The Portuguese universal access program to direct-acting antivirals (Sovaldi® and Harvoni®) for the treatment of Hepatitis C:

A financial analysis of the first 2 years

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Dissertation written under the supervision of Professor Susana Frazão Pinheiro

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Abstract

Title: The Portuguese universal access program to direct-acting antivirals (Sovaldi® and Harvoni®) for the treatment of Hepatitis C: A financial analysis of the first 2 years

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Nowadays, 350.000 people die annually due to the direct or indirect action of the Hepatitis C virus, responsible for many acute and chronic hepatitis worldwide and their further progression to more severe diseases like Hepatic Cirrhosis and Hepatocellular Carcinoma. Portugal is no exception as 150.000 people are estimated to be infected with related deaths up to 1.200 annually.

Two years ago, after Gilead's development of two new drugs - Sovaldi® (Sofosbuvir) and Harvoni® (Sofosbuvir + Ledipasvir) - with treatment success rates around 95%, the Portuguese government took the decision of granting universal access to this drugs to all patients infected with the HCV, regardless of the stage of progression of the disease.

The objective of this thesis is therefore to perform an economic analysis of this measure, understanding the impact, costs and benefits for the patients and healthcare system, what conclusions are willing to be taken and how can it influence future deals.

The collection of data from the Infarmed press releases as well as previous studies enabled the comparison of the economic profit for the government when treating patients with Sovaldi® / Harvoni® versus Pegylated Interferon and Ribavirin. The results showed that the new therapy is cost-effective, increasing HCV infected patients' life expectancy while avoiding many severe occurrences.

Key Words: Hepatitis C, Sovaldi, Harvoni, Sofosbuvir, Ledipasvir, Markov Model

Resumo

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Actualmente, 350.000 pessoas morrem anualmente devido à acção directa ou indirecta do vírus da Hepatite C. Portugal não é excepção, uma vez que se estima que 150.000 pessoas estejam infectadas e que ocorram anualmente 1.200 mortes relacionadas com este vírus.

Há dois anos atrás, após o desenvolvimento por parte da Gilead de dois novos fármacos – Sovaldi® (Sofosbuvir) e Harvoni® (Sofosbuvir + Ledipasvir) – com taxas de sucesso de tratamento à volta dos 95%, o governo português tomou a decisão de garantir o acesso universal destes fármacos a todos os pacientes infectados com o VHC, independentemente do estádio de progressão da doença.

Esta tese pretende realizar uma análise económica desta medida, tentando calcular o impacto, os custos e os benefícios que pode trazer para os pacientes e para o Sistema Nacional de Saúde, tendo a noção que as conclusões obtidas poderão influenciar decisões futuras.

Os dados recolhidos do Infarmed conjugados com o de estudos anteriores permitiram comparar os ganhos económicos para o Estado ao tratar pacientes com Sovaldi® / Harvoni® quando comparado com Interferão Peguilado e Ribavirina. No final, os resultados mostraram que a nova terapia é custo-efectiva, aumentando a esperança média de vida dos pacientes infectados com VHC e permitindo evitar um grande número de ocorrências graves.

Palavras-chave: Hepatite C, Sovaldi, Harvoni, Sofosbuvir, Ledipasvir, Modelo de Markov

Preface - Acknowledgments

Although every student knows that at some point in their Master they must write a dissertation, it does not become an easy task. Throughout this journey, many people with their knowledge, advices and support, helped me complete this thesis successfully.

I would like to express my deepest gratitude to my father for being my mentor all along this dissertation process, as well as to my mother and brother for all the support throughout all this time. A special thanks to Carolina, undoubtedly the person who listened to me the most and that through her advices and kind words manage to encourage me to keep going.

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Finally, a last thank you to all my friends that with their support and concern pushed me to complete this dissertation effectively.

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1. Introduction

Nowadays, 350.000 people die annually due to the direct or indirect action of the Hepatitis C virus, responsible for many acute and chronic hepatitis worldwide and their further progression to more severe diseases like Hepatic Cirrhosis and Hepatocellular Carcinoma. This virus is spread out worldwide infecting 2,2% of the world population. Portugal is no exception as 150.000 people are estimated to be infected with related deaths up to 1.200 annually.

Two years ago, after Gilead's development of two new drugs - Sovaldi® (Sofosbuvir) and Harvoni® (Sofosbuvir + Ledipasvir) - with treatment success rates around 95%, the Portuguese government took the decision of granting universal access to these drugs to all patients infected with the HCV, regardless of the stage of progression of the disease. The main purpose of this thesis is therefore to perform an economic analysis of this historical decision, considering the patients treated during the first two years.

To evaluate this decision, a few analysis were done around its impact for the core stakeholders, the patients, as well as the economic benefits for the Government. Also important is whether this measure can be the basis for future similar decisions. The main research questions to focus on, are:

RQ1: What are the impact, cost and benefits of this measure for:

- Patients
- Healthcare system

RQ2: What conclusions are achieved and how they can influence:

- The near future
- Similar measure (co-participation) for different diseases

This thesis aims to have both academic and managerial relevance. As the government decision is relatively recent, this study will provide both the opportunity and the challenge to economically evaluate the first program of its kind. Also, if results are positive, it might serve as future ground for many other similar decisions in the healthcare sector.

The dissertation is structured in five chapters: Introduction, Literature Review, Methodology and Data Collection, Results' Analysis and Main Conclusions and Further Research.

It will start with an overview of the dissertation's topic and context, followed by a second chapter aiming to present some facts and figures about HCV, both in Portugal and worldwide. It explains the natural history of the disease and its associated costs, as well as the evolution of the treatments and an attempt to contextualize the Portuguese government decision. The last subchapter is related with the methods used by economists to choose between different measures.

The third chapter explains the processes of data collection used to obtain the results and to answer the research questions. It also clarifies the methodology used to perform this economic analysis, splitting it between benefits and costs. The following chapter briefs the results gathered during the analysis of the results, once more separated between costs and benefits and applying the methods described previously. Its core function is to support the last chapter where the conclusions will be listed.

In this last chapter, a summary of the answers to the research questions will be provided, stating the main results obtained and how can they influence future deals. Finally, the potential limitations that could affect results will be stated as well as possible research to be developed in the future.

2. Literature Review

2.1 Facts and Figures

Since its discovery in 1989, the Hepatitis C Virus (HCV) has been quickly spreading out around the world. Data from 2010 suggests that around 185 million individuals (2,2% of the world's population) are infected with this disease and that 350 000 patients die every year (World Health Organization, 2014). Asia is considered the continent with the highest number of infected individuals, followed by Africa and Europe (Lavanchy, 2011).

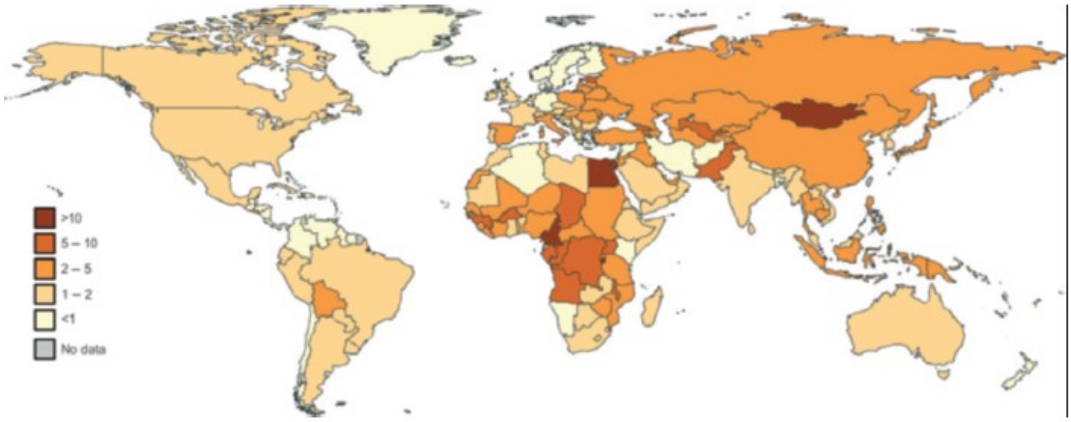


Figure 1 - Hepatitis C global prevalence 2010 (%)

(Lavanchy, 2011)

Since HCV is primarily transmitted through exposure to contaminated blood (Alter, 1995), population groups that have an increased risk of exposure to this disease include recipients of blood transfusions and derivatives before 1992, injection drug users, healthcare workers and HIV infected patients (Chak, Talal, Sherman, Schiff, & Saab, 2011). Nevertheless, it is fair not to forget high-risk sexual exposure as another means of transmission of the disease, as well as piercings and tattoos, accounting for 10-20% of HCV infections (Alter, 1997).

According to a panel of experts, in 2013, 1-1,5% of the Portuguese population, or 100.000 to 150.000 patients, is infected with HCV. However, only 30% (~37.500) are assumed to be diagnosed (Anjo et al., 2014; Baptista Leite, 2014). The annual HCV incidence rate in Portugal is one new case per 100.000 inhabitants, meaning 100 new cases per year (Anjo et al., 2014), while 900-1200 HCV related deaths are estimated annually (Baptista Leite, 2014).

Furthermore, high percentages of HCV were found in endovenous drug users (50%), especially in long duration users (80%) and HIV co-infected patients (30%). Patients in hemodialysis (5%), blood transfusions receptors before 1992 (2%) and babies from HCV infected mothers (1,5%) were other identifiable risk groups (Anjo et al., 2014).

2.2 Natural History of HCV

The Natural History of Hepatitis C is highly variable, ranging from acute and chronic hepatitis, to cirrhosis, hepatocellular carcinoma (HCC) and death (EASL, 2015). When entering the human body, HCV lasts around 15-150 days to incubate (Aranda da Silva, 2006). During its acute stage, the majority of the patients are still asymptomatic and while some spontaneously eradicate the virus, the majority (54-86%) establish a chronic infection (Maasoumy & Wedemeyer, 2012). In this stage, 15-51% of the patients develop cirrhosis at a given moment in life, influenced by several factors like alcohol consumption, diabetes, aging or HIV co-infection (Maasoumy & Wedemeyer, 2012). The Metavir scoring system is currently accepted for the liver fibrosis staging.

METAVIR stage	F0	F1	F2	F3	F4
Definition	No fibrosis	Portal fibrosis without septa	Portal fibrosis with septa	Numerous septa without cirrhosis	Cirrhosis

Figure 2 - METAVIR liver biopsy scoring system

(WHO, 2014)

At F4 stage, patients have already developed cirrhosis and can progress from a compensated phase of the disease to a decompensated one associated with portal hypertension and hepatic insufficiency, causing jaundice, ascites, digestive bleeding and infections (Anjo et al., 2014). Annually, 3-6% of the cirrhotic patients have a severe liver decompensation, which increases the mortality ratio to 18% in the next year and 50% in a 5 year period (Maasoumy & Wedemeyer, 2012).

