

## COMMENT FROM THE EDITOR

**The End of Hepatitis C**

*Go on till you come to the end; then stop.*

Lewis Carroll

We are at a turning point in the management of the hepatitis C virus (HCV) epidemic. HCV can be cured, but treatment up to this point has required a toxic combination of drugs. This is about to change; the second generation of direct-acting antiviral agents promises high cure rates with few side effects. This gives us the historical opportunity to eradicate HCV from the entire population. Our article addresses the advantages of universal eradication of HCV infection from the United States and the steps required to achieve this goal.

**Hepatitis C Virus**

HCV is a small, hepatotropic RNA virus that infects an estimated 3–7 million people in the United States<sup>1</sup> and 170 million worldwide.<sup>2</sup> Transmission is almost entirely parenteral, and the most predictive risk factor for chronic infection in the United States is current or past injection drug use. The transmission efficiency of HCV is high, and exposure is followed by chronic infection in 65%–85% of cases. Most HCV cases in the United States are caused by genotype 1; other genotypes may predominate in other countries. HCV genotype 1 has traditionally been the most difficult to treat because of interferon nonresponsiveness, and attempts to create a vaccine for HCV have been unsuccessful to date.

The consequences of HCV infection are serious; recent studies show a major impact on health-related quality of life, liver-related mortality, all-cause mortality, and medical resource utilization among patients with HCV infection.<sup>3–5</sup> Studies also show that successful treatment of HCV infection improves health-related

quality of life and reduces mortality in patients with HCV.<sup>6,7</sup>

**Antiviral Therapy**

HCV has 3 nonstructural proteins that are essential for viral replication, an NS3/4A protease, an NS5B polymerase, and the NS5A protein. Each of these proteins is an excellent target for antiviral therapy.

Antiviral therapy for HCV has improved incrementally since 1986, beginning with thrice-weekly interferon monotherapy and progressing to a 3-drug regimen consisting of weekly pegylated interferon injections with oral ribavirin and a protease inhibitor (boceprevir or telaprevir). These improvements have been associated with a sustained virologic response in up to 72% of patients in randomized trials.<sup>8</sup> Treatment-induced sustained virologic response is durable; late relapse has been described but is rare.<sup>9–11</sup> Thus, HCV is one of the few—and possibly the only—chronic viral infection that can be cured.

Exciting changes are about to take place with the recent Food and Drug Administration approval of a new class of once-daily protease inhibitor (simeprevir) and the first-in-class once-daily polymerase inhibitor (sofosbuvir).<sup>12</sup> Other drugs including alternative protease inhibitors, polymerase inhibitors, and NS5A inhibitors are in different phases of clinical trials.<sup>13</sup> Although interferon remains part of the antiviral arsenal for the moment, combinations of oral agents have proven effective, and interferon-free treatment is likely to become the new standard of care within the next 12–18 months.<sup>14–16</sup>

**Other Infectious Epidemics**

Several epidemic or endemic diseases have been controlled or

eliminated and serve as useful case studies as we make the case for HCV eradication. The most spectacular example was smallpox, a worldwide scourge responsible for millions of deaths. A primitive form of vaccination (variolation) started around 1670, but true vaccination only gained popularity after Edward Jenner's experiments with cowpox in 1796. The last naturally acquired case of smallpox occurred in Somalia in 1977, and the last human case occurred as the result of a laboratory exposure at the University of Birmingham in 1978. Smallpox was declared officially eliminated on May 8, 1980 when the 33rd Assembly of the World Health Organization accepted the Final Report of the Global Commission for the Certification of Smallpox Eradication.<sup>17</sup>

Polio is another important case. The Global Polio Eradication Initiative of the World Health Organization was launched in 1988 at a time when polio was endemic in 125 countries, with an estimated 350,000 new cases annually. The incidence of polio has since been reduced by more than 99%, and only 3 countries (Nigeria, Pakistan, and Afghanistan) have failed to eradicate the virus.<sup>18</sup> Despite this amazing achievement, endemic disease is a threat to other nations, as demonstrated by an outbreak in China in 2011, 17 years after the last reported case of paralytic polio in that country.<sup>19</sup> As pointed out in the accompanying editorial, no country is safe without global eradication.<sup>20</sup>

An example of a successful national disease elimination program is universal hepatitis B vaccination in Taiwan, instituted in 1984. At the 25th anniversary of the program, the prevalence of hepatitis B surface antigen had declined from 10% to 0.9%, hepatitis B surface antibody (protective antibodies) had increased from 24.5% to 55.9%, and hepatitis B core antibody (evidence of prior infection) had decreased from 28% to 7%.<sup>21,22</sup> These

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data highlight the gains as well as the fact that vaccination takes time to change the prevalence of a disease, especially if the goal is complete elimination.

