The direct-medical costs associated with interferon-based treatment for Hepatitis C in Vietnam [version 1; peer review: 2 approved]

Huyen Anh Nguyen<sup>1</sup>, Graham S. Cooke<sup>2</sup>, Jeremy N. Day<sup>1,3</sup>, Barnaby Flower<sup>1</sup>, Le Thanh Phuong<sup>4</sup>, Trinh Manh Hung<sup>1</sup>, Nguyen Thanh Dung<sup>4</sup>, Dao Bach Khoa<sup>4</sup>, Le Manh Hung<sup>4</sup>, Evelyne Kestelyn<sup>1,3</sup>, Guy E. Thwaites<sup>1,3</sup>, Nguyen Van Vinh Chau<sup>4</sup>, SEARCH Investigators, Hugo C. Turner<sup>1,3</sup>

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

**Corresponding author:** Huyen Anh Nguyen (huyenna@oucru.org)

**Author roles:**

- **Nguyen HA:** Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing
- **Cooke GS:** Funding Acquisition, Supervision, Writing – Review & Editing
- **Day JN:** Supervision, Writing – Review & Editing
- **Flower B:** Supervision, Writing – Review & Editing
- **Phuong LT:** Supervision
- **Hung TM:** Writing – Review & Editing
- **Dung NT:** Supervision
- **Khoa DB:** Supervision
- **Hung LM:** Supervision
- **Kestelyn E:** Project Administration, Supervision
- **Thwaites GE:** Funding Acquisition, Supervision, Writing – Review & Editing
- **Chau NVV:** Supervision
- **Turner HC:** Conceptualization, Investigation, Methodology

**Competing interests:** No competing interests were disclosed.

**Grant information:** The MRC GCRF (MR/P025064/1), a Wellcome Trust Collaborative Award (206296) and the Wellcome Trust core grant (106680) supported this work. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Copyright:** © 2019 Nguyen HA et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

**How to cite this article:** Nguyen HA, Cooke GS, Day JN et al. The direct-medical costs associated with interferon-based treatment for Hepatitis C in Vietnam [version 1; peer review: 2 approved] Wellcome Open Research 2019, 4:129
https://doi.org/10.12688/wellcomeopenres.15408.1

**First published:** 04 Sep 2019, 4:129 https://doi.org/10.12688/wellcomeopenres.15408.1
Introduction

The World Health Organization (WHO) estimates that there are 71 million people living with chronic hepatitis C infection globally. Hepatitis C virus (HCV) is typically transmitted through intravenous drug use, unsafe injection practice and the transfusion of unscreened blood/blood products. 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 Vietnam.

Interferon-based therapies have been used to treat HCV since 1991. The original interferon (IFN) intramuscular injections had to be administered daily and were associated with poor cure rates and unpleasant side effects. Pegylated IFN (Peg-IFN) was first licensed in 2001 and has improved pharmacokinetics, requiring only weekly injections. Additionally, Peg-IFN is more effective than IFN and is associated with fewer adverse effects. 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). 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%). The tablets have almost no side effects and forgo the need for weekly injections. 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 licenses. In 2016, 86% of people starting HCV therapy worldwide received DAA drugs rather than interferon-based therapy. Recently, the WHO recommended that interferon-based therapy should no longer be used where DAA drugs are available.

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 2030. 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 mortality. In 2015, only 7% of the 71 million people living with chronic HCV infection were treated. 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 uptake. 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. 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.

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). However, until very recently (June 2019), DAAs were not covered by national health insurance. In addition, 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. |
| Co-payment | The proportion of the total billed healthcare costs that insured patients pay. |
| 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 | 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 viewpoint adopted for Table 1 was 1.5 μg/kg once per week 180 μg once per week 3 million IU three times per week Genotype 1/4/6: 1000mg per day 17 24 16 18 22 17 24 16 21 22 23. The dosages of Peg-IFN α-2a and Peg-IFN α-2b were calculated assuming an average body weight of 58 kilograms for men and 50 kilograms for women.

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 22. 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 22. Both of these regimens were considered in our analysis.

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 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 23. 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 23.

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$) following the average 2017 exchange rate where 22,370 Vietnamese dong (VND) equal 1 US$ 24.

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-2b 22. 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) 22. The dosage of Peg-IFN α-2b was calculated assuming an average body weight of 58 kilograms for men and 50 kilograms for women 22.

### Methods

#### Study location

Vietnam is a lower-middle-income country in Southeast Asia with a population of over 95 million people 25 and a 2017 gross per capita income of US$2160 26. The seroprevalence of HCV in the general population has been estimated to be between 1 and 4.7% 18,19, which is high relative to other countries in the region. In Vietnam, genotypes 1 and 6 predominate 18,20. 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) 21.

