Clinical and economic consequences of antiviral treatment for Hepatitis C chronic infection in Europe: analysis of England, Italy, Romania and Spain data

X. TATA[1,2], A. MARCELLUSI[3], G. FABIANO[3,4], S. RYDER[5], M. BUTI[6], L. GHEORGHE[7], C. COPPOLA[8], A. CRAXI[9], F.S. MENNINI[3], L.A. KONDILI[1]

1Istituto Superiore di Sanità, Rome, Italy, 2Universiteti" Zoja e Keshillit te Mire",3University of Tor Vergata, Rome, Italy, 4Institute for Leadership and Management in Health, London, Italy, 5NIHRNottinghamBiomedical Research Centre, Nottingham, United Kingdom, 6Hospital Universitario Valle Hebron, Barcelona , Spain, 7Carol Davila University of Medicine and Pharmacy Fundeni ClinicalInstitute, Bucharest, , 8Gragnano Hospital, Naples, Italy, 9University of Palermo, Palermo, Italy

1 INTRODUCTION

The effect of antiviral therapy, in terms of the impact on clinical-related outcomes rather than virological efficacy, changes over time according to the epidemiological profile of the disease and specific patient characteristics. These factors vary by country, meaning country-specific epidemiology of HCV infection, DAA treatment guidelines, and treatment access are expected to impact the burden of HCV-liver related outcomes following viral eradication. In this study, we built country-specific models using real-life data of fibrosis stage, genotype distribution, and treatment eligibility for England, Italy, Romania, and Spain. These countries have varying epidemiological patterns of infection, treatment eligibility, and gross domestic product (GDP), thus providing a comprehensive evaluation on how treatment access in these different landscapes can influence their clinical and economic burden of HCV.

2 AIM

The main objectives were: (1) to compare the disease burden outcomes (development of decompenstated cirrhosis (DC), HCC, and necessity for orthotopic liver transplantation (LT) in these countries over a 20-year time horizon; (2) to assess, by country, the impact of antiviral therapy on the direct cost of HCV-related disease management; (3) to predict the necessary time to recover the initial investment for treatment in each country.

3 METHOD

A country-specific Markov model, grounded in country-specific parameters (to real-life fibrosis stage and genotype distribution data) was used to evaluate HCV disease progression and related costs for 1000 standardized treated patients over a 20 year time horizon, was designed to estimate the clinical and economic outcomes of expanded access to DAA therapy, considering the direct costs of HCV treatment in the European context (England, Italy, Romania, and Spain) [1-6]. The model structure considers 13 disease states (fibrosis stages from F0 to F4, DC, HCC, first-year transplant and subsequent years transplant, SVR from F0 to F3, SVR from irreversible liver damage (ILD), HCV-related death, and death from other causes) and 41 transition probabilities. Events constituting advanced liver disease, such as ILD or DC, were considered as cumulative events in the model and not mutually exclusive[1]. Model inputs are reported in **Table 1** and **Table 2**. All transition probabilities are adjusted for competing probabilities of death from other causes according to the official data from each country.

Scenarios. The model simulates three different scenarios considering 1,000 standardized patients over a 20-year time horizon:

1. No treatment (base case): patients in disease stages F0-F4 follow the natural history of HCV without any therapy;
2. 2015/2016: prioritized treatment using the country-specific genotype and fibrosis stage distribution of patients;
3. 2017/2019: no treatment restrictions or restrictions according to the eligibility criteria (in Romania).

Economic results were reported as the absolute difference between the estimated cost of the 2015/2016 and 2017/2019 scenarios to the "no treatment" scenario. The break-even analysis considers the time (in years) needed to minimize this difference to zero. Costs were expressed in Euros and were discounted at a rate of 3% annually.

Sensitivity analysis. To estimate the uncertainty of the economic results, deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA) were performed (5000 Monte Carlo simulation to provide 95% confidence intervals (95% CIs) for case and cost reduction at 20 years, break-even point, and case reduction at the break-even point.

