Hepatitis C Virus: The 25-Year Journey
From Discovery to Cure

Since the Institute of Medicine's call for a national response to viral hepatitis in 2010, prevention of hepatitis C virus (HCV) infection and associated illness has received much-needed attention from public health officials, clinical care providers, the media, and the community at large. Momentum for this burgeoning interest has been fueled by the progressive rise in HCV-related mortality; epidemics of new HCV infections among young adults; expanded U.S. recommendations for HCV testing; and most recently, licensure of safe HCV therapeutics capable of curing almost all persons of their HCV infection. In this context, it is remarkable to recall that over the course of 25 years, the field of viral hepatitis advanced from discovery of the virus to the beginning of the curative era for HCV infection (Fig. 1).

By the early 1980s, screening patients for hepatitis A virus or hepatitis B virus (the known causes of viral hepatitis at the time) revealed that a substantial number of hepatitis cases were not related to either infection. Harvey Alter and colleagues at the National Institutes of Health (NIH) identified this new form of hepatitis as non-A, non-B hepatitis (NANB). However, the cause of this new clinical entity remained elusive. Subsequently, Michael Houghton and associates (Chiron Corporation) and Daniel Bradley (Centers for Disease Control and Prevention [CDC]) cloned the putative agent, publishing their work in 1989 and calling the new agent "hepatitis C virus." Identification of HCV was accomplished by extraction of RNA and DNA from large volumes of chimpanzee sera with high infectious titers; complementary DNA was made from the extracted RNA and inserted into a cloning vector for viral replication and protein synthesis. Immunoassays were then produced to detect protein products of these clones. The expressed proteins were screened with sera from a patient with NANB; a single clone was identified among millions screened. Cloning of multiple overlapping regions of the genome led to development of an immunoassay that detected antibody in all but one specimen drawn from a panel of well-characterized specimens of sera known to contain the NANB infectious agent. Subsequently, the entire HCV genome was mapped and seven genotypes identified.

The impact of the discovery of HCV has been enormous. The addition of HCV antibody testing improved the precision of epidemiologic studies, which confirmed the major modes of HCV transmission as blood-borne and identified persons at risk: primarily those who received unscreened blood products, those with parenteral exposures to HCV in healthcare settings, and persons who inject drugs (PWID). In 1990, HCV antibody testing of blood and plasma donors was immediately adopted to protect the nation's blood supply. Second-generation assays introduced in 1992 virtually eliminated transfusion-associated HCV transmission. These tests also are important tools for national health surveys, which estimate that at least 3 million persons are currently living with HCV infection in the United States, 76% of whom were born during 1945-1965 (i.e., baby boomers), reflecting the substantial incidence of infection before viral discovery. Natural history studies of HCV-infected persons reveal the high likelihood of chronicity following viral acquisition (55%-85%), and the significant risk of cirrhosis and hepatocellular carcinoma (HCC) after 20 years or more of infection.

Discovery of HCV also spurred research for virologic targets of candidate vaccines and therapeutic agents. Development of hepatitis B vaccines raised hope for similar success with hepatitis C; however, the genetic diversity of HCV and the relatively weak immune response elicited by HCV infection have posed formidable barriers to vaccine development.

The absence of promising vaccine candidates increased the focus on drug development to reduce the burden of disease. Beginning in the early 1990s, initial treatment for HCV infection consisted of interferon...
alpha-2b, but few patients receiving treatment achieved a sustained virologic response (SVR) (signifying persistent viral clearance and a cure of their HCV infection). Subsequently, the introduction of pegylated interferon and the addition of ribavirin into treatment regimens raised the likelihood of viral clearance after 48 weeks of therapy to ~50% of treated patients. However, the toxicities of the therapeutic agents were considerable, resulting in many patients deferring treatment.6

Continued research of the virus made possible the identification of antiviral agents that act directly on the nonstructural proteins of HCV to interrupt viral replication and assembly in host hepatocytes. Licensed in 2011, the first generation of these agents, when combined with 24-48 weeks of pegylated interferon and ribavirin, improved cure rates among persons infected with HCV genotype 1 to 70%, although not without continued toxicities. The treatment landscape brightened considerably in 2013 with licensure by the U.S. Food and Drug Administration (FDA) of the latest generation of HCV treatments. These treatments expanded the viral genetic targets of therapy, broadening activity against additional genotypes. When used in combination as all-oral therapies or together with pegylated interferon and ribavirin, ~90% of treated patients achieved cure after 12-24 weeks of therapy with few major adverse events; shorter courses of therapy appear to be equally effective. Additional agents are expected to be approved by the FDA in 2014.