The Hepatitis C Virus has also an oncogenic potential and estimations state that the virus causes approximately 25% of the Hepatocellular Carcinomas (HCC) worldwide (Tanaka et al., 2006). Plus, the incidence of HCC cases is higher in cirrhotic patients (1,4 - 4,9% per year), being the overall five-year HCC risk between 7-30%. (Lok et al., 2009).

Concerning Portugal, estimations showed that 60% of the diagnosed patients were in the chronic hepatitis C state (CHC), while the rest of the patients were split between compensated cirrhosis (30%), decompensated cirrhosis (6%) and HCC (4%) (Anjo et al., 2014). Although in the last years a reduction on the number of new infected patients has been noticed, until 2030

there will be an increase on the number of patients in the higher stages of the disease (45%, 100% and 80%), respectively (Baptista Leite, 2014).

Also, HCV is considered the main cause for transplants associated to viral infections while in Portugal a panel of experts estimated that 20% of the hepatic transplants were due to HCV, meaning 50 out of an annual average of 250 liver transplants, expecting to increase in the near future (Baptista Leite, 2014).

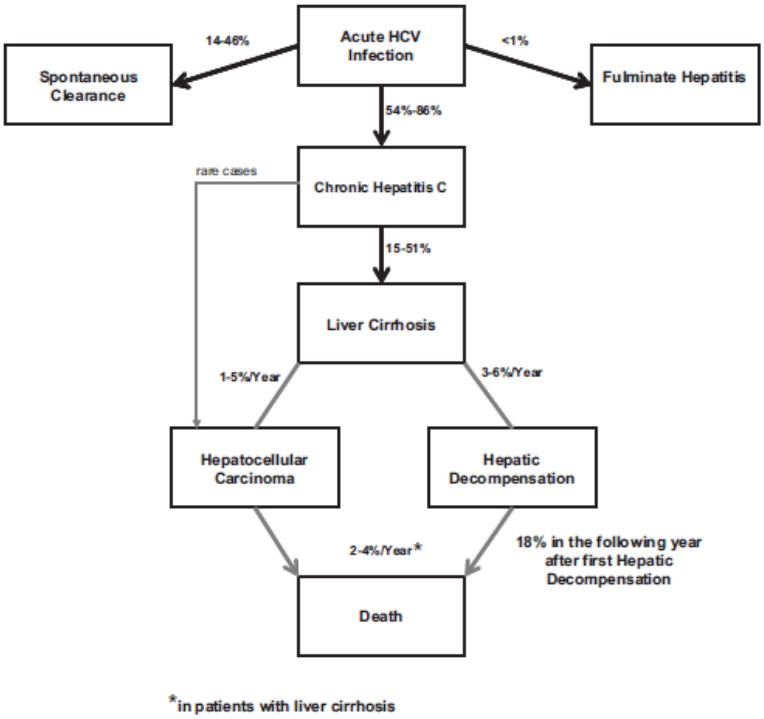


Figure 3 - Natural History of HCV infection

(Maasomy and Wedemeyer, 2012)

2.3 Associated costs

To analyze the economic impact of the HCV infection, both direct and indirect costs should be calculated. As far as direct costs are concerned, both the costs of medication exclusive for hospitals and in ambulatory are included. Furthermore, specialized appointments, diagnostic and therapeutic complementary exams and medication for transplanted patients are also considered. As indirect costs, absenteeism or the loss of productivity are included in the list (Anjo et al., 2014).

In Portugal, the most recent studies estimate that the annually HCV associated costs are around 70 million euros (Anjo et al., 2014; Baptista Leite, 2014). These are mainly related to the more advanced stages of the disease and do not include anti-viral costs. Taking into account

the estimations to 2030, annual direct costs will ascend as high as 2.100 million euros.(Baptista Leite, 2014).

In a study from 2013, the annual average cost per patient and per stage in Portugal was estimated in 432€ for CHC, 522€ for compensated hepatic cirrhosis, 11.103€ for decompensated hepatic cirrhosis and 17.128€ for HCC. Regarding transplanted patients, the average annual costs were estimated as 116.154€ in the first year and 6.886€ for the following years. The annual costs per stage of the disease are summarized on the plot below **(Figure 4)**. Indirect costs were not considered, as there is no absenteeism in chronic hepatitis and compensated cirrhotic patients, only less than 20% of the decompensated hepatic cirrhosis were workers (from the 10% in that stage) and with an advanced average patient age (Anjo et al., 2014)

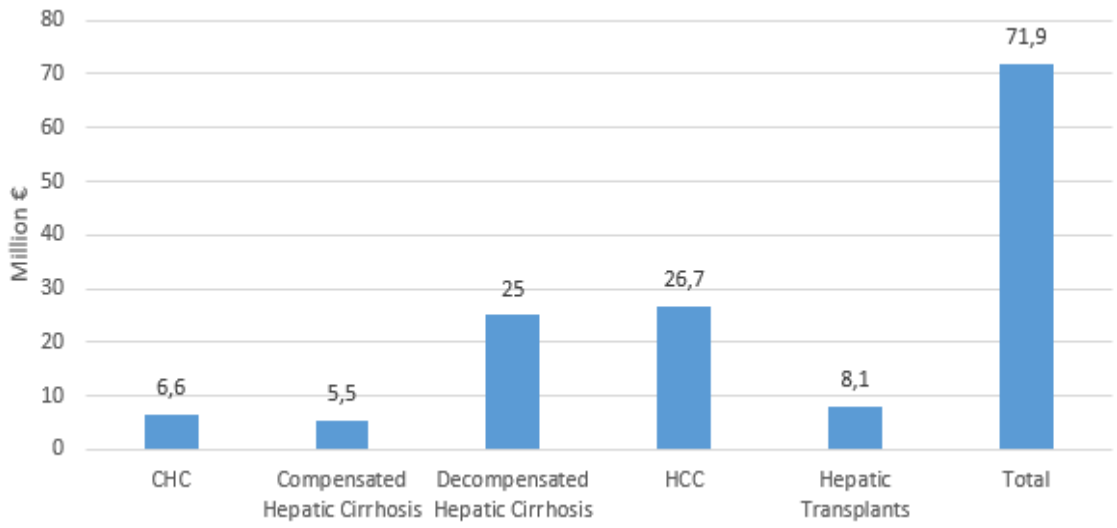


Figure 4- Annual Costs per Stage of the disease in Portugal

(Adapted from Anjo et al. 2014)

2.4 HCV Treatment

Currently, 6 different HCV genotypes (G) have been identified (Naggie, 2012), as well as 50 subtypes (Aranda da Silva, 2006). Determining each patient genotype is crucial as it influences the type of treatment and its duration (José Velosa, Caldeira, Lopes, Guerreiro, & Marinho, 2012). Genotype 1 is predominant in the USA and in Europe, G4 and G5 in Africa and G6 in Asia. Portugal is no exception in the European continent, as studies show that the dominant genotype is G1 (60%), followed by G3 (30%), G4 (10-15%) and G2 (2%) (Baptista Leite, 2014; J. Velosa et al., 2011).

The goal of the HCV therapy is to eradicate the virus. Nowadays, it is considered that the infection is cured in patients who achieve a Sustained Virological Response (SVR): undetectable HCV RNA, 12 - 24 weeks after treatment completion. Nevertheless, cirrhotic patients remain at risk of having severe complications, even after curing the infection (EASL, 2015).

Before 2011, the standard treatment for chronic hepatitis C was a combination of Pegylated Interferon alfa (PegIFN) and Ribavirin (RBV) for 24 or 48 weeks (José Velosa et al., 2012). However, while for patients infected with G2, G3, G5 or G6, SVR rate was 80% or higher, for patients with genotype 1 rates were around 40-50% (Antaki et al., 2010). Plus, this treatment was contra-indicated in several groups of patients (EASL, 2011; José Velosa et al., 2012).

In 2011, in order to suppress the gap in the HCV G1 treatment effectiveness, Boceprevir (BOC) and Telaprevir (TVR) were licensed to the market. These two drugs were the first of a new generation of direct-acting antivirals (DAA), and together with PegIFN and RBV, were able to increase SVR to rates to 65-75% (Bacon et al., 2011). Still, the side effects and the high costs of this triple combination influenced its weak market acceptance and success (EASL, 2015).

Currently, Sofosbuvir (SOF), a drug produced by Gilead and licensed in 2014, is recommended by the most recent international guidelines for the treatment of CHC patients (EASL, 2015), as it showed unparalleled SVR rates and tolerability (European Medicines Agency, 2013). Plus, combined with ribavirin and/or Simeprevir and Daclatasvir, two other DAA licensed in 2014, it showed rates of 60-100% depending on the HCV genotype (EASL, 2015). The combination of Sofosbuvir with another Gilead owned medicine, Ledipasvir (LDV), resulted in SVR rates around 94% for G1 HCV patients (Afdhal, Reddy, et al., 2014; Afdhal, Zeuzem, et al., 2014; Guzman Sabrina, 2014; Kowdley et al., 2014). These new drugs had the advantage of being taken as a pill once per day when compared with the former treatments: 5-6 pills per day (RBV) or subcutaneous (PegIFN) (Aranda da Silva, 2006; EASL, 2015).

