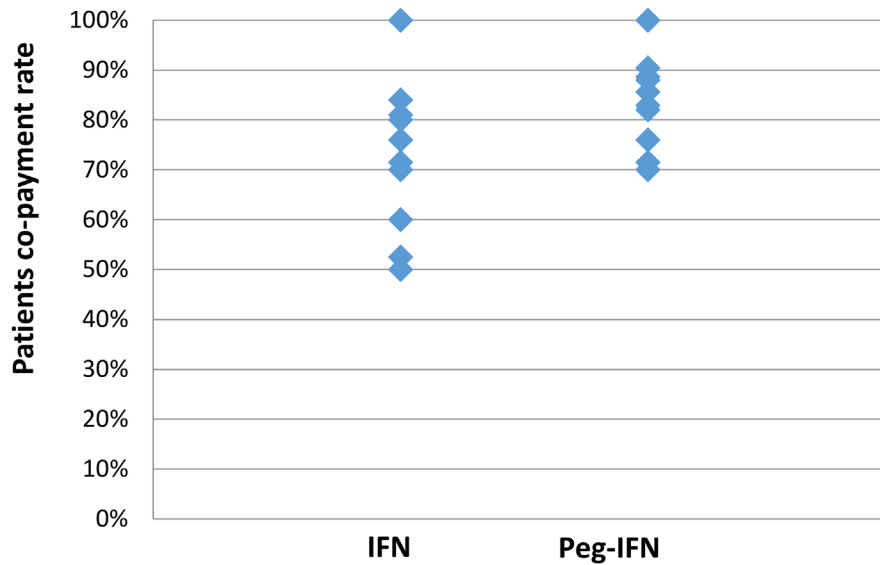


Figure 3. The possible co-payments required by patients for the drug costs relating to interferon-based treatment. The values summarize the different potential patient co-payment rates for the drug costs relating to interferon-based treatment (based on Figure 2 and Equation 2). Note, these only pertain to the drugs and not the other resources/services.

the same for the non-drug costs, but the drug related rates are superseded by the relevant non-drug rates (see Equation 3).

Catastrophic health expenditures

In Vietnam, the average income in 2016 was US\$136 per month³⁴. In comparison, the estimated costs of HCV treatment with IFN or Pre-IFN ranged between US\$200 and US\$480 per month (Table 3). Given that even patients receiving the maximum level of support from the NHI incur substantial out-of-pocket payments for these treatments (Figure 3), it is likely that many patients will have been unable to afford interferon-based HCV treatment. This financial barrier may have led to many patients not being able to access treatment, as well as what is known as “catastrophic health expenditures” (Box 1) (this is when medical spending of a household reaches a point such that the household has to cut down on necessities (such as food, clothing, and their children’s education))³⁵. A variety of different thresholds are used to define this, such as 25% of total household expenditure/income or 40% of a household’s non-subsistence expenditure^{35,36}. Regardless of the exact threshold used, our results indicate that interferon-based treatments were causing catastrophic health expenditures in Vietnam. The importance of reducing such financial barriers is recognised in the Sustainable Development Goals³⁷.

The move towards using DAAs

DAAs were initially very expensive, thereby restricting their use to high-income countries³⁸. However, the emergence of low-cost generic versions of the drugs, has led to steep price reductions. It has been estimated that widespread access to combinations of HCV DAAs is feasible, with potential target prices approximately US\$50–\$250 per person for a standard

12-week treatment course, significantly cheaper than the longer treatment regimens with IFN and Peg-IFN^{39–41}. The new DAA drugs are ‘pangenotypic’, meaning they are similarly efficacious for different genotypes, removing the need for expensive genotype testing in specialist labs or prolongation of therapy for the predominant strains in Vietnam. Because DAA treatment regimens are shorter, with fewer side effects, there will also be cost savings associated with the medical monitoring and consultations required during treatment compared to interferon-based therapy (Figure 1).

A further potential advantage of DAAs is that they may allow the possibility of decentralising hepatitis C treatment to primary health care facilities in some settings⁴², which could also bring additional cost savings⁴³. This benefit will depend on the local health system and needs further investigation.

This cost data related to interferon-based therapy indicates that switching to generic DAAs may lead to potential cost savings.

The most recent Vietnamese MoH treatment guidelines (released in 2016) recommend DAAs as the first-line therapy⁴⁴. However, the costs of DAA drugs only became subsidised by the NHI in June 2019.

