

Cost-effectiveness analysis of chronic hepatitis C treatment in the prison population in Spain

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ABSTRACT

Objectives: To evaluate the cost-effectiveness of direct-acting antiviral (DAAs) treatment versus non-treatment in prisoners awaiting treatment for chronic hepatitis C (CHC) and to analyse the clinical and economic impact of the treatment on liver complications and mortality.

Material and method: A lifetime Markov model was developed to simulate treatment and disease progression from an estimated cohort of 4,408 CHC prisoners treated with DAAs over 2 years (50% of patient each year) versus no treatment. In the treated cohort, a sustained viral response of 95% was associated. Patient characteristics, transition probabilities, utilities and costs (pharmacological and healthcare states) were obtained from published literature. The model estimated healthcare costs and benefits, incremental cost-utility ratio (ICUR) based on total costs and the quality-adjusted life year (QALY) and avoided clinical events. A National Healthcare System perspective was adopted with a 3% annual discount rate for both costs and health outcomes. Sensitivity analyses were performed to assess uncertainty.

Results: In the DDA treated cohort, the model estimated a decrease of 92% of decompensated cirrhosis and 83% of hepatocellular carcinoma, 88% liver-related mortality cases were reduced, 132 liver transplants were avoided. The treatment achieved an additional 5.0/QALYs (21.2 vs. 16.2) with an incremental cost of €3,473 (€24,088 vs. €20,615) per patient with an ICUR of €690 per QALY gained.

Discussion: Considering the willingness-to-pay threshold used in Spain (€22,000-30,000/QALY), DAAs treatment for prisoners with CHC is a highly cost-effective strategy, reduces infection transmission, increases survival and reduces complications due to liver disease, as well as the cost associated with its management.

Keywords: prisons, chronic hepatitis C, cost-effectiveness analysis, public health.

Text received: 01/10/2019

Text accepted: 28/10/2019

INTRODUCTION

The World Health Organization (WHO) and the Strategic Plan for tackling Hepatitis C in the Spanish National Health System (*Plan Estratégico para el Abordaje de la Hepatitis C en España*, PEAHC) consider the hepatitis C virus (HCV) infected prison inmates as a risk population that must be prioritized in order to eliminate hepatitis C^{1,2}. This is because prisoners have a much higher prevalence of HCV infection compared to the non-incarcerated population and because successful treatment implies redu-

cing both the risk of transmission and the burden of the disease. In particular, in Spain it is estimated that HCV infection is 8-14 times more prevalent in prisoners than in non-prisoners (8.2%-14.8% vs. 0.8%-1.2%)³⁻⁷, despite the fact that the incidence in prisons has been greatly reduced in recent years^{8,9}.

The high prevalence of HCV infection in the prison population is mainly due to the frequent history of intravenous drug use present in this group. In addition to the habit of sharing injection materials, there are other possible transmission routes among inmates, such as unhygienic tattooing and piercing, as well as

risky sexual behaviours^{10,11}. It is estimated that 70% of intravenous drug users (IDUs) enter prison at least once and that 35.3% of Spanish IDU prisoners and 16.5% of foreign IDU prisoners admit to using an intravenous drug during their stays in prison¹². This consumption is maintained and even tends to increase during leave times and after release¹³, which implies a risk of HCV transmission both inside and outside prison¹⁴.

The availability in recent years of new direct-action antivirals (DAAs), with a high efficacy, a favourable safety profile and a shorter administration period, has led to extraordinary changes in the morbidity and mortality associated with chronic hepatitis C (CHC) as well as in the quality of life of patients.

Several recent studies have shown that treating prisoners in Spanish prisons with CHC using current DAAs can be successful^{15,16} and have a similar effectiveness to that observed in the non-incarcerated population¹⁵. Therefore, optimizing CHC treatment in prison inmates is an opportunity to improve the health of these patients and has a great epidemiological importance given the ability of this group to transmit the infection.

On the other hand, CHC has an impact at an individual and collective level, and in prisoners and non-prisoners alike, representing a substantial economic burden for the Spanish National Health System (NHS)¹⁷. Thus, although the treatment of chronic patients is associated with the cost of DAAs, it should not be forgotten that not treating them also involves costs for the NHS deriving from disease management as well as its complications. In recent years, new DAAs have induced a change in the use of health resources and in the costs of care for these patients¹⁷.

The objective of this study was to estimate the cost-effectiveness and health gains associated with the use of direct-acting antivirals (DAAs) for the treatment of CHC in the prison population in Spain.

