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ECONOMIC CONSEQUENCES OF INVESTING IN ANTI-HCV ANTIVIRAL TREATMENT FROM THE ITALIAN NHS PERSPECTIVE: a real-world-based analysis of PITER data

Running heading: Economic consequences of the anti-HCV strategy in Italy

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Abstract

Objective: We estimated the cost consequence of the Italian National Health System (NHS) investment in Direct-acting Antiviral drugs (DAA) according to hepatitis C virus (HCV) treatment access policies in Italy.

***Methods*:** A multistate 20-year time horizon Markov model of HCV liver disease progression was developed. Fibrosis stage, age and genotype distributions were derived from the Italian Platform for the Study of Viral Hepatitis Therapies (PITER) cohort. The treatment efficacy, disease progression probabilities and direct costs in each health state were obtained from the literature. The break-even point in time (BPT) was defined as the period of time required for the cumulative costs saved to recover the Italian NHS investment in DAA treatment. Three different PITER enrolment periods, which covered the full DAA access evolution in Italy, were considered.

***Results*:** The disease stages of 2657 patients who consecutively underwent DAA therapy from January 2015 to December 2017 at 30 PITER clinical centres were standardized for 1,000 patients. The investment in DAAs was considered to equal €25 million, €15 million, and €9 million in 2015, 2016 and 2017, respectively. For patients treated in 2015, the BPT was not achieved due to the disease severity of the treated patients and high DAA prices. For 2016 and 2017, the estimated BPTs were 6.6 and 6.2 years, respectively. The total cost savings after 20 years were €50.13 and €55.50 million for 1,000 patients treated in 2016 and 2017, respectively.

***Conclusions*:** This study may be a useful tool for public decision makers to understand how HCV clinical and epidemiological profiles influence the economic burden of HCV.

Key points for decision makers

- Following the Direct-acting Antiviral drugs (DAA) treatment in patients who had severe liver disease, treated in 2015, only a significant health benefit, with no break-even point to recover the investment in DAA across 20 years was estimated.
- The time required for the cumulative costs saved to recover the initial Italian NHS investment in DAA treatment was estimated to be 6.6 years and 6.2 years for patients treated in 2016 and 2017 respectively.
- The overall results of this cost-consequence analysis, based on real-life HCV treatment data from a representative sample of Italian patients in care, confirm an overall health benefit of DAA anti-HCV treatment.

1. Introduction

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease worldwide [1]. According to recent estimates, more than 71 million people around the world are infected with HCV [2, 3]. Despite declining HCV infection rates, the burden of HCV is still high [4]. The effects of therapies on morbidity and mortality and as well as their economic consequences vary significantly between countries due to the different epidemiological profiles of HCV infection. Regarding the epidemiology of HCV, past incidence of infection was assumed to follow a logistic function until infection rates peaked in 1989 in different countries. However, in Italy, a more intense epidemic wave occurred from the 1950s to the 1960s via iatrogenic transmission due to the use of unsterilized materials [5, 6]. For this reason, a longer exposure time suggests a potential higher prevalence of advanced liver disease stages among individuals with chronic HCV infection in Italy compared to those in countries in which the epidemic waves occurred later. In fact, Italy has the highest prevalence of HCV in Europe and the highest death rate due to hepatocellular carcinoma (HCC) and liver cirrhosis [7]. Each year, more than 20,000 chronic liver disease-complicated deaths are reported, and in more than 65% of them, HCV is the main aetiological factor. HCC is the 5th leading cause of death from cancer in Italy [8]. Genotype 1 occurs most frequently in Italian patients with chronic HCV infection (and in more than 50% of infected people in the general population), followed by genotype 2c. Both genotypes are related to the nosocomial transmission mode of HCV infection, the principal route of HCV transmission in Italy [9, 10]. Considering this transmission peculiarity, Italy represents an interesting epidemiological context in that severe stages of liver disease and the corresponding economic burden in Italy are higher than those in countries with different epidemiology of infection. During the past four years, the AIFA policy perspective has radically changed. In 2015, the AIFA decided reimbursement policies based on the prioritization of symptomatic individuals with moderate-to-severe liver fibrosis and a few other patients categories. Since 2017, the AIFA's access to therapy has become universal independent of the liver fibrosis stage, and treatment has become available for all chronically infected HCV patients [11].

From the economic perspective, cost-effectiveness and cost-sustainability have been studied in Italy [12-15], and the data demonstrated the economic efficiency and sustainability of the Direct-Acting Antiviral (DAA) therapy investment. Apart from these studies, no specific analysis has estimated the economic consequences of the Italian National Health System (NHS) investment and access to treatment. In 2014, an initial study proposed by Mennini et al. [16] attempted to provide decision makers with fundamental information for reflection and discussion and allow them to plan the implementation of rational and economically sustainable actions with the aim of controlling and eradicating the infection. In that study, the authors calculated the economic effect in terms of the direct and indirect costs (excluding drug costs) of DAA treatment in Italy, estimating a cost savings between €192 and €198 million depending on the access scenario [16].

The high number of DAA treated patients has resulted in an increased investment associated with drug acquisition costs from the NHS and, consequentially, increased healthcare cost savings due to the avoidance of diseases related to HCV. However, whether the two costs offset each other over time remains in question.

The aim of this work was to estimate the cost consequence of the NHS investment in DAA-based anti-HCV treatment in Italy according to the fibrosis stage and access to DAA treatment information based on real-life data from a representative sample of patients treated in Italy. The final goal was to estimate the amount of time required for the initial NHS investment in DAA treatment to achieve cumulative cost savings due to HCV-related disease avoidance.

2. Methods

A specific Markov model was designed to estimate the clinical and economic consequences of HCV treatment in the Italian setting. [17]. The model simulated the cost sustained by the Italian NHS for DAA treatment of HCV chronically infected patients during the years 2015, 2016 and 2017. The liver disease progression of treated patients was evaluated through the model over 20 years' time horizon. Direct medical costs were estimated according to the fibrosis and HCV genotype stratification of the HCV chronically infected patients, consecutively treated in the PITER (Piattaforma Italiana per lo studio della Terapia delle Epatiti ViRali) real life cohort [17].