Patients	PegIFN-α, RBV and sofosbuvir	PegIFN-α, RBV and simeprevir	Sofosbuvir and RBV	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombit-asvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Genotype 1a	12 wk	12 wk, then PegIFN-α and RBV 12 wk (treatment-naïve or relapsers) or 36 wk (partial or null responders)	No	8-12 wk, without RBV	12 wk with RBV	No	12 wk without RBV	12 wk without RBV
Genotype 1b					12 wk without RBV			
Genotype 2	12 wk	No	12 wk	No	No	No	No	12 wk without RBV
Genotype 3	12 wk	No	24 wk	No	No	No	No	12 wk without RBV
Genotype 4	12 wk	12 wk, then PegIFN-α and RBV 12 wk (treatment-naïve or relapsers) or 36 wk (partial or null responders)	No	12 wk without RBV	No	12 wk with RBV	12 wk without RBV	12 wk without RBV
Genotype 5 or 6	12 wk	No	No	12 wk without RBV	No	No	No	12 weeks without RBV

Figure 5 - Treatment recommendations for HCV-monoinfected or HCV/HIV coinfected patients with chronic hepatitis C without cirrhosis

(EASL 2015)

Patients	PegIFN-α, RBV and sofosbuvir	PegIFN-α, RBV and simeprevir	Sofosbuvir and RBV	Sofosbuvir and ledipasvir	Ritonavir-boosted paritaprevir, ombit-asvir and dasabuvir	Ritonavir-boosted paritaprevir, and ombitasvir	Sofosbuvir and simeprevir	Sofosbuvir and daclatasvir
Genotype 1a	12 wk	12 wk (treat-ment-naïve or relapsers) or 24 wk (partial or null re-sponders)	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	24 wk with RBV	No	12 wk with RBV, or 24 wk without RBV	12 wk with RBV, or 24 wk without RBV
Genotype 1b					12 wk with RBV			
Genotype 2	12 wk	No	16-20 wk	No	No	No	No	12 wk without RBV
Genotype 3	12 wk	No	No	No	No	No	No	24 wk with RBV
Genotype 4	12 wk	12 wk (treat-ment-naïve or relapsers) or 24 wk (partial or null re-sponders)	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	No	24 wk with RBV	12 wk with RBV, or 24 wk without RBV	12 wk with RBV, or 24 wk without RBV
Genotype 5 or 6	12 wk	No	No	12 wk with RBV, or 24 wk without RBV, or 24 wk with RBV if negative predictors of response	No	No	No	12 wk with RBV, or 24 wk without RBV

Figure 6 - Treatment recommendations for HCV-monoinfected or HCV/HIV coinfected patients with chronic hepatitis C with compensated cirrhosis

(EASL 2015)

2.5 The Portuguese Government Decision

Before 2014, the standard HCV treatment was similar to the rest of the world: Pegylated Interferon alfa combined with Ribavirin at first, followed by a triple treatment with both combined with Boceprevir or Telaprevir when they became available (Anjo et al., 2014; José Velosa et al., 2012). From the moment Gilead obtained its license to sell Sofosbuvir and Ledipasvir, the interest demonstrated by Portuguese patients in these new drugs was significant.

However, the fact that it was only accessible by wealthy patients (40.000 euros /patient) (Favreau, 2014) and the incapacity of the Portuguese government to reach an agreement with Gilead lead many patients to demonstrate their dissatisfaction in the media and even in the Portuguese parliament (Lusa, 2015). The government had at the time an emergency plan, consisting in treating with this medicine only patients with decompensated cirrhosis awaiting for a liver transplant (Castanho, 2014).

In February 2015, after one year of negotiations, the Portuguese Ministry of Health initiated a new HCV treatment policy, granting universal access to this new generation of direct-acting antivirals, specifically Sovaldi® (Sofosbuvir) and Harvoni® (Sofosbuvir + Ledipasvir), to all patients registered in the National Healthcare System. (Infarmed, 2015). It was considered an unprecedented measure, aiming to increase the life expectancy of HCV infected patients, while decreasing public expenditures (Infarmed, 2015).

Previous treatment	Regimen	Non-cirrhotic			Cirrhotic			Source*
		Maximum Duration (weeks)	Pts. (%)	SVR (%)	Maximum Duration (weeks)	Pts. (%)	SVR (%)	
No	LDV/SOF	12	18.4	96.2	24	51.0	96.9	ION-3
	LDV/SOF	8	81.6	96.7	12	49.0	97.0	ION-3
	P+R	48	-	48.8	48	-	25.9	Various
	BOC+P+R	48	-	67.7	48	-	41.7	Poordad et al. 2011
	SOF+P+R	12	-	92.7	12	-	79.6	SPC Sovaldi®†
	SOF+R	24	-	67.6	24	-	36.4	SPC Sovaldi®‡
	No treatment	-	-	0.0	-	-	0.0	-
Yes	LDV/SOF	12	79.2	95.4	24	87.1	100	ION-2
	LDV/SOF	24	20.8	98.9	12	12.9	86.4	ION-2
	P+R	48	-	38.1	48	-	26.3	Forns et al. 2014
	BOC+P+R	48	-	64.4	48	-	35.3	Bacon et al. 2011
	No treatment	-	-	0.0	-	-	0.0	-

BOC: boceprevir; LDV: ledipasvir; P: pegylated interferon; Pts: patients; R: ribavirin; SOF: sofosbuvir.

Figure 7- Modelled regimens and respective SVR estimates for HCV genotype 1 subgroups (Almeida JM, Felix J et al. 2015)

According to the former Portuguese Health Minister, Paulo Macedo, the Government had granted "Europe's best deal", explaining that Gilead would only be paid per patient as long as the treatment proved to be successful. Plus, regardless of the duration of the treatment, 8, 12 or 24 weeks, the government would always pay the same, less than 20.000 € per patient (RTP, 2015). The agreement would have the duration of two years, expecting to treat 7000 to 8000 patients in this time span (Carriço, 2015), while a national registry would be created for collecting information about the success of the treatment, the so-called Portal of Hepatitis C (Tato Marinho, 2016).

At the end of July 2015, Infarmed (the Portuguese national authority for drugs and health products) had estimated that around 5000 patients had been treated, while 2184 premature

deaths were spared. Furthermore, 217 hepatic transplants, 1200 HCC and 3204 cirrhosis incidents were avoided, resulting in treatment cost savings of 166 million euros (Infarmed, 2015).

2.6 Economic Evaluation in Healthcare

Different forms of economic evaluation are used to assist economists in decision making between different courses of action. Although the most appropriate method of economic evaluation depends always on the context, the most straight-forward approach should always be applied (Robinson, 1993d).

2.6.1 Cost-Benefit Analysis

Being the most comprehensive of all the economical evaluations, the cost-benefit analysis consists on listing the potential advantages and disadvantages of an option, so that the best choice can be made (Robinson, 1993d). Monetary values are put on both inputs (costs) and outputs (benefits), making it possible to say if a program offers a net gain to society whenever total benefits are higher than total costs. Although early valuation of benefits' methods were based on the human capital approach, being outcomes valued in terms of productivity gains, recent methods adopted valuations based on peoples' preferences, their willingness to pay.

Nevertheless, when using this method economists need to be capable to understand that the value people give to money is often included in the valuation of the benefits of the healthcare program (Robinson, 1993a). Since the 1930s, it has been applied to healthcare programs and become a framework for all other forms of economic evaluations, such as the cost-effectiveness or the cost-utility analysis (Robinson, 1993d).

2.6.2 Cost-Effectiveness Analysis

The cost-effectiveness analysis is used to compare the costs of different programs when outcomes are in common natural units. When measuring healthcare procedures, data is ideally collected from economical evaluations in clinical trials, being the outcomes returned in life years gained, cases cured or even occurrences avoided. Procedures are then expressed in costs per unit of outcome. Although there is some disagreement among economists about whether benefits should be discounted, the traditional view still requires it, so that long-term effects do not become so cost effective. Furthermore, whenever there is uncertainty about the outcomes, a sensitive analysis should be performed. (Robinson, 1993b). Despite being the most applied approach until 10 years ago, this type of analysis have certain limitations, not being able to help

economists decide between treatments for different diseases or to analyze reductions in morbidity and mortality in a single index (Robinson, 1993d).

2.6.3 Cost-Utility Analysis

To overcome cost-effectiveness analysis limitations, economists developed the cost-utility evaluation, a more sophisticated approach. It enable economists to choose between different strategies in the healthcare sector using utility, the level of well-being experienced by people in different states of health. Life scales such as the Quality-Adjusted Life Years (QALYs) **(Appendix 1)**, have been created so that a single measure of lifetime utility can be obtained from a utility-based quality of life in a given health state and a quantitative measure of life years (Robinson, 1993d).

In order to compare different program's outcomes, indexes such as the Rosser's combined categories of two dimensions, disability and distress, obtaining different health states. Scores were then expressed in terms of 0 = Dead to 1 = Perfect Health, becoming possible to assign a Quality of Life (QoL) score, to any health state (Robinson, 1993c). This index has later become the role model for more complex questionnaires, such as the EuroQoL 5 Dimensions Questionnaire (EQ-5D) **(Appendix 2)**.

By obtaining a common unit of utility, different interventions can be compared and ranked using an index measured in cost per QALYs gained, called Incremental Cost-Effectiveness Ratio (ICER) **(Appendix 3)**. Nevertheless, there are some controversy about this type of analysis as it is not consensual how to value a health status or an improvement in health status. (World Health Organization, 2003).

2.6.4 Markov Models in Economical Evaluations

Markov models **(Appendix 4)** are used to evaluate random processes that evolve over time. In healthcare, they are often employed for decision making, particularly when modelling the progression of chronic diseases (Briggs & Sculpher, 1998).

In order to be a realistic and effective model, the disease must be divided into different states, representing mutually exclusive events (clinically and economically). Transition probabilities should also be assigned between the states, being constant over time. The probability of moving to states in each cycle must sum 1, as the probability of staying in the same state is also calculated (1-Probability of Leaving). . Therefore, by running the model over a selected number of cycles (discrete time period), it is possible to estimate long term costs and outcomes associated with the intervention (Briggs & Sculpher, 1998).

QALYs and costs for the given interventions can then be calculated using these models. For QALYs the procedure is to attach a QoL weight to for a given state of health, generating a result in the end of several cycles. Costs however are easier to be calculated if they are attached to transition probabilities as well, representing treatments.

Nevertheless, when computing the model both costs and outcomes should be discounted. By applying a rate of discount, they can therefore be compared in terms of a Net Present Value. As an outcome of the model, it is possible to calculate the incremental costs or the incremental effectiveness of a drug therapy by computing the ICER, using the costs and the effects (normally the QALYs) estimated in the Markov model (Briggs & Sculpher, 1998).

3. Methodology and Data Collection

3.1 Study Design

This economic analysis aimed to analyze the impact of the Portuguese government decision of granting universal access to the new direct-acting antivirals to all patients infected with HCV.

For that matter, primary data was requested to Infarmed regarding information about Portuguese patients collected by the agency on their HCV portal. Given the reluctance of the institution on providing data, the same was retrieved from a poster for EASL 2016 congress from Professor Rui Tato Marinho, using data from the database and revealing patients' distribution per HCV genotype and degree of liver fibrosis (Tato Marinho, 2016). This information was of great importance so that costs and benefits could be calculated with more accuracy.

