

## Hepatitis C

### Understanding Factors That Influence the Physicians' Treatment Decisions

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#### Introduction

The Hepatitis C virus (HCV) is a blood-borne virus and a leading cause of chronic liver disease, end-stage cirrhosis, and liver cancer. Prevalence rates in Western Europe, according to the European Association for the Study of the Liver (EASL), are estimated at from 0.4% to 3% of the population, and it is estimated that the burden of HCV is likely to increase in Europe in the coming years. The clinical course of HCV differs; about 25% of patients resolve it without treatment over time, while the remaining 75% develop chronic infection.

The standard of care for chronic infection is peginterferon and ribavirin combination therapy (PEG-IFN/RBV), with treatment lasting from 24 to 72 weeks. While PEG-IFN/RBV reduces the risk of complications, such as cirrhosis, treatment initiation rates are low—about 10% of the diagnosed population—and discontinuation is an issue, mainly because of treatment side effects and the resistance of some forms of the disease to treatment. As a result, success rates vary between 40% and 80% depending on the patient disease genotype (from 1 to 6). Barriers to treatment include low platelet counts, because patients with HCV are at a higher risk of developing thrombocytopenia (TCP) given the side effects of HCV treatment and/or the biology of late stage liver disease. If platelet counts in patients with HCV and TCP can be increased, potentially treatment initiation, adherence to treatment and patient outcomes could improve.

While clinical trials provide accumulating evidence on treatment efficacy for different patient profiles and the clinical implications of treatment, we know very little about the physician treatment decision process and the factors that influence physicians' to initiate, continue, or stop treatment (i.e., how important low platelet count is in the physician decision to treat or not treat HCV patients).

This study's goal was to improve HCV treatment by (1) better understanding the nexus of factors physicians consider—e.g., clinical, social and behavioural, demographic, physician–experience-related, health and social care systems, regulatory, and policy—when making HCV treatment decisions; (2) investigating the comparative influence and importance of specific factors and combinations of factors and the trade-offs implicated in the decisionmaking process; and (3) examining how much TCP impacts treatment decisions and how it impacts treatment (e.g., its influence on decisions to begin or terminate treatment or adjust dosage and duration of treatment).

To meet this goal, we conducted five analyses, focusing on four European countries characterised by different approaches to healthcare organisation and financing, which alongside cultural differences may have potential implications for treatment pathways for patients with HCV infection. These were: France, Italy, Spain, and the United Kingdom. These analysis included:

1. Review the academic literature and of relevant national and European guidelines;
2. Conduct key informant interviews (KIIs) with national experts to contextualise the data from the literature review and further explore some emerging themes;
3. Map the patient journey in the four countries to identify stages HCV patients pass through once they have entered the healthcare system and map, for each stage, potential points of departure from the typical journey;

4. Design and conduct of Discrete Choice Experiments (DCEs) to quantitatively assess the importance of factors that influence treatment decisions;
5. Conduct expert workshop to help build scenarios identifying challenges to HCV treatment.

The five analyses build on one another, with the first three providing evidence that fed into the design of the DCEs and with the DCE results in turn serving as the key inputs into building the scenarios for the expert workshop.

### **Key Findings**

The findings from each set of analyses are summarised below.

#### **Literature Review Findings**

Based on the literature review, two broad categories of factors have a role in influencing physicians' treatment decisions. The first relate to the **patient's profile** and include: (1) clinical factors, such as viral genotype and haematological abnormalities (including TCP and anaemia); (2) comorbidities and related conditions, such as HIV, Hepatitis B (HBV) and depression, side effects; (3) special population groups (including injecting drug users, alcohol-dependents, prison inmates, and migrants) and age-related groups, including the elderly and children; (4) sociodemographic factors, such as administrative region, income levels, and social inclusion; and (5) factors related to patient behaviour, such as issues with adherence to treatment or substance misuse.