#### The resources and services required for HCV treatment

The MoH treatment guidelines from the MoH 2013 treatment guidelines (Table 1) 22. The dosages of Peg-IFN α-2a and Peg-IFN α-2b were calculated assuming an average body weight of 58 kilograms for men and 50 kilograms for women 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 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 23. 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 23.

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$) following the average 2017 exchange rate where 22,370 Vietnamese dong (VND) equal 1 US$ 24.

### 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

| Perspective                  | The viewpoint adopted for deciding which types of costs and health benefits are to be included within an economic evaluation. |
|------------------------------|------------------------------------------------------------------------------------------------------------------------|
| Productivity 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.                          |

| 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 2013 22.

IU, international unit.

Table 1. The Vietnam MoH treatment guidelines for HCV drugs.
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 | No | No |
| | Fibro-scan | Every 12 weeks | No |
| **Group 3: X-ray** | Chest X-ray | No | Every 4 weeks |
| **Group 4: Blood tests** | Full blood count | No | No |
| | The international normalized ratio | No | No |
| | Prothrombin | | |
| **Group 5: Immunoassay** | Alpha-fetoprotein | No | No |
| | Free thyroxine | Every 12 weeks | No |
| | Thyroid - Stimulating Hormone | | |
| | Hepatitis B surface antigen | | |
| | Human immunodeficiency virus | | |
| **Group 6: Biochemical tests** | Electrolytes | No | No |
| | Albumin | | |
| | Bilirubin | | |
| | Creatinine (urine and blood) | Every 4 weeks | No |
| | Urea | No | |
| | Alanine transaminase | Every 4 weeks | No |
| | Aspartate aminotransferase | No | No |
| | Gamma-glutamyl transferase | No | 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.[22]

Table 3. The estimated cost of the different regimens.

| Treatment | Drugs (US$) | Tests (US$) | Consultation fees (US$) | Total (US$) |
|-----------|-------------|-------------|-------------------------|-------------|
| **Genotype 2/3: 24-week treatment regimen** | | | | |
| IFN α-2a + ribavirin | 619.17 – 655.17 | 498.18 | 13.95 | 1,155.29 – 1,167.31 |
| IFN α-2b + ribavirin | 607.75 – 619.77 | 498.18 | 13.95 | 1,119.88 – 1,131.90 |
| Peg-IFN α-2a + ribavirin | 1,644.14 – 2,617.89 | 498.18 | 13.95 | 2,156.27 – 3,130.02 |
| Peg-IFN α-2b + ribavirin | 1,680.07 – 1,967.78 | 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 | 613.24 | 24.41 | 1,953.84 – 1,961.90 |
| IFN α-2b + ribavirin | 1,254.71 – 1,262.97 | 613.24 | 24.41 | 1,882.83 – 1,892.09 |
| Peg-IFN α-2a + ribavirin | 3,327.48 – 5,259.20 | 613.24 | 24.41 | 3,955.60 – 5,887.32 |
| Peg-IFN α-2b + ribavirin | 3,375.89 – 3,950.73 | 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 3). Costs are in 2017 prices.
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.

### Table 4. The assumed input and unit cost for the direct medical cost based on interferon.

| Item                          | Total Quantity          | Unit cost (VND) | Unit cost (US$) |
|-------------------------------|-------------------------|-----------------|-----------------|
| Drug                          |                         | Genotype 2/3    | Genotype 1/4/6  |
| Feronsure (3x10⁶ IU)          | 216x10⁶                 | 432x10⁶         | 189000          | 8.32 |
| Superferon (3x10⁶ IU)         | 216x10⁶                 | 432x10⁶         | 178000          | 7.84 |
| 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-intron (50 μg)a           | Man: 2088 Woman:1900    | 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 |
| 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 |
| Group 6: Biochemical tests    |                         |                 |                 |
| Electrolytes                  | 1                       | 1               | 28600           | 1.26 |
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\(^2\). The drug-related costs contributed the most (54–89%) to the total treatment cost (Table 1). The drug-related costs for treating HCV genotypes 1/6 were approximately US$25 per week for IFN plus ribavirin and between US$68-108 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)\(^2\), which is similar to our finding. Another study reported that in China\(^3\), the Peg IFN-2a and ribavirin for treating HCV genotype 1, cost US$174 per week (2016 prices), almost double our estimate.

**Payment from the national health insurance programme**

In Vietnam, the proportion of the population covered by the national health insurance programme as of December 2016 is estimated to be 81.7%\(^3\). However, even the patients covered by the national health insurance programme incur significant out-of-pocket costs (Box 1) for HCV treatment (the co-payment process is outlined in Figure 2). For example, 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 (Figure 2)\(^3\). 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) (Figure 2 and Figure 3)\(^3\).

