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## Comment on Nuño Solinís R, et al. “Value of Treating All Stages of Chronic Hepatitis C: A Comprehensive Review of Clinical and Economic Evidence”

Patrice Cacoub

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### INTRODUCTION

Although the liver is the primary target for hepatitis C virus (HCV) infection, it is well established that many other organ systems are affected, increasing the overall burden of disease [1–3]. In a recent article, Nuño Solinís and co-authors assessed the overall disease burden of chronic HCV across 354 clinical studies in over 500,000 patients, including the impact of early versus late treatment [4]. Their article included some valuable insights into the contributions that extrahepatic manifestations (EHMs) make towards the overall morbidity and mortality of the disease. The authors concluded that early treatment leads to a strong and consistent reduction in the burden of chronic hepatitis C infection, from both clinical and economic perspectives. The economic argument for early treatment has been addressed by Nuño Solinís and colleagues [4]. In this response, I highlight the burden of HCV EHMs

and present an ethical argument for treating HCV early to minimize both the individual and collective burdens of HCV-related diseases.

In the face of insurmountable evidence for the benefit of treating patients early, a concerted effort is required to alter the actions of governments and policymakers to realize real-world changes in clinical practice. As the current infected population ages, the burden of decompensated cirrhosis and hepatocellular carcinoma is set to rise until at least 2030, and potentially beyond this in countries such as Russia, where the number of new infections continues to increase [5]. In a series of publications that modeled the future burden of HCV in 47 countries [5–7], the authors found rare exceptions such as the Netherlands, where the future burden of HCV is predicted to decrease because the country has a high treatment rate using newer therapies with high viral cure rates [5].

Although the majority of governments provide limited access to newer and highly effective direct-acting antivirals (DAAs), Nuño Solinís and colleagues highlight examples of government programs designed to widen access to diagnosis and treatment of HCV infection [4]. These countries include Georgia, Mongolia, Egypt, Australia, and France, and the outcomes

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of these programs should be closely monitored to inform other countries' health policy and effect real-world changes to eliminate HCV infection and reduce future HCV-related disease burden.

## HIGH COST OF EXTRAHEPATIC DISEASE

EHMs such as neuropsychiatric conditions, glomerulonephritis, and insulin resistance can increase morbidity and mortality at all stages of liver disease, not only when liver disease is advanced [3]. The implications of extrahepatic disease have far-reaching consequences, both individual and societal. Studies have shown a substantial negative effect of HCV on health-related quality of life, including general health and social functioning, which also impacts work productivity [8, 9]. Viral eradication was associated with improved health-related quality of life and work productivity, independent of liver fibrosis stage [9]. The economic burden of HCV EHMs is considerable: a recent meta-analysis reported that the estimated direct costs were in the order of US\$1.5 billion per year [10]. The cost is a reflection of the diverse extrahepatic diseases associated with HCV and the high proportion (up to 74%) of patients with chronic HCV that are affected by these diseases. The prevailing practice is to delay treating patients with mild liver disease. However, if patients are treated earlier, treatment duration can potentially be shorter and more effective, the progression towards cirrhosis and decompensated disease is reduced, and the contribution of EHMs to all-cause morbidity and mortality is diminished. Indeed, Nuño Solinís et al. illustrate that a significant mortality benefit is gained in patients who achieve SVR, at all stages of fibrosis [4]. The practice of delaying HCV therapy also raises ethical issues because it potentially allows the development of avoidable extrahepatic diseases and denies an improved quality of life after viral clearance [10]. Evidence presented by Nuño Solinís and colleagues show that delaying treatment could substantially increase morbidity, mortality, and medical costs [4]. The combined evidence from

this systematic review of the literature suggests that early treatment intervention has a demonstrable impact on morbidity and mortality for patients with chronic HCV infection.

Reasons for delaying treatment are various, but a significant motivation includes the short-term economic cost of providing these drugs. The evidence base presented shows that treatment with DAAs is more cost-effective than older, interferon-based regimens; it also shows that treating patients with mild liver disease (METAVIR; F1–2 fibrosis) is more cost-effective than treating patients with more advanced liver disease (F3–4 fibrosis). Taken together, these two findings must call into question the value of delaying treatment. Interestingly, this corroborates the findings of a 2014 study by Younossi et al. [11] suggesting that the most cost-effective strategy is to treat patients without staging liver disease at all. Delaying treatment also ignores the considerable cost of treating and caring for patients with decompensated liver disease and hepatocellular carcinoma.