A final example with relevance to HCV is infection with human immunodeficiency virus (HIV), a virus that cannot be cured by vaccination but can be controlled with effective treatment. Unlike polio and smallpox and similar to HCV, HIV is not easily transmitted to the general population but is associated with certain types of behavior. Progress in the control of HIV has required high levels of community awareness, timely linkage to care, and highly effective antiretroviral therapy. These factors have reduced the prevailing level of HIV.<sup>23</sup> A study of men who have sex with men in San Francisco (a group that comprises 90% of cases of HIV/acquired immunodeficiency syndrome in that city) reported a marked decline in number of patients who reported being unaware of their infection from 21.7% in 2004 to 7.5% in 2011.<sup>24</sup> As a result, the community viral load, described as the mean, median, or total viral load of a population living with HIV, showed a similar decline, with commensurate declines in the incidence of HIV and newly diagnosed and reported cases of HIV.<sup>25,26</sup>

### How Do We Apply These Lessons to Hepatitis C Virus?

Eradication of a disease has never occurred through individual or commercial action; it has always required a concerted and large-scale population-based approach. The examples above have all been achieved by mobilizing massive resources, including funding of antiviral therapy in the Ryan White program to control HIV. These lessons can be

applied to HCV with some interesting variations on the theme. On the positive side:

1. HCV can be cured, so the benefits of treatment are nearly instantaneous instead of the decades required for a successful vaccination program or the need for lifelong therapy in the case of HIV.
2. The entire epidemic in the United States is confined to 3–7 million. Identifying and treating this cohort can potentially eliminate HCV from the U.S. population<sup>27,28</sup> and may prevent a second epidemic that is likely to accompany drug use among teens and young adults.

On the negative side:

1. Most infected persons in the United States are unaware of their infection; ongoing education and large-scale screening will be necessary.
2. HCV therapy is currently complicated and is delivered by a relatively small number of providers, too few to manage the problem. Treatment must be simplified,<sup>29</sup> and the number of competent treating providers must be increased through innovative programs.<sup>30,31</sup>
3. Patients who are cured are not immune and may become reinfected, as described in a prison population.<sup>32</sup> In the absence of herd immunity, universal eradication of HCV is the only way to prevent reinfection.
4. Worldwide elimination of HCV is a daunting task; targeted treatment has been proposed,<sup>33,34</sup> but it remains too complicated and costly in developing countries. Global elimination of HCV will require

very simple therapy or an effective vaccine.<sup>35</sup>

### Business as Usual or a Bold Step Forward?

Enthusiasm over the availability of the new direct-acting antiviral agents is dampened by concerns about cost; sofosbuvir has a retail cost of \$1,000 per tablet (\$84,000 for a 3-month course). This is similar to the cost of the recently obsolete triple drug regimens, which average \$84,063 per course (including adverse event management) and a median cost of \$195,000 per cure.<sup>36</sup> The newer drug regimens will have higher cure rates, shorter courses, and lower adverse events and may cost less per cure. Nevertheless, treating 3.2 million infected individuals in the United States with sofosbuvir carries a price tag of about \$270 billion in drug costs alone.

Controlling the cost of HCV therapy will require a random approach to treatment (treat those who show up), rationed care (make deliberate choices about whom we treat), or an innovative plan that attempts to treat everyone. The current approach has features of the first 2 options. Calls for treating only patients with advanced or advancing liver disease ignore 3 important facts. First, HCV is associated with extrahepatic disease; focusing only on the liver ignores the effect on non-hepatic disease and mortality. Second, following infected patients is expensive, requiring decades of office visits, lab tests, scans, and intermittent liver biopsies in some patients. Third, failure to address the problem proactively has a significant cost; Centers for Disease Control and Prevention projects that costs for the 10-year period from 2010–2019 will exceed \$10.7 billion, with an additional \$54.2 billion in premature

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mortality and \$21.3 billion in morbidity and disability.<sup>37</sup>

With so much money at stake, it seems that all parties might profit from universal treatment, but it will require a new way of thinking. Instead of retail sales, we might look to something like the defense industry where the government awards contracts for goods and services that serve the public interest. We could replace low-volume, high-price sales with a strategy that spreads the same money over a much larger population. Skeptics may say that universal treatment is unnecessary; not all infected persons progress to advanced liver disease. These same voices may have had the same arguments about other diseases, but we find no written opinion that mourns the disappearance of smallpox or polio.

### What Will It Take?

Two big government programs of similar scale are the Centers for Medicare and Medicaid's program for free access to chronic hemodialysis and the Ryan White program for HIV care. Curing HCV is a smaller project because it has a defined population that is approaching the end of an epidemic. Furthermore, unlike the existing programs, an HCV treatment program holds the promise of complete eradication of the targeted condition (HCV) from the United States. However, the plan will require a proactive and bold approach.

Safe and effective oral antiviral agents are already available,<sup>12,15,16</sup> but the drugs are made by different companies, and many are not yet on the market. We must ask whether companies can be incentivized to cooperate as they have on drugs such as Bactrim/Septra and the combination antiviral agents Truvada and Atripla. In return for cooperation and reasonable pricing, the federal and state

funding agencies and private insurers must agree to fund universal therapy. The government can provide additional incentives such as expedited Food and Drug Administration review of promising agents and protection from groundless lawsuits.

### Conclusion

Safe oral combination therapy will allow us the historic opportunity to clear HCV from the U.S. population. The arguments can be summarized as the cost of health vs the cost of healthcare. We will hear arguments on both sides, but we must ask ourselves whether we should let a historic opportunity pass without at least considering the possibility.

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**Conflicts of interest**

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