The second broad category of factors described in the literature relates to **health system features**, which include: (1) health financing and cost-effectiveness; (2) awareness and adherence to guidelines; and (3) access to care through eligibility criteria, collaboration between healthcare professionals and the wider health system stakeholders, and access to educational interventions to improve practice and alleviate fear and discrimination.

#### **KII Findings**

Although the literature defines the two broad categories of important factors in influencing physicians' treatment decisions, there was a lack of evidence on how physicians actually make decisions, and on the weight they attribute to the different factors in practice. Therefore, we conducted KIIs to elaborate on the information obtained from the literature, give a country-specific perspective to that information, and start to understand the tradeoffs made when undertaking treatment decisions.

KIIs with five experts in HCV in the clinical and advocacy areas from each country—France, Italy, Spain, and the UK—highlight the **importance of the patient's profile in physician decisionmaking**. In general, the opinions of the experts were similar across the four countries. Genotype is a strong determinant for treatment in all four countries, and comorbidities (in particular, HIV, depression, diabetes, HBV and cirrhosis) influence decisions. Interviewees also highlighted the **role of demographic and behavioural factors in treatment decisionmaking, mainly in treatment initiation**, across all four countries. Most interviewees noted that the factors influencing the decision to treat special population groups are different from society at large because of complications surrounding adherence, the stigma of HCV, and different entry points and referral systems for these populations. For example, migrant status plays a role because of access to care and education barriers. When considering side effects, experts from all countries note that this involved tradeoffs depending on their level of severity.

Interviewees were also able to provide information about their country's **healthcare system and the impact of this on HCV treatment and decisions**. Interviewees report variation in the quality of care across and within countries, and under-diagnosis is viewed as a major problem, although diagnosis levels are increasing in some countries. However, interviewees also note that an increase in diagnosis would inevitably constrain resources and that the resource constraints would be exacerbated by the imminent arrival of new, more expensive therapies. Government support and funding appear to vary within countries, with, for example, large regional diversity in the UK and Spain.

### **Mapping the Patient Journey Findings**

The mapping of the typical patient journey for each of the four countries under study partly drew on evidence extracted from the literature review and, more specifically, on the KIIs. This information was complemented by a targeted review of (national) policy documents and hospital guidelines for HCV and/or the treatment of HCV infection in the four countries. Drawing on this information enabled us to build a picture of the “typical” journey and to highlight the barriers and gaps patients encounter as they pass from diagnosis to treatment.

In general, **the referral process is two-phase**, with patients undergoing a preliminary diagnosis in primary care, often incidentally through a routine health check or by being treated for another ailment and then being referred to a specialist centre where the full diagnosis is given. Treatment is then provided in this specialist setting, such as a secondary care unit in a hospital or by outpatient specialist care, depending on the healthcare system, stage of disease, and clinical and behavioural characteristics.

**There are some points of departure from this “typical” journey**; they result mainly from general practitioners' (GPs') limited knowledge about HCV diagnostic tools and decisions, the capacity of the specialist providers to follow up with patients and offer continuity of care, the quality of care coordination and intra-professional collaboration across units, and the motivation and commitment of the individual patient.

### **DCE Findings**

The findings from the literature review, KIIs, and path mapping highlighted a research gap where new empirical research could add value, i.e. the tradeoffs made by physicians in their decisions whether to treat different patients. These earlier stages of research also uncovered a range of possible factors that could be used as the basis of DCEs, from which the influence of each factor could then be quantified. DCEs provide a method for gaining *quantitative* insights into how different factors influence decisionmaking. Within a DCE, respondents are asked, in a survey context, to consider a range of hypothetical choice scenarios, each described by specific attributes, and indicate the decisions they would make in these scenarios. Respondents are forced to make tradeoffs and have to make pragmatic judgements about how they would respond in each situation, thus reflecting real-world decisionmaking.

In this case, 210 physicians—including gastroenterologists, hepatologists, infectious disease specialists, GPs, and specialist nurses—were surveyed across the four countries. There were two DCEs—one focused on the **factors influencing the decision to begin treatment**, and one focused on the **decision about if and when to make changes to the regimen of patients already being treated**; the two DCEs were presented in the context of a survey designed to also obtain information about the physicians themselves.