2.1 Model structure

Starting from the mortality-morbidity multistate model recently developed by Marcellusi et al. in 2016 [12], a new Markovian process was implemented. It included 13 disease states [fibrosis stages from F0 to F4, decompensated cirrhosis (DC), hepatocellular carcinoma (HCC), first-year transplant and following years transplant, sustained virologic response (SVR) from F0 to F3, SVR from irreversible liver damage (ILD), HCV-related death, and death from other causes] and 41 transition probabilities (Figure 1). The SVR from ILD states represent patients treated in the states F4, DC and HCC that achieve an SVR after one year of treatment. Patients can be entered into the Markov process from different fibrosis stages (F0-F3), compensated and DC states and the HCC state. The proportions of disease stages were defined according to the PITER distribution of the fibrosis stage of treated patients for each period considered in the analysis. An NHS perspective was considered (only direct medical costs). Simulations for a 20-year period for each of the three treatment years, 2015, 2016 and 2017, were performed.

2.2 Epidemiological and clinical parameters

Data stratifications for the disease states, genotypes and ages of DAA-treated patients were retrieved from the PITER database. PITER is a structured network that benefits from an integrated collaboration involving Italy's National Institute of Public Health (Istituto Superiore di Sanità), the Italian Society for the Study of the Liver (AISF), the Italian Society for Infectious Diseases (SIMIT) and their affiliated clinical centres. The PITER database comprises an ongoing cohort of consecutively enrolled patients from hospital centres across Italy linked to care for chronic HCV infection who are not on an HCV treatment regimen at the time of enrolment. The cohort can be reasonably considered to be a representative sample of patients in care with no treatment access restrictions on the basis of sociodemographic and healthcare system reimbursement criteria [17].

Treatment initiations occurring among enrolled patients covered the full evolution of DAA access in Italy since 2015. The first round of enrolment began in May 2014 and lasted 6 months, and three rounds of enrolment were conducted through December 2017. Treated patients were grouped into 3 time periods for analysis: 2015 (patients treated from January-December 2015), 2016 (patients treated from January–December 2016) and 2017 (patients treated from January–December 2017).

The three-time period analysis represented the AIFA reimbursement policies of prioritization for symptomatic individuals with moderate-to-severe liver fibrosis and a few other categories of patients until the year 2016. In 2017, the AIFA expanded the access to treatment to all patients with no fibrosis stage or other restrictions [11].

2.3 Transition probabilities

Progression of HCV liver disease was considered to be an increase in the severity of liver fibrosis (from F0 to F4 according to the Metavir classification) or progression to ILD stages. The probabilities of the various stages of progression are based on the literature review (Table 1). Throughout annual cycles, patients can remain in their current stage or progress to a worse disease state coherently with the natural history of the disease. This progression can be stopped or slowed down by treatment. The DAA efficacy is expressed in terms of probability to reach an SVR state. If patients are cured in stages F0-F3 (they move to the SVR state), the model assumes that liver damage is reversed. Patients achieving an SVR in stages F4, DC and HCC are no longer infectious, but they may incur additional liver damage (F4 and DC could progress to HCC) or need a liver transplant (LT). The probabilities of moving from SVR-irreversible liver damage to HCC or LT are weighted for the percentages of patients with compensated cirrhosis, DC and HCC. Patients can die due to HCV-related diseases from only the states DC, HCC, LT (procedure) and LT (following years). All probabilities are adjusted for competing probabilities of death from other causes [18].

The efficacy parameters of interferon (IFN)-free HCV regimens of second-generation DAAs are stratified by the presence or absence of cirrhosis (Table 1). Three different periods, which covered the full evolution of different DAA accesses in Italy since 2015, were considered. The SVR of each period was estimated in accordance with the

availability of DAAs in the Italian context (Appendix). The SVR rate of each treatment was derived from the literature and used to estimate the mean rates of SVR according to the HCV RNA genotype and fibrosis stage weighted for real-life PITER cohort characteristics. For the F0, F1, F2, F3, F4 and DC states, the probabilities of achieving SVR, disease progression and HCV-related death were estimated. For the HCC state, the probability of death due to HCV and the probability of transplant were assumed to be independent. All the parameters of base-case analysis were discussed and validated by the clinical expert involved in this study and by all the co-authors.

2.4 Economic parameters

The yearly direct healthcare costs were derived from the literature and considered aggregate costs for the management of HCV-related diseases (specialist visits, analyses and check-ups), pharmacological therapies and hospitalization costs. The averages costs and ranges (MIN–MAX), available from national literature, are reported in Table 1.

The average treatment cost per DAA was derived from assumptions made from the literature [19] and added to the average cost of the patient's management. Costs are expressed in euros at the 2017 price level.

2.5 Economic analysis

The outcomes of the model are expressed in terms of HCV-related diseases (DC and HCC), transplant and HCV-related death avoidance. Costs were discounted at an annual rate of 3% according to Italian AIES guidelines [20]. The economic analysis was performed by standardizing 1,000 patients stratified by fibrosis stage, age and genotype as reported in the treated PITER cohort in the three time periods considered.

One of the main model outputs was the break-even point in time (BPT), which was an evaluation of the time required to incur hepatitis C treatment cost savings. This index was derived from the financial discounted payback period, a method that estimates the point in time at which the cumulative, discounted positive cash flows offset the initial capital investment [21]. From our perspective, the BPT was defined as the period of time required for the cumulative, discounted value of costs saved to recover the initial NHS investment in DAA treatment, which indicates how long it takes to break even. The annual costs saved were calculated as the cost difference, including the average cost of patient management during the natural history of the disease minus the real-world treatment estimates for each period of the analysis.

