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

Huyen Anh Nguyen¹, Graham S. Cooke², Jeremy N. Day¹,³, Barnaby Flower¹, Le Thanh Phuong⁴, Trinh Manh Hung¹, Nguyen Thanh Dung⁴, Dao Bach Khoa⁴, Le Manh Hung⁴, Evelyne Kestelyn¹,³, Guy E. Thwaites¹,³, Nguyen Van Vinh Chau⁴, SEARCH Investigators, Hugo C. Turner¹,³

¹Oxford University Clinical Research Unit, Ho Chi Minh, Vietnam
²Division of Infectious Diseases, Imperial College London, London, UK
³Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, UK
⁴Hospital for Tropical Diseases, Ho Chi Minh, Vietnam

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
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

This article is included in the **Oxford University Clinical Research Unit (OUCRU) gateway.**
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 products². There are six major HCV strains, genotypes 1–6, and the prevalence of each genotype varies significantly between regions. 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 available¹².

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 2030¹³. 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 mortality¹⁴. In 2015, only 7% of the 71 million people living with chronic HCV infection were treated¹⁵. 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 uptake¹⁶. 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 services¹⁷. 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 countries¹⁸,¹⁹.

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)²⁰. 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. |
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 μg once per week   |
| Peg-IFN α-2b  | 1.5 μg/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 2013⁴. IU, international unit.

Methods

Study location

Vietnam is a lower-middle-income country in Southeast Asia with a population of over 95 million people⁷, and a 2017 GDP per capita of US$2365⁸. The seroprevalence of HCV in the general population has been estimated to be between 1 and 4.7%,⁹,¹⁰ which is high relative to other countries in the region. In Vietnam, genotypes 1 and 6 predominate¹⁹,²¹. 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
HCV treatment guidelines from the MoH (Table 1)\textsuperscript{23}. The dosage of Peg-IFN α-2b was calculated assuming an average body weight of 58 kilograms for men and 50 kilograms for women\textsuperscript{24}.

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 guidelines\textsuperscript{23}. 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 1/4/6\textsuperscript{23}. 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 | No | No |
| **Group 2: Ultrasound** | Abdominal ultrasound | Every 12 weeks | No |
| | Fibro-scan | No | No |
| **Group 3: X-ray** | Chest X-ray | No | No |
| **Group 4: Blood tests** | Full blood count | Every 4 weeks | No |
| | The international normalized ratio | | |
| | Prothrombin | | |
| **Group 5: Immunoassay** | Alpha-fetoprotein | Every 12 weeks | No |
| | Free thyroxine | | |
| | Thyroid-Stimulating Hormone | | |
| | Hepatitis B surface antigen | | |
| | Human immunodeficiency virus | | |
| | Electrolytes | No | No |
| | Albumin | | |
| | Bilirubin | | |
| **Group 6: Biochemical tests** | Creatinine (urine and blood) | Every 4 weeks | |
| | Urea | No | |
| | Alanine transaminase | Every 4 weeks | No |
| | 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 MoH\textsuperscript{23}.
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 programme. One exception to this was the costs relating to the IFN drugs which were obtained from a 2017 report from the Drug Administration of Vietnam.

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$) following the average 2017 exchange rate where 22,370 Vietnamese dong (VND) equal 1 US$.

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 therapy. 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$) | Total treatment cost (US$) |
| Genotype 2/3: 24-week treatment regimen | | | | |
| IFN α-2a + ribavirin | 619.17 – 655.17 | 25.79 - 27.30 | 498.18 | 1,155.29 – 1,167.31 |
| IFN α-2b + ribavirin | 607.75 – 619.77 | 25.32 - 25.82 | 498.18 | 1,119.88 – 1,131.90 |
| Peg-IFN α-2a + ribavirin | 1,644.14 – 2,617.89 | 68.50 - 109.07 | 498.18 | 2,156.27 – 3,130.02 |
| Peg-IFN α-2b + ribavirin | 1,680.07 – 1,967.78 | 70.00 - 81.99 | 498.18 | 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 | 1,953.84 – 1,961.90 |
| IFN α-2b + ribavirin | 1,254.71 – 1,262.97 | 26.14 - 26.31 | 613.24 | 1,882.83 – 1,892.09 |
| Peg-IFN α-2a + ribavirin | 3,327.48 – 5,259.20 | 69.32 - 109.57 | 613.24 | 3,955.60 – 5,887.32 |
| Peg-IFN α-2b + ribavirin | 3,375.89 – 3,950.73 | 70.33 - 82.30 | 613.24 | 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)^b | 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           |
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)\(^{16}\), which is similar to our finding. Another study reported that in China\(^{11}\), 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).