**Physician Sample Findings.** In our physician sample, a larger proportion of the individuals interviewed in Spain and France compared to the UK and Italy report that they make decisions on their own and are solely responsible for decisions in their unit, suggesting a greater degree of autonomy in these systems. Interestingly, these physicians were more likely to cease treatment than those without overall responsibility for a unit. In terms of physician perceptions of their healthcare systems, physicians generally feel positive about access to care, but opinions were mixed when specifically considering special populations—a particular issue in Spain and Italy.

**Findings Regarding the Decision Whether to Commence Treatment.** [Figure 1](#) shows an example of the one of the scenarios (or vignettes) provided to physicians for the first DCE experiment, regarding the decision whether to commence treatment; each scenario contains a range of attributes that briefly characterise the patients' clinical history, their clinical and demographic characteristics, and their social characteristics. Each physician was asked to consider nine such vignettes and indicate for the patient in question whether they would decide to begin treatment.

The findings from this first DCE experiment show that **a wide range of factors has a statistically significant influence on decisions to begin treatment:**

- Patient's age;
- Whether patients are severely obese;
- History of drug or alcohol misuse;
- Whether patients have stable living arrangements;
- Whether patients have dependents who require support;
- Level of motivation;
- Any history of psychosis;
- Clinical considerations, such as patients' genotype, the stage of the disease, and their haemoglobin, platelet, and white cell counts.

**A number of patient factors were not found to have a statistically significant influence on the decision to treat; these include gender, social support network, and comorbidities.**

The value added of DCEs and the modelling process that utilises the data is that we can quantify the relative weight placed on each factor in physicians' decisions to treat. For example, platelet count is identified as an important factor in influencing the decision to treat, and a number of studies focus on agents that can increase platelet counts in patients to ensure they are eligible for antiviral HCV therapy. In the KIIs, TCP is mentioned as an important factor influencing decisions to initiate and continue treatment, in particular in Italy, Spain, and the UK. The DCEs provides further insight and allow us to quantify the relative importance placed on TCP compared to other patient characteristics in both the decisions about whether to initiate treatment and continue it. [Figure 2](#) shows the value of each of the factors found to be significant in the decision to treat, in units of equivalent change in platelet count.

For example, if a physician has two patients who are identical in all other ways apart from one having a past history of drug or alcohol misuse, then the figure shows that that patient would need a platelet count that was in excess of 14,000/mm<sup>3</sup> higher than the other patient to be considered for treatment over them. The model from physicians choices also shows that a patient having an ongoing drug or alcohol misuse problem would require a platelet count in excess of

59,000/mm<sup>3</sup> higher than a patient without any history of misuse to be considered for treatment over them (all else being equal).

The relationship between platelet count and decision to treat is non-linear. The evidence from our study suggests that TCP leads to reductions in the likelihood of treatment, and that interventions that can increase platelet counts up to 70,000/mm<sup>3</sup> will act to increase the likelihood that any patient will be considered for initiation of treatment.

Findings regarding the decision whether to continue treatment. The second experiment concentrates on the factors influencing the decisions around continuing treatment, presenting the physicians with vignettes like the one shown in Figure 3.

At this point, we find that **very few of the patients' background characteristics play a significant role in the decision to continue treatment**, with only their blood test results at treatment initiation (haemoglobin, platelet, and white blood cell counts) influencing the decision to continue, adjust, or terminate treatment. However, the patient's physiological response to treatment influences the decision whether to continue treatment, and patients are less likely to remain in treatment as time elapses, and if they do not have an appropriate RNA response. Deterioration in the levels of blood counts from baseline is a significant determinant in decreasing dose or ceasing treatment, but an increase in blood count levels from baseline does not increase the probability of continuing treatment. **Patient adherence to the treatment is another factor** observed to influence the decision. Those stated to be unreliable were more likely to have their treatment ceased. However, **side effects were not a significant factor** in the decision to decrease dose or cease treatment, perhaps because physicians use adherence as an indication of how much side effects can be tolerated.