MATERIALS AND METHOD

A cost-effectiveness analysis of CHC patients awaiting treatment who are inmates in Spanish prisons was conducted. The target population was estimated at 4,408 inmates. For the calculation of this population, the total annual prison population was used, not including readmissions obtained from two Prison Administrations (4,001-4,713 inmates)^{2,3}, and seroprevalence of Ac HCV and positive viral load in this population of 45-53%^{2,3} and 9.1% was associated, respectively.

The characteristics of the population (age, genotype and degree of fibrosis [F0, F1, F2, F3 y F4]) were identified from published studies of prisoners in Spain (Table 1)¹⁸. For the analysis, a previously validated Markov^{19,20} model was adapted (Figure 1) to simulate the progression of the disease through the different mutually exclusive health states at the end of each annual cycle or remaining in the same health state. Patients enter the model based on the state of their fibrosis. In the treated cohort, it was considered that 50% were treated in the first year and 50% in the second year, and the average rate of sustained viral response (SVR) was 95%² which was derived from Spanish real-world data. Patients in SVR stages F0, F1 and F2 are considered cured patients and continue in that state until their death. Patients in SVR stages F3 and F4 remain at risk of developing hepatocellular carcinoma (HCC), and, in the case of SVR F4, are also at risk of decompensated cirrhosis (DC). Untreated patients progressed in the model according to the natural history of the disease. Patients who undergo liver transplantation (LT) only remain for one cycle at state. The transition probabilities between the different health states were obtained from published literature¹⁹⁻²⁰.

Mortality associated with the analysis depended on each health state and, in some cases, on the age range. In patients with DC, HCC or LT, liver-related mortality¹⁹⁻²⁰ were assigned for each state, and non-liver-related mortality was calculated from data from the National Institute of Statistics²¹. In the rest of the stages, all-cause mortality was considered according to the age range²¹.

The utility values are associated with the preferences of the patients for a given health state, oscillating between 0 (worst perceived state) and 1 (perfect health state). The values were obtained from published studies when utilities for the general population were used¹⁹⁻²⁰ (Table 1).

The study was conducted from the perspective of the NHS. Therefore, only direct health costs expressed in euros and with values based on those from the year 2018 were incorporated. The average pharmacological cost of DAAs per patient (€ 20,594) was calculated from the total number of patients treated since the PEAHC started and the total costs for the same period^{2,22}. The costs associated with monitoring during treatment and disease management^{19,20}, as well as the costs of each health state^{19,20}, were updated with respect to the year of the study (€, 2018) using the Price Index of Consumption (PIC)²³.

The results for effectiveness were expressed in terms of life years gained (LY) and quality-adjusted life

years (QALYs). The latter was estimated as the product of the LY due to the utility of the patients in each health state. The efficiency was expressed as follows:

- as an incremental cost-effectiveness ratio (ICER) per patient, which was calculated as follows:

$$ICER = \frac{Cost_{Treatment} - Cost_{No\ treatment}}{LY_{Treatment} - LY_{No\ treatment}}$$

- as an incremental cost-utility ratio (ICUR) per patient, by dividing the incremental difference of the total cost and the QALY of the two alternatives:

$$ICUR = \frac{Cost_{Treatment} - Cost_{No\ treatment}}{QALY_{Treatment} - QALY_{No\ treatment}}$$

The option of treating all prisoners with CHC was considered efficient if the result of the ICUR was below the willingness-to-pay (WTP) threshold used in Spain, which ranges between € 21,000 and € 30,000 per QALY^{24,25}.

The incidence of liver complications in each of the alternatives studied was also analysed; this was shown as the “number of cases avoided” with the option of treatment versus no treatment.

The time horizon was defined as the entire life of patients. For this reason and to assess the results in a present value, an annual discount rate of 3% was used for both costs and health outcomes²⁶.

Finally, to evaluate the model’s uncertainty and the robustness of the results, several univariate and multivariate sensitivity analyses were performed by modifying the most significant parameters. These parameters were: a) the SVR rate (93% and 98%)²; b) the percentage of patients at F4 stage (15% and 25%); c) the probability of receiving LT for presenting with DC (0.01 and 0.06)^{19,20} or HCC (0.0 and 0.14)^{19,20}; d) the utilities of the SVR stages (0.98 and 1.00 for SVR F0 and SVR F1, 0.92 and 1.00 for SVR F2, 0.82 and 0.90 for SVR F3, and 0.79 and 0.87 for SVR F4)^{19,20}; and e) the pharmacological cost (\pm 20%), the cost of LT (\pm 20%) and f) the variation of the discount rate (0% and 5%)²⁶.

