



Treating Hepatitis C in Lower-Income Countries

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Just two decades after the identification of hepatitis C virus (HCV), an improved understanding of the viral lifecycle has led to several new classes of highly promising therapies. By as early as 2015,

sustained virologic response rates will be in the 90% range for most HCV genotypes, and this effective “cure” will be achieved through short, convenient courses of interferon-free, fixed-dose, single-pill regimens with adverse-effect profiles that are markedly better than those of past treatments. The use of these agents is expected to reduce the intensity of follow-up monitoring, the rate of hospitalizations for adverse effects, dependence on specialist care, and resource demands associated with disease progression, including those for liver transplantation and management of end-stage liver disease and liver cancer. However, with drug costs that may exceed \$90,000 per course, it remains to

be seen how these remarkable advances will extend to the estimated 150 million people with HCV infection living outside the target high-income markets for these agents.

HCV is implicated in 28% of cases of cirrhosis and 26% of cases of liver cancer globally, accounting for almost 500,000 deaths per year.¹ Low- and middle-income countries account for more than 80% of the global HCV burden, with the most infections in South Asia, East Asia, North Africa, the Middle East, and Southeast Asia.² HCV genotypes 4, 5, and 6 are particularly common in these areas, but the new treatment regimens can achieve responses in patients infected with those geno-

types that are similar to those achieved in patients with the genotype 1 infections that predominate in the United States and Europe.

Most patients with HCV infection in low- or middle-income countries remain untreated. HCV treatment has traditionally required weekly interferon injections, used in combination with ribavirin. This treatment involves numerous challenges in resource-constrained settings, including the cost of interferon formulations, protracted treatment courses of 6 to 12 months, and adverse effects including an influenza-like syndrome, cytopenias, infection, depression, and liver decompensation. In 2011, the first generation of direct-acting antivirals (DAAs) — telaprevir and boceprevir — were approved, and sustained virologic response rates, which had been 40 to 50% with past regimens, rose to 65 to 75%. These drugs have not been wide-

ly adopted in low- and middle-income countries, however, because they still depend on a prolonged interferon-and-ribavirin “backbone” and have been approved only for use against HCV genotype 1. They also have clinically significant adverse effects, a low genetic barrier to the development of viral resistance, peculiar dosing requirements, and numerous drug interactions — particularly when used with antiretrovirals needed in patients who are coinfecting with the human immunodeficiency virus (HIV).

Second-generation DAAs that have completed phase 2 trials or beyond include NS3 protease inhibitors, NS5A inhibitors, nucleoside NS5B polymerase inhibitors, nonnucleoside NS5B polymerase inhibitors, and combinations of these drugs. Besides markedly improved rates of sustained virologic response (frequently >90%),

minimal adverse effects and drug interactions, short treatment courses of 2 to 3 months, and the possibility of single-pill, fixed-dose combinations, the most notable advancement is a high cure rate without the need for interferon. Moreover, many of these agents have excellent in vitro efficacy against several, if not all, HCV genotypes. These developments are highly relevant to untreated patients in low- and middle-income countries.

The promise of this wave of all-oral DAAs comes with a substantial up-front financial burden. Health insurance is expected to insulate patients in high-income countries, and these drugs are thought to be cost-effective at the expected prices of approximately \$90,000 per course.³ Conversely, in lower-income countries where more than two thirds of drug costs are traditionally borne out

of pocket, drug cost is likely to be the single biggest barrier to treatment. However, the manufacturing cost of an all-oral, DAA-based, 3-month treatment course is conservatively estimated to be between \$100 and \$270.⁴ The global rollout of antiretroviral therapy (ART) against HIV has taught us that it is possible to make these agents broadly available and affordable (see box).

Annual costs for first-line ART have decreased from more than \$20,000 in the mid-1990s to often less than \$100 per person. The task of ART delivery has shifted from specialist physicians to primary care physicians, medical assistants, nurses, and public health officers, and nearly 10 million people in low- and middle-income countries are currently receiving treatment. Access expansion was achieved thanks to a combination of strident activism, high-level national and global policymaking, and the participation of the pharmaceutical industry. Key solutions included the World Health Organization's incorporation of ART regimens into its Model Lists of Essential Medicines, licensing of manufacturing for generics and fixed-dose combinations, differential pricing of the original brand-name drugs, and removal of barriers to the uptake of generics.⁵ Treatments for other conditions have also enjoyed similar successes. In India, because of legal pathways allowing the manufacture of generics, the costs of drugs such as imatinib for chronic myelogenous leukemia and sorafenib for liver cancer have dropped from \$2,000 to \$5,000 a month to less than \$200 a month.