Limitations

Our study has several limitations, for example, we focused on quantifying only the direct medical costs of HCV treatment. This includes the costs covered by the insurance system and the patient’s co-payment (Box 1). However, the direct non-medical costs (such as the patient’s travel costs) and the patient’s productivity costs (indirect costs) were not quantified. The total

cost of HCV treatment under the societal perspective (Box 1) would therefore be even higher. It was also not possible to capture the costs associated with the specific side-effects of IFN/Peg-IFN treatment. In our study, we focused only on patients with HCV infection; in practice, the prevalence of co-infections with other hepatotropic viruses or HIV can be high, and this is likely to influence the treatment costs.

Our analysis was performed in the context of the HTD in Ho Chi Minh City, which is a large hospital specialising in infectious disease. Whilst it is possible that there may be some minor variations in costs in other provinces in Vietnam, as the costs of both healthcare services and drugs are regulated centrally by the NHI department and MoH, our cost estimates are likely to be robust. Although the precise results and cost estimates of our study are not directly generalizable to other countries, they are consistent with reports from neighbouring countries, such as Thailand³⁰. It is important that further HCV treatment costing studies are conducted in other low- and middle-income countries, particularly relating to the use of DAAs.

The cost estimates were predominantly based on the price lists from HTD relating to 2017. However, it is possible that the costs, particularly those relating to the drugs, will vary over time.

We have focused on conducting a costing study, hence further evaluation regarding the cost-effectiveness of the different treatments is required.

Conclusion

A deeper understanding of the costs of the different treatment options is vital for supporting HCV policy decisions. Currently, there are few costing studies and economic evaluations of HCV treatment in low- and middle-income countries^{15,45,46}.

We found that treating HCV with IFN or Peg-IFN results in significant direct medical costs. We estimated that a 48-week Peg-IFN treatment regimen costs between US\$3,956–5,887 in Vietnam. The majority of this figure relates to the cost of the drugs.

Although the role of interferon-based therapy is diminishing, this cost data provides a foundation for evaluating the economic benefits and cost-effectiveness of switching to using DAAs.

Of concern, we found that even patients receiving the maximum level of support from the NHI incur substantial out-of-pocket costs for their HCV treatment (Figure 3). Consequently, many patients will not be able to afford the IFN or Peg-IFN treatments, leading to “catastrophic health expenditures” (Box 1). This raises important issues regarding the health insurance payment mechanism for HCV patients. Once newer interferon-free regimens are included in the government’s insurance coverage, out-of-pocket expenses for patients could be reduced, but details of how this will be managed are not yet available. Crucially, minimising costs to patients will be an important part of reaching the ambitious 2030 treatment targets¹².

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Acknowledgements

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 **Rodolfo Castro** 

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In summary, the research can be considered a critical previous step towards improving access to DAAs in Vietnam. It was concluded that treating HCV with IFN or Peg-IFN results in high direct medical costs. DAAs are subsidised by the local National health insurance programme from June 2019.

Some discretionary suggestions to improve the paper's quality are listed below:

It would be useful to have a supplemental spreadsheet that could be used as a parameter for further economic evaluations; this spreadsheet could have citations (or weblinks to the sources used) to allow quick update and checking by future researchers.

An update regarding the actual use of IFN-based regimens for Hepatitis C treatment in Vietnam would be useful.

Authors' could also discuss, as another potential advantage of DAAs, the possibility of decentralising Hepatitis C treatment to primary health care¹; this could bring additional savings if associated with the use of effective generic drugs².

References

1. Castro R, Perazzo H, de Araujo LAMM, Gutierrez IG, et al.: Effectiveness of implementing a decentralized delivery of hepatitis C virus treatment with direct-acting antivirals: A systematic review with meta-analysis. *PLoS One*. 2020; **15** (2): e0229143 [PubMed Abstract](#) | [Publisher Full Text](#)
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Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Not applicable

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Public Health; Health Technology Assessment; Epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 31 Aug 2020

Huyen Nguyen, Oxford University Clinical Research Unit, Ho Chi Minh, Vietnam

In summary, the research can be considered a critical previous step towards improving access to DAAs in Vietnam. It was concluded that treating HCV with IFN or Peg-IFN results in high direct medical costs. DAAs are subsidised by the local National health insurance programme from June 2019.

Some discretionary suggestions to improve the paper's quality are listed below:

It would be useful to have a supplemental spreadsheet that could be used as a parameter for further economic evaluations; this spreadsheet could have citations (or weblinks to the sources used) to allow quick update and checking by future researchers.

Response: We have included the full detail of the costs used within the analysis within Table 4.