RESULTS

The treatment of the entire cohort of patients was associated with 3.8 LY and 5.0 QALY per patient compared to no treatment and with an incremental cost for treatment of €3,473, which implies an ICUR of 690 € per QALY gained and an ICER of € 913 per

LY per patient, which is well below the WTP threshold commonly used in Spain (Table 2).

The health outcomes measured in terms of the number of avoided cases of DC, HCC, LT and liver-related deaths (Figure 2) showed much greater reductions with the option of treating versus not treating (92, 83, 90 and 88%, respectively). These reductions also implied a decrease in the costs associated with the management of these complications.

The sensitivity analyses showed that the results described above were robust. The maximum variation occurred when the probability of receiving LT due to DC or HCC increased and when the pharmacological cost was reduced by 20%, revealing a negative ICUR, this means that treating the entire cohort, compared to the non-treatment option, is a dominant strategy (lower cost and higher effectiveness). The variation in the discount rate also had a significant impact on the results. The highest ICUR was € 1,497/QALY (below the WTP threshold), while the lowest was € -507/QALY. The detailed results are presented in a tornado diagram showing the variation in the ICUR when each parameter included in the sensitivity analysis varies between its maximum and minimum values (Figure 3).

DISCUSSION

To our knowledge, only one recent study²⁷ has assessed the efficiency of increasing the number of DAAs treatments used for prisoners in Spain. In that study a different methodology was used to evaluate the long-term effects of the disease and costs, however it had similar results to this one. In this sense, the results of our analysis also show that treating CHC infected prisoners is an efficient strategy, with a cost per QALY that is significantly lower than the efficiency threshold used in Spain. In addition, treating all CHC prisoners reduces infection transmission, increases survival, improves quality of life, significantly reduces the incidence of liver complications and avoids future economic costs. In our opinion, these results are relevant and consistent in the sensitivity analyses carried out.

Studies published in other countries that evaluate the economic impact of treatment for CHC in the prison population are scarce^{14,28,29}. However, the results of these studies are in line with those obtained in this study, even if evaluations were performed when the standard treatment was pegylated interferon plus ribavirin²⁷ or if more recent treatments were used, having taken place during the DAA treatment era^{14,29}.

Table 1. Analysis parameters.