If $i = \{2015; 2016; 2017\}$ is the period of analysis, t = 0, 1, … 20 is the cycles used in the Markov-model simulation, CF_t is the cash flow in period t (avoided costs due to HCV-related disease reduction), I_t is the initial investment in period t for DAA acquisition and r is the discount rate, then the BPT can be defined as follows:

$$\mathrm{BPT}_i = \min(x) : \sum_{t=0}^{x} \left(\frac{{CF_t}^i}{(1+r)^t} - \frac{{I_t}^i}{(1+r)^t} \right) \cong 0$$

2.6 Sensitivity analysis

To estimate the uncertainty of the economic results, probabilistic sensitivity analysis (PSA) and deterministic sensitivity analysis (DSA) were performed.

For PSA, the probabilistic distribution choice was made by applying what is generally reported for the development of economic evaluation models, distinguishing between costs (gamma distribution) and epidemiological parameters (beta distribution) and considering the range available from the literature (Table 1) [22]. Furthermore, 5000

Monte Carlo simulations were performed to provide 95% confidence intervals (95% CIs) for the primary economic results (case and cost reduction at 20 years, BPT and case reduction at the BPT).

To highlight the effects of the main model parameters, DSA was conducted via a one-way deterministic analysis in which the parameters were changed by arbitrary constant variation:

- Transition probabilities (-20% to +20%)
- Treatment costs (-20% to + 20%)
- Healthcare medical costs (-20% to +20%)
- % F3, F4, DC and HCC (-20% to +20%)
- Transplant probability for SVR (0 to +50%)
- SVR (minimum from the literature to 1)

Finally, due to the heterogeneity of different transition probabilities applied in the literature, we performed a specific DSA considering the HCV disease progressions estimated from two different Italian studies [4, 23] and from a US model that performed a similar analysis (expressed as return to cost-effectiveness) [26]. One-way DSA is represented by a tornado diagram, and the specific-transition-probability DSA is presented as the BPT evolution for each year.

Table 1 – Transition probabilities and efficacy of treatments and costs.

Annual probability of disease progression	**Base-case**	**Min**	**Max**	**Source**
F0 to F1	0.117	0, 09	0.140	[27]
F1 to F2	0.085	0.070	0.102	[27]
F2 to F3	0.120	0.100	0.144	[27]
F3 to F4	0.100	0.080	0.120	[28]
F4 to Decompensated Cirrhosis (DC)	0.030	0.020	0.036	[28]
F4 to HCC	0.050	0.040	0.060	[28]
Decompensated Cirrhosis to HCC	0.100	0.080	0.120	[28]
Decompensated Cirrhosis to Transplant	0.110	0.090	0.132	[28]
HCC to Transplant	0.200	0.160	0.240	[29]
SVR to HCC[a]	0.008	0.007	0.009	Assumption from [30]
SVR to Transplant[a]	0.016	0.011	0.020	Assumption from [30]
Annual probability of progressing to death	**Base-case**	**Min**	**Max**	**Source**
Decompensated Cirrhosis to Death (liver-related)	0.090	0.070	0.108	[30]
HCC to Death (liver-related)	0.430	0.340	0.516	[29]
Transplant (procedure) to Death (liver-related)	0.150	0.120	0.180	[29]
Transplant (following years) to Death (liver-related)	0.057	0.050	0.068	[29]
Death from all other causes	0.074	0.070	0.108	[18]
Efficacy of treatments - 2015	**Base-case**	**Min**	**Max**	**Source**
F0-F3 to SVR (Genotype 1)	0.879	0.643	0.97	Appendix [25, 31][c]
F4-DC to SVR (Genotype 1)	0.834	0.643	0.954	Appendix [25, 31][c]
F0-F3 to SVR (Genotype 2)	0.742	0.500	0.984	[25, 31][c]
F4-DC to SVR (Genotype 2)	0.742	0.500	0.984	Assumed equal to F0-F3
F0-F3 to SVR (Genotype 3)	0.758	0.606	0.910	[25, 31][c]
F4-DC to SVR (Genotype 3)	0.758	0.606	0.910	Assumed equal to F0-F3
F0-F3 to SVR (Genotype 4 and more)	0.525	0.000	0.950	[25, 31][c]
F4-DC to SVR (Genotype 4 and more)	0.525	0.000	0.950	Assumed equal to F0-F3
Efficacy of treatments - 2016	**Base-case**	**Min**	**Max**	**Source**
F0-F3 to SVR (Genotype 1)	0.983	0.963	1.000	Appendix [25][c]
F4-DC to SVR (Genotype 1)	0.928	0.760	1.000	Appendix [25][c]

F0-F3 to SVR (Genotype 2)	0.960	0.920	1.000	Appendix [25][c]
F4-DC to SVR (Genotype 2)	0.952	0.710	0.975	Appendix [25][c]
F0-F3 to SVR (Genotype 3)	0.960	0.940	0.970	Appendix [25][c]
F4-DC to SVR (Genotype 3)	0.860	0.710	0.890	Appendix [25][c]
F0-F3 to SVR (Genotype 4 and more)	0.963	0.940	1.000	Appendix [25][c]
F4-DC to SVR (Genotype 4 and more)	0.943	0.800	0.970	Appendix [25][c]
Efficacy of treatments - 2017	**Base-case**	**Min**	**Max**	**Source**
F0-F3 to SVR (Genotype 1)	0.980	0.784	1.000	Appendix [25][c]
F4-DC to SVR (Genotype 1)	0.931	0.745	1.000	Appendix [25][c]
F0-F3 to SVR (Genotype 2)	0.980	0.784	1.000	Appendix [25][c]
F4-DC to SVR (Genotype 2)	0.970	0.776	1.000	Appendix [25][c]
F0-F3 to SVR (Genotype 3)	0.950	0.760	1.000	Appendix [25][c]
F4-DC to SVR (Genotype 3)	0.884	0.707	1.000	Appendix [25][c]
F0-F3 to SVR (Genotype 4 and more)	0.970	0.776	1.000	Appendix [25][c]
F4-DC to SVR (Genotype 4 and more)	0.961	0.769	1.000	Appendix [25][c]
Cost of treatment	**Base-case**	**Min c**	**Max c**	**Source**
Treatment 2015	€ 25,000.00	€ 20,000	€ 29,000	Assumption from [19]
Treatment 2016	€ 15,000.00	€ 12,000	€ 17,400	Assumption from [19]
Treatment 2017	€ 9,000.00	€ 7,200	€ 10,440	Assumption from [19]
Other direct medical costs	**Base-case**	**Min**	**Max**	**Source**
F0	€ 222	€ 176	€ 292	[24, 25]
F1	€ 241	€ 176	€ 292	[24, 25]
F2	€ 215	€ 176	€ 292	[24, 25]
F3	€ 604	€ 292	€ 942	[24, 25]
F4	€ 904	€ 397	€ 1,354	[24, 25]
Decompensated Cirrhosis (DC)	€ 5,961	€ 4,385	€ 8,868	[24, 25]
HCC	€ 13,336	€ 5,792	€ 20,000	[24, 25]
Transplant (procedure)	€ 76,036	€ 62,648	€ 84,900	[24, 25]
Transplant (following years)	€ 1,870	€ 0	€ 4,729	[24, 25]
SVR	€ 0	€ 0	€ 0	[24, 25]
SVR to ILD states [b]	€ 2,186	€ 397	€ 2,483	Assumption from [23]

