

# Early Treatment of Hepatitis C Virus Improves Health Outcomes and Yields Cost-Savings: A Modeling Study in Argentina

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## Abstract

**Objective:** Most untreated hepatitis C virus (HCV) patients develop chronic infection and severe complications, including death. Direct-acting antivirals in early stages of liver fibrosis reduce complications and healthcare costs. However, therapy is often delayed, and patients in early stages have limited access to effective treatments. We assessed the clinical and economic effect of treating chronic HCV at early versus late stages of disease in Argentina.

**Methods:** A Markov model of the natural HCV history was used to forecast lifetime liver-related and economic outcomes from social security sector perspective. Healthcare use and transition probabilities were drawn from literature. Demographic characteristics of the patients and treatment attributes were based on data from registrational trials of glecaprevir/pibrentasvir.

**Results:** Lower rates of all hepatic complications and liver-related mortality were predicted when treatment was initiated in mild versus advanced disease. Sustained virologic response rates were similar among all stages. Higher quality-adjusted life years (QALYs) were predicted when treatment was initiated in mild (F0-F1) versus moderate (F2-F3) or advanced (F4) liver disease (11.5, 9.9, and 7.5 QALYs, respectively). Delaying treatment increased long-term total lifetime costs (F4: AR\$ 1 437 816; F2-F3: AR\$ 967 673; F0-F1: AR\$ 954 018; 37.10 AR\$=1 USD, Nov 2018 exchange rate) and provided fewer QALYs.

**Conclusions:** Our study show early treatment was a dominant strategy compared with treatment in advanced stages of liver disease. These results may help health policy makers take actions to reduce health and economic burden of HCV in Argentina.

**Keywords:** Hepatitis C virus, cost-effectiveness, direct-acting antiviral, pan-genotype, Argentina

## 1. Introduction

Hepatitis C virus (HCV) infection is considered a highly important healthcare problem (World Health Organization [WHO], 2017). This transmissible viral infection usually remains asymptomatic in the disease early stages but may lead to serious complications, including compensated cirrhosis (CC) and decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), and liver failure linked to significant morbidity and mortality rates (Moreno et al., 2017). The cost burden derived from HCV is associated with hepatic complications, as well as severe extrahepatic complications (eg, type 2 diabetes mellitus, depression and cognitive impairment, renal insufficiency, non-Hodgkin lymphoma) (Reau, Vekeman, Wu, & Sánchez-González, 2017).

The global prevalence rate of HCV infection has been estimated at 1% by the World Health Organization (WHO, 2017). Data from Argentina are scarce, and the exact HCV prevalence rate remains unknown; it has been calculated at 0.8%, according to several studies, ranging from 0.17% to 5.6%. However, in high endemic areas,

prevalence may be higher. Most data have been obtained by extrapolation and may not represent the real HCV infection prevalence (Ridruejo et al., 2016).

The main goal of antiviral treatment of HCV is to achieve sustained virologic response (SVR), defined as an absence of detectable HCV RNA  $\geq 12$  weeks after treatment (Pearlman & Traub, 2011). The choice of the best treatment scheme for each individual patient depends on the clinical situation, presence of comorbidities, use of concomitant treatments, evaluation of liver damage, HCV genotype/subtype, and treatment efficiency. Currently, direct-acting antivirals (DAAs) are the reference therapies for chronic HCV in Argentina (Asociación Argentina para el Estudio de las Enfermedades del Hígado [AAEEH], 2020). HCV treatment can be very effective, especially if HCV is diagnosed in the early stages of the infection (Alomar et al., 2018). In addition, HCV treatment in early stages of the disease was associated with decreased liver-related complications and healthcare costs when compared with treatment in later stages of liver fibrosis (Pearlman & Traub, 2011; Reau, Vekeman, Wu, & Sánchez-González, 2017). Nevertheless, treatment start is often delayed due to several factors (patient level: lack of awareness, fear of side effects, poor adherence, and comorbidities; provider level: limited knowledge, lack of availability, and communication difficulties; payer level: lack of promotion, surveillance, and costs) (Mendizábal, Alonso, & Silva, 2019). As a consequence, patients in early fibrosis stages may have restricted access to effective treatment regimens. Specific actions to increase accessibility to HCV diagnosis and timely treatment are still pending in most Latin American countries, including Argentina. It is estimated that less than one-third of infected patients have been diagnosed (Kershenobich et al., 2011); according to recent epidemiologic data, only 8.9% of diagnosed patients currently are being treated in Latin America (Viola et al., 2020).