In February 17th 2017 the total of initiated treatments was 10.168 (Infarmed, 2017b), being the distribution of treated patients per genotype and degree of liver fibrosis as follows:

Treated Patients per HCV Genotype		
G1	6921	68,07%
G2	129	1,27%
G3	1821	17,91%
G4	1275	12,54%
G5/G6	21	0,21%

Table 1- Treated Patients per HCV Genotype (designed from data)

Treated Patients per degree of Liver Fibrosis						
	G1	G2	G3	G4	G6	Total
F0	208	8	36	38	0	290
F1	1453	31	291	293	4	2073
F2	1592	28	364	281	6	2271
F3	1523	19	382	281	4	2209
F4	2146	43	747	383	8	3326

Table 2 - Treated Patients per degree of Liver Fibrosis (designed from data)

3.2 Costs

There were two main types of direct costs considered on this analysis. The cost of the new medication consists on the total Hepatitis C treatment costs of the new therapy for this cohort of patients. The cost of non-treated patients included all the costs associated with patients that did not respond to treatment throughout the progression of the disease along its natural history.

3.2.1 Medication Costs

The cost of the new medication (Harvoni® and Sovaldi®) was not disclosed by the Health Ministry. Nevertheless, values close to 20.000€ - 24.000€ per treatment became public (Carriço, 2015; RTP, 2015), even without quantity discounts, so a sensitivity analysis with cost levels close to this amount will be used to assess the predictable gains for the government (24.000€, 20.000€ and 15.000€).

On the other side, the old medication (Pegylated Interferon and Ribavirin) cost was estimated for the Portuguese case, taking into account estimations from 2013 actualized for 2017. Experts assumed that 70% of patients infected with genotypes 1-4 took Pegylated Interferon 2a + Ribavirin, while 30% Pegylated Interferon 2b + Ribavirin. The average duration of treatments was also estimated, ranging from 30 weeks for G2 and G3 patients and 36 weeks for G1 and G4 patients (Anjo et al., 2014). In the end of treatments, a total of 6.077.531€ for all patients in medical appointments and complementary diagnostic exams would have to be added to total medicine costs **(Table 3)**. Portuguese HCV genotypes 5 and 6 patients are residual, so inherent costs were not calculated.

PegIFN + RBV				
Genotype	Patients	Medication	Weekly cost	Average duration (weeks)
1, 4	70%	PegIFN 2a + RBV	225,48 €	36
	30%	PegIFN 2b + RBV	170,06 €	
2, 3	70%	PegIFN 2a + RBV	223,76 €	30
	30%	PegIFN 2b + RBV	168,35 €	

Table 3 - Old Medication therapy schematics (designed from data)

3.2.2 Non-treated patients' costs

Concerning the cost of non-treated patients, two groups were considered. The first one included all patients with F0-F3 liver fibrosis and the second gather all the patients with F4, that is, hepatic cirrhosis. The rationale behind this decision was that HCV patients treated before cirrhosis had minimal chances of evolving to higher stages of the disease. F0-F2 patients are considered cured. F3 patients are only kept into periodical analysis for Hepatocellular Carcinoma screening. Also, cirrhotic and non-cirrhotic patients respond differently to the two treatments as SVR is lower in cirrhotic patients (Floreani, 2008; Rodrigues, 2016).

Although this new therapy has increased substantially the overall success rate to levels close to 100% (96,5% SVR) (Infarmed, 2017a), there are still patients whom the new medicine was not successful. They continue progressing through the natural history of the disease to more advanced stages.

In order to understand how progression was made, a Markov model of the disease was followed **(Figure 8),** considering a period of 60 years. The reason behind this lifetime span was to give enough time for all the patients in the model to reach the death stage so that costs could be calculated with more certainty. In order to do so, the average age of the cohort (51,2 years) and INE mortality tables were taken into consideration, so that the probability of mortality from other causes could be added to the model.

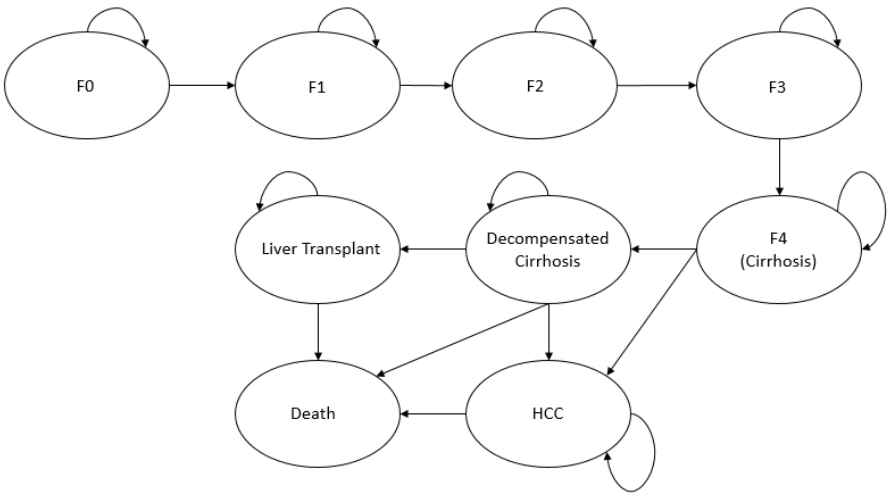


Figure 8 - Simplified HCV Markov model (designed from data)

The number of patients in every stage, from F0 to F4, was multiplied by the non-SVR rate of this treatment for both cirrhotic and non-cirrhotic patients and then by the annual percentage of evolution to further stages of the disease **(Table 4)** for every year of the model.

Stages	% Evolution/year	Source
F0-F1	11,7%	Thiem et al. 2008
F1-F2	8,5%	Thiem et al. 2008
F2-F3	12,0%	Thiem et al. 2008
F3-F4	11,6%	Thiem et al. 2008
Cirrhosis - Hepatic Decompensation	3,9%	Fattovich et al. 1997
Cirrhosis - HCC	1,4%	Fattovich et al. 1997
Hep. Decompensation - HCC	1,4%	Fattovich et al. 1997
Hep. Decompensation - Liver transplant	2,0%	Grieve et al. 2006
Hep. Decompensation -Death	13,0%	Fattovich et al. 1997
HCC - Death	43,0%	Fattovich et al. 1997
Liver transplant - Death (1y)	15,0%	Grieve et al. 2006

Table 4 - Percentage of Evolution/year between HCV stages (designed from data)

After 60 years, the amount of occurrences in every stage of the disease unable to be avoided were then multiplied by the cost per stage per year per patient of the disease (Anjo et al., 2014). These costs had into consideration medical appointments, blood tests, complementary exams, abdominal ultrasounds and even hospitalizations and were actualized at a 5% rate according to

Infarmed specifications **(Table 5)** becoming higher as the disease continues to progress. Liver transplantations had also into consideration costs for the first 10 years after the procedure, as well as the annual probability of death on the first year. Although there is no consensual decision among economists about how and whether or not to value a death, the decision of not accounting those costs was taken.

Since this cohort of patients is relatively similar to the one used in the previous study, including also the Portuguese HCV infected patients (Anjo et al., 2014) and that concluded that indirect costs were not relevant, they were not considered in this analysis.

Lastly, in order to compare the total non-responding patients' costs with the new treatment with the old treatment the same procedure was computed. Different SVR rates for both cirrhotic and non-cirrhotic patients were taken into consideration, when being treated with the two medications, 91,6% / 98,2% for the new therapy and 45,9% / 65,8% for the old therapy (Floreani, 2008; Rodrigues, 2016).

It is fair not to forget that many patients now treated with DAA agents are in reality non-responders to PEG-IFN, ~40% (Martins et al., 2016). Some could not bear its side-effects and a few have medical conditions that contra-indicated the old treatment.

Stages of the disease	Cost / stage /year / patient
CHC (F0 - F3)	432 €
Cirrhosis (F4)	522 €
Hepatic Decompensation	11.103 €
HCC	17.128 €
Liver Transplant	185.014 €
Death	0 €

Table 5- Cost per HCV stage per year per patient for 2017
(Adapted from Anjo et al. 2014)

3.3 Benefits

3.3.1 Lifetime Savings and Reduction of Occurrences

As far as benefits are concerned, a reduction on the number of patients with cirrhosis, hepatocellular carcinomas, liver transplants and premature HCV-related deaths are among them. Lastly, the most important economic benefit to be taken into account by the Portuguese government are the lifetime savings.

With a non-cirrhotic SVR of 98.2%, almost all group 1 patients (F0-F3) become cured (Rodrigues, 2016), not evolving to further stages of the disease and contributing to a decrease

on the number of cirrhosis, HCC and even deaths taking into account the annual transition probabilities. Nonetheless, the 1.8% non-treated non-cirrhotic patients will be accounted as costs and progress to further stages of the disease.

On the other side, SVR for cirrhotic patients (Group 2) is 91.6% (Rodrigues, 2016) what can enlarge the number of HCC, Decompensated Cirrhosis and deaths avoided, considering HCV transition probabilities. Once again, non-responding patients (8.4%) will be considered as costs and progress to further stages of the disease.

After obtaining these numbers for a 60 years lifetime span, it will be possible to calculate the lifetime savings by multiplying the costs per stage per year per patient discounted at a 5% rate by the number of occurrences avoided annually in each stage of the disease, throughout the lifetime of the model. Nevertheless, to compare with the previous treatment, the same method will have to be computed taking into account SVR for both cirrhotic and non-cirrhotic patients.

3.3.2 QALYs and ICER

The Quality-Adjusted Life-Years estimate the years of life remaining for a patient following a particular treatment or intervention. QALYs for a given treatment are calculated by multiplying the average number of years spent by a patient in a given stage of the disease by a quality-of-life score on a 0 to 1 scale. The Quality of Life utilities (QoL) were attributed by patients and measured in terms of the person's ability to perform daily life routine and freedom from pain and mental disturbance in the different states of health (NICE, n.d.). By obtaining the different QALYs per treatment, it was possible to understand whether the new treatment is more effective than the old one and how is it reflected in the average life expectancy of HCV infected patients.

In this analysis, utility values were retrieved from a previous study, and showed a quality of life of 0,81 for HCV infected non-cirrhotic patients, 0,55 for HCV infected cirrhotic patients and the same utility, 0,45, for patients with Decompensated Cirrhosis, Hepatocellular Carcinoma and Liver Transplant **(Table 6)**.

Stages	Utility /QoL	Source
Non-cirrhotic	0,81	Siebert U et al. 2002
Compensated Cirrhosis	0,55	Siebert U et al. 2002
Decompensated Cirrhosis	0,45	Siebert U et al. 2002
Hepatocellular Carcinoma	0,45	Siebert U et al. 2002
Liver Transplant	0,45	Siebert U et al. 2002

Table 6 - Old Medication costs per genotype (Designed from data)

In order to understand whether the new treatment is cost-effective when comparing with the old one, the Incremental Cost-Effectiveness Ratio (ICER) indicator should be taken into consideration. It is the ratio of the change in costs of the two different therapies with the change in the effects of the intervention measured in quality-adjusted life-years.