a - Only for SVR to ILD

b - Weighted average of states F4, DC and HCC (HCC costs are assumed equal to those of DC)

c - Source [25] reports the rates of SVR obtained using an evidence-based review of information on the DAA regimen classified as “Recommended” or “Alternative” by the AASLD HCV guidelines [32] and the European Association for the Study of the Liver (EASL) [33]

DC: decompensated cirrhosis; ILD: irreversible liver damage

3. Results

Of 5282 patients enrolled and evaluated for their access to DAA therapy (coming from 30 clinical centres distributed all over Italy), 2657 (51%) had consecutively undergone DAA therapy from January 2015 to December 2017. Genotype (G) distribution analysis during this period showed that G1 represented the most frequent genotype in Italy in all 3 of the periods analysed (67% in 2015, 64% in 2016 and 62% in 2017), followed by G2 and G3. In 2015, over 60% of the treated patients were in the F4+ stage, while no more than 19% were in stages F0-F3 (Table 2). The distribution of treated patients in F0-F3 increased to 44% in 2016 and to 77% in 2017 (Table 2).

Table 2 – Patient distribution by genotype, disease stage and year of starting treatment

Genotype distribution in treated patients	**2015 N 1390 (%)**	**2016 N 553 (%)**	**2017 N 665 (%)**
G1	938 (67%)	352 (64%)	415 (62%)
G2	186 (13%)	100 (18%)	135 (20%)
G3	154 (11%)	61 (11%)	65 (10%)
G4 and Other	112 (8%)	40 (7%)	51 (8%)
Fibrosis	Year 2015 N 1340 (%)	Year 2016 N 553 (%)	Year 2017 N 665 (%)
F0	72 (5%)	75 (14%)	192 (29%)
F1	72 (5%)	75 (14%)	192 (29%)
F2	131 (9%)	88 (16%)	127 (19%)
F3	232 (17%)	115 (21%)	64 (10%)
F4	722 (52%)	171 (31%)	77 (12%)
DC	110 (8%)	19 (4%)	9 (1%)
HCC	50 (4%)	10 (2%)	4 (1%)
Total	100%	100%	100%

Table 3 reports the clinical and economic results for a standardized population of 1,000 patients estimated by the model. The number of avoided HCV-related disease complications (DC, LT) was significantly higher in the first treatment period (2015) (980, 95% CI: 778-1221 avoided liver disease complications per 1,000) than in the subsequent years (722 and 374 avoided liver disease complications in 2016 and 2017, respectively). Regarding costs, the potential clinical outcomes reduction on time estimated for patients treated in 2016 and 2017 reflect important cost savings over 20 years period of time (-€50.1, 95% CI: -21.4 to -79.3; and -€55.5, 95% CI: -30.4 to -85.5, respectively). For patients

treated in the year 2015, the liver disease complications avoided, , do not compensate the initial investment in DAA . (€12.97 million increased costs, 95% CI: 3.4–42.5 million).

In the BPT analysis, the period of time required for the cumulative costs saved to recover the initial NHS investment in DAA treatment was estimated to be 6.6 years (95% CI: 5.4–9.1) for the 2016 treated patient cohort and 6.2 years (95% CI: 5.3–7.6) for the 2017 cohort. This estimation means that the initial investment for drug acquisition by the Italian NHS will be compensated after 6.6 years for patients treated in 2016 and after 6.2 years for those treated in 2017.

Table 3 – Base-case results and probabilistic sensitivity analysis

Results	BPT	Avoided cases (BPT)	Increasing costs after 20 years (€ million)	Avoided cases (after 20 years)
2015 *(Min-Max)*			€12.97 *(€ 2.35 - € 42.25)*	980 *(778 - 1221)*
2016 *(Min-Max)*	6.6 *(5.36 - 9.15)*	377 *(328.25 - 470.91)*	- €50.12 *(-€21.39 - -€ 79.26)*	722 *(558 - 918)*
2017 *(Min-Max)*	6.2 *(5.33 - 7.61)*	145 *(129.33 - 170.98)*	- €55.50 *(-€30.37 - -€85.49)*	374 *(279 - 493)*

Figure 2 reports the break-even results in 2017 based on the DSA. The graph represents the variation in the time to recover the initial investment compared to the base-case results (line in the middle). The SVR rate of new DAAs represents the input parameter with the greatest impact on the BPT results (a lower level of SVR increased the BPT to 7.2 years). Treatment costs, drug costs and transition probabilities had a moderate impact on the years needed for the return on investment (range 5.4–7.2), while transition probabilities and the distribution of the F3+ disease state had marginal impacts.

Considering the different models available in the literature on the disease progression of HCV patients, specific analyses were conducted on the BPT results using different transition probabilities. Figure 3 shows the BPT analysis for each cohort and the cost difference between the scenario with DAA treatment and the natural history of the disease. In all the analysed simulations, the distribution of the cost difference over time was consistent with the base-case analysis (cost increase between €11 and €25 million at 20 years of follow-up; Figure 3.a). The uncertainty regarding the BPT and estimated cost reduction could make the return on investment become 6.5-9.2 years for patients treated in 2016 and 6.1–8.0 years for those treated in 2017 depending on the model used (Figure 3.b and Figure 3.c).