An update regarding the actual use of IFN-based regimens for Hepatitis C treatment in Vietnam would be useful.

Response: We have added the following into the introduction.

"We conducted a detailed analysis of the costs of treating chronic HCV with the pre-existing standard of care in Vietnam, IFN and Peg-IFN therapy. Since 2016, Vietnam has started to move away from interferon-based therapy towards DAA treatment regimens (in keeping with WHO guidelines). In June

2019, DAAs started to be covered by national health insurance³². Consequently, due to its side effect profile and the increasing availability of DAAs, interferon-based therapy is becoming more infrequently used in Vietnam. However, data on the costs of interferon-based therapy are still essential for conducting accurate economic evaluations of DAA treatment, as interferon-based treatment will likely be the comparator (Box 1) within the analysis.”

Unfortunately, there is currently no data on the exact numbers receiving interferon-based therapy nationally.

Authors’ could also discuss, as another potential advantage of DAAs, the possibility of decentralising Hepatitis C treatment to primary health care¹; this could bring additional savings if associated with the use of effective generic drugs².

Response: We agree and really appreciate your suggestion. We have added the following with your suggested references:

“A further potential advantage of DAAs is that they may allow the possibility of decentralising hepatitis C treatment to primary health care facilities in some settings [3], which could also bring additional cost savings [4]. This benefit will depend on the local health system and needs further investigation.”

Competing Interests: No competing interests were disclosed.

Reviewer Report 30 January 2020

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Josephine Walker 

Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK

This article presents important information on the cost of treatment for Hepatitis C virus with the older drug regimens that have been in use since 1991 (IFN and Peg-IFN). Although new recommendations are to use direct acting antiviral (DAA) treatments when available, it is important to understand the baseline or previous cost of treatment to accurately estimate the impact of transitioning to new treatment regimens.

There are a few points it would be helpful to address in the discussion:

- The results include a range of uncertainty in the cost of the drugs, based on different brands available, but there is no uncertainty or variation included in the cost of the tests or in the number of tests received per patient. Perhaps comment on whether all patients are expected to receive the same tests or if some will fail to complete treatment.
- The total cost per week and cost per month are referred to in the discussion, it would be clearer if these estimates are included in the results so that the reader doesn't have to

calculate it themselves.

- The point about catastrophic health expenditure is interesting, but made me wonder whether it means patients aren't able to access treatment at all rather than spending beyond their means. Would this change with DAA treatment? Is there any information available about access to healthcare and how this varies according to the distribution of income in the country?
- Furthermore, the change to DAA drugs may result in changes to the number of tests and consultations required due to fewer side effects, which may be worth mentioning.
- It is stated that there are few costing studies and economic evaluations of HCV treatment in LMIC, but no references are included in the discussion to show the few that are available. Some are referenced earlier in the paper regarding IFN treatment, and there are published papers of economic evaluation of DAAs in Egypt and India (plus others in press).

Figure 2 - I think some text is needed to explain this figure as I couldn't follow it. Do the uses of the words "co-payment" vs "out-of-pocket payment" here match the definitions in Box 1? Perhaps converting this into a box instead of a figure would allow for additional explanation of how the co-payment mechanism works? In addition, it wasn't clear to me how the co-payment applies to non-drug costs, and this will also apply to the discussion of catastrophic health expenditures.

Minor changes including editorial points:

- Introduction first paragraph contains an extra close brackets at the end of line 7.
- Methods first paragraph refers to gross per capita income but cites a source of GDP per capita. Clarify if referring to GDP, GNI, or per capita income which is referred to in discussion with a different source cited.
- Table 3 footnote refers to itself, should this refer to Table 4?
- Table 4, please indicate which class of drugs each brand name refers to so that it can be cross-referenced with Table 3.
- Figure 3 caption refers to itself, should this refer to Figure 2?
- The reference for the cost of DAAs is fairly old, unfortunately there is not much published on this but MSF's [press release](#) on what price they pay may be helpful.
- Discussion states that cost data related to IFN supports economic case to increase access to DAAs. Perhaps rephrase to indicate that the cost data provides a foundation for evaluating the economic case to treat with DAAs, as the case for use of DAAs is not made in this paper. Or remove as this is stated later in discussion as well (bottom of page 9 column 1).

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Not applicable

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: I am a co-investigator on an investigator sponsored research grant funded by Gilead Sciences. I am also involved in a research project evaluating the cost and cost-effectiveness of treatment for HCV with DAAs in HaiPhong, Vietnam, funded by ANRS.

