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## Curing Chronic Hepatitis C — The Arc of a Medical Triumph

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Related articles, pages 1594 and 1604

Chronic hepatitis C is a major cause of liver cirrhosis and hepatocellular carcinoma worldwide. Some 130 million to 170 million people, or about 3% of the world's population, are chronically infected with the hepatitis C virus (HCV). In the United States, chronic hepatitis C, the most common cause of liver-related death and reason for liver transplantation, recently eclipsed human immunodeficiency virus (HIV) infection as a cause of death. The development of direct-acting antiviral agents (DAAs) has revolutionized HCV treatment by offer-

ing genuine prospects for the first comprehensive cure of a chronic viral infection in humans. This success can be traced to important scientific, clinical, and regulatory developments.

The history of HCV's discovery and antiviral-drug development offers a striking example of the effect of advances in biomedical research on disease outcome (see table). The discovery of HCV 25 years ago showed the importance of new scientific approaches: whereas past virus discovery had relied on direct visualization of viral particles, the previously elu-

sive HCV was isolated with the use of a new expression-cloning approach that generated a library of complementary DNA from infectious plasma.<sup>1</sup>

The subsequent molecular characterization of the viral genome enabled several important discoveries. First, it revealed HCV to be a positive-stranded RNA virus that replicates its genome directly into RNA without traversing a DNA intermediate, so that unlike HIV or hepatitis B virus, it lacks a latent, nuclear form that defies ready immunologic clearance. Instead, it requires continuous rep-

**Key Milestones and Their Effects on the Development of Curative Antiviral Treatment for Chronic Hepatitis C.\***

Key Milestone	Effects
<b>Scientific</b>	
Expression cloning of HCV	Discovery of viral genome, genomic organization, and viral genotypes; diagnostic assays; safety of blood products
Model systems for viral replication in cell culture (replicons) and ultrastructural characterization of nonstructural proteins	Screening and discovery of direct-acting antiviral agents targeting the HCV NS3/4A protease, NS5B polymerase, and nonstructural protein NS5A
HCV infectious-tissue culture model	Entry and assembly inhibitors; host-targeting agents as adjunctive therapies
<b>Clinical</b>	
Interferon-based treatment	Discovery that HCV infection is curable; starting point for initial add-on combinations with direct-acting antiviral agents
Successful HIV drug development	Combination of potent agents from two or more classes with nonoverlapping resistance profiles produced effective viral suppression without resistance selection
<b>Regulatory</b>	
FDA policy	Enabled rapid clinical development of direct-acting antiviral agents by permitting phase 2 studies of all oral regimens without standard-of-care comparators

\* FDA denotes Food and Drug Administration, HCV hepatitis C virus, and HIV human immunodeficiency virus.

lication for its existence — an observation that would be leveraged for the design of strategies to permanently clear the virus. In addition, molecular characterization resulted in an appreciation of viral genotypes, which led to critical epidemiologic discoveries and the development of appropriate genotype-specific therapeutic regimens.

Finally, it fostered the creation of several cell-culture systems to explicate the viral life cycle, virus–host interactions, and pathogenesis.<sup>2</sup> Because of initial difficulty in cultivating the virus, an important milestone was the construction of subgenomic selectable replicons harboring the viral non-structural proteins (NS3–5) responsible for genome replication. The use of replicons permitted efficient screening, testing, or both of several classes of DAAs that blocked these proteins, whose structures were themselves successfully crystallized and elucidated. These include inhibitors of NS3/4A protease, NS5A, and both nucleoside and nonnucleoside NS5B polymerase inhibitors.<sup>3</sup>

The subsequent discovery of a viral isolate that efficiently infected a human hepatoma cell line enabled the expansion of the arsenal of therapeutic classes to include inhibitors of viral entry, translation, and assembly, as well as inhibitors that block host proteins or microRNAs that are essential for maintenance of the viral life cycle. Because replicons and tissue-culture models largely recapitulate in vivo viral-replication behavior, researchers were able to develop DAA candidates rapidly by circumventing lengthy and costly efficacy studies in the chimpanzee, the only viable animal model of HCV.

In many ways, antiviral development in HCV was guided by the HIV therapeutic experience and, accordingly, quickly moved to more practicable paradigms. HCV encodes a highly error-prone RNA polymerase that generates extraordinary heterogeneity of the viral species within infected persons. Thus, it came as little surprise that initial monotherapy trials of

was clinically effective. It amounted to a holding strategy, however, since its effectiveness was limited by the side-effect profile of injected interferon regimens and first-generation protease inhibitors, which induce cytopenias, depression, autoimmunity, and rash; these toxic effects were particularly prominent in patients with cirrhosis.