Parameter	Value	Reference	Parameter	Value	Reference
Distribution (%) of genotypes (GT)			Costs of health status		
• GT1	49	PEAHC ²	• F0	272.10 €	Turnes J et al. ¹⁹⁻²⁰
• GT2	1		• F1	272.10 €	Turnes J et al. ¹⁹⁻²⁰
• GT3	24		• F2	314.82 €	Turnes J et al. ¹⁹⁻²⁰
• GT4	26		• F3	314.82 €	Turnes J et al. ¹⁹⁻²⁰
Level (%) of fibrosis (F)			• F4	572.76 €	Turnes J et al. ¹⁹⁻²⁰
• F0 and F1	44	Daivozadeh G et al. ¹⁸	Costs of health statuses		
• F2	19		• SVR F0	115.71 €	Turnes J et al. ¹⁹⁻²⁰
• F3	16		• SVR F0 (second year onwards)	0€	Assumption
• F4	20		• SVR F1	115.71 €	Turnes J et al. ¹⁹⁻²⁰
Probabilities of transition (yearly)			• F1 SVR (second year onwards)	0€	Assumption
• From F0 to F1	0.131	Turnes J et al. ¹⁹⁻²⁰	• F2 SVR	115.71 €	Turnes J et al. ¹⁹⁻²⁰
• From F1 to F2	0.080	Turnes J et al. ¹⁹⁻²⁰	• F2 SVR (second year onwards)	0€	Assumption
• From F2 to F3	0.133	Turnes J et al. ¹⁹⁻²⁰	• F3 SVR	115.71 €	Turnes J et al. ¹⁹⁻²⁰
• From F3 to F4	0.134	Turnes J et al. ¹⁹⁻²⁰	• F3 SVR (second year onwards)	115.71 €	Assumption
• From F3 to HCC	0.011	Turnes J et al. ¹⁹⁻²⁰	• F4 SVR	166.46 €	Turnes J et al. ¹⁹⁻²⁰
• From SVR F3 to HCC	0.003	Turnes J et al. ¹⁹⁻²⁰	• F4 SVR (second year onwards)	166 €	Assumption
• From F4 to DC	0.040	Turnes J et al. ¹⁹⁻²⁰	• Regr C	116 €	Assumption
• From F4 to HCC	0.015	Turnes J et al. ¹⁹⁻²⁰	• Regr C (second year onwards)	0€	Assumption
• From SVR F4 to DC	0.003	Turnes J et al. ¹⁹⁻²⁰	• Decompensated cirrhosis	2332.38 €	Turnes J et al. ¹⁹⁻²⁰
• From SVR F4 to HCC	0.006	Turnes J et al. ¹⁹⁻²⁰	• Liver cell carcinoma	8884.02 €	Turnes J et al. ¹⁹⁻²⁰
• From SVR F4 to Regr. C	0.055	Turnes J et al. ¹⁹⁻²⁰	• Liver transplant	125294.15 €	Turnes J et al. ¹⁹⁻²⁰
• From DC to HCC	0.068	Turnes J et al. ¹⁹⁻²⁰	• Post-LT	36622.95 €	Turnes J et al. ¹⁹⁻²⁰
• From DC to LT	0.023	Turnes J et al. ¹⁹⁻²⁰	• Post-LT (following years)	18331 €	Turnes J et al. ¹⁹⁻²⁰
• From DC to liver-related death	0.138	Turnes J et al. ¹⁹⁻²⁰			
• From HCC to LT	0.040	Turnes J et al. ¹⁹⁻²⁰			
• From HCC to liver-related death	0.430	Turnes J et al. ¹⁹⁻²⁰			
• From TH to post-LT	1.000	Assumption			
• From LT to liver-related death	0.210	Turnes J et al. ¹⁹⁻²⁰			
• From post-LT liver-related death	0.057	Turnes J et al. ¹⁹⁻²⁰			
Utilities					
• F0	0.98	Turnes J et al. ¹⁹⁻²⁰			
• F1	0.98	Turnes J et al. ¹⁹⁻²⁰			
• F2	0.92	Turnes J et al. ¹⁹⁻²⁰			
• F3	0.79	Turnes J et al. ¹⁹⁻²⁰			
• F4	0.76	Turnes J et al. ¹⁹⁻²⁰			
• SVR F0	1.00	Turnes J et al. ¹⁹⁻²⁰			
• SVR F1	1.00	Turnes J et al. ¹⁹⁻²⁰			
• SVR F2	0.93	Turnes J et al. ¹⁹⁻²⁰			
• SVR F3	0.83	Turnes J et al. ¹⁹⁻²⁰			
• SVR F4	0.83	Turnes J et al. ¹⁹⁻²⁰			
• Reg. C	0.86	Turnes J et al. ¹⁹⁻²⁰			
• DC	0.69	Turnes J et al. ¹⁹⁻²⁰			
• HCC	0.67	Turnes J et al. ¹⁹⁻²⁰			
• LT	0.50	Turnes J et al. ¹⁹⁻²⁰			
• Post-LT	0.77	Turnes J et al. ¹⁹⁻²⁰			

Note. DC: decompensated cirrhosis; HCC: hepatocellular carcinoma; PEAHC: Spanish Strategic Plan for Combating Hepatitis C; Post-LT: post- liver transplant; Reg. C: regression of cirrhosis; SVR: sustained virologic response; LT: liver transplant.