Several countries define different cost-effectiveness thresholds (WTP), above which treatments are no longer cost-effective. In the United Kingdom the National Institute for Health and Care Excellence (NICE) sets a threshold of £30.000 per QALY (Appleby, 2007), so this rule will be used in order to assess whether this new therapy is cost-effectiveness.

4. Results' Analysis

4.1 Medication Costs

Old medication therapy costs were calculated taking into account the distribution of the cohort by genotype. HCV G1 and G4 therapy lasted 36 weeks on average, while HCV G2 and G3 lasted 30. In the end, adding up monitoring costs, total costs amount 79.822.699€ **(Table 7)**.

PegIFN + RBV							
Genotype	Patients	Medication	Weekly cost	Average duration (weeks)	Costs	Monitoring costs	Total
1, 4	70%	PegIFN 2a + RBV	225,48 €	36	46.572.130,93 €	6.077.531,25 €	79.822.699,28 €
	30%	PegIFN 2b + RBV	170,06 €		15.054.078,18 €		
2, 3	70%	PegIFN 2a + RBV	223,76 €	30	9.164.121,30 €		
	30%	PegIFN 2b + RBV	168,35 €		2.954.837,62 €		

Table 7 - Old Medication costs per genotype (designed from data)

Since new therapy costs are still not disclosed, a sensitivity analysis was conducted so that it could be possible to calculate whether the decision of treating patients with Sofosbuvir or Sofosbuvir + Ledipasvir was economically profitable to the government.

As it is observable on the table below **(Table 8)**, patients infected with HCV genotypes 1, 4, 5 and 6, representing the majority of the cohort, were treated only with Sofosbuvir or Sofosbuvir + Ledipasvir, while for patients infected with G2 and G3, Ribavirin (65€ per week) had also to be taken into account. For these two HCV genotypes, the treatment duration is 12 and 24 weeks.

Total medication costs were then tested for three different cost levels of Sofosbuvir / Sofosbuvir + Ledipasvir. In the first scenario, 24.000€, total costs for the new medicine would amount 244.034.336€. In the second scenario, a cost level of 20.000€ per patient would return total costs of 203.362.336€. Lastly, a lower cost of 15.000€ per patient would result in 152.522.336€ in costs.

New Medication							
Genotype	Patients	Treatment	Average duration (weeks)	Cost SOF / LDV	Cost RBV / Week (a)	Cost per Genotype	Total
1, 4-6	8218	SOF / LED	12	24.000 €	65 €	197.226.662 €	244.034.336 €
2	129	SOF / LDV + RBV	12			3.099.985 €	
3	1821	SOF / LDV + RBV	24			43.707.688 €	
1, 4-6	8218	SOF / LED	12	20.000 €		164.355.552 €	203.362.336 €
2	129	SOF / LDV + RBV	12			2.583.451 €	
3	1821	SOF / LDV + RBV	24			36.423.333 €	
1, 4-6	8218	SOF / LED	12	15.000 €		123.266.664 €	152.522.336 €
2	129	SOF / LDV + RBV	12			1.937.783 €	
3	1821	SOF / LDV + RBV	24			27.317.889 €	

(a) Source: Prontuário Infarmed

Table 8 - Cost of treating HCV patients with the new medicine for different costs per treatment levels (designed from data)

4.2 Non-treated patients' costs

Costs representing the non-responding patients to the new treatment were computed, taking into consideration the new SVR rates for a 60 years period. In the beginning (Y=0), 403 patients did not respond to the treatment, split between 123 untreated CHC and 279 cirrhosis. From this point on, for a period of 60 years and according to the annual transition probabilities supra mentioned **(Table 4)**, 11 Hepatic Decompensations and 4 Hepatocellular Carcinomas will occur in Year 1. Sixty years from now, all patients will be on the death stage, resulting in a present value of total non SVR patient costs of 22.602.901€ **(Table 9)**.

As a means of comparison between treatments, costs representing non-responding patients to the old treatment were also computed. Taking into consideration the former SVR rates for both cirrhotic and non-cirrhotic patients for a lifespan of 60 years, it is clear to see that costs will be higher, as 4140 patients were incapable of becoming cured with the old therapy, being 99 HCV infected patients in F0 liver fibrosis stage, as well as 709 F1, 777 F2 and 755 F3 and 1799 cirrhotic patients. This will result in more occurrences of further stages of disease. The present value of total non-responding patients to the old medicine costs will amount 191.994.899€ sixty years from now **(Table 9)**.

New Medication (SVR Cir = 91,6% | SVR NCir = 98,2%)								
Stages of the disease	Cost / stage /year / patient	0	1	2	3	4	60	
F0	525 €	5	5	4	4	3	0	
F1		37	35	32	30	27	0	
F2		41	39	37	35	33	0	
F3		40	40	40	39	39	0	
Cirrhosis (F4)	634 €	279	268	258	248	238	0	
Hepatic Decompensation	13.496 €		11	19	26	31	0	
HCC	20.819 €		4	6	7	8	0	
Liver Transplant	224.886 €			0	1	1	0	
Death	0 €		1	6	13	21	403	
	PV Costs	241.946 €	438.041 €	599.690 €	732.810 €	840.049 €	0 €	22.602.091 €

Old Medication (SVR Cir = 45,9% | SVR NCir = 65,8%)								
Stages of the disease	Cost / stage /year / patient	0	1	2	3	4	60	
F0	525 €	99	87	77	67	59	0	
F1		709	658	610	565	522	0	
F2		777	741	705	670	634	0	
F3		755	758	756	750	740	0	
Cirrhosis (F4)	634 €	1799	1785	1771	1758	1744	0	
Hepatic Decompensation	13.496 €		70	128	175	214	0	
HCC	20.819 €		25	40	49	55	0	
Liver Transplant	224.886 €			1	4	7	0	
Death	0 €		14	51	102	164	4140	
	PV Costs	2.370.579 €	3.598.188 €	4.645.876 €	5.542.847 €	6.298.025 €	0 €	191.994.899 €

Table 9 - Progression of non-responding patients in New vs Old Medication and its cost for a 60 year period (designed from data)

As it is clear to understand, a higher SVR new medication rate influences the amount of non-responding patients' costs to decrease significantly, less 169.392.808€ when comparing to the former therapy. The maximum difference between costs happens in year 10, when non-SVR

costs for the old medication represent 8.187.907€, while the maximum new medication costs spent in a year was 1.053.315€ **(Figure 9)**.

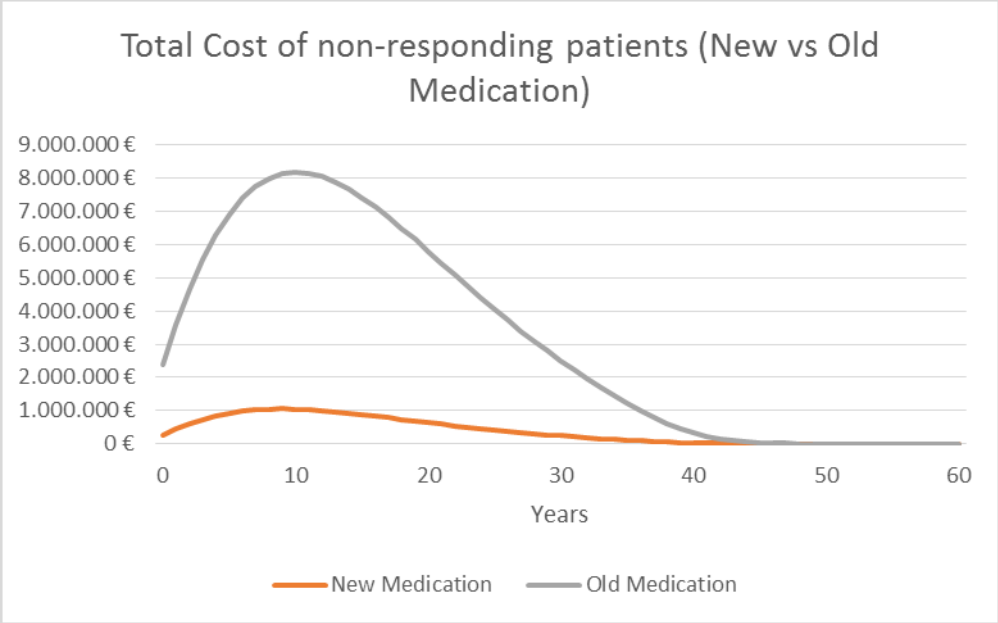


Figure 9 - Progression of Total Costs for non-responding patients in New vs Old Medication for a 60 year period (designed from data)

4.3 Lifetime Savings in Occurrences Avoided

Regarding Lifetime Savings in Occurrences Avoided, by treating the cohort of patients with the old medication (Pegylated Interferon + Ribavirin), splitting patients according to its degree of fibrosis and applying the correspondent SVR rates for both cirrhotic and non-cirrhotic, 6029 patients, 4503 Chronic Hepatitis C (191 F0, 1364 F1, 1494 F2, 1454 F3) and 1527 cirrhosis would have been treated successfully. That would have prevented 59 Hepatic Decompensations and 21 Hepatocellular Carcinomas from happening in the end of the first year. Sixty years from now, the Present Value of the lifetime savings for the government, concerning this cohort of patients and applying annually discounted prices, would have summed 238.434.133€ **(Table 10)**.

By treating patients with the new treatment, SVR rates increase significantly, which will result in 9766 successfully treated patients, distributed by 6720 chronic hepatitis C (285 F0, 2036 F1, 2230 F2, 2169 F3) and 3047 cirrhosis. 118 Hepatic Decompensations and 43 Hepatocellular Carcinomas were avoided in the end of the first year. In a 60 years period, Lifetime Savings for the new medication would amount 407.826.941€ **(Table 10)**.