\[
\text{Equation 1: Out-of-pocket payment for the drugs} = \text{Price of the drug} \times \text{Patient’s co-payment rate}
\]

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.

\[
\text{Equation 2: Patients co-payment rate} = 1 - \text{proportion covered by the NHI}
\]
\[
\text{Equation 3: Proportion covered by the NHI} = \text{Drug related rate} \times \text{Group related rate} \times \text{Referral related rate}
\]

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

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**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 month\(^34\). 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 Goals\(^37\).

The move towards using DAAs
DAAs were initially very expensive, thereby restricting their use to high-income countries\(^38\). 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 settings\(^42\), which could also bring additional cost savings\(^43\). 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 therapy\(^44\). 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 generalisable to other countries, they are consistent with reports from neighbouring countries, such as Thailand. 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.

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 targets.

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

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References

1. World Health Organization: Global hepatitis report 2017. World Health Organization; 2017. Reference Source
2. Thu Thuy PT, Bunchoorntavakul C, Tan Dat H, et al.: A randomized trial of 48 versus 24 weeks of combination pegylated interferon and ribavirin therapy in genotype 6 chronic hepatitis C. J Hepatol. 2012; 56(5): 1012-8. PubMed Abstract | Publisher Full Text
3. Carithers R1 Jr, Emerson SS: Therapy of hepatitis C: meta-analysis of interferon alfa-2b trials. Hepatology 1997; 26(3 Suppl 1): S35-S85. PubMed Abstract | Publisher Full Text
4. Sleijfer S, Bannink M, Van Gool AR, et al.: Side effects of interferon-alpha therapy. Pharm World Sci. 2005; 27(1): 423-31. PubMed Abstract | Publisher Full Text
5. Shepherd J, Jones J: A systematic review of the cost-effectiveness of peginterferon alfa-2b in the treatment of chronic hepatitis C. Expert Rev Pharmacoecon Outcomes Res, 2007; 7(6): 577-95. PubMed Abstract | Publisher Full Text
6. Manns MP, McHutchison JG, Gordon SC, et al.: Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet. 2001; 358(9286): 958-65. PubMed Abstract | Publisher Full Text
7. Manns M, Wedemeyer H, Cornberg M: Treating viral hepatitis C: efficacy, side effects, and complications. Gut. 2006; 55(9): 1350-9. PubMed Abstract | Publisher Full Text | Free Full Text
8. World Health Organization: WHO Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection. Geneva, 2018. Reference Source
9. World Health Organization: Key facts on hepatitis C treatment. Reference Source
10. Simmons B, Cooke G, Miraldo M: The impact of voluntary licences for hepatitis C on access to treatment: a difference-in-differences analysis. Reference Source
11. World Health Organization: Progress report on access to hepatitis C treatment: focus on overcoming barriers in low-and middle-income countries. 2018. Reference Source
12. World Health Organization: Global health sector strategy on viral hepatitis 2016-2021. Towards ending viral hepatitis. 2016. Reference Source
13. Cooke GS, Andrieux-Meyer I, Applegate TL, et al.: Accelerating the elimination
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Rodolfo Castro

1 Oswaldo Cruz Foundation, FIOCRUZ, Rio de Janeiro, Brazil
2 Federal University of the State of Rio de Janeiro, UNIRIO, Rio de Janeiro, Brazil

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 care\(^1\); this could bring additional savings if associated with the use of effective generic drugs\(^2\).

References
1. Castro R, Perazzo H, de Araujo LAMM, Gutierres IG, et al.: Effectiveness of implementing a decentralized delivery of hepatitis C virus treatment with direct-acting antivirals: A systematic review with meta-analysis.\textit{PLoS One.} 2020; 15 (2): e0229143 PubMed Abstract | Publisher Full Text
2. Perazzo H, Castro R, Luz PM, Banholi M, et al.: Effectiveness of generic direct-acting agents for the treatment of hepatitis C: systematic review and meta-analysis.\textit{Bull World Health Organ.} 2020; 98 (3): 188-197K PubMed Abstract | Publisher Full Text

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.

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**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 insurance. 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 care; this could bring additional savings if associated with the use of effective generic drugs.

**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.

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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 month\(^34\). 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 blanket.

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.