Reviewer Expertise: Evaluation of health interventions in low and middle income countries, particularly related to the impact and cost-effectiveness of scaling up treatment for Hepatitis C virus.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 31 Aug 2020

Huyen Nguyen, Oxford University Clinical Research Unit, Ho Chi Minh, Vietnam

This article presents important information on the cost of treatment for Hepatitis C virus with the older drug regimens that have been in use since 1991 (IFN and Peg-IFN). Although new recommendations are to use direct acting antiviral (DAA) treatments when available, it is important to understand the baseline or previous cost of treatment to accurately estimate the impact of transitioning to new treatment regimens.

There are a few points it would be helpful to address in the discussion:

The results include a range of uncertainty in the cost of the drugs, based on different brands available, but there is no uncertainty or variation included in the cost of the tests or in the number of tests received per patient. Perhaps comment on whether all patients are expected to receive the same tests or if some will fail to complete treatment.

Response: The costs were calculated in relation to a standard treatment (based on the treatment guidelines). There will be some variation and we have added the following to the discussion.

"These cost estimates relate to a standard treatment (based on MoH guidelines). It should be noted that in practice there will be variations in these treatment costs and resources utilized, such as for those not finishing the treatment regimen, experiencing treatment failure or those with co-infections such as HIV."

The total cost per week and cost per month are referred to in the discussion, it would be clearer if these estimates are included in the results so that the reader doesn't have to calculate it themselves.

Response: We agree that this would be clearer and have added a column for the average cost per week for the drug cost in Table 3.

The point about catastrophic health expenditure is interesting, but made me wonder whether it means patients aren't able to access treatment at all rather than spending beyond their means. Would this change with DAA treatment? Is there any information available about access to healthcare and how this varies according to the distribution of income in the country?

Response: This is a very good point. We have added more in the text that the high costs may have meant that many patients were not accessing treatment, as well as leading to catastrophic health expenditure. Unfortunately, there is currently no information available about access to healthcare and how this varies according to the distribution of income in the country and we are planning to explore how it may change with DAA treatment in future work.

"In Vietnam, the average income in 2016 was US\$136 per month³⁴. In comparison, the estimated costs of HCV treatment with IFN or Pre-IFN ranged between US\$200 and US\$480 per month (Table 3). Given that even patients receiving the maximum level of support from the national health insurance programme incur substantial out-of-pocket payments for these treatments (Figure 3), it is likely that many patients will have been unable to afford interferon-based HCV treatment. This financial barrier may have led to many patients not being able to access treatment, as well as what is known as "catastrophic health expenditures" (Box 1) (this is when medical spending of a household reaches a point such that the household has to cut down on necessities (such as food, clothing, and their children's education))³⁵. A variety of different thresholds are used to define this, such as 25% of total household expenditure/income or 40% of a household's non-subsistence expenditure^{35, 36}. Regardless of the exact threshold used, our results indicate that interferon-based treatments were causing catastrophic health expenditures in Vietnam. The importance of reducing such financial barriers is recognised in the Sustainable Development Goals"

Furthermore, the change to DAA drugs may result in changes to the number of tests and consultations required due to fewer side effects, which may be worth mentioning.

Response: We have added the following in the "The move towards using DAAs" section *"The new DAA drugs are 'pangenotypic', meaning they are similarly efficacious for different genotypes, removing the need for expensive genotype testing in specialist labs or prolongation of therapy for the predominant strains in Vietnam. Because DAA treatment regimens are shorter, with fewer side effects, there will also be cost savings associated with the reduced medical monitoring and consultations required during treatment compared to interferon-based therapy."*

It is stated that there are few costing studies and economic evaluations of HCV treatment in LMIC, but no references are included in the discussion to show the few that are available. Some are referenced earlier in the paper regarding IFN treatment, and there are published papers of economic evaluation of DAAs in Egypt and India (plus others in press).

Response: We have added appropriate references for this statement – including two

systematic reviews.

"Currently, there are few costing studies and economic evaluations of HCV treatment in low- and middle-income countries [REFS 1-3]"

REF 1: 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):551-67.

REF 2: He T, Lopez-Olivo M, Hur C, Chhatwal J. Systematic review: cost-effectiveness of direct-acting antivirals for treatment of hepatitis C genotypes 2-6. *Alimentary pharmacology & therapeutics*. 2017;46(8):711-21.

REF 3: Chaillon A, Mehta SR, Hoenigl M, Solomon SS, Vickerman P, Hickman M, et al. Cost-effectiveness and budgetary impact of HCV treatment with direct-acting antivirals in India including the risk of reinfection. *PLoS one*. 2019;14(6):e0217964.