In our opinion, the greatest asset of the new generation of DAAs for HCV is their unprecedented practical applicability in

Examples of Key ART Access Strategies Applicable to Second-Generation DAA Access in Low- and Middle-Income Countries.*

Affordability

Recognition as essential medicines

Creating novel international funding streams (e.g., the Global Fund to Fight AIDS, Tuberculosis, and Malaria and the U.S. President's Emergency Plan for AIDS Relief); prioritization within national budgets

Allowing legal pathways for generic-agent manufacture, including fixed-dose, once-daily combinations; World Health Organization prequalification program for quality control

Differential pricing of branded originator drugs

Task shifting of testing and treatment away from physicians

Introducing simplified testing and treatment guidelines and drug regimens; expanding use of cheap point-of-care laboratory technologies

Availability

Allowing manufacture and export of generics

Creating global, multi-stakeholder efforts to expand access (e.g., the 3 by 5 Initiative and the Treatment 2015 Initiative)

Decentralizing testing and treatment; integrating care into community and primary care services, such as antenatal care programs

Task shifting of testing and treatment away from physicians

Establishing antidiscrimination and anti-stigma policies

* ART denotes antiretroviral therapy, and DAA direct-acting antiviral.

resource-limited settings. In fact, these agents may present fewer hurdles on the ground than the rollout of ART did. First, patients are likely to adhere to DAA regimens, because they typically entail once-daily combinations, with or without ribavirin. Second, DAAs have had few adverse effects in trials thus far and have had minimal drug interactions — even with the ART needed in patients with HCV–HIV coinfection, which has been a problem with past HCV treatments. Third, to achieve an end point of cure, the required treatment course will probably not exceed 3 months, which limits the need for protracted follow-up, testing, and adverse-effect management. Fourth, the DAAs are expected to have similar efficacy against all HCV genotypes, which limits the need for resource-intensive genotype testing and complicated genotype-tailored regimens. Finally, as with the prescribing patterns for ART in resource-limited settings, the simplicity of these once-daily, fixed-dose, well-tolerated DAA regimens is likely to minimize dependence on specialist physicians. In fact, to minimize redundancies, DAAs may be excellent candidates for incorporation into existing HIV primary care delivery and surveillance infrastructures.

HCV prevalence is five times that of HIV, and a large proportion of infected people remain unaware of their status — one of

several challenges to the expansion of access to DAA therapy. It may be necessary to initially target higher-prevalence countries and prioritize higher-risk groups, such as patients with advanced liver fibrosis, cirrhosis, and HIV or hepatitis B coinfection. The greatest challenge, however, may stem from poor global advocacy, perhaps due in part to a false perception of the indolent course of HCV. The global mortality burden of viral hepatitis (A, B, C, and E) is similar to that of HIV and higher than that of tuberculosis or malaria, but the differences in the political and social climate surrounding these infections could not be starker. For example, the Global Fund to Fight AIDS, Tuberculosis, and Malaria received almost \$30 billion in pledges between 2002 and 2015, whereas no dedicated international agencies or well-funded, broad-based campaigns exist for eradication of viral hepatitis. In contrast to the groundswell of HIV activism, HIV's place in the United Nations Millennium Declaration in 2000, and consequent public health “exceptionalism” — which led to impressive gains — there have been few calls to list DAAs as essential medicines, create nimbler fund-raising mechanisms, or engage low- and middle-income countries that stand to benefit from these developments.

The charge is onerous. But seldom in the history of medicine

have such definitive, curative therapies been developed for a disease so widespread and consequential to human health. We believe that robust efforts toward equitable access to these advancements are imperative.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Responding to Hepatitis C through the Criminal Justice System

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The United States is in the midst of a hepatitis C virus (HCV) epidemic, with an estimated 2.7 million to 3.9 million

Americans currently infected.¹ Untreated HCV leads to cirrhosis, liver failure, and hepatocellular carcinoma and is the lead-

ing cause of the need for liver transplantation. Most Americans with HCV became infected decades ago and are unaware of