International HCV treatment guidelines acknowledge a priority for treating patients with EHMs owing to the clinical impact of extrahepatic disease and the subsequent benefits of treatment [12, 13].

This is a great step forward in reducing the long-term morbidity and mortality of HCV, but it is arguable that the best way to mitigate the impact of extrahepatic diseases is to treat early, before these complications are given a chance to arise, an approach that the current evidence base would suggest is both clinically validated and cost-effective.

## EHMS AND SCREENING

If the ultimate goal is to eradicate HCV, then a greater effort is required to screen and treat patients with HCV infection and prevent ongoing transmission. In the US alone, up to 75% of people infected with HCV are unaware of their infection [14]. The majority of patients are diagnosed incidentally during evaluation of liver transaminases or of at-risk populations such as people who inject drugs [15].

Furthermore, the majority of screening programs restrict coverage to known high-risk groups, e.g. injection drug users and prisoners [16]. An additional benefit—beyond reducing long-term costs—for an increased recognition of HCV EHMs could be an expansion of the population of patients screened for HCV. This is in part supported by international guidelines stating that patients should be prioritized for treatment if they have EHMs of HCV infection [12]. An international group of experts [the International Study Group of Extrahepatic Manifestations Related to Hepatitis C Virus (ISG-EHCV)] recently published an expert consensus statement highlighting the need for a multidisciplinary assessment of patients with HCV infection to better diagnose EHMs [2]. Those EHMs with a strong or significant association with HCV based on epidemiological, clinical, and laboratory evidence include mixed cryoglobulinemia, diabetes, and cardiovascular disease. A meta-analysis of 102 published studies found that diabetes and depression were diagnosed in 15% and 25% of patients, respectively [10]. These disorders could be included alongside other high-risk groups or combined with other negative predictors to improve HCV screening [2].

## COST-EFFECTIVENESS IN THE DAA ERA

DAA regimens have been shown to be more cost-effective partly owing to the superior efficacy and safety profiles compared with those of interferon-containing regimens. However, the majority of the studies reviewed by Nuño Solinís and colleagues were of interferon-containing regimens and so there is still a need for a systematic review of the cost-effectiveness of DAAs. Regardless of current strategies towards HCV treatment, the cost to healthcare systems is set to rise in the near future as we enter an era in which patients who have long-standing HCV infection will require greater access to care. This is evidenced by new data showing that HCV is an independent risk factor for increased mortality and resource utilization in the baby-boomer cohort (adults born in 1945–1965) [17]. For this

well-defined group, who are five times more likely to have chronic HCV [18], there is a strong argument for widespread screening of baby boomers and treating all those with chronic HCV in order to substantially reduce the future impact of hepatic and extrahepatic disease. In the US, the Center for Disease Control has issued recommendations that all baby boomers should be given a one-time HCV test [18]. Although there has been mixed success in delivering this recommendation, with low uptake in primary-care settings, the use of electronic notification systems in a variety of medical settings has resulted in substantial increases in the number of people screened [19, 20]. A recent study in the US showed that investments in HCV screening and treatment are expected to “break even” from a social perspective after only 8–9 years when treatment is expanded to include stages F0–F2, compared with 20–22 years when treatment is limited to fibrosis stages F3–F4 [21].

## SUMMARY

As demonstrated in the review by Nuño Solinís et al. [4], we now have highly effective, well-tolerated, and cost-effective therapies to treat essentially anyone who is infected with HCV. With these tools, we can prevent not only hepatic but also many extrahepatic diseases caused by HCV. As such, I believe that interferon-free DAA therapy should be offered to most patients that have HCV EHMs as well as to all patients at risk of developing them. This stands out as the best approach to deal with the serious complications of chronic HCV infection and to speed the way to a world in which HCV is effectively eradicated.

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**Compliance with Ethics Guidelines.** This article does not contain any new studies with human or animal subjects performed by any of the authors.

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