The combination of glecaprevir (GLE 300 mg, a NS3/4A protease inhibitor) and pibrentasvir (PIB 120 mg, a NS5A viral protein inhibitor) administered once daily is indicated for the treatment of adult patients with genotypes 1 to 6 HCV chronic infection with or without CC. According to current guidelines, this pangenotypic scheme is indicated in an 8-week schedule in selected populations (AAEEH, 2020).

Availability of optimized treatment schemes may lead to even better responses with the goal of a complete eradication of this disease. However, there is a need to evaluate the financial healthcare impact of DAA schemes. In the present study, we assessed the clinical and economic consequence of treating patients with HCV at early versus late stages of liver disease in Argentina.

## 2. Method

A Markov model of the natural history of HCV was used to forecast liver-related and economic outcomes over a lifetime; the model scheme has been described elsewhere (Liu et al., 2012). The model was run from the perspective of Argentina's social security sector, which represents approximately one-third of the total healthcare system. The social security sector in Argentina covers all employers of the formal economy and their families, is financed with payroll contributions of employers and employees, and often operates through contracts with private providers (Bello & Becerril-Montekio, 2011). Healthcare use and transition probabilities were drawn from published literature (Bardach et al., 2019; Saraswat et al., 2015). Demographic characteristics of the patients and treatment attributes were based on data from clinical trials of GLE/PIB (Forns et al., 2017; Wyles et al., 2018; Asselah et al., 2018; Zeuzem et al., 2018).

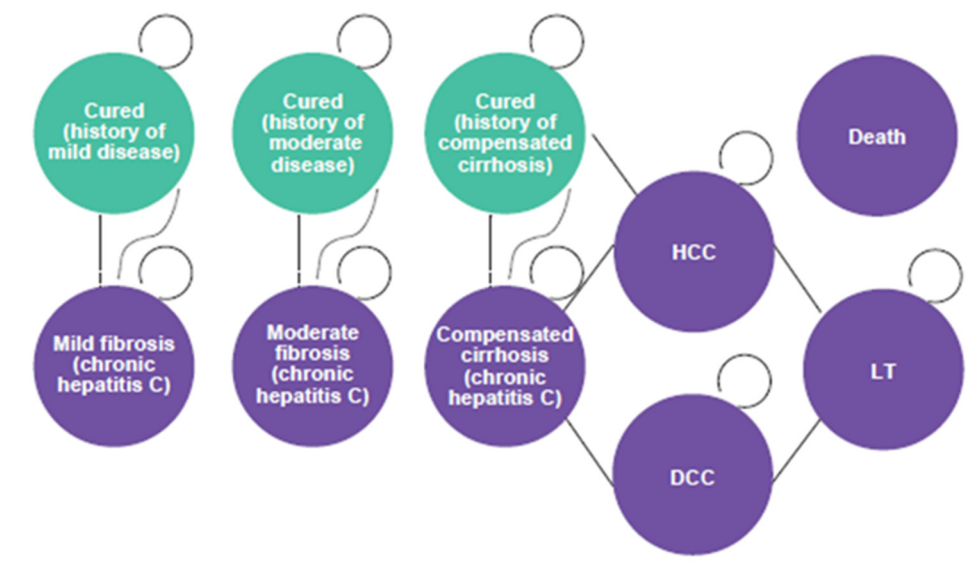


Figure 1. Markov model scheme

DCC: decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplantation

Analyses were performed for patients with all HCV genotypes and distinct fibrosis stages of liver disease, defined by Metavir score: mild (F0: no fibrosis; F1: portal fibrosis without septa), moderate (F2: portal fibrosis with few septa; F3: numerous septa with incomplete nodules), and severe disease (F4: CC), both in naive or treatment-experienced patients (Bedossa & Poynard, 1996). DCC, HCC, and need for liver transplantation were also included. Without treatment, spontaneous viral clearance is only possible from F0 stage. Death may occur in any model stage (Figure 1). The main demographic and virologic data of naive and treatment-experienced patients are shown in Table 1.

Table 1. Demographic characteristics

Variable	Patients treatment-naïve	Patients treatment experienced
Percentage of patients	75	25
Age, years	44.15	56
Male sex, %	57.7	58.6
GT distribution, %		
GT1	59.0	
GT1a	34.5	
GT1b	65.5	
GT2	22.0	
GT3	18.0	
GT4	1.0	
GT5 and 6	0.0	

Abbreviations: GT, genotype.