New Medication (SVR Cir = 91,6% | SVR NCir = 98,2%)								
Stages of the disease	Cost / stage /year / patient	0	1	2	3	4	60	
F0	525 €	285	251	220	194	170	0	
F1		2036	1889	1751	1621	1499	0	
F2		2230	2128	2025	1923	1822	0	
F3		2169	2178	2171	2154	2125	0	
Cirrhosis (F4)	634 €	3047	3126	3200	3268	3330	0	
Hepatic Decompensation	13.496 €		118	220	307	383	0	
HCC	20.819 €		43	69	87	99	0	
Liver Transplant	224.886 €			2	6	12	0	
Death	0 €		34	107	206	326	9766	
	PV Costs	5.461.632 €	7.477.186 €	9.262.848 €	10.852.166 €	12.245.784 €	0 €	407.826.941 €
	PV QALYs	7119	6679	6247	5831	5433	0	89.161

Old Medication (SVR Cir = 45,9% | SVR NCir = 65,8%)								
Stages of the disease	Cost / stage /year / patient	0	1	2	3	4	60	
F0	525 €	191	168	148	130	114	0	
F1		1364	1266	1173	1086	1005	0	
F2		1494	1426	1357	1288	1221	0	
F3		1454	1459	1455	1443	1424	0	
Cirrhosis (F4)	634 €	1527	1609	1686	1758	1824	0	
Hepatic Decompensation	13.496 €		59	112	159	200	0	
HCC	20.819 €		21	35	45	52	0	
Liver Transplant	224.886 €			1	3	6	0	
Death	0 €		21	62	117	183	6029	
	PV Costs	3.332.999 €	4.317.039 €	5.216.662 €	6.042.129 €	6.787.808 €	0 €	238.434.133 €
	PV QALYs	4487	4209	3938	3678	3429	0	56.592

Table 10 - Progression of responding patients in New vs Old Medication and its cost for a 60 year period (designed from data)

Once more, as it is clear to observe, as a result of a more effective SVR, the new medication increases substantially the savings in occurrences. It will always return higher savings during the lifetime span of the model, reaching its peak 11 years from now, when the government will be able to save 16.523.804€ **(Figure 10)**. On the other side, treating patients with the old therapy will return a maximum of 9.424.527€ on savings in the end of year 12.

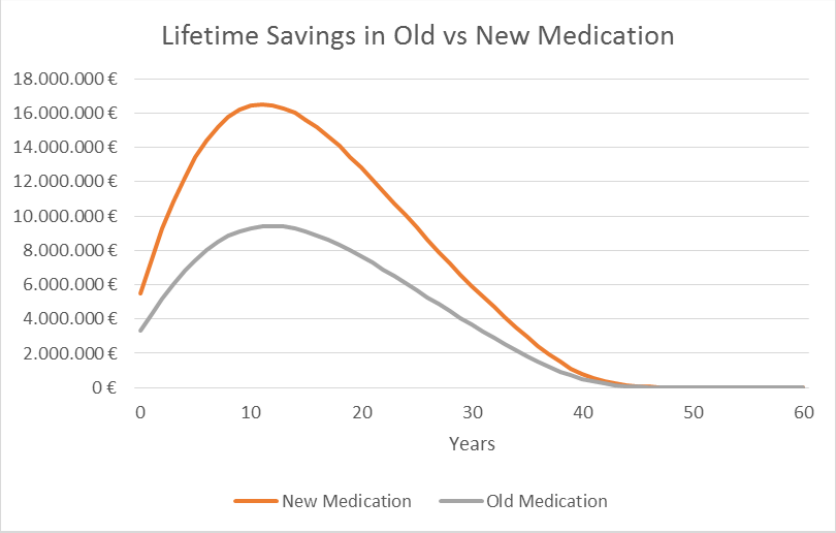


Figure 10 - Progression of Lifetime Savings for responding patients in New vs Old Medication for a 60 year period (designed from data)

4.4 Reduction in Occurrences

By treating HCV infected patients with the new medication (Harvoni® and Sovaldi®), it will be possible to observe in the long-term that a larger number of occurrences will not happen.

The table below **(Table 11)** resumes the difference in the number of occurrences avoided, being the new treatment capable of preventing 3693 cirrhosis, 2458 Hepatic Decompensations, 1083 Hepatocellular Carcinomas, 286 Liver Transplants and 3737 premature HCV-related deaths from happening during the 60 years lifetime span.

Ocurrences Avoided	New Medication	Old Medication	Diference btw treatments
Cirrhosis (F4)	9634	5940	3693
Hepatic Decompensation	6345	3887	2458
HCC	2792	1710	1083
Liver Transplant	735	449	286
Premature HCV-related deaths	9766	6029	3737

Table 11- Number of occurrences in a 60 years period (New vs Old Medication) (designed from data)

On the other hand, the higher number of occurrences avoided with the new therapy will be also reflected in higher savings per HCV stage at the end of the 60 years. In the table below, it is possible to observe that 169.392.808€ in total will be saved by treating patients with Sovaldi® and Harvoni® when compared to the former therapy, being the total difference between treatments of be 16.659€. By saving 11.556.121€ in the F0-F3 stage, as well as 14.456.779€ in the Cirrhosis stage, 51.599.019€ in Hepatic Decompensations, 15.631.903€ in Hepatocellular Carcinomas and 169.392.808€ in Liver Transplants, the government can therefore save money when treating Hepatitis C infected patients **(Table 12)**.

Lifetime Savings	New Medication	Old Medication	Diference btw treatments
F0-F3	35.025.033 €	23.468.912 €	11.556.121 €
Cirrhosis (F4)	34.487.034 €	20.030.256 €	14.456.779 €
Hepatic Decompensation	122.268.038 €	70.669.019 €	51.599.019 €
HCC	37.147.936 €	21.516.032 €	15.631.903 €
Liver Transplant	178.898.901 €	102.749.915 €	76.148.986 €
Total	407.826.941 €	238.434.133 €	169.392.808 €
Total per Patient	40.109 €	23.449 €	16.659 €

Table 12 - Savings in occurrences for a 60 years period in New vs Old Medication (designed from data)

4.5 Sensitivity Analysis

In order to analyze total costs for both therapies, three different scenarios were built taken into consideration the different cost levels for the new therapy (24.000€, 20.000€ and 15.000€). The old therapy cost (Pegylated Interferon + Ribavirin) remains unaltered, amounting 79.822.699€. Also, as previously seen, non-responding patients' costs are 191.994.899€ with the old therapy and 22.602.091€ with the new therapy.

In the first scenario, when the new medication costed 24.000€ per treatment, the total cost per treatment amounted 244.034.336€, resulting in a total difference in savings in costs between therapies of 5.181.172€ and a difference in total cost per patient of -510€. The second scenario,

20.000€ per treatment, is the more realistic according to the press and results in a total cost of therapy of 203.362.366€, which allows the government to save 45.853.172€ in costs between treatments and 4.510€ per patient. Lastly, a more unrealistic scenario of 15.000€ per treatment would prevent the government from spending more 96.693.172€ fighting the disease, saving 9.510€ per patient.

As it is possible to observe, since costs with non-SVR patients in old medication are way higher than with new medication, in all scenarios a higher cost per treatment with the new therapy is not enough for the government to lose money in the long-run, resulting in a great amount of savings. **(Table 13)**.

SOF / LDV = 24.000€	New Medication	Old Medication	Diference
Cost of therapy	244.034.336 €	79.822.699 €	164.211.636 €
Costs of non-responding patients	22.602.091 €	191.994.899 €	-169.392.808 €
Total	266.636.426 €	271.817.598 €	-5.181.172 €
Total Cost per patient	26.223 €	26.733 €	-510 €

SOF / LDV = 20.000€	New Medication	Old Medication	Diference
Cost of therapy	203.362.336 €	79.822.699 €	123.539.636 €
Costs of non-responding patients	22.602.091 €	191.994.899 €	-169.392.808 €
Total	225.964.426 €	271.817.598 €	-45.853.172 €
Total Cost per patient	22.223 €	26.733 €	-4.510 €

SOF / LDV = 15.000€	New Medication	Old Medication	Diference
Cost of therapy	152.522.336 €	79.822.699 €	72.699.636 €
Costs of non-responding patients	22.602.091 €	191.994.899 €	-169.392.808 €
Total	175.124.426 €	271.817.598 €	-96.693.172 €
Total Cost per patient	17.223 €	26.733 €	-9.510 €

Table 13- Sensitivity analysis for different costs of the new therapy (designed from data)

4.6 QALYs and ICER

The new medication will increase the number of Quality-Adjusted Life-Years in a sixty years period to 89.161, when comparing with the 56.592 QALYs obtained with the old therapy. The difference between treatments is therefore 32.568, being QALYs discounted at a 5% rate, increasing average life expectancy of HCV infected patients in 3.2 years. Expected costs with the new medication are lower, a result of a higher SVR rate with the new treatment.

For the three scenarios **(Table 14)**, different Incremental Cost-Effectiveness Ratios were calculated, being -159€/QALY in the first one, -1.408€/QALY in the second one and -2.969€ in the last hypothesis. If respecting NICE rules of a maximum threshold of £30.000/QALY, the three scenarios would fit the regulations, being the new treatment considered as cost-effective.

Plus, given the great amount of benefits brought by the new medication in terms of occurrences avoided, reduction in public expenditure or even non-responding patients to the old treatment that become cured, the recommendation is very positive.

SOF / LDV = 24.000€	New Medication	Old Medication	Diference btw treatments
Expected Cost	266.636.426 €	271.817.598 €	-5.181.172 €
Expected QALYs	89.161	56.592	32.568
ICER (€ per QALY)			-159 €
QALY per patient	8,77	5,57	3,20

SOF / LDV = 20.000€	New Medication	Old Medication	Diference btw treatments
Expected Cost	225.964.426 €	271.817.598 €	-45.853.172 €
Expected QALYs	89.161	56.592	32.568
ICER (€ per QALY)			-1.408 €
QALY per patient	8,77	5,57	3,20

SOF / LDV = 15.000€	New Medication	Old Medication	Diference btw treatments
Expected Cost	175.124.426 €	271.817.598 €	-96.693.172 €
Expected QALYs	89.161	56.592	32.568
ICER (€ per QALY)			-2.969 €
QALY per patient	8,77	5,57	3,20

Table 14 - Expected QALYs and ICER for the two treatments given the three different cost levels (designed from data)

4.7 Sensitivity Analysis for different discount rates

Taking into consideration Infarmed regulations for economic healthcare analysis, two different Sensitive Analysis were performed for 0% and 3% discount rates.

4.7.1 Sensitivity Analysis for a 0% discount rate

With a 0% discount rate, costs for non-responding patients will be significantly higher than for 5%, increasing the reduction in public expenditure when comparing to the former discount rate **(Table 15)**. Considering the three different new therapy cost levels, when the price of medication is 24.000€, the total savings between therapies amount 146.141.357€, or 14.373€ per patient, while when cost is 20.000€, the government can save 186.813.357€, 18.373€ per patient. Lastly, when Sofosbuvir / Ledipasvir costs 15.000€ per treatment, the government saves 237.653.357€, meaning 23.373€ per patient.