The availability of safe curative regimens for HCV holds promise for rapid adoption into clinical practice. To make this vision a reality, public health officials, clinical care providers, and policymakers must be cognizant of current prevention challenges and apply the advances in diagnostics and therapies needed to overcome them. HCV testing of risk populations, first recommended in 1998, has met limited success; at least half of the 3 million persons living with HCV are unaware of their infection status, and few are in care or receiving treatment.4,13 For the first time since discovery of the virus, the incidence of HCV infection in the U.S. is increasing—up 50% since 2011. Most of this increase appears to be related to injection-drug use in suburban and rural areas where harm reduction, drug treatment, and HCV testing services are sparse to nonexistent.14,15 Thus, there is much room for improvement regarding all phases of the HCV test,
care, and cure continuum in settings providing routine primary care as well as those serving populations with ongoing risk of HCV transmission. Although CDC funds a few states to monitor HCV infection and disease, most states lack the capacity to collect the data needed to target and evaluate HCV prevention, including care and treatment. National health surveys omit high-risk subpopulations (e.g., the homeless and incarcerated), rendering the true prevalence among these populations unknown.

HCV testing linked to care and treatment reduces the risk of HCC by 70% and all-cause mortality by 50%. HCV testing linked to care and treatment can avert an estimated 121,000 deaths and is cost-effective, with health benefits comparable to screening for colorectal cancer, breast cancer, and cervical cancer. Market prices of the new direct-acting antivirals (DAAs) have raised cost-related issues around access to care; however, prescribing these new curative therapies after diagnosis of HCV-infected persons with moderate-severe liver disease continues to be cost-effective.

Over the next 25 years, the nation can set ambitious goals for reductions in HCV disease and transmission and implement the programs and interventions required to reach them. First, given the long period between HCV infection and onset of clinically significant disease, prevention of HCV disease can one day become the status quo in the United States. With full implementation of expanded HCV testing recommendations for persons born during 1945-1965, along with improved access to recommended treatment, populations experiencing the highest rates of HCV-related mortality can learn of their infection status and be treated and cured of their HCV infection before they become severely ill. Second, as with HIV “treatment as prevention” programs, health models project the potential impact of employing HCV therapies to interrupt viral transmission, thereby reducing incident cases. Given the lack of serologic markers for acute HCV infection and the limited surveillance, testing, and care capacity for the growing number of young persons at risk for new HCV infection, successful integration of HCV therapies with other prevention strategies will require investments in research and programs designed to prevent HCV exposures and promote access to therapy among at-risk populations (e.g., PWID and HIV-positive men who have sex with men).

Since the discovery of HCV, the nation has reached a public health landmark: the opportunity to save hundreds of thousands of lives through HCV testing and cure (Fig. 2). Twenty-five years from now, will scientists and medical historians document missed opportunities and needless HCV-related illness and death? Or will they celebrate the successful prevention of morbidity and lives saved? To be successful, policymakers and the public must understand the urgency of HCV as a public health issue and commit to building capacity for surveillance, prevention, and care. All levels of the health system can work together to prevent new HCV infections, identify HCV-infected persons, and provide appropriate care and

Fig. 2. Mike Luckovich cartoon presented to participants at the CDC observance of the 25th anniversary of the discovery of HCV, June 17, 2014. © Mike Luckovich/CDC Foundation. Reprinted with permission.
treatment. With a national commitment to capacity building, the U.S. can markedly reduce HCV transmission and disease, setting the nation on a course toward the elimination of hepatitis C.

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