Probability rates of fibrosis progression and health condition were obtained from available literature (Table 2) (Thein, Yi, Dore, & Krahn, 2008; Wright et al., 2006; Shepherd et al., 2007; Hartwell, Jones, Baxter, & Shepherd, 2011).

Table 2. Model inputs for the base case and PSA

Variable	Base-case value	Sensitivity Low	Sensitivity High	Distribution in PSA
<b>Transitional probabilities (annual)</b>				
<i>Fibrosis Progression</i>				
F0 to F1	0.110	0.088	0.132	Beta
F1 to F2	0.088	0.070	0.105	Beta
F2 to F3	0.176	0.141	0.211	Beta
F3 to F4 (CC)	0.143	0.114	0.172	Beta
<i>Non-fibrosis Disease Progression</i>				
SVR, history of F4 (CC) to HCC (first year)	0.012	0.003	0.022	Beta
CC to DCC	0.039	0.029	0.049	Beta
CC to HCC (First Year)	0.014	0.004	0.024	Beta
DCC to HCC (First Year)	0.014	0.004	0.024	Beta
<i>Liver Transplant</i>				
DCC to Liver Transplant (First Year)	0.020	0.016	0.024	Beta
HCC to Liver Transplant (First Year)	0.020	0.016	0.024	Beta
<i>Liver-related Mortality</i>				
DCC to Liver Death	0.130	0.120	0.140	Beta
Liver Transplant to Liver Death	0.150	0.120	0.180	Beta
After Liver Transplant to Liver Death	0.057	0.046	0.068	Beta
HCC to Liver Death	0.430	0.400	0.460	Beta
<b>Health state utilities</b>				
Mild fibrosis (F0 – F1)	0.770	0.616	0.924	Beta
Moderate fibrosis (F2 – F3)	0.660	0.528	0.792	Log-normal
Severe fibrosis, F4 (CC)	0.550	0.440	0.660	Log-normal
No HCV	0.820	NA	NA	NA
SVR, history of mild fibrosis	0.820	NA	NA	NA
SVR, history of moderate fibrosis	0.710	NA	NA	NA
SVR, history of severe fibrosis (CC)	0.600	NA	NA	NA
DCC	0.450	0.360	0.540	Beta
HCC	0.450	0.360	0.540	Beta
Liver transplant (first year)	0.450	0.360	0.540	Beta
Liver transplant (subsequent year)	0.670	0.536	0.804	Beta

Abbreviations: F0-F1: mild liver disease (no fibrosis-portal fibrosis without septa); F2-F3: moderate liver disease (portal fibrosis with few septa-numerous septa with incomplete nodules); F4: severe liver disease (compensated cirrhosis); GT, genotype; SVR, sustained virologic response; CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; NA, not applicable.

Health outcomes included lifetime risk of CC, DCC, HCC, liver transplantation, and liver-related death. Other outcomes included lifetime costs and quality-adjusted life years (QALYs), both discounted at a 5% rate, with a time horizon of 70 years (Augustovski et al., 2010; MERCOSUR, 2009). An analysis strategy with a portfolio approach was performed, considering a pangenotypic HCV patient population, regardless of treatment history and presence of cirrhosis. Costs of the model were obtained from reimbursement tariffs of the social security

institutions and expressed in Argentine pesos (exchange rate 37.10 AR\$ = 1 USD, November 2018) (Table 3).

Table 3. Direct costs considered in our model

Variable	Base-case cost, AR\$	Sensitivity Low	Sensitivity High	Distribution in PSA
<i>Direct medical cost for each health condition</i>				
Mild fibrosis (F0 – F1)	1831	916	2747	Gamma
Moderate fibrosis (F2 – F3)	1967	984	2951	Gamma
Severe fibrosis, F4 (CC)	5076	2538	7614	Gamma
SVR, history of mild fibrosis	1000	500	1501	Gamma
SVR, history of moderate fibrosis	1416	708	2124	Gamma
SVR, history of severe fibrosis (CC)	4827	2414	7241	Gamma
DCC	96 629	48 314	144 943	Gamma
HCC (first year)	24 543	12 272	36 815	Gamma
HCC (subsequent years)	14 942	7471	22 413	Gamma
Liver transplantation (first year)	356 244	178 122	534 366	Gamma
Liver transplantation (subsequent years)	37 826	18 913	56 740	Gamma
<i>Treatment cost</i>				
Drug cost (glecaprevir/pibrentasvir) by day	15 768	NA	NA	NA
<i>Treatment-related costs</i>				
Anemia	28 076	14 038	42 114	Gamma
Rash	119	59	178	Gamma
Depression	9810	4905	14 715	Gamma
Neutropenia	7261	3630	10 891	Gamma
Thrombocytopenia	4694	2347	7 042	Gamma

Abbreviations: PSA, probabilistic sensitivity analysis; SVR, sustained virologic response; CC, compensated cirrhosis; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NA, not applicable.