SOF / LDV = 24.000€ (DR=0%)	New Medication	Old Medication	Diference
Cost of therapy	244.034.336 €	65.670.332 €	178.364.003 €
Costs of non-responding patients	40.845.321 €	365.350.681 €	-324.505.360 €
Total	284.879.656 €	431.021.013 €	-146.141.357 €
Total Cost per patient	28.017 €	42.390 €	-14.373 €

SOF / LDV = 20.000€ (DR=0%)	New Medication	Old Medication	Diference
Cost of therapy	203.362.336 €	65.670.332 €	137.692.003 €
Costs of non-responding patients	40.845.321 €	365.350.681 €	-324.505.360 €
Total	244.207.656 €	431.021.013 €	-186.813.357 €
Total Cost per patient	24.017 €	42.390 €	-18.373 €

SOF / LDV = 15.000€ (DR=0%)	New Medication	Old Medication	Diference
Cost of therapy	152.522.336 €	65.670.332 €	86.852.003 €
Costs of non-responding patients	40.845.321 €	365.350.681 €	-324.505.360 €
Total	193.367.656 €	431.021.013 €	-237.653.357 €
Total Cost per patient	19.017 €	42.390 €	-23.373 €

Table 15 - Sensitivity analysis for different costs of the new therapy using a 0% discount rate (designed from data)

Discounted QALYs will suffer a reduction, influenced by the drop of the discount rate, amounting 155.688 in the new therapy and 99.171 in the old therapy. The difference between treatments will therefore increase to 56.517 rising the life expectancy for Hepatitis C infected patients to 5,56 years.

The Incremental Cost-Effectiveness Ratio will also be influenced by the increase in total costs and decrease substantially to -2.586€ per QALY in the first scenario, -3.305€ per QALY in the second and -4.205€ per QALY in the third situation **(Table 16)**. However, the outcome is still negative, meaning that the change in therapies is still cost effective.

SOF / LDV = 24.000€ (DR=0%)	New Medication	Old Medication	Diference btw treatments
Expected Cost	284.879.656 €	431.021.013 €	-146.141.357 €
Expected QALYs	155.688	99.171	56.517
ICER (€ per QALY)			-2.586 €
QALY per patient	15,31	9,75	5,56

SOF / LDV = 20.000€ (DR=0%)	New Medication	Old Medication	Diference btw treatments
Expected Cost	244.207.656 €	431.021.013 €	-186.813.357 €
Expected QALYs	155.688	99.171	56.517
ICER (€ per QALY)			-3.305 €
QALY per patient	15,31	9,75	5,56

SOF / LDV = 15.000€ (DR=0%)	New Medication	Old Medication	Diference btw treatments
Expected Cost	193.367.656 €	431.021.013 €	-237.653.357 €
Expected QALYs	155.688	99.171	56.517
ICER (€ per QALY)			-4.205 €
QALY per patient	15,31	9,75	5,56

Table 16 - Expected QALYs and ICER for the two treatments given the three different cost levels (0% Discount Rate) (designed from data)

Total lifetime savings will also increase to 324.505.360€, a result of the significant drops in costs sixty years from now. With this discount rate, the difference in savings per patient when using the new therapy will be 31.914€ **(Table 17)**.

Lifetime Savings (DR=0%)	New Medication	Old Medication	Diference in treatments
Total	800.909.609 €	476.404.249 €	324.505.360 €
Total per Patient	78.768 €	46.853 €	31.914 €

Table 17 - Lifetime Savings given a 0% Discount Rate (designed from data)

4.7.2 Sensitivity Analysis for a 3% discount rate

On the other side, when using a 3% discount rate the results are between the ones calculated for the 0% and 5% discount rates. In the first scenario, a 24.000€ cost level returns a total difference in savings between therapies of 43.228.776€ and savings of 4.251€ per patient, while the second scenario of 20.000€ in costs allows the government to save 83.900.776€, 8.251€ per patient in the end of the 60 years. The last scenario, 15.000€ per therapy, returns a profit of 134.740.776€, 13.251€ per patient **(Table 18)**.

SOF / LDV = 24.000€ (DR=3%)	New Medication	Old Medication	Diference
Cost of therapy	244.034.336 €	73.912.537 €	170.121.798 €
Costs of non-responding patients	27.870.065 €	241.220.639 €	-213.350.574 €
Total	271.904.400 €	315.133.176 €	-43.228.776 €
Total Cost per patient	26.741 €	30.993 €	-4.251 €

SOF / LDV = 20.000€ (DR=3%)	New Medication	Old Medication	Diference
Cost of therapy	203.362.336 €	73.912.537 €	129.449.798 €
Costs of non-responding patients	27.870.065 €	241.220.639 €	-213.350.574 €
Total	231.232.400 €	315.133.176 €	-83.900.776 €
Total Cost per patient	22.741 €	30.993 €	-8.251 €

SOF / LDV = 15.000€ (DR=3%)	New Medication	Old Medication	Diference
Cost of therapy	152.522.336 €	73.912.537 €	78.609.798 €
Costs of non-responding patients	27.870.065 €	241.220.639 €	-213.350.574 €
Total	180.392.400 €	315.133.176 €	-134.740.776 €
Total Cost per patient	17.741 €	30.993 €	-13.251 €

Table 18 - Sensitivity analysis for different costs of the new therapy using a 3% discount rate (designed from data)

QALYs will also rise when compared to the previous analysis (0% discount rate), a result of the increase in the discount rate. New Medication will return QALYs of 108.465 and Old Medication of 68.932. The difference in QALYs gained between treatments is lower when compared to the 0% discount rate, 39.534, which will extend life expectancy in 3,89 years **(Table 19)**.

The ICER increases when facing a 3% discount rate, and is -1.093€/QALY in the first scenario, -2.122€/QALY in the second scenario and -3.408€/QALY in the third scenario. The three ICER results calculated for the different therapy cost levels are still negative, meaning that the treatment is still cost-effective.

SOF / LDV = 24.000€ (DR=3%)	New Medication	Old Medication	Diference btw treatments
Expected Cost	271.904.400 €	315.133.176 €	-43.228.776 €
Expected QALYs	108.465	68.932	39.534
ICER (€ per QALY)			-1.093 €
QALY per patient	10,67	6,78	3,89

SOF / LDV = 20.000€ (DR=3%)	New Medication	Old Medication	Diference btw treatments
Expected Cost	231.232.400 €	315.133.176 €	-83.900.776 €
Expected QALYs	108.465	68.932	39.534
ICER (€ per QALY)			-2.122 €
QALY per patient	10,67	6,78	3,89

SOF / LDV = 15.000€ (DR=3%)	New Medication	Old Medication	Diference btw treatments
Expected Cost	180.392.400 €	315.133.176 €	-134.740.776 €
Expected QALYs	108.465	68.932	39.534
ICER (€ per QALY)			-3.408 €
QALY per patient	10,67	6,78	3,89

Table 19- Expected QALYs and ICER for the two treatments given the three different cost levels (3% Discount Rate) (designed from data)

Lifetime savings are now 518.439.502€ with New Medication and 305.088.939€ with the Old Medication, meaning that the difference between treatments is 213.350.563€. The difference in savings by treating patients with the new therapy decreases to 20.983€ when compared to a 0% discount rate **(Table 20)**.

Lifetime Savings (DR=3%)	New Medication	Old Medication	Diference in treatments
Total	518.439.502 €	305.088.939 €	213.350.563 €
Total per Patient	50.987 €	30.005 €	20.983 €

Table 20 - Lifetime Savings given a 3% Discount Rate (designed from data)

4.8 Decision to change therapies

Summing up, as it is possible to understand from the table below **(Table 21)**, differences between therapies' total costs decrease as the discount rate increases. The same phenomenon is possible to detect when the cost of the new therapy decreases. As a result, the total difference in costs between therapies and therefore the difference per patient is negative, meaning that the government will always save money with the new medication.

Total Costs		NM	OM	Difference	Difference / Patient
15.000 €	DR = 0%	193.367.656 €	431.021.013 €	-237.653.357 €	-23.373 €
	DR = 3%	180.392.400 €	315.133.176 €	-134.740.776 €	-13.251 €
	DR = 5%	175.124.426 €	271.817.598 €	-96.693.172 €	-9.510 €
20.000 €	DR = 0%	244.207.656 €	431.021.013 €	-186.813.357 €	-18.373 €
	DR = 3%	231.232.400 €	315.133.176 €	-83.900.776 €	-8.251 €
	DR = 5%	225.964.426 €	271.817.598 €	-45.853.172 €	-4.510 €
24.000 €	DR = 0%	284.879.656 €	431.021.013 €	-146.141.357 €	-14.373 €
	DR = 3%	271.904.400 €	315.133.176 €	-43.228.776 €	-4.251 €
	DR = 5%	266.636.426 €	271.817.598 €	-5.181.172 €	-510 €

Table 21- Differences in costs for different discount rates and different cost levels (designed from data)

Lifetime Savings from responding patients become higher as the discount rate decrease. Difference between treatments is 16.659€ per patient in the worst case scenario, a positive indicator. Plus, costs are always higher with the new medication rather than with the old one, meaning that there will be always a surplus to the government.

Lifetime Savings		New Medication	Old Medication	Diference btw treatments
DR = 0%	Total	800.909.609 €	476.404.249 €	324.505.360 €
	Total per Patient	78.768 €	46.853 €	31.914 €
DR = 3%	Total	518.439.502 €	305.088.939 €	213.350.563 €
	Total per Patient	50.987 €	30.005 €	20.983 €
DR = 5%	Total	407.826.941 €	238.434.133 €	169.392.808 €
	Total per Patient	40.109 €	23.449 €	16.659 €

Table 22 - Differences in Lifetime Savings for different discount rates (designed from data)

The difference between expected QALYs decreases with the growth of the discount rate, being the maximum difference in QALYs achieved of 56.517. QALYs per patient vary between 5,56 and 3,20. The Incremental Cost-Effectiveness Ratio is always negative for the different cost levels and discount rates, meaning that investing in the new therapy (Sovaldi® and Harvoni®) is always cost-effective **(Table 23)**. ICER is the lowest for a 24.000€ cost level and a 5% discount rate, and the highest for a 15.000€ cost level and 0% discount rate.

Differences in QALYs and ICER (NM vs OM)		0%	3%	5%
QALY	Total	56.517	39.534	32.568
	Per Patient	5,56	3,89	3,20
ICER	15.000 €	-4.205 €	-3.408 €	-2.969 €
	20.000 €	-3.305 €	-2.122 €	-1.408 €
	24.000 €	-2.586 €	-1.093 €	-159 €

Table 23- Differences in QALYs and ICER for different discount rates and cost levels (designed from data)

In the end, regardless of the discount rate or the new therapy cost per patient, it will always be worth to the government to grant universal access to Sofosbuvir and Sofosbuvir + Ledipasvir. The average life expectancy of Hepatitis C infected patients will increase and the new therapy will always be cost effective, meaning that, 60 years from now, the government will have saved more lives with less money.