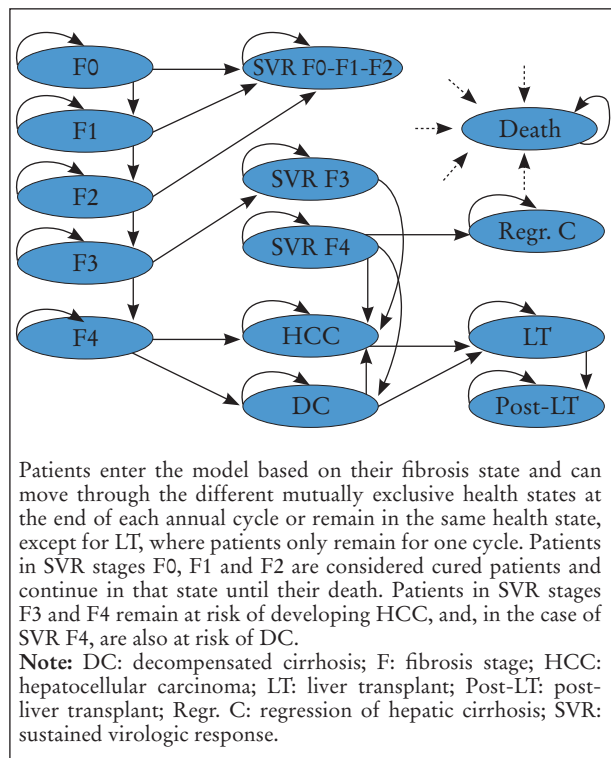


Figure 1. Markov model diagram.

Table 2. Results of cost effectiveness analysis per patient.

	Treated cohort	Not treated cohort	Incremental difference Treatment vs. not treatment
LYG	22.9	19.1	3.8
QALY	21.2	16.2	5.0
Total costs	24.088 €	20.615 €	3.473 €
Pharmacological	20.294 €	0 €	20.294 €
Treatment monitoring	1.028 €	0 €	1.028 €
Disease management	2.766 €	20.615 €	-17.848 €
Incremental cost-effectiveness ratio	913 €		
Incremental cost-utility ratio	690 €		

Note. QALY: quality adjusted life years; LYG: life year gained.

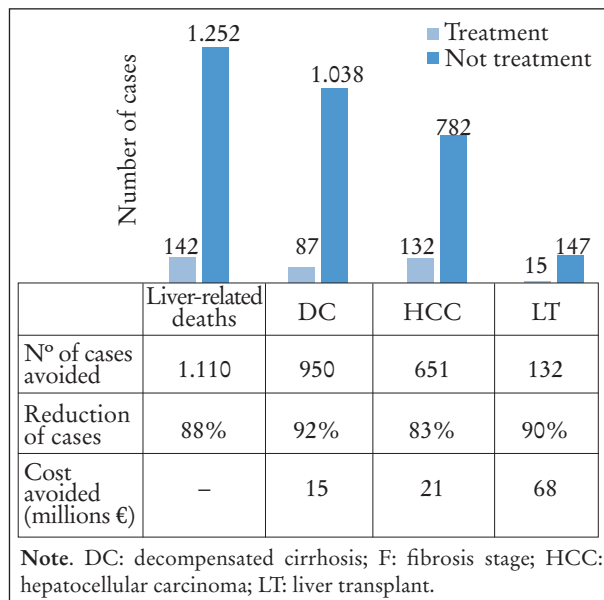


Figure 2. Clinical results of the analysis for the entire cohort according to treatment hypothesis.

In this analysis, a scenario was assessed in which the option of treating prisoners with CHC would be carried out quickly (i.e., 100% within 2 years). The time factor is a significant element because of the epidemiological relevance to reduce the possibility of viral transmission between subjects. In addition, it is also important from an economic perspective as there is a decrease in the costs associated with the management and liver-related complications of the disease when treatment is initiated and successful³⁰.

The analysis also examined the treatment of all affected inmates regardless of their degree of fibrosis, which is what the PEABC has recommended since June 2017² for epidemiological, therapeutic and cost-effectiveness reasons³⁰.

Treatment with current DAAs for CHC has demonstrated that they generate benefits at epidemiological, clinical and economic levels¹⁹⁻²⁰. Therefore, the main strategy for eliminating HCV infection should be to provide unrestricted access to DAA therapies. This strategy can and should be complemented with others of a preventive and educational nature, as recommended by prison experts in a recent publication³¹. However, access to this treatment is access to this is restricted in many countries³² and even more so to even more in prisoners³³, essentially for economic reasons^{34,35}. As we have observed in the inmate and non-incarcerated populations¹⁷, the cost of treatment is amply compensated by individual benefits (improved quality of life, increased survival and fewer liver complications), collective benefits (reduction in trans-

