Published in final edited form as:

J Hepatol. 2016 July ; 65(1): 5–6. doi:10.1016/j.jhep.2016.03.015.

Doing the math on hepatitis C virus treatment

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One of the greatest breakthroughs in medicine is our current capability to cure nearly everyone with chronic hepatitis C virus (HCV) infection. With a few months of taking well tolerated pills, more than 90% of HCV-infected persons eradicate infection, eliminating the concern of spreading the virus to others, reducing by 80–90% the risks of liver failure and liver cancer, and improving survival [1–6]. These, and an array of additional less-well-documented treatment benefits, make an overwhelming case for treatment. There is no patient who is better off with HCV infection than without, and no health care provider we know who would not treat each patient given the opportunity. Accordingly, the medical guidance provided by the American Association for the Study of Liver Diseases and Infectious Diseases Society of America concludes that, “Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy [7].” Likewise, the guidance from the European Association for the Study of Liver Disease concludes, “All treatment-naïve and –experienced patients with compensated or decompensated chronic liver disease related to HCV, who are willing to be treated and who have no contraindications to treatment, should be considered for therapy [8].”

So, why complicate such a simple subject with complex math? Because the treatments are expensive. The core issue should not be obfuscated by questions about whether treatment is medically indicated. It is. The relevant question is how can we get that life-saving medication to everyone, and that’s where it can be challenging to make the math work. For example, we think there are about 3.2 million persons with chronic HCV infection in the United States. If it costs \$50,000 per person to cure HCV infection and everyone were treated, then the total cost of medication alone would be greater than the entire 2014 gross domestic product of more than 100 countries. That math won’t work and is the reason the World Health Organization correctly concludes, “it is important to have a framework to help policy-makers decide who to prioritize for treatment” and the European Association for the Study of Liver Disease to concludes, “Because not every HCV-infected patient can be treated within the next year or so, prioritization is necessary [9, 10].”

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However, that ‘framework’ doesn’t exist and prioritization is complex and can be unjust. Treating first those with the most need makes sense. But, what if those who need it most also are those who benefit the least because they already have extensive liver damage, have comorbid conditions, are older than other candidates, or have already developed cancer? Then, there is the question of determining that ‘need’. If the person with F1 (a low liver fibrosis score) is denied and the one with F2 treated, shouldn’t we have more than 70% accuracy in making that crucial determination [11]? Treating those most likely to spread infection to others also makes sense. But, those most likely to transmit to others often have low disease stage and are the ones most likely to abrogate the personal benefits of treatment by being re-infected. Treating those who have the most symptoms also makes sense, but what if those symptoms don’t always improve with cure? Then there is the question of who gets to decide whom to prioritize. Health care providers often impose socioeconomic and racial biases when prioritizing treatments [12]. Moreover, health care providers prefer not to be the barrier between patients and life-saving therapies.

Mathematical models aim to answer some of these questions by helping to build that decision-making framework, reducing treatment prioritization to a complex calculation of economics; past disease history and future progression risk; treatment effect on disease outcomes and quality of life; and in some cases, reinfection risk [13, 14]. Each of these parameters can alter the cost-benefit ratio by enough to move the needle of whether treatment can be considered cost-effective by the commonly-used threshold of <\$100,000 per quality-adjusted life year (QALY) gained. For example, models that assume that the impact of chronic hepatitis C on quality of life (and thus the impact of treatment on quality of life) is comparable for someone with no disease (F0) and someone with severe disease (F4) find that treating everyone regardless of disease stage is cost-effective [15]. On the other hand, models that assume a more modest impact of treatment on quality of life find that only treatment of F3 disease and greater is cost effective. In this scenario where the impact on quality of life is more modest, earlier treatment was more cost-effective when treatment was more effective and cheaper, disease progression faster, and impact on quality of life more substantial [16].

In the most recent issue, work by Martin and Zahnd extend modeling by considering the impact of delaying treatment among HIV-coinfected men who have sex with men (MSM) and incorporating the preventive benefits of therapy among people who inject drugs [13, 14]. Importantly, both models considered the impact of reinfection. Both studies support that the benefits in terms of disease prevention and cost are greatest when treating those with severe disease (those who ‘need it most’). However, Zahnd et al demonstrate that delaying treatment until later disease stage will substantially increase the risk of liver complications even when considering reinfection rates of up to 22% in three years. Martin et al demonstrate that the cost-effectiveness of treating persons with mild or moderate disease varies by the potential prevention benefit. Treating people who are currently injecting drugs with mild or moderate disease was more cost-effective than treating those who had stopped the practice with mild to moderate disease except in settings with high disease prevalence and high reinfection risk.

How do these models change our approach to control of HCV infection? The impact of reinfection in the models underscores the importance of prevention. New infections still occur, and worldwide most are not aware of their HCV infection. Reinfection risk is unknown in the new HCV treatment era, but as demonstrated by both Zahnd and Martin, reinfection can have significant impact on disease and cost [13, 14]. Treating people also means that they have to be aware of their status and linked into care. Therefore, we need to massively expand prevention services as well as testing and linkage to care efforts simultaneously with treatment expansion.

Another obvious step is to reduce the price of medications. Hill calculated that it costs \$10–\$30 to make daclatasvir and \$68–\$136 for sofosbuvir, two of the new HCV treatments whose AWP in the USA is almost \$1000 USD per pill [17]. Fortunately, drug prices are already dropping. In India, where up to 20 million may be infected, and generic versions of sofosbuvir, ledipasvir and daclatasvir are already available, \$1000 USD is the cost of a 12-week treatment course and in Egypt where nearly 9 million are infected. Even in the USA where prices are notoriously high and often opaque, 50–75% reductions in the ‘sticker’ price of drugs are being reported. Lower prices will be crucial to justifying cost effectiveness in more settings and expanding treatment.

The multiple parameters in these models also reveal how complex these calculations can be. When societal resources are being used to pay for treatment (vs for example private insurance), groups of stakeholders (and not just individual health care providers) should make recommendations based on thoughtful calculations of benefits, societal priorities, and financial capacity. The United Kingdom National Institute for Health and Care Excellence is an example of a broad societal approach to consider the results of complex models such as those published by Zahnd and Martin as well as other factors to produce guidance on which persons should be allowed to benefit from HCV treatments.

There also has to be global philanthropy and commitment. Global commitments to treatment of HIV, tuberculosis, and malaria have markedly expanded treatment uptake around the world. Similar coordinated, sustained, well-funded efforts are needed now for HCV. Accordingly, the United Nations 2030 Sustainable Development Goal should be rewritten not just ‘to combat’ but ‘to end’ the epidemic of HCV, mirroring the language for HIV, tuberculosis, and malaria.

How do we make the math work? Like a complicated algebra problem, there may be many ways to get the right answer, and that may depend on the setting. The key is to solve this problem now to prevent the incalculable harms of failing.

Acknowledgments

Supported by US NIH grants: R01DA012568, R37DA013806, and R01DA026727

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