4 RESULTS

Characteristics of treated patients by country, according to fibrosis stage

Because the four European countries have different treatment eligibility criteria, the distribution of fibrosis stages among treated patients varied significantly. (**Figure 1**).

Evaluation of clinical outcomes from 2015-2035

By expanding access to DAA therapies in 2017/2019, the model estimated a decrease in end-stage disease in all countries. There would be 640 fewer events of advanced liver disease in England, 626 fewer events in Italy, 643 fewer events in Spain, and 739 fewer events in Romania over the next 20 years. More cases of irreversible liver disease are avoided in 2015/2016 as compared to 2017/2019 (**Table 3**).

Evaluation of costs and return on investment from 2015-2035

The potential reduction in clinical events over the next 20 years for patients treated between 2015-2019 is cost saving in all countries. The overall savings for 1000 standardized treated patients over 20 years are shown in **Table 3**. In all countries, it would take less than 10 years to reach a break even point The Break Even Points are similar to the base case values in all countries except Romania in which the max variation is almost double the time estimated in base case analysis. Higher variation is reported during the first treatment period (prioritized) versus the second treatment period (universal).

Table 3 - Economic outcomes of expanding access to direct-acting antiviral therapy over a 20-year time horizon in England Italy, Romania and Spain)

	Year	Break Even Point (95% confidence interval)	Avoided cases (BEP) (95% confidence interval)	Avoided cases (after 20 years) (95% confidence interval)	Avoided costs after 20 years (€ million) (95% confidence interval)
England	2015 - 2016	7,8	667	1.057	€ 43,88
	(Min-Max)	(4,14 - 12,59)	(534 - 815)	(868 - 1264)	(€ 17,52 - € 82,13)
	2017 - 2019	5,8	250	640	€ 106,28
	(Min-Max)	(4,49 - 7,27)	(215 - 288)	(522 - 770)	(€ 73,74 - € 144,66)
	Overall	6,5	405	820	€ 81,48
	(Min-Max)	(4,46 - 8,92)	(335 - 481)	(678 - 975)	(€ 51,27 - € 118,56)
Italy	2015 - 2016	7,7	797	1.221	€ 16,54
	(Min-Max)	(4,76 - 11,34)	(625- 988)	(987 - 1478)	(€ 0,55 - € 58,74)
	2017 - 2019	4,4	179	626	€ 83,81
	(Min-Max)	(3,43 - 5,49)	(147- 215)	(486 - 783)	(€ 51,74 - € 123,49)
	Overall	5,4	383	886	€ 63,50
	(Min-Max)	(3,43 - 7,81)	(292 - 488)	(705 - 1087)	(€ 30,41 - € 108,57)
Romania	2015 - 2016	6,8	750	1.211	€ 45,29
	(Min-Max)	(3,74 - 10,77)	(479 - 1080)	(917 - 1545)	(€ 3,15 - € 142,08)
	2017 - 2019	6,4	337	739	€ 50,57
	(Min-Max)	(3,08 - 10,91)	(191 - 526)	(541 - 967)	(€ 14,1 - € 109,89)
	Overall	6,7	510	€ 934	45,40
	(Min-Max)	(2,96 - 11,94)	(291- 789)	(697 - 1204)	(€ 7,68 - € 115,98)
Spain	2015 - 2016	4,8	394	1.103	€ 289,63
	(Min-Max)	(3,36 - 6,5)	(316- 479)	(903 - 1323)	(€ 172,87 - € 436,04)
	2017 - 2019	3,7	130	643	€ 241,50
	(Min-Max)	(2,68 - 4,88)	(99 - 166)	(509 - 792)	(€ 146,9 - € 359,24)
	Overall	4,5	265	877	275,56
	(Min-Max)	(3,38 - 5,77)	(213- 323)	(708 - 1064)	(€ 170,9 - € 404,83)

€ - Euro; BEP - Break even point; Min – minimum; Max - maximum

Table 1. Transition probabilities and efficacy of treatment (Base-case and Deterministic Sensitivity analysis parameters)