**Catastrophic health expenditures**

In Vietnam, the per capita average income in 2016 was US$136 per month\(^4\). 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 be unable to afford HCV treatment. This may lead to what is known as “catastrophic health expenditures” (Box 1), 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)\(^5\). A variety of

| Item | Total Quantity | Genotype 2/3 | Genotype 1/4/6 | Unit cost (VND) | Unit cost (US$) |
|------|----------------|--------------|---------------|-----------------|----------------|
| Albumin | 1 | 1 | 21200 | 0.93 |
| Bilirubin | 1 | 1 | 21200 | 0.93 |
| Creatinine (urine) | 6 | 12 | 15900 | 0.93 |
| 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 |

*The dosage is prescribed following average body weight for men is 58 kg and for women is 50 kg\(^2\). 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 Figure 1. The unit costs of the different types of tests are shown in Table 3. Costs are in 2017 prices.

Out-of-pocket payment = Price of the drug × Patients co-payment rate
Patients co-payment rate = 1 - (Drug related rate × Group related rate × Referral related rate)

The health insurance programme 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 health insurance programme has different group specific payment rates. This grouping is based on the individuals 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 health insurance programme 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 co-payment mechanism for interferon (IFN) and pegylated (Peg)-IFN. Information adapted from 32, 33.
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 HCV treatment is 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. A recent study\(^{39}\) suggested that widespread access to combinations of HCV DAAs is feasible, with potential target prices of US$100–$250 per person for a standard 12-week treatment course, significantly cheaper than the longer treatment regimens with IFN and Peg-IFN. 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 required during treatment compared to interferon-based therapy (Figure 1).

This cost data related to interferon-based therapy indicates the potential savings of generic DAAs and further supports the economic case to increase access to generic DAAs in low- and middle-income countries.

The most recent Vietnamese MoH treatment guidelines (released in 2016) recommend DAAs as first-line therapy\(^{40}\). However, the costs of DAA drugs only became subsidised by the national health insurance programme 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 hepatotrophic 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 national health insurance 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\(^{29}\). It is important that

Figure 3. The possible co-payments required by patients for the hepatitis C virus (HCV) drugs. The values summarise the different potential co-payment rates by patients for the HCV drugs (based on Figure 3). Note, these only pertain to the drugs and not the other resources/services.
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 very 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 is needed for economic evaluation of new DAA treatment strategies. Many countries are struggling to scale up access to DAAs. This cost data highlights the potential cost savings of using DAAs further supports the importance of increased access to generic DAAs in low- and middle-income countries.

Of concern, we found that even patients receiving the maximum level of support from the national health insurance programme 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.

Grant information
The MRC GCRF (MR/P025064/1), a Wellcome Trust Collaborative Award (206296) and the Wellcome Trust core grant (106680) supported this work.

Acknowledgements
SEARCH Investigators (alphabetical order): Barnaby Flower, Eleanor Barnes, Evelyne Kestelyn, Graham S Cooke, Guy E Thwaites, Hugo C Turner, Jeremy N Day, Joel Tarning, Leanne McCabe, Motiur Rahman, Nguyen Van Vinh Chau, Nicholas J White, Sarah L Pett, A Sarah Walker, and Timothy B Hallett.

References
1. World Health Organization: Global hepatitis report 2017. World Health Organization; 2017. Reference Source
2. Thu Thuy PT, Bunchomtavakul C, Tan Dai 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 RL Jr, Emerson SS: Therapy of hepatitis C: meta-analysis of interferon alfa-2b trials. Hepatology. 1997; 26(3 Suppl 1): 835–88S. PubMed Abstract | Publisher Full Text
4. Steijler S, Bannink M, Van Gool AR, et al.: Side effects of interferon-alpha therapy. Pharm World Sci. 2005; 27(6): 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 Pharmacoeconomics 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, Wiedemeyer 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. 2019. 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, Andrioux-Meyer I, Applegate TL, et al.: Accelerating the elimination of viral hepatitis: a Lancet Gastroenterology & Hepatology Commission. Lancet Gastroenterol Hepatol. 2019; 4(2): 135–84. PubMed Abstract | Publisher Full Text
14. Luhnen M, Waffenschmidt S, Gerber-Grote A, et al.: Health Economic Evaluations of Sofosbuvir for Treatment of Chronic Hepatitis C: a Systematic Review. Appl Health Econ Health Policy. 2016; 14(5): 527–43. PubMed Abstract | Publisher Full Text
15. 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): 561–87. PubMed Abstract | Publisher Full Text
16. The World Bank: World Bank Country and Lending Groups. 2017. Reference Source
17. The World Bank: GDP per capita data: Vietnam. 2017. Reference Source
18. Berto A, Day J, Van Vinh Chau N, et al.: Current challenges and possible solutions to improve access to care and treatment for hepatitis C infection in Vietnam: a systematic review. *BMC Infect Dis.* 2017; 17(1): 260. PubMed Abstract | Publisher Full Text | Free Full Text