4. Discussion

The fibrosis stage distribution in the treated patients represents one of the main drivers for the return on investment from the Italian NHS perspective. Consistent with other studies published in the Italian context [12, 16], our work demonstrates that access to HCV treatment in earlier fibrosis stages of liver disease, which correspond to no or minimal liver damage, correlates with better outcomes from a clinical perspective and cost reduction over time.

In the pre-DAA era, Marcellusi et al. (2015) [24] estimated a total burden of disease between 0.61 and 1.63 billion euros per year, of which 60.6% was associated with indirect costs (productivity loss) and 39.4% was associated with direct medical costs. No economic burden data are available regarding the post-DAA era. To our knowledge, this is the first study aiming to quantify the clinical and cost consequences of DAA investment and return from the NHS perspective. Moreover, this is the first cost-consequence analysis that is based on real-life data from a large sample of the Italian population for three different time periods.

Analysis of the clinical events potentially avoided over 20 years indicated a significant impact of the prioritized treatment (year 2015) on the reduction of severe clinical outcomes, such as progression of cirrhosis to DC, HCC and LT, and a less impact of DAA treatment on the reduction of these clinical events estimated by the model in patients treated in 2016 and 2017 Liver fibrosis is generally a slowly progressive disease characterized first by persistent hepatic inflammation, which could lead to the development of cirrhosis and HCC in the final stages of the disease progression. However, fibrosis progression is not linear, and its rates are extremely variable and can be influenced by host, viral and environmental factors [34-36]. Published data regarding the progression rates during HCV chronic infection are variable; progression rates to cirrhosis are as low as 2–3% to as high as 51% over 22 years [37, 38]. Once cirrhosis is established, a high risk of HCC or hepatic decompensation (variceal haemorrhage, ascites, encephalopathy) and, following an episode of decompensation, a high risk of death have been reported [27, 39, 40]. For this reason, the clinical effect of treatment across this time period was obviously visible in patients treated in the first period (2015), as these patients mainly had advanced liver fibrosis with fast liver disease progression without an effective treatment. On the other hand, the clinical effect of treatment was less visible in the other two periods (2016 and 2017) because the treated patients were mainly in the fibrosis stage F0-F3, therefore the severe liver disease outcomes would only appear in some of them in 20 years, even without treatment .

From the economic prespective, the nonprogression of liver disease following treatment in patients with liver fibrosis stages lower than F3, will consecutively have a cost reduction in their management over time. This explains the tendency of the relationship between the lower number of severe clinical outcomes avoided and the higher amount of costs saved as well as the BPT for patients treated in 2016 and 2017. In contrast, treating prioritized patients in 2015 led to a greater estimated reduction in severe clinical outcomes but a lower cost savings because the main management

costs persists regardless of virus eradication in patients with severe liver disease stage. This result, in combination with the higher drug costs in the first period, explain the not achievement of the BPT for patients treated in 2015. Considering instead the final two periods, the difference in the severe clinical outcomes avoided was significantly higher for patients treated in 2016 due to the higher proportion of patients with fibrosis stages higher than F3 compared to those treated in 2017 (377% vs 145%).. However, this result does not translate to a significantly different amount of time required to recover the investment in DAA therapy because the DBT is related to two factors, drug cost and liver disease progression cost. Specifically, the cost of drugs administered to patients in 2016 was higher than that administered to patients in 2017, and the liver disease progression costs were also modelled to be higher due to the higher proportion of patients with a fibrosis stage >F3 in 2016 than in 2017 (37% vs 14%). These differences in both components of costs from which the DBT was derived explains the similar times required to reach the break-even points in both periods despite the different drug and disease costs in each of the periods analysed.

Moreover, as observed in the sensitivity analysis, considering different disease progressions compared to the base case, a lack of a BPT within the 20-year period cannot be ruled out. In fact, fibrosis progression in chronic HCV infection is not a linear process; it depends on several host factors, such as alcohol use, coinfection patterns, and metabolic disorders. Consequently, for a fibrosis stage higher than F3, different progression probabilities should be considered for economic evaluations. Considering the different progression probabilities available in the literature [4, 23, 26] and the results reported in Figure 3.a and in Table 3, the return on investment in monetary terms could also never be fulfilled for patients treated in the severe liver disease stage, but a great return in terms of severe clinical outcmes avoided is observable.

Real-life clinical data suggest that following viral eradication due to DAA treatment, in the cirrhosis stage, some patients have significantly improved liver function tests, though some could still deteriorate, and HCC surveillance needs to continue despite virus elimination [31]. In several studies, improved liver function and reduction of LT necessity following HCV eradication after DAA treatment have been reported [31, 41-43]. On the other hand, treatment of patients with mild or no liver disease does not carry additive costs of management. In fact, comparing the third period (year 2017), in which a higher proportion of patients were treated in the F0-F2 fibrosis stage, to the first and second treatment periods (prioritized treatment), the reduction of liver-related events was lower in the third period, but the avoided costs were proportionally significantly higher. The real-life data clearly indicate the drastic reduction of costs for these latter patients compared to that for the others (PITER data not shown). In 2016, Linthicum et al. [26] investigated the value of expanding screening and treatment for HCV infection in the United States using the net social value of varying levels of access to treatment after diagnosis. This study demonstrated that such a “test-and-treat” strategy is likely to entail higher short-term costs but also yield the greatest social benefits.