### Findings from Applying the Models

We have implemented these models of how factors influence physician decisions to begin and continue treatment into a forecasting system, which we use to calculate the likelihood of treatment in each of the countries for a patient with given characteristics. The forecasting system can examine the change in probability of treatment as different characteristics change, thus showing the influence of a given characteristic on the decision and presenting potential areas of future investigation to increase the number of patients undergoing successful treatment.

For example, for the patient shown in Figure 4, we can explore the difference in probability of being accepted for treatment if he were instead experiencing severe TCP. Although the probabilities of being treated will vary according to the specific patient profile under consideration, we can show the influence that platelet count can have on the probability of treatment for an otherwise attractive patient and how this influence differs between countries. This illustrates the power of DCEs in not only showing which factors are important in influencing treatment decisions, but also in *quantifying* the level of influence that each are likely to have based on the responses obtained from the structured choice experiments undertaken with a sizeable sample of physicians across the four countries of interest.

### Expert Workshop Findings

The results of the previous tasks were discussed in an expert workshop focusing on the current issues and how these might develop over time. Scenarios were developed around the common elements of context and uncertainty to illustrate the potential challenges and to examine shaping actions that could be taken to improve treatment prospects and patients' outcomes given the current clinical, policy, and innovation environments.

Workshop participants contributed to the development of the scenarios through systematically categorising the list of key factors influencing physicians' decisions, based on the perceived level of impact and the level of uncertainty of the factor. The scenarios were then focused on those factors that had a high impact and high level of certainty, and these were used to develop key shaping actions which could be adopted to support the development of each situation described. The scenarios were developed by RAND Europe around different models of care delivery: (1) **community primary care**, targeted at hard to reach population groups; (2) **care delivered in a network of specialist practices**; and (3) **highly specialised centre-based care**. All these scenarios have different outcomes, advantages, and challenges. Depending on the scenario realised, there will be different impacts on the factors that are significant in treatment decisions today.

For example, in a community-based system, there will be less of an issue with living arrangements because the system will include local initiatives to help patients find suitable accommodation during treatment. Blood counts will no longer be a limitation in the specialist care systems because close monitoring, along with specialist care and new medications to manage levels, will alleviate this. We would also anticipate that the influence of genotype on the decision to begin treatment will be reduced in specialised environments because of the presence of new medications and experienced physicians.

All scenarios could reduce the impact of psychological issues on treatment, through spillover improvements, close monitoring, or integrated care. Patient motivation could be improved in all scenarios by a variety of interventions, including the development of strong social networks at a community level, the promotion of one-to-one support by specialist nurses, and the introduction of new drugs with fewer side effects in specialised settings.

Such scenarios-based futures thinking can be used as a guide to inform **shaping actions**—future strategic decisions that might be taken to either help situate oneself in any of the given scenarios and make plans or help take an active role in shaping different scenarios that might come to light in the future. Some examples of shaping actions addressing some of the relevant factors among clinical, lifestyle, and healthcare system-related characteristics include the following:

- **Clinical:** Current barriers to starting treatment and to deciding whether to continue treatment include levels of platelets and red and white blood cells. Thus, **developing treatments that alleviate these issues would increase the number of patients who could commence and continue treatment**. The issue of genotype could also be addressed if a new drug compatible with all forms of the disease were developed.
- **Lifestyle:** The main lifestyle factors identified as impacting the decision to initiate treatment were living arrangements, motivation, and a history of alcohol and substance misuse. Living arrangements were consistently highlighted as an issue, because of the current need to refrigerate medication. But such concerns may be alleviated with the move toward an oral pill rather than an injection. **All these factors require coordinated interaction with other parts of the health and social care systems, and with the voluntary sector (e.g. patient associations)**. Support from psychiatrists throughout therapy could help patients with adherence issues, those with chaotic lifestyles, or those with current or previous alcohol or substance misuse.
- **Healthcare system:** There are major differences in physicians' propensity to treat across countries, and available resources and system organisation play a role in influencing these decisions. Interventions seeking to **reshape elements of care standards and care delivery**