19. Polaris Observatory HCV Collaborators: Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. *Lancet Gastroenterol Hepatol.* 2017; 2(3): 161–76. PubMed Abstract | Publisher Full Text

20. Dunford L, Carr MJ, Dean J, et al.: Hepatitis C virus in Vietnam: high prevalence of infection in dialysis and multi-transfused patients involving diverse and novel virus variants. *PLoS One.* 2012; 7(8): e41266. PubMed Abstract | Publisher Full Text | Free Full Text

21. Cartwright EJ, Miller L: Novel drugs in the management of difficult-to-treat hepatitis C genotypes. *Hepat Med.* 2013; 5: 53–61. PubMed Abstract | Publisher Full Text | Free Full Text

22. Vietnam Ministry of Health: Decision on promulgating of guidelines “The instruction of treatment and diagnosis for hepatitis C”. In: Health Mo, editor. 2013.

23. World Data: Average sizes of men and women. Reference Source

24. The Hospital for Tropical Diseases: Services and drug price list covered by health insurance. 2017.

25. Drug Administrative of Vietnam Department: A result of drug procurement bidding in each province during period 2016-2017. National reports, 2017. Reference Source

26. OFX: Historocal Exchange rate. Reference Source

27. World Data: Average sizes of men and women. Reference Source

28. Kamal SM: Hepatitis C in Developing Countries: Current and Future Challenges. Academic Press; 2017. Publisher Full Text

29. Kapol N, Lochid-amnuay S, Teerawattananon Y: Economic evaluation of pegylated interferon plus ribavirin for treatment of chronic hepatitis C in Thailand: genotype 1 and 6. *BMC Gastroenterol.* 2016; 16(1): 91. PubMed Abstract | Publisher Full Text | Free Full Text

30. Chen H, Chen L: Estimating cost-effectiveness associated with all-oral regimen for chronic hepatitis C in China. *PLoS One.* 2017; 12(4): e0175189. PubMed Abstract | Publisher Full Text | Free Full Text

31. Vietnam Ministry of Health and Health Partnership Group: Joint annual health review 2016: Towards healthy aging in Vietnam. Hanoi; 2017. Reference Source

32. Vietnam Ministry of Health: Promulgate the list, rate conditions of payment for pharmaceutical medicines, biochemicals, radioactive medicines and substances subject for participants of government health insurance 30/2018/TB-YTT. 2018. Reference Source

33. The rule of Social Health Insurance 58/2014/GH13 (2014). Reference Source

34. Monthly average income per capita at current prices by residence and by region [Internet]. 2016. Reference Source

35. Xu K, Evans DB, Kawabata K, et al.: Household catastrophic health expenditure: a multicountry analysis. *Lancet.* 2003; 362(9378): 111–7. PubMed Abstract | Publisher Full Text | Free Full Text

36. Global Burden of Disease Health Financing Collaborator Network: Future and potential spending on health 2015-40: development assistance for health, and government, prepaid private, and out-of-pocket health spending in 184 countries. *Lancet.* 2017; 389(10083): 2005–30. PubMed Abstract | Publisher Full Text | Free Full Text

37. World Health Organization: Monitoring Sustainable Development Goals –Indicator 3.8.2. Reference Source

38. Rosenthal ES, Graham CS: Price and affordability of direct-acting antiviral regimens for hepatitis C virus in the United States. *Infect Agent Cancer.* 2016; 11(1): 24. PubMed Abstract | Publisher Full Text | Free Full Text

39. Hill A, Khoo S, Fortunak J, et al.: Minimum costs for producing hepatitis C direct-acting antivirals for use in large-scale treatment access programs in developing countries. *Clin Infect Dis.* 2014; 58(7): 928–36. PubMed Abstract | Publisher Full Text | Free Full Text

40. Vietnam Ministry of Health: Decision on promulgating of guidelines “The instruction of treatment and diagnosis for hepatitis C”. In: Health Mo, editor. 2016.
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. *PLoS One*. 2020; 15 (2): e0229143 PubMed Abstract I 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. *Bull World Health Organ*. 2020; 98 (3): 188-197K PubMed Abstract I 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.

Reviewer Report 30 January 2020
https://doi.org/10.21956/wellcomeopenres.16845.r37603

© 2020 Walker J. This is an open access peer review report distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

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.