As is common in this type of analysis, different limitations exist related to the assumptions and adaptations needed to model the disease progression. First, this is a baseline analysis based on real-life data from treated patients, and several inputs in the model (disease progression, drug costs, drug efficacy in 2017) are based on literature data. This mixture of data is not perfectly coherent methodologically but considers all the available evidence and represents a proxy of what decision makers could expect from their public health decisions. Moreover, for the disease progression probabilities, no data are available for the specific Italian population chronically infected with HCV, but the use of different disease progressions reported in the literature in the DSA seems to limit this potential assumption bias. Second, antiviral treatment is considered effective if an SVR is reached at 12 weeks, which is a surrogate outcome. In fact, the outcome after SVR depends primarily on the fibrosis stage at treatment onset as well as on host-related and concomitant risk factors. Following HCV eradication after IFN-based treatment in noncirrhotic patients and patients without liver damage cofactors, no fibrosis progression or fibrosis regression has been reported [44, 45]. Regarding HCV eradication due to DAA use, no data are available to confirm this hypothesis, as HCV DAAs have been utilized for only a short time. However, real-life short-term DAA efficacy (SVR12) data from the PITER cohort confirm the assumption made in this model regarding patients with fibrosis in stages F0-F3 and partially confirm the assumption made for patients with a fibrosis stage higher than F3 [31]. A potential bias in not considering possible liver disease progression in patients with fibrosis at stages F0-F3 regardless of whether the virus is eradicated due to other liver disease cofactors should be considered in terms of the costs of liver disease in these patients and in future analyses. The uncertainties on the input were considered in the sensitivity analysis, and no significant variations were estimated. The lowest range of each parameter did not differ significantly from the result obtained in the base case, and moreover, very narrow differences in the BPT were estimated. Thirdly, DAA treatment costs were assumed to decrease over time to €10,000 and €6,000 in the first and second years of commercialization in Italy, respectively. This decrease represents the main driver in the BPT analysis, but no official references are available in Italy regarding the real DAA costs during this period (prices were covered by an agreement between the AIFA and pharmaceutical companies). However, based on nonofficial communications with the AIFA, these assumptions reflect, to a good approximation, the real-life costs paid by the Italian NHS for each DAA treatment per patient. Considering the lack of real-life medium- and long-term data on DAA effectiveness for patients with different profiles of chronic HCV liver disease and the overall morbidity stage, this analysis could help decision makers, as it reflects the real-life epidemiological and clinical patterns of treated patients in relation to overall patients in care.

Finally, the model considered health effects and cost reductions for patients treated from 2015-2017. No assumptions were made for indirect effects on the general population (such as avoiding infections and eradication), and indirect costs

were not considered in the analysis. Therefore, the results might represent an underestimation of the actual health effects and avoided costs.

5. Conclusion

The results of this cost-consequence analysis, which was based on real-life HCV treatment data from a representative sample of Italian patients in care, confirm an overall health benefit of treatment. This benefit is inversely correlated with cost savings in patients with severe liver disease over a 20-year evaluation period. The break-even point in time analysis demonstrated that following the emergency treatment of patients with severe liver disease, in whom only a health benefit was estimated, the current investment in universal DAA treatment is broadly cost saving. It is plausible to assume that the increasing trend in the Italian NHS return on investment estimated in this study will continue in the future, entailing lower investments and faster returns. This study may be a useful tool for public decision makers to understand how HCV epidemiological profiles influence the economic burden of HCV.

Data Availability Statement

PITER is a multicentric prospective study that was approved by the Ethical Committee of Istituto Superiore di Sanità and the local Ethical Committees of the 90 centers involved in the study. By protocol, the property of the data is of participating clinical centers while Istituto Superiore di Sanità acts as coordinating center for data management and analysis. Cumulative data are reported within the paper whereas each patient data are not fully available and without restrictions for ethical reasons. The datasets generated and analyzed during the current study could be available upon request to all interested researchers.

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Conflicts of interest: AM, RV, LAK, SR, FM and SV have no competing interests to declare regarding the content of this article.

Authors’ contributions: AM, RV**,** LAK, designed the study, conducted the analysis and finalized the draft of the manuscript. FM and SV provided guidance on the methodology, reviewed the results and critically assessed the

manuscript. All the authors provided data and/or reviewed the results of the final draft of the manuscript. All authors approved the final version of the manuscript. LAK had full access to all the data used in the study and had final responsibility for the decision to submit for publication

Compliance with ethical standards

The PITER cohort study protocol was approved by the Ethics Committee of Istituto Superiore di Sanità (Italian National Institute of Public Health) and by the local ethics committees of each clinical centre. Patient data were evaluated via an anonymous analysis, adopting codes generated by the electronic case-report form. Informed consent was obtained from each patient participating in this study.

AM, RV, LAK, SR, FM and SV have no competing interests to declare regarding the content of this article.

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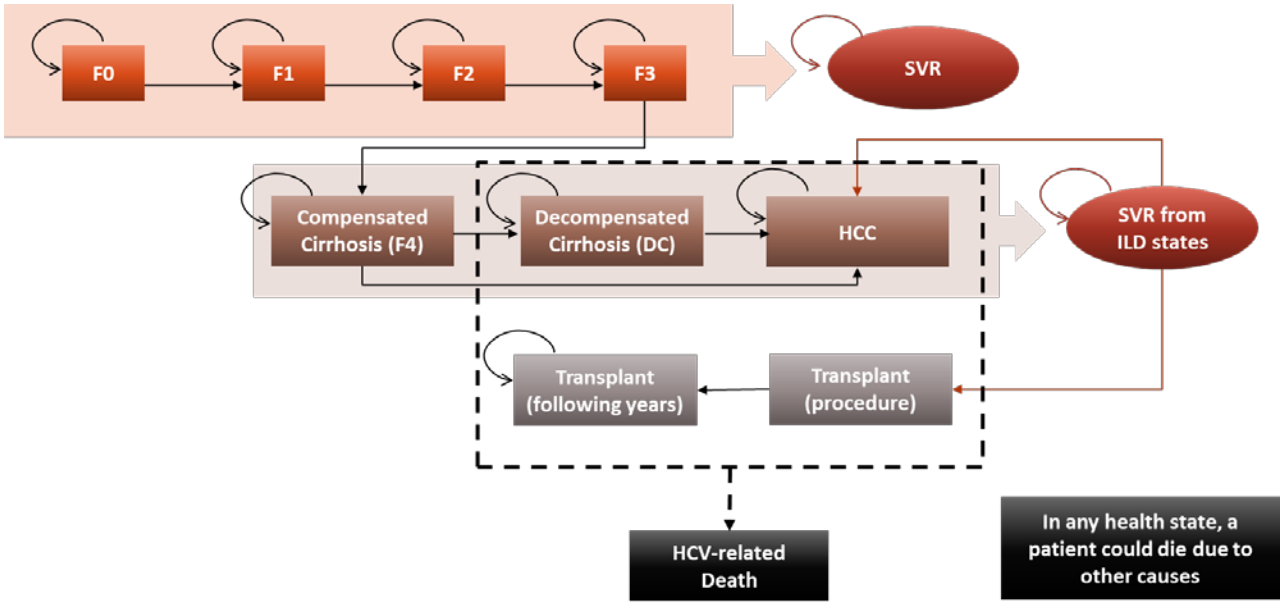
Fig 1 – State transition Markov model