Figure 2 - I think some text is needed to explain this figure as I couldn't follow it. Do the uses of the words "co-payment" vs "out-of-pocket payment" here match the definitions in Box 1? Perhaps converting this into a box instead of a figure would allow for additional explanation of how the co-payment mechanism works? In addition, it wasn't clear to me how the co-payment applies to non-drug costs, and this will also apply to the discussion of catastrophic health expenditures.

Response: We have changed Figure 2 to make it clearer and add more explanation of how the co-payment mechanism works within the text.

"In Vietnam, the proportion of the population covered by the national health insurance programme (NHI) as of December 2016 is estimated to be 81.7%³¹. However, even the patients covered by the NHI can incur significant out-of-pocket payments (Box 1) for HCV treatment. For the drug costs relating to HCV treatment, the patient's out-of-pocket payment will be based on the price of the drug and the patient's co-payment rate (the proportion of the billed costs that insured patients pay) (Equation 1).

Equation 1: Out-of-pocket payment for the drugs = Price of the drug × Patient's co-payment rate
The patient's co-payment rate is what is remaining after subtracting the proportion covered by the NHI (Equation 2). In the case of these drug costs, the proportion covered by the NHI (Equation 3) is given by three components (the drug related rate, group related rate and referral related rate). These are outlined in Figure 2.

Equation 2: Patients co-payment rate = 1 - proportion covered by the NHI

Equation 3: Proportion covered by the NHI = Drug related rate × Group related rate × Referral related rate

Based on these rates, even with the maximum level of insurance cover, patients still have to pay 50% of the cost of the IFN drugs and 70% of the cost of the Peg-IFN drugs (See Drug related rate within Figure 2)³². Furthermore, if patients attend the HTD without a formal referral from their primary health care facility, they have to pay for the full cost of the treatment (as though uninsured) (See Referral related rate within Figure 2 and Figure 3)³³. The payment mechanism within the NHI is the same for the non-drug costs, but the drug related rates are superseded by the relevant non-drug rates (see equation 3)."

The co-payment mechanism of the non-drug costs is the same but with different rates. We used the drug cost as an example to show the general idea of how national health insurance works. We have made this clearer in the text.

Minor changes including editorial points:

Introduction first paragraph contains an extra close brackets at the end of line 7.

Response: We have deleted the bracket.

Methods first paragraph refers to gross per capita income but cites a source of GDP per capita. Clarify if referring to GDP, GNI, or per capita income which is referred to in discussion with a different source cited.

Response: We have fixed the references for this and changed the values to GDP per capita.

Table 3 footnote refers to itself, should this refer to Table 4?

Response: We have fixed this (changing Table 3 to Table 4).

Table 4, please indicate which class of drugs each brand name refers to so that it can be cross-referenced with Table 3.

Response: We have fixed by adding subcategory for column 1 within Table 4.

Figure 3 caption refers to itself, should this refer to Figure 2?

Response: We have fixed this (changing Figure 3 to Figure 2).

The reference for the cost of DAAs is fairly old, unfortunately there is not much published on this but MSF's [press release](#) on what price they pay may be helpful.

Response: We have updated the references related to the cost of DAAs

"It has been estimated that widespread access to combinations of HCV DAAs is feasible, with potential target prices approximately US\$50–\$250 per person for a standard 12-week treatment course, significantly cheaper than the longer treatment regimens with IFN and Peg-IFN [REF 1-2]"

REF 1: Hafez TA. Public Health and Economic Burden of Hepatitis C Infection in Developing Countries. *Hepatitis C in Developing Countries*; Elsevier; 2018. p. 25-32.

REF 2: Barber MJ, Gotham D, Khwairakpam G, Hill A. Price of a hepatitis C cure: cost of production and current prices for direct-acting antivirals in 50 countries. *Journal of Virus Eradication*. 2020.

Discussion states that cost data related to IFN supports economic case to increase access to DAAs. Perhaps rephrase to indicate that the cost data provides a foundation for evaluating the economic case to treat with DAAs, as the case for use of DAAs is not made in this paper. Or remove as this is stated later in discussion as well (bottom of page 9 column 1).

Response: Thank you for this suggestion. We have rephrased the statements in the discussion and conclusion.

"This cost data related to interferon-based therapy indicates that switching to generic DAAs may lead to potential cost savings"

"Although the role of interferon-based therapy is diminishing, this cost data provides a foundation for evaluating the economic benefits and cost-effectiveness of switching to DAAs."

Competing Interests: No competing interests were disclosed.