Probabilistic sensitivity analysis (PSA) was carried out to examine the robustness of model results. In the PSA, it was assumed that each input parameter are associated with a certain probabilistic distribution. The parameters of the variables considered in the PSA are shown in Table 2 and Table 3. For the PSA, 500 simulations were drawn from the variables' distributions. The results are summarized graphically using the cost-effectiveness plane, where the horizontal axis indicates the total QALYs, and the vertical axis indicates the discounted total cost of each fibrosis stages of liver disease.

### 3. Results

In base-case, when treatment was initiated in milder versus advanced stages, lower rates of DCC, HCC, liver transplant, and liver-related death were predicted in HCV patients (Figure 2).

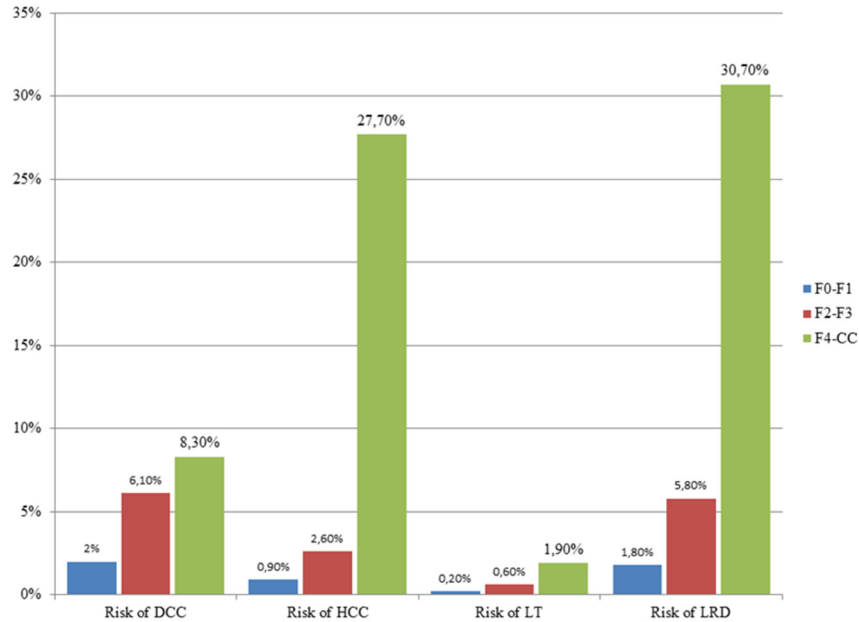


Figure 2. Lifetime risks of liver morbidity and mortality from GLE/PIB

DCC, decompensated cirrhosis; F0-F1: mild liver disease (no fibrosis-portal fibrosis without septa); F2-F3: moderate liver disease (portal fibrosis with few septa-numerous septa with incomplete nodules); F4/CC: severe liver disease/compensated cirrhosis; GLE/PIB, glecaprevir/pibrentasvir; HCC, hepatocellular carcinoma; LrD: liver-related death; LT: liver transplantation.

Rates of SVR were similar among patients with mild (F0-F1: 97.9%), moderate (F2-F3: 97.9%), and severe disease (F4-CC: 98.9%). Nevertheless, higher QALYs were predicted in the Markov model when GLE/PIB scheme was started at early stages, accounting for 11.5, 9.9, and 7.5 lifetime QALYs for mild, moderate, and advanced liver disease, respectively (Figure 3). Lower direct medical costs were also predicted in a context of early treatment with GLE/PIB when compared with patients starting therapy in moderate or advanced liver disease (F0-F1: AR\$ 954 018; F2-F3: AR\$ 967 673; and F4: AR\$ 1 437 816).