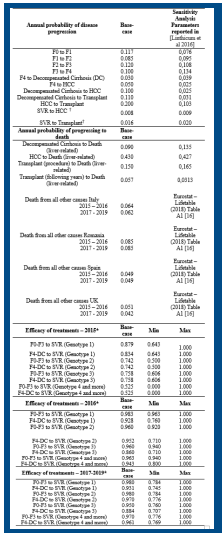


Table 2. Cost parameters (Base-case and Deterministic Sensitivity analysis parameters)

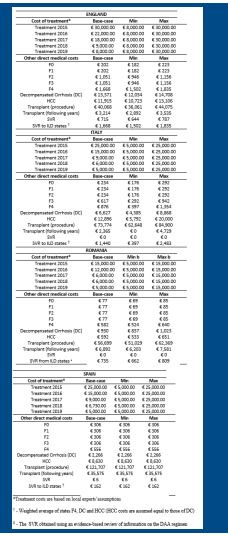
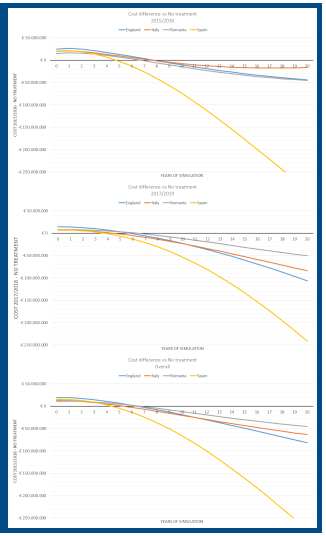


Fig 2. Differences in costs by treatment scenario in Italy, Romania, Spain, and England over a 20-year time horizon.



The costs avoided and break even estimations over the next 20 years based on the DSA analysis are reported in **Figure 3**. Transition probabilities had the highest impact on both the number of years needed until the break event point and the total costs saved over the 20-year time horizon for Italy, Spain, and Romania (36%, 59%, and 86%, respectively). For England, the variation of treatment cost led to a higher level of variability (-23% in the minimum scenario).

Fig 1. Proportion of patients by disease stage in Italy, Romania, Spain, and England in 2015/2016 and 2017/2018.

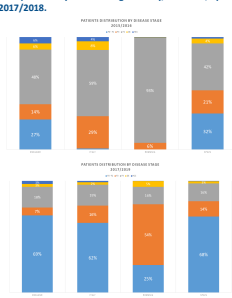
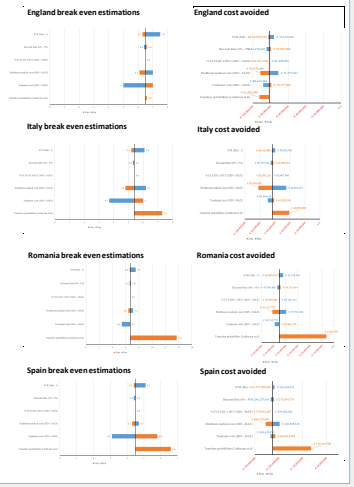


Fig 3. Deterministic Sensitivity Analysis assessing the impact of the variation in model parameters on the total costs avoided and break even time point



5 CONCLUSIONS

Results of this study show that despite the country-specific dynamics and natural history of HCV infection in Italy, Spain, Romania, and England, there will be a positive return on investment and expanding access to treatment is cost saving in less than 10 years in the countries analyzed. Universal access to therapies in all infected individuals will result in stronger economic returns and less disease burden. It should be noted though, that not treating or delaying treatment of infected individuals will result in higher disease burden and consecutively higher costs for the NHS. Policy makers could consider these efforts when determining the most cost-effective methods for managing HCV infection across Europe.

6 ACKNOWLEDGEMENTS

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7 REFERENCES

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8 CONTACT

Loreta Kondili. Center for Global Health, Istituto Superiore di Sanità.
Viale Regina Elena 299- 00161 Rome, Italy
Tel: +39 0649903813 - E-Mail: loreta.kondili@iss.it