**within healthcare systems** are likely to optimise treatment rates. For example, identifying steps to facilitate the **updating of guidelines to reflect best practice** would constitute a system improvement. This can be complemented by **implementing positive changes in the patient's journey in terms of flow and support**; doing so could increase adherence and also improve physicians' confidence in the system which, from our results, would in turn lead to an increase in treatment continuation.

## Conclusions

Based on the results of this study we have identified key factors in physicians' decisions to treat Hepatitis C and have quantified the impact of TCP on treatment decisions. We have also looked at some of the policy implications of such factors in treatment decisions through scenario analysis. Below we summarise our key findings.

### Factors Important in Influencing Physicians' Decisions to Treat Hepatitis C

We used a multi-method approach to identify a number of factors important in affecting physicians' decisions to initiate HCV treatment for patients. As shown in Table 1, DCEs provide a valuable empirical way of confirming factors identified in the literature review and KIIs as important (e.g., age, country, genotype, history of alcohol/substance abuse), but DCEs were also useful in showing that factors important in the literature review and/or KIIs (e.g., comorbidities and gender) are not important to physicians and that factors not shown as important (or as important) in the literature review and KIIs (e.g., BMI, living arrangement, stage of disease) are more important to physicians.

Interestingly, the factors involved in continuing treatment often differed from those influencing treatment initiation. At the continuation stage, for patients that had already been accepted for treatment, the patient's profile and circumstances were no longer important factors, and the decision focused on the clinical response to treatment. For example, significant factors include the duration of the treatment so far, the patient's adherence to therapy, and a reduction in haemoglobin, white blood cell, and platelet counts. However, although severe side effects were mentioned in the KIIs as a factor influencing the decision to continue treatment, this was not reflected in the DCE results.

### Focus on the Impact of TCP on Treatment Decisions

Platelet count was identified as an important factor in influencing the decision to treat, and a number of studies in the literature review focus on agents that can increase platelet counts in patients to ensure they are eligible for antiviral HCV therapy. In the KIIs, TCP was mentioned as an important haematological factor influencing treatment decisions to initiate and continue treatment in Italy, Spain, and the UK. Interviewees in both Italy and the UK mentioned issues with the guidelines around the treatment of patients with low platelet counts, stating that the threshold levels were too high compared to reality. The views on the importance of TCP did vary across countries, with French interviewees stating that it was rare to interrupt treatment based on TCP.

The models estimated from the data collected through the DCEs provide further insight and allow us to quantify the relative importance placed on TCP alongside other patient characteristics in both the decisions about whether to initiate treatment and whether to continue treatment should TCP occur during treatment. One can examine a range of different patient profiles and, for each, to look at the difference that having, or not having, TCP will have on the patient's probability of receiving treatment. This can be used to illustrate the possible impact that may be achieved with new therapies that could reduce the onset of TCP.

## **Relative Importance of Factors and Policy Implications**

While the DCEs illustrate the influence that each factor has on treatment decisions independent of each other, some of these factors are interrelated in actual patients, and a change in one factor may also lead to a change in another. Thus, in interpreting the findings, it is important to take this into account if considering how interventions may seek to influence these factors to improve the probability that certain patient groups will be judged as eligible or appropriate for treatment.

To validate the relationship between factors and assess their future impact on treatment decision, we explored the emerging findings with a workshop of experts and developed a set of scenarios. In the scenario building, blood counts, genotype, patient commitment (motivation at initiation, adherence at continuation), living arrangements, severe psychological issues, and collaboration within the healthcare system were considered as factors that may have a high impact on treatment decision, but whose impact could be decreased by appropriate interventions, including investment into new drug development, public health education campaign, etc.

## **Footnotes**

The research described in this article was conducted by RAND Europe.