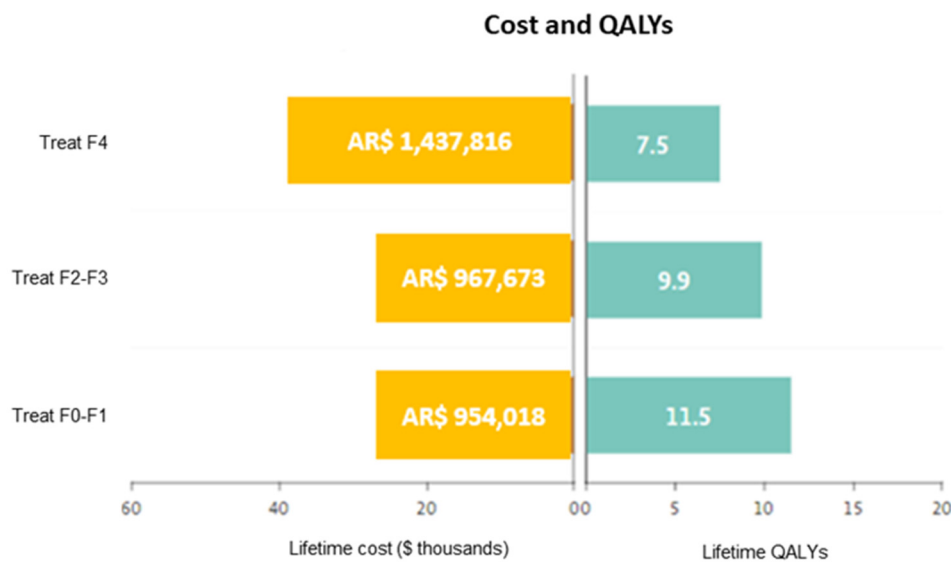


Figure 3. Lifetime per-patient direct medical costs and QALYs from treatment with GLE/PIB

Exchange rate 37.10 AR\$ = 1 USD, November 2018. Direct costs included extrahepatic complication. F0-F1: mild liver disease (no fibrosis-portal fibrosis without septa); F2-F3: moderate liver disease (portal fibrosis with few septa-numerous septa with incomplete nodules); F4: severe liver disease /compensated cirrhosis; GLE/PIB, glecaprevir/pibrentasvir; QALY, quality-adjusted life year.

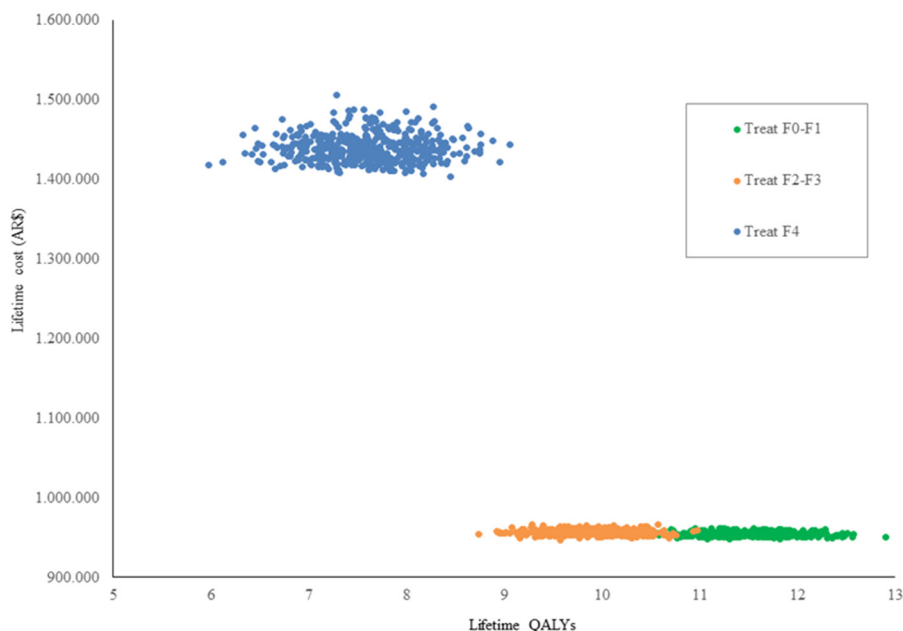


Figure 4. Probability sensitivity analysis scatter plot of expected cost and QALYs

Exchange rate 37.10 AR\$ = 1 USD, November 2018. Direct costs included extrahepatic complication. F0-F1: mild liver disease (no fibrosis-portal fibrosis without septa); F2-F3: moderate liver disease (portal fibrosis with few septa-numerous septa with incomplete nodules); F4: severe liver disease /compensated cirrhosis; QALY, quality-adjusted life year.