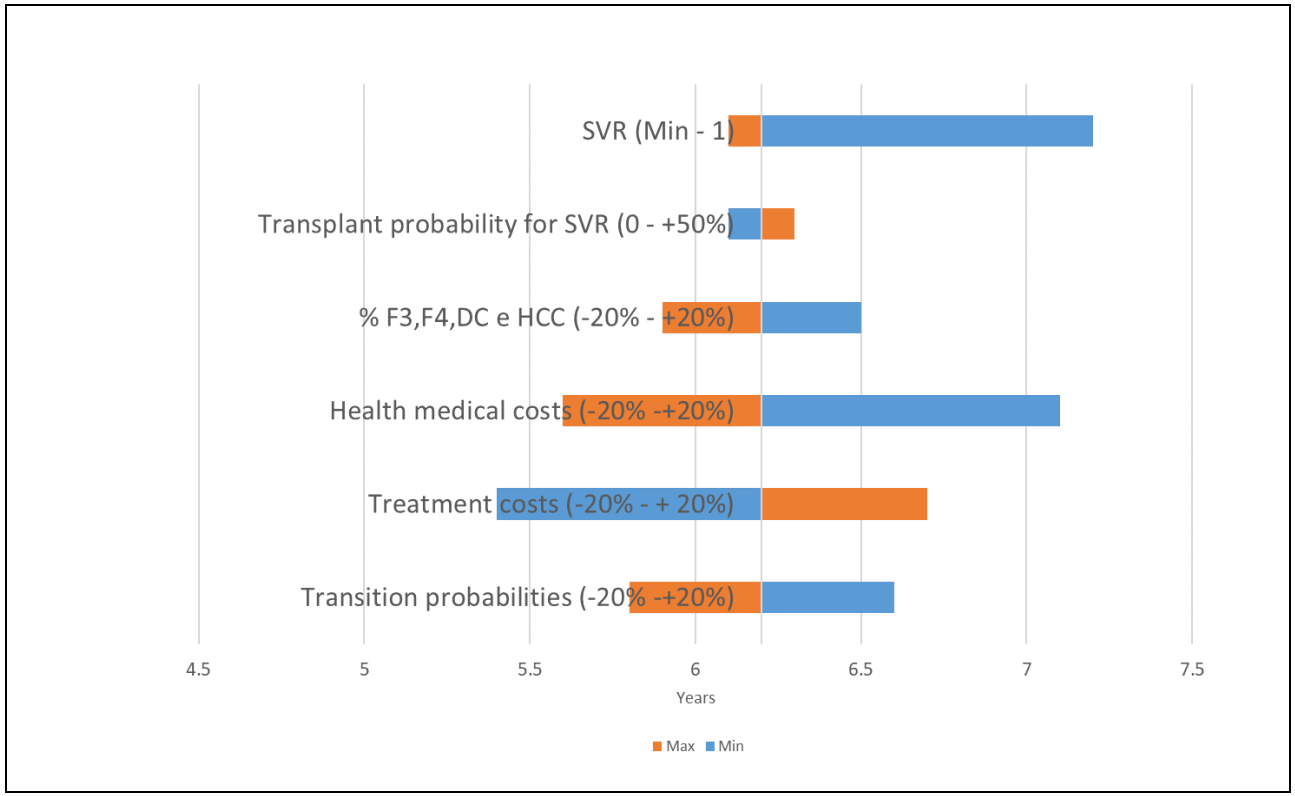
Legend: F: fibrosis stage; SVR: sustained virologic response; HCV: hepatitis C virus; HCC: hepatocellular carcinoma.

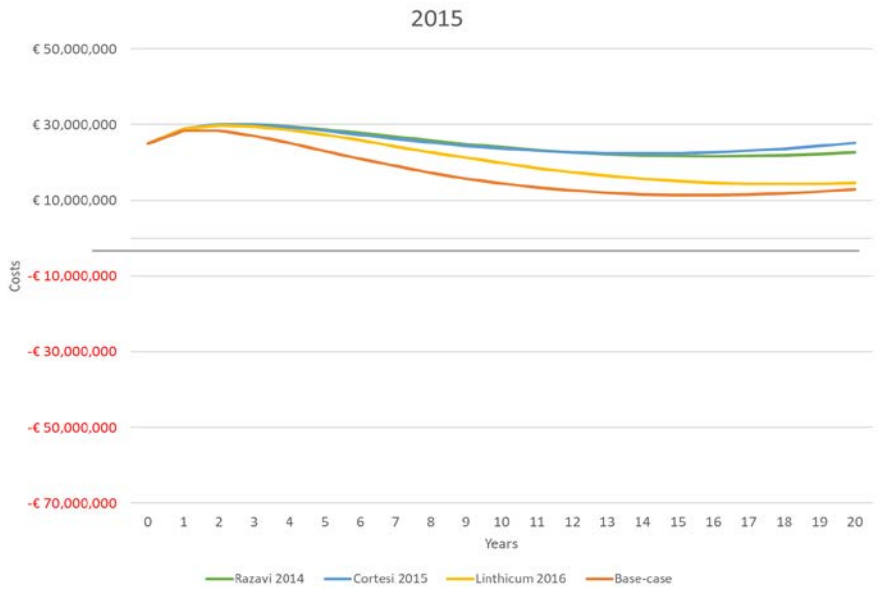
Fig 2 – Deterministic sensitivity analysis of the discounted break-even point in time (2017): tornado diagram

Legend: F: fibrosis stage; SVR: sustained virologic response; DC: decompensated cirrhosis; HCC: hepatocellular carcinoma.