***It may be possible to imagine the global eradication of HCV infection, but three major challenges remain: infection is often diagnosed at a late stage, the high cost of direct-acting antivirals may lead to selective use, and reinfection remains possible.***

the first HCV protease inhibitors were thwarted by rapid selection of preexisting resistant variants. Fortunately, the long-running standard of care, the broadly acting antiviral cytokine interferon alfa, which inhibits HCV replication not by binding viral proteins but by inducing hundreds of host genes to produce an antiviral intracellular state, combined with ribavirin, an agent with both antiviral and immunomodulatory properties, showed activity against both protease-inhibitor-resistant and wild-type virus. Thus, a key first step in the therapeutic revolution was the addition of a protease inhibitor to the backbone of peginterferon and ribavirin. This strategy succeeded in boosting rates of sustained virologic response, or viral cure, from about 45% to approximately 75% among patients with HCV genotype 1 infection and proved that a DAA

Against this backdrop, the development of HCV nucleoside inhibitors, nonnucleoside inhibitors, and NS5A inhibitors presented the opportunity to apply to HCV the HIV combination-therapy principle, whereby a combination of potent agents from two or more classes with nonoverlapping resistance profiles could provide rapid and potent suppression of viral replication and prevent emergence of resistant variants. In theory, this regimen, applied for sufficient duration, could achieve the goal of high cure rates and freedom from dependence on interferon.

But additional steps were required to get from these interferon-tethered regimens to trials of investigational DAAs in combination. Traditional study designs had, until recently, used a standard-of-care comparator for new agents, which in the case of HCV meant using an interferon-based

therapy in the control group — an unappealing prospect for many patients. Buoyed by the success of combination HIV therapies and the knowledge that resistance variants in HCV were not predicted to persist as they do in HIV, the Food and Drug Administration agreed to permit phase 2 trials to use new combinations of HCV DAAs without requiring a standard-of-care comparator. This decision proved catalytic. Because of the short durations of, and rapid enrollment in, these studies, the pace of ensuing clinical drug development has been breathtaking.

These trials have shown that the combination approach is not only viable in concept, but also capable of producing sustained virologic response rates exceeding 90%, with the use of interferon-free, all-oral combinations. Just as impressively, several roads appear to be capable of leading to the same destination; combinations of several different classes have all yielded high rates of sustained virologic response in phase 2 studies. Phase 3 studies of many of these combinations are completed or under way, and approvals of the first of these regimens should be forthcoming within the year. Late-phase studies also show that DAA combinations are capable of bridging most of the performance gap between more-conventional populations of previously untreated patients and populations that have historically been difficult to treat, including patients with cirrhosis, HIV-coinfected persons, and patients who have not had a response to conventional interferon-based therapies.<sup>4</sup>

 An audio interview with Dr. Chung is available at [NEJM.org](http://NEJM.org)

Still, some drug-development hurdles lie ahead. Although they have achieved spectacular response rates in late-stage clinical trials, DAAs must fulfill their promise in the real world. Given historical trends in real-world populations, a minor but substantial fraction of some patient groups will probably need alternative approaches; these include patients with coexisting conditions such as renal failure, hepatic decompensation, or a liver transplant, as well as those with previous failure of a DAA combination. For such patients, new treatments may be required, including host-targeting agents or inhibitors of viral entry or assembly.<sup>5</sup>

It may now be possible to imagine the global eradication of HCV infection, but three major challenges remain. First, in the absence of effective screening programs, HCV infection is often diagnosed at a late stage (in high-income countries) or seldom diagnosed at all (in low- or middle-income countries). Second, the high cost of DAAs will preclude their use in most infected patients in low- or middle-income countries; in high-income countries, the need for payers to provide major resources for HCV treatment may lead to the selective use of DAAs for certain patient subgroups. Third, reinfection remains possible even after successful curative therapy.

Ultimately, a preventive vaccine would be desirable for the global eradication of HCV, but the virus's extraordinary sequence heterogeneity and ability to evade host immune responses pose challenges for the development of a broadly protective vaccine. In the mean-

time, effective HCV screening programs, including full implementation of birth-cohort screening in the United States, the establishment of access to affordable treatment in low- and middle-income countries, and strategies for reducing the risk of transmission (e.g., safe injection practices) will probably be needed to control HCV infection on a global scale. The introduction of DAAs represents a major breakthrough, but it is only a first step toward eliminating HCV globally.

Disclosure forms provided by the authors are available with the full text of this article at [NEJM.org](http://NEJM.org).

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