Perspective editorial
Innovative strategies for hepatitis C in Belgium integrating treatment efficacy, public disease burden, and healthcare costs

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Hepatitis C is a leading cause of chronic liver disease, end-stage cirrhosis and liver cancer worldwide (1). Thus far, the standard of care approved for hepatitis C in Belgium shows relatively limited efficacy and is usually associated with serious, not always reversible side effects. As a consequence, patients who are of utmost need for therapy are often not eligible for these treatments. A number of new generation therapies with extremely high efficacy and a good safety profile are in the pipeline (2) which likely will revolutionize (near) future HCV treatment. So, gaining good insight into the health-, economic- and societal burden associated with HCV and its sequelae is of key importance to appropriately assess the value of these new innovative treatments (2,4). As Belgium has been found to lag behind with respect to HCV disease detection and treatment, the Belgian Working Group on HCV aimed to contribute to a better understanding of the burden associated with HCV infection in Belgium through assessing HCV-related prevalence and attributable mortality, and through assessing the health and economic impact using different innovative scenarios of diagnosis and treatment rates (5-7). The development of public health strategies will allow us to predict the global impact of new treatment and prevention initiatives, all correctly informing health policy.

The project discussed in this introductory perspective overview used a highly reliable and validated simulation model that was built upon sound epidemiological data collection, consultation of expert opinion, and country-specific mathematical modeling. Several interesting current and future trends emerged. It was projected that there were likely 70,000 viremic HCV infections in 1994 (5) with, however, only 23,000 individuals being diagnosed with viremic HCV by 2010. Regarding genotype distribution, it was found that genotype 1 predominated (59%), followed by genotypes 3 (19%) and 4 (14%) and that a considerable proportion of liver transplants (nearly 15 per 100) were attributable to HCV. In 2011, about 700 patients were treated on an annual base. Although the overall HCV prevalence is decreasing, particularly the burden of advanced stage HCV is expected to increase under current treatment rates (6). It was estimated that this rise in advanced stage disease would be associated with increasing healthcare costs, which are expected to peak in 2024 (7). By 2025, one-third of HCV-related healthcare costs will be attributable to advanced liver disease. Moreover, the lifetime cost of HCV was projected to increase with life expectancy, with highest future costs anticipated among young females suffering early stage liver disease (7).

In aim to circumscribe the problem in the future, different innovative strategies were explored projecting the impact of treating a larger proportion of people living with HCV with next generation antiviral therapy (5). By increasing sustained virological response (SVR) rates to 85-90% as well as the number of treated cases (from 700 to almost 2,000) from 2016 onward, the cases with advanced stage HCV would be significantly lower in 2030 as compared to 2013, and would result in substantial cost savings mainly due to the decreased need for high-tech and expensive interventions. This scenario was found most efficient when applied to patients with advanced stage liver disease (respectively, F2-F4 cases). Extending therapy to patients with only mild liver disease (F0-F1) would imply treating much higher numbers of patients to obtain comparable outcomes. Importantly, a two year delayed access was found to increase HCV-related morbidity and mortality by 16% and would significantly decrease potential cost savings. In addition, the positive impact of early initiation of treatment (start in 2015) would persist even if a lower number of patients (1,000 patients) are treated and would still result in significant cost savings.

The upcoming next generation of antivirals for HCV seems to hold great promise both for public health and clinical medicine, as hypothetically it could be possible to eliminate HCV. Indeed, the threshold to treatment will be very low considering the evolution towards once daily intakes of all oral therapy with almost no side effects, a short treatment duration, and emergence of resistance not being a hurdle. However, there are still some key challenges that remain. The projected data suggest that successful diagnosis and treatment of patients currently