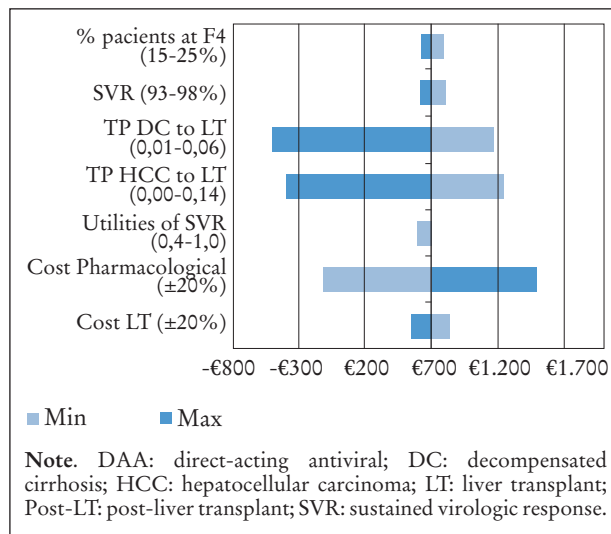


Figure 3. Sensitivity analysis results: Tornado Diagram.

mission) and the savings in long-term health expenditure. It is possible that these benefits are even greater among prisoners since the age of inmates in treatment is much lower: in one Spanish study, they were 15 years younger, and there were no cases treated in those older than 63 years¹⁵. Additionally, treatment of younger and more affected patients obtained greater clinical benefits³⁵. It has even been recommended that the treatment of patients with these characteristics take priority in cases of budgetary difficulties³⁶.

In Spanish prisons, there are improvements to be made in access to treatment. A recent parliamentary response⁴ reported that almost 40% of the prison population with CHC and fibrosis stages F2-F4 were still awaiting treatment. The results of our analysis show that treating prisoners is an efficient strategy and should help to change this situation and encourage the treatment of all infected inmates. There are already examples in Spanish prisons^{16,37}, where almost all infected prisoners have been treated, that show that universal treatment is feasible if there is administrative support along with a team of professionals that is involved and motivated. In some regions, such as Catalonia, in which access to treatments for infected prisoners is unrestricted, those infections can be eliminated in a very short period of time⁹. If we add to all of these practical experiences the results of the economic assessment of this work, there should be no doubt that treating CHC in prisoners is a political priority. Some authors have suggested, in countries such the United States, that the use of specific budgetary items for this purpose should be analysed³⁵.

This study presents some limitations related to its methodology. The first is that specific characteristics of patients co-infected with HIV were not included, and the data that model the influence of this infection were not considered. There are studies that have shown that transition probabilities and utilities are similar in patients with and without co-infection with HIV³⁸, except in the progression of cirrhotic patients, which is more pronounced in co-infected patients³⁹. The second is that the transmission of the disease has not been included in the analysis. The exclusion of both assumptions makes the analysis more conservative and minimizes the benefit of the option to treat, but this does not alter the conclusion since, in any case, the option to treat turned out to be more beneficial.

Another possible limitation of this work is that cases of post-SVR reinfection were not taken into account. In Spain, reinfection has recently been studied in more than 600 prisoners treated with SVR for whom monitoring was possible, and it was found that the estimated reinfection rate for this group was 2.9 per 100 patients/year⁴⁰. These data are epidemiologically relevant and should support the preferably early re-treatment of these patients. Including re-treatment in the analysis would result in an increase in the pharmacological cost, but also increase the clinical benefits, assuming no significant modification was made to the presented economic analysis.

Finally, if the social perspective had been used instead of that of the Spanish Health System and the loss of productivity in patients with CHC had been considered, the option of treating could be assumed to have greater clinical and economic benefits⁴¹. Therefore, one would expect the results of the analysis to further favour the option to treat.

As a relevant aspect and something that, in our opinion, provides strength to this study, is that a previously validated model representing the natural history of the disease and based on real-life patient data that reflects the inmate population with HCV in Spain has been used. We also believe that the results can be extrapolated to other countries in our economic environment with similar infected populations.

In short, political decisions and organizational programming can improve the treatment of CHC prison population, which is essential to overcoming the challenge of eliminating HCV. The treatment of this population improves the health of those affected, decreases health complications, reduces economic costs and is a cost-effective strategy because it involves a cost per QALY that is significantly lower than the efficiency

WTP threshold used in Spain. Therefore, to test and treat this population quickly and without restrictions should be the way forward.

CONFLICT OF INTEREST

Andrés Marco has made oral presentations for Abbvie, Bristol-Myers Squibb, Gilead, Janssen-Cilag and MSD, and has also participated in advisory boards of Gilead, Janssen-Cilag and MSD.

Raquel Domínguez-Hernández and Miguel Ángel Casado are employees of Pharmacoconomics & Outcomes Research Iberia, a consultancy firm specialised in the economic evaluation of healthcare interventions, which has received unconditional funding from Gilead Sciences for the development of the analysis.

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