Results of the PSA prove the robustness of the base-case findings. These confirm that treating chronic HCV infection at early fibrosis stages has better outcomes and lower total healthcare costs than treatment in the severe liver disease stage (Figure 4).

#### 4. Discussion

Hepatitis C is considered a global public health problem. According to the Centers for Disease Control and Prevention, up to 70% of people infected with HCV will develop chronic liver disease, 5% to 20% will develop cirrhosis in a period of 20 to 30 years, and 1 to 5 subjects will die from cirrhosis or HCC (Stasi, Silvestri, & Voller, 2020). The World Health Organization recommends treating all persons with chronic HCV infection older than 12 years with pangenotypic DAAs, with the goal of cure (WHO, 2021). Evaluation of costs is highly relevant for inclusion of these treatment schemes in healthcare systems.

Although in Argentina there is no formal centralized and consolidated instance for health technology assessment, this type of analysis (integrating clinical information with economic data in connection with a new clinical intervention) is essential for rational decision-making that is not based only on implicit health coverage. In our study, which used a Markov model for the social security sector of the Argentine healthcare system, early treatment with GLE/PIB generated more QALYs at lower cost and was therefore a dominant strategy.

Our data showed that treating chronic HCV infection at early fibrosis stages has better health outcomes in terms of lifetime risks of DCC, HCC, liver transplantation, and liver-related mortality. In addition, early pangenotypic treatment with GLE/PIB was related to a reduction of total healthcare costs in Argentina, especially when comparing both mild and moderate stages with patients with F4 Metavir score or CC. This benefit in medical costs included extrahepatic complications of HCV.

Our results are in line with previously published research by other authors from developed countries (Ahmed,

Gordon, Saab, & Younossi, 2014; Buti et al., 2016; Nuño Solinís, Arratibel Ugarte, Rojo, & Sanchez-Gonzalez, 2016). In the United States, Ahmed et al. showed that treatment with a DAA at the F2 stage rather than F3-F4 is projected to have greater efficacy, decreasing the average number of cases of DCC by 63.3%, HCC by 89.0%, liver transplants by 83.3%, and HCV-related deaths by 84.5% (Ahmed, Gordon, Saab, & Younossi, 2014). Furthermore, Buti et al. reported similar results using a model in the Spanish setting. They showed that, when compared with delayed administration of therapy at the F4 stage, initiating DAA treatment at stages F2–F3 reduced the incidence of liver-disease complications and was associated with cost-savings for the Spanish National Health System in previously untreated patients with genotype 1 HCV (Buti et al., 2016).

In our model, the GLE/PIB treatment regimen has been associated with very high overall SVR rates in all stages of the disease, as previously reported in real-world studies (Hsu et al., 2019; Lampertico et al., 2020; Ridruejo et al., 2020). However, higher QALYs were predicted when treatment was started in mild stages versus moderate or advanced liver disease. The QALYs estimation is useful to assess both the effect of a treatment on life expectancy and quality of life (Ogden, 2017). As a consequence, QALYs represent time alive, scaled to reflect health state desirability (Neumann & Cohen, 2018).

Considering these data and that the coronavirus disease 2019 has placed a significant strain on national healthcare systems at a critical moment in the context of hepatitis elimination (WHO, 2016), this analysis may help decision makers to reprioritize programs and resources to achieve HCV elimination targets and reap the full benefits of early HCV treatment (Blach et al., 2021).

In conclusion, from a perspective of social security of Argentina, treating chronic HCV infection at early fibrosis stages improves health outcomes and reduces total healthcare costs. Our results may help public health authorities take actions to reduce the relevant health and economic burden of HCV in Argentina by avoiding delays and restrictions in HCV treatment accessibility.

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#### Competing Interests Statement

The authors declare that Diego Kanevsky and Maria Florencia Rodriguez are employees of AbbVie Argentina and may own AbbVie stock or stock options. Yuri Sanchez Gonzalez is an employee of AbbVie Inc. and may own AbbVie stock or stock options. Mariana Glanczspigel is director of 3eff, a health consultancy that offers services for the pharmaceutical industry including Abbvie. She has given conferences for the pharmaceutical industry that also includes Abbvie. Natalia Albaytero is manager in 3eff, a consultancy that offers services for the pharmaceutical industry including Abbvie. She has no other financial relationships relevant to disclose. Jorge Elgart: advisor in 3Eff; no other financial relationships relevant to disclose. Manuel Mendizabal received speaker honoraria from Gador.

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