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infected with HCV can positively impact the disease burden. However, the most significant impact, both from the health and economic perspective, will be reached when increased treatment rates with highly effective next generation antivirals (SVR rate of 90% or above) are combined together with substantial diagnostic efforts. Indeed, more effective treatments are an important but only one part of the solution. Owing to the slow progression and asymptomatic character of the disease, many people are unaware of being infected with the hepatitis C virus. So, effective preventive programs as well as screening efforts (mainly at the primary care level) will, therefore, be crucial to detect HCV infection in an earlier stage or to prevent people from acquiring it, and to subsequently ensure that those who are infected will get the opportunity for cure. Such a required boost in diagnosis rates will make a markedly reorganization of public health capacity necessary. For Belgium, where the advanced liver disease burden is expected to increase, the approaching burden could be largely prevented by introducing improved treatment strategies. According to the most recent European Association for the Study of the Liver (EASL) guidelines, it is recommended to prioritize treatment in patients with significant fibrosis (Metavir score F3-F4) and treatment is justified for patients with moderate fibrosis (Metavir score F2). For patients with no or mild disease (Metavir score F0-F1) the indication for and timing of therapy can be individualized (8). Moreover, through combining increased HCV treatment efficacy and uptake, major reductions in chronic HCV prevalence can be reached as well, even with the potential to move toward elimination of HCV over the next decades. Notwithstanding this, it is important to keep in mind that even after successful therapy HCV-reinfection is possible. In the economic scenarios shown in the papers of this issue, the cost of antiviral therapy was excluded (7). Given uncertainty concerning the real treatment costs, all actors in the field should take care that the next generation antivirals with high SVR are not to become a kind of 'luxury drug' that would only be available to selected individuals. Yet, there is quite some discussion regarding the price of these new therapies which in turn has led to concerns about the ability of our already overburdened healthcare system to implement and target these treatments even to those in greatest need. The global rollout of HIV treatment is an inspiring case as it teaches us that it is possible to make these regimens broadly available and affordable. Also, to better understand this, it is necessary to frame this discussion in the larger context of the public and economic burden of chronic liver disease against the retail cost of therapy. Adequate cost-effectiveness analyses would, therefore, be warranted and first evidence seems overall encouraging (9-11). In medicine, success is often hard to define. However, when it comes to hepatitis C therapy, SVR is a well-established surrogate indicator for treatment success, and has even been equated with cure (12). Besides a less than 1% chance for late relapse, decreased incidence rates of cirrhosis, transplant, liver cancer and mortality have been associated with SVR. Although increasing access to the upcoming next generation antiviral regimens would initially be associated with an increase in healthcare costs overall (due to the costs attributable to antiviral treatment), these will most likely be compensated by a fall in the costs of treatment of the long-term sequelea of (untreated) HCV. In addition, increasing the proportion of antiviral treatment with high SVR would lead to improved quality of life and a reduction in HCV-related productivity losses. This gain in quality of life and productivity would largely outweigh the initial investment required to cover the cost of antiviral treatment if treatment rates would almost be quadrupled. Based on the current findings outlined in this project it might be supposed that for Belgium increasing diagnosis and subsequent treatment rates of people with HCV infection will be associated with more welfare (better quality of life and productively, respectively), given the decline in the overall number of persons carrying the infection, and consequently, the number of patients progressing to advanced stage HCV (5-7). Hence, it is difficult to argue this would not be success, both for the patients as well as society. However, the impacts will only become visible on mid- or even long-term and immediate impacts in terms of benefits to the healthcare system and public health have to be balanced against the societal willingness to make the initial required investments widely available. These prospects create a new and challenging framework for all actors in the field extending from policy makers to patients. Taking their responsibilities, government, healthcare professionals, and drug companies will have to constructively work together to make sure that treatment is within reach of all in need, so that people living with HCV will be properly screened, cared for, and treated. Concretizing the initiative to come up with a hepatitis C plan similar to the existing HIV plan could be a first, however, important step toward such a well-thought and consensus-based strategy of managing the hepatitis burden in Belgium. In conclusion, with the introduction of the new highly effective next generation antivirals together with concerted action, hepatitis C may no longer be considered a serious public health problem within the next few decades.

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