5. Conclusions, Limitations and Future Research

5.1 Conclusions

The old medication for the treatment of Hepatitis C, Pegylated Interferon + Ribavirin, was in the past a great improvement in the eradication of the virus allowing HCV infected patients to become cured. However, this treatment has only a modest efficacy for most patients and important side effects, preventing many people to be cured.

After a failed experience with two new drugs, Boceprevir and Telaprevir, mainly due to its serious side effects, Gilead developed Sofosbuvir (Sovaldi®) and Sofosbuvir + Ledipasvir (Harvoni®), promising SVR rates around 95%. These new medications gave a new hope for many patients unable to become cured from the infection and motivated several public demonstrations while the government and the pharmaceutical company were agreeing on prices.

After some months of expectation, the Portuguese Health Minister informed the Portuguese citizens that the agreement with Gilead was signed, being the best in Europe until that moment. The government would only pay for the treated patients and the same per patient regardless of the duration of the treatment. The cost of the therapy was not disclosed although press rumors pointed to 20.000€-24.000€. Therefore, in order to do a complete economic evaluation of this political action, a sensitivity analysis for the three different levels of price had to be performed.

Since Hepatitis C is a disease with multiple stages, in order to calculate the costs and the savings of the new therapy when compared to the old one, a Markov model had to be computed. Annual transition probabilities between states were attributed to the model, as well as Quality of Life Utilities. This way, it was possible to calculate the results for a 60 years period, the time all the patients in the model needed to transit to the death stage. In the end, by attributing cost values to all the states, obtained in literature, and discounting to the present value both the costs and the QALYs it was possible to obtain the outcomes of the model.

When performing this economic analysis, it was interesting to analyze whether the fact that being the new therapy cost per patient significantly higher than the old one, could be enough to overcome the potential difference gained in lifetime savings in patients between the two therapies, therefore not being cost-effective. Results however completely dismissed this questions as they showed that the therapy is cost-effective for all discount rates applied to the model, since the more effective SVR rate influences costs of non-treated patients with the new medication to decrease substantially when compared to the former medication.

What is more, this new therapy will provide savings in occurrences of 169.392.808 €, 16.659 € per patient when compared with the old therapy. Even when computing a sensitivity analysis for the three different new therapy cost levels chosen for comparison, 15.000€, 20.000€ and 24.000€, costs were always inferior to the previous medicine, still a consequence of the difference in the non-treated patients. Treating patients with this new therapy will allow the government to save 510€ per patient for the highest old therapy cost level, the worst case scenario. Nevertheless, the more realistic cost levels will allow savings in the order of 4.510€ per patient and 9.510€ per patient, respectively.

As it is clear to understand, this new medicine is extremely cost effective for the government, as not only it is able to reduce costs when compared to the old therapy, as it will provide several benefits by allowing the National Healthcare System to save a great amount of money. Nevertheless, one should not forget that when taking healthcare political decisions, most of the times the economical factor is not the most important to take into consideration. This new therapy will be able to reduce the number of occurrences, especially in the most advanced stages of the disease, avoiding up to 1083 Hepatocellular Carcinomas, 286 Liver Transplants and 3737 premature HCV-related deaths. Sovaldi® and Harvoni® will also contribute for an increase in the life expectancy of HCV infected patients of 3,2 years. Plus, several patients that did not cured the infection when using the old treatment have now a second chance of becoming cured.

In conclusion, it is worth for the government to invest in this new therapy. Initial costs will be higher, a consequence of treating all patients not only those on the more advanced stages and of a higher cost per treatment. Nevertheless, the difference in the costs of non-responding patients in the long term completely justifies this measure, allowing savings in the long run.

This measure will also definitely reshape the way businesses between the Health Ministry and pharmaceutical companies are conducted. By paying exclusively the amount per treated patient, the government can use this deal as a role model for future drugs negotiations. Also, the government learned that by negotiating in a mass scale, curing all patients infected with the disease instead of those in the most advanced stages, benefits can be very significant in the long term.

5.2 Limitations and Future Research

Throughout this dissertation, some limitations affected the way the study was conducted, preventing a deeper analysis.

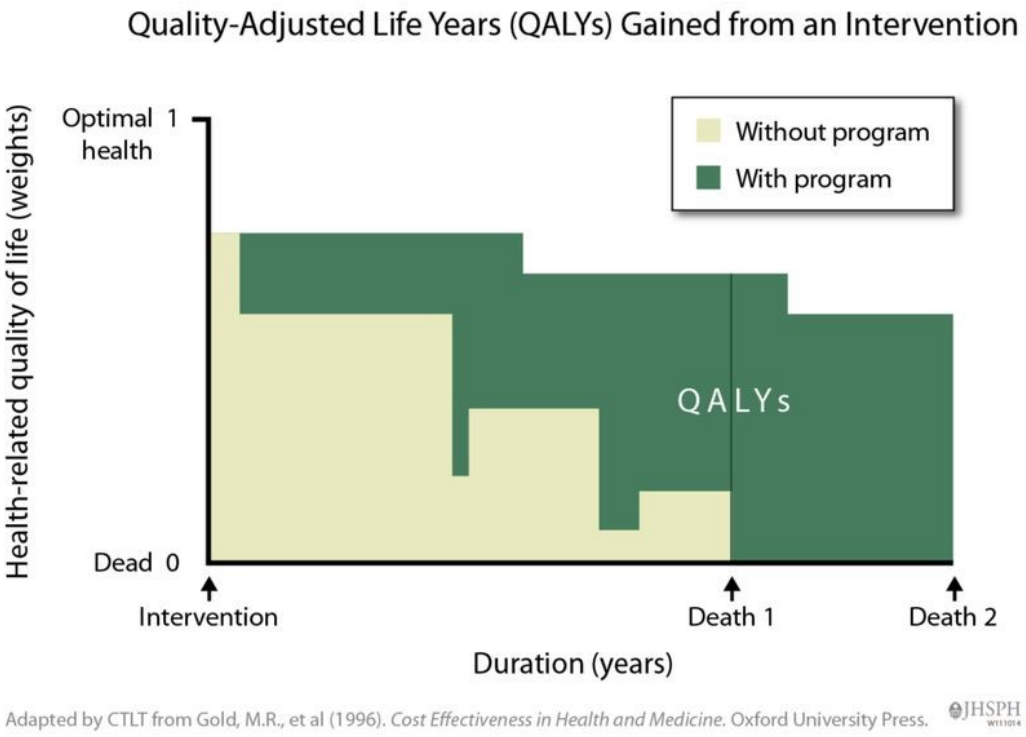
The first one was the reluctance of the Infarmed on providing the data contained in its portal what would allow a better characterization of the patients and the response to treatment.

Some simplifications regarding the Markov model were conducted, so that the numeric analysis become easier. Concerning the cirrhotic patients with SVR, for instance, the reduced risk for progression to HCC was not considered. The transition probability after Liver Transplantation to the death stage was related only to the first year, despite being the year more people died as consequence of it.

In the future, a more detailed analysis of the patients could be helpful. By getting the HCV portal data, researchers can easily estimate SVR rates for different age groups and gender. This is essential to observe and analyze the impact of medications over a time period. Also, by increasing more and more the complexity of the Markov model, it is possible to obtain even more accurate results, closer to the reality.

6. Appendixes

6.1 Appendix 1 – QALYs



6.2 Appendix 2 - Example of a EQ-5D Questionnaire

Medscape® www.medscape.com

EQ-5D	SF-8 scale median score
Mobility	Physical functioning
No problems	48.3
Moderate problems	40.1
Extreme problems	21.5
Self-care	Physical functioning
No problems	48.3
Moderate problems	30.3
Extreme problems	21.5
Usual activities	Role physical
No problems	54.0
Moderate problems	38.7
Extreme problems	28.3
Pain/discomfort	Bodily pain
No problems	60.8
Moderate problems	40.1
Extreme problems	31.5
Anxiety/depression	Mental health
No problems	56.8
Moderate problems	41.5
Extreme problems	31.6

*$p < 0.001$ in all comparisons for Kruskal–Wallis H test

6.3 Appendix 3 - ICER

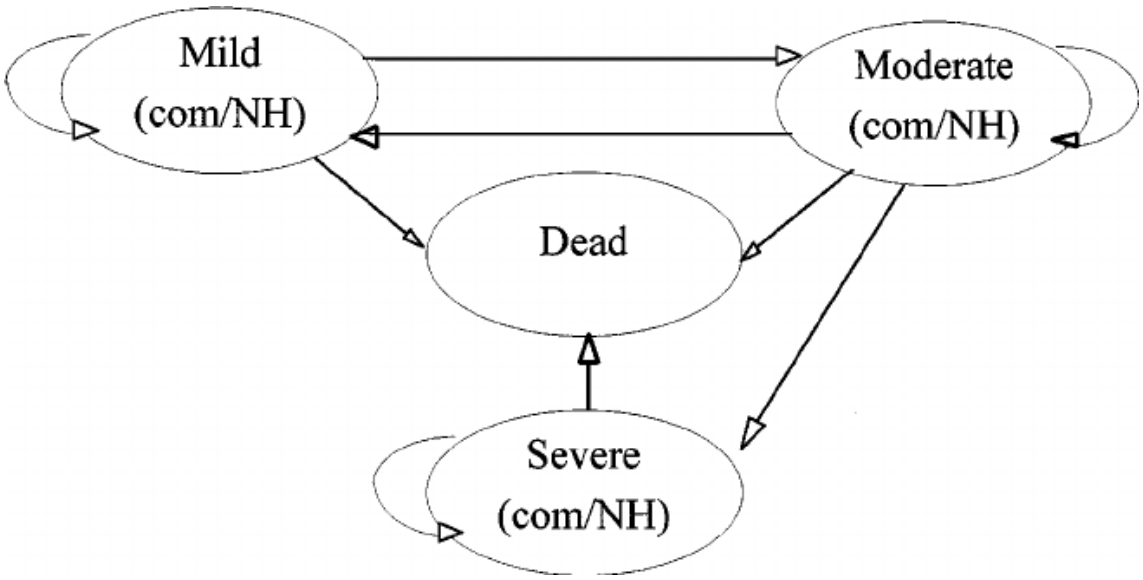
Incremental Cost-Effectiveness Ratio (ICER)

$$\text{ICER} = \frac{(C_n - C_0)}{(QALY_n - QALY_0)}$$

C_1 = cost of new hepatitis C therapy
C_0 = cost of old hepatitis C therapy
$QALY_n$ = quality adjusted life years with new hepatitis C therapy
$QALY_0$ = quality adjusted life years with old hepatitis C therapy

Source: Hepatitis C Online – University of Washington

6.4 Appendix 4 – Markov Model



Source: Bayesian Value-of-Information Analysis: An Application to a Policy Model of Alzheimer's disease

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