EDITORIAL

Simple, Effective, but Out of Reach? Public Health Implications of HCV Drugs

John W. Ward, M.D., and Jonathan H. Mermin, M.D., M.P.H.

The results of four clinical trials showing the excellent safety and efficacy of a 12-week course of sofosbuvir (an NS5B inhibitor licensed in the United States in 2013) and velpatasvir (a new NS5A inhibitor) in treating patients with hepatitis C infection (HCV) are reported now in the *Journal*.[1-3] In two of these studies, ASTRAL-1 and ASTRAL-2, 97 to 100% of patients with HCV genotype 1a, 1b, 2, 4, 5, or 6 had a sustained virologic response at 12 weeks after the end of therapy, a marker that is indicative of virologic cure. Similar efficacy was observed among patients in whom previous treatment had failed and those with compensated cirrhosis, factors that have been associated with a reduced response to the treatment of HCV infection.[4]

In the ASTRAL-3 study, sofosbuvir–velpatasvir was 95% efficacious in achieving a sustained virologic response among patients with genotype 3 (the viral strain associated with a reduced treatment response).[4] Efficacy was 89 to 91% for patients with cirrhosis or previous treatment failure.

In these three studies, sofosbuvir–velpatasvir was associated with few serious adverse events, high study-completion rates, and rates of sustained virologic response that were superior to those with selected study comparators. In addition, the data suggest that the pretreatment presence of NS5A resistance-associated variants was not a major factor in treatment outcomes but that more study is needed, particularly in patients with genotype 3.

For HCV-infected patients with decompensated cirrhosis, ASTRAL-4 showed 94% efficacy with the addition of ribavirin, as compared with a sustained virologic response of 83% for the 12-week regimen of sofosbuvir–velpatasvir alone. The proportions of patients with serious adverse events were similar across treatment regimens (16 to 19%). Indicators of liver function improved in nearly half the patients. Together, these studies indicate that this drug regimen can achieve high rates of HCV cure regardless of genotype.

The public health implications of simple, safe, and curative HCV therapies could be profound. HCV chronically infects 2.7 million to 3.5 million persons in the United States and 130 million to 150 million persons globally,[5,6] causing more than 700,000 deaths from cirrhosis or primary liver cancer worldwide every year.[6] In the United States, the rate of new HCV infection has risen by more than 150% in recent years, fueled by increases in injection-drug use.[6] HCV treatment could dramatically reverse these trends. A cure of HCV infection reduces the risk of liver cancer by 76% and of death from any cause by 50%. Theoretically, such a cure could reduce the force of infection and HCV transmission within a population.[7,8] Given the benefits of safe, simple, and curative therapy, why are we still concerned about the public's health with respect to HCV treatment?

Patients do not benefit from a drug they cannot afford. Although studies by the Centers for Disease Control and Prevention have shown that treating all HCV-infected persons is cost-effective from a societal perspective,[9] the price of current medications is a formidable barrier for many. Despite U.S. recommendations that all HCV-infected persons should receive treatment,[10] health plans and payers have responded to the cost of HCV medications ($83,000 to $153,000 per course of treatment) by instituting restrictive reimbursement policies. In 33 state Medicaid programs, only patients in whom the infection

has progressed to severe liver disease qualify for HCV treatment.[11] Drug expenditures for the treatment of HCV infection have declined as a result of mandated 23% rebates for Medicaid and privately negotiated prices by health plans, but inequities in patient access to such therapies persist.

In response, on November 5, 2015, the Centers for Medicare and Medicaid Services (CMS) notified state programs that limitations on drug coverage should not deny access to clinically appropriate antiviral therapy for beneficiaries with chronic HCV infection. CMS also requested that manufacturers disclose value-based pricing agreements so that states can participate in such arrangements.[6] Globally, a generic version of sofosbuvir has been licensed for use in 91 low-resource countries.[12] Access to these drugs is also a challenge in middle-income countries, in which more than 60% of HCV-infected persons reside.[13] Licensure of sofosbuvir–velpatasvir and other HCV regimens that are now being studied creates opportunities for innovative pricing strategies that increase affordability of new HCV medications and of those already on the market.

Benefits of curative therapy can be realized only for persons who have been tested and know they are infected with HCV. In the United States, HCV infection remains undiagnosed in at least half of all persons with the disease,[7] and the proportions are even higher in other countries.[14] A combination of testing strategies is recommended to identify persons with ongoing transmission risks (e.g., those who inject drugs) and those who were infected in the distant past who are at highest risk for dying from HCV infection. In the United States, even a modest increase in the capacity to implement HCV testing for all persons who were born from 1945 through 1965 could avert more than 320,000 deaths[9] but only when testing is linked to care and curative treatment.

The progressive steps in HCV care from viral detection to HCV cure are poor in the United States and in many other countries.[11,14] Education for providers and creation of models for care improve quality.[6,7] Although currently licensed therapies require that HCV-infected persons undergo genotyping and disease staging before the initiation of treatment, most HCV-infected persons do not receive this level of care. The sofosbuvir–velpatasvir regimen could simplify HCV management by reducing the need for these steps, paving the way for simple "test and cure" strategies appropriate for primary care and other settings, such as addiction-treatment programs.

The availability of simple, safe, and curative regimens creates opportunities for improving the health of the millions of patients living with HCV infection. At a population level, the effect of HCV medications will be determined by affordability and equitable access to HCV testing, care, and treatment. Only through these improvements can our focus be directed to what matters most: reducing the morbidity and mortality associated with HCV infection, stopping HCV transmission, and ultimately eliminating HCV as a public health threat in the United States and worldwide.

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From the Centers for Disease Control and Prevention, Atlanta.

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