Fig 3 – Deterministic sensitivity analysis: Markov cost tracking with the input transition probabilities of Razavi 2014 [4], Cortesi 2015 [23] Lithicum 2016 [26] and base-case.


F0
F1
F2
F3
SVR
Compensated Cirrhosis (F4)
Decompensated Cirrhosis (DC)
HCC
SVR from ILD states
Transplant (following years)
Transplant (procedure)
HCV-related Death
In any health state, a patient could die due to other causes


SVR (Min - 1)
Transplant probability for SVR (0 - +50%)
% F3,F4,DC e HCC (-20% - +20%)
Health medical costs (-20% -+20%)
Treatment costs (-20% - + 20%)
Transition probabilities (-20% -+20%)
4.5
5
5.5
6
6.5
7
7.5
Years
Max
Min


2015
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-€ 30,000,000
-€ 50,000,000
-€ 70,000,000
Costs
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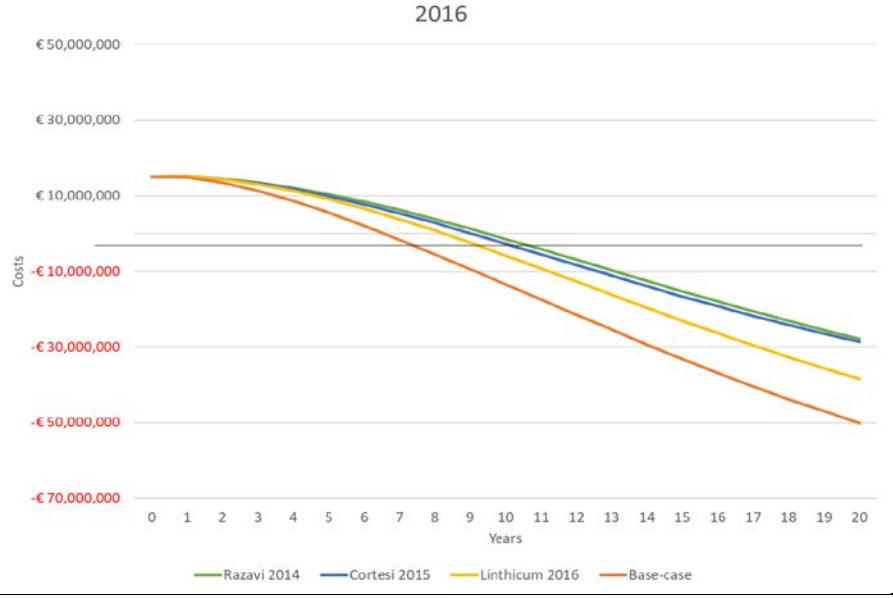
Years
Razavi 2014
Cortesi 2015
Linthicum 2016
Base-case


2016
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-€ 50,000,000
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Costs
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Years
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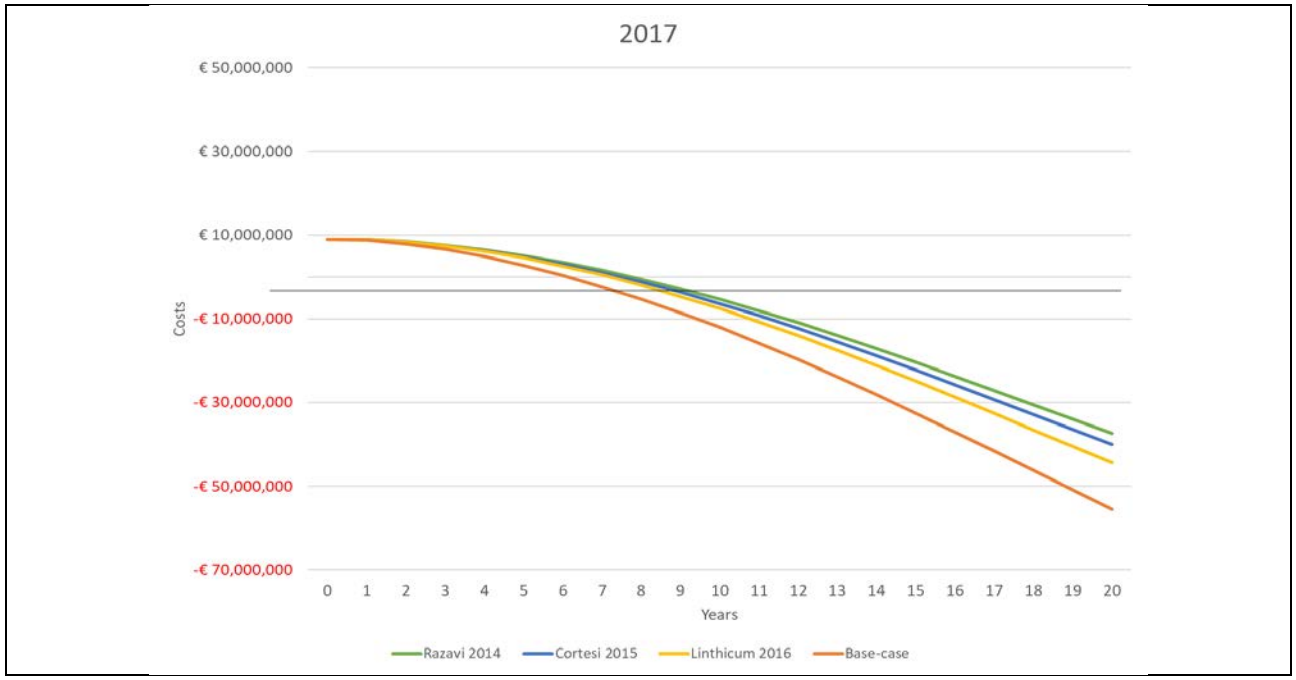
Linthicum 2016
Base-case


2017
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Costs
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Years
Razavi 2014
Cortesi 2015
Linthicum 2016
Base-case