

Overcoming Barriers to Care for Hepatitis C

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Thanks to steady scientific and therapeutic advances related to hepatitis C virus (HCV), now is a time of much optimism regarding the care of HCV-infected patients.¹ Many seminal developments have been documented, and the number of new agents and regimens being studied in clinical trials suggests that gains will continue to be made in the tolerability and efficacy of treatments for HCV infection.¹ These advances raise the hope that we may overcome the barriers created by the relatively poor efficacy and tolerability of peginterferon alfa plus ribavirin, the historical backbone of treatment in hepatitis C. Although optimism is justified, so is some degree of caution, for as treatment improves, the true rate-limiting factor in achieving better outcomes may turn out to be access to diagnosis and treatment.

To better understand progress in the care of patients with hep-

atitis C, one must consider the populations we treat and the health system context in which we treat them. According to a 2010 strategic report from the Institute of Medicine (IOM),² lack of knowledge and awareness on the part of health care providers, persons at risk for infection, health policymakers, and the public contributes to the risk of ongoing transmission and lost opportunities for diagnosis, treatment, and prevention. Although therapy that has limited efficacy and harsh side effects provides minimal incentive for patients and clinicians to pursue diagnosis and treatment, the greatest barrier to treatment is lack of diagnosis: estimates suggest that about half of the approximately 3.2 million Americans infected with HCV are unaware of their infection, and only a tiny fraction are treated (see table).^{3,4} At the population level, this low rate of disease detection limits

the possibility that new therapies can deliver potential downstream economic and public health benefits of the interruption of increases in HCV-related mortality and in liver transplantation for such complications of HCV infection as end-stage liver disease and hepatocellular carcinoma.

The challenge of improved diagnosis and treatment is made more acute by the disproportionate distribution of the burden of hepatitis C among vulnerable groups. The risk of HCV infection is highest among blacks and Hispanics, people with lower levels of education, and the poor.⁴ Analysis of data from the National Health and Nutrition Examination Survey (NHANES) indicates that as compared with non-Hispanic whites, non-Hispanic blacks have nearly twice the odds, and Mexican Americans have more than two and a half times the odds, of having HCV antibodies. In addition, people with a family income

Trends in Hepatitis C–Related Mortality, Liver Transplantation, and Treatment in the United States, 2002–2007.*

Year	Deaths to which Hepatitis C Contributed <i>no. of patients</i>	Transplantation for HCV-Related Primary Indication (Excluding Hepatoma) <i>number</i>	Transplantation for HCV-Related and HBV- or HCV-Related HCC	Patients Treated with Antiviral Therapy for Hepatitis C in U.S. (95% CI) <i>number</i>
2002	4839	1904	752	126,040 (125,449–126,649)
2003	4616	1862	829	144,276 (143,616–144,943)
2004	4586	2022	889	107,131 (106,653–107,614)
2005	4767	2040	988	114,197 (113,580–114,823)
2006	6415	1942	1149	88,083 (87,685–88,486)
2007	6572	1799	1247	83,270 (82,897–83,647)

* Data in the column on mortality are from the Centers for Disease Control and Prevention, National Center for Health Statistics, Multiple Cause of Death 1999–2009 (<http://wonder.cdc.gov/mcd-icd10.html>), and are based on hepatitis C infection (ICD-10, 17.1 and 18.2) declared as a contributing cause on the death certificate; data in the columns on transplantation are from the Organ Procurement and Transplantation Network (as of May 2012); and data in the column on antiretroviral therapy are from Volk et al.³ CI denotes confidence interval, HBV hepatitis B virus, HCC hepatocellular carcinoma, and HCV hepatitis C virus.

below the poverty line had nine times the odds of testing positive for HCV antibodies, as compared with people who had a household income two times the poverty threshold or higher.⁴ The IOM's strategy report cites numerous studies indicating that whites are more likely than blacks to be evaluated for HCV infection and to undergo and complete treatment for it, and there are similar disparities with regard to treatment of, and mortality associated with, hepatocellular carcinoma, a major complication of hepatitis C.²

According to another analysis of NHANES data, only marginally more than one third of patients with hepatitis C who were medically eligible for treatment had private medical insurance.⁵ In fact, infection with HCV was independently associated with the likelihood of being uninsured, even after adjustment for socioeconomic and demographic factors. Uninsured patients with hepatitis C may also be more likely to seek care in emergency rooms than in clinics or health centers — a finding that has important implications for programs aimed at improving diagnosis and treatment in vulnerable groups.⁵

Taken together, these data suggest that many people with hepatitis C may be at a disadvantage in terms of health literacy, which limits their capacity to successfully engage with health care services to obtain a diagnosis and treatment. Engagement in the health system is a necessary though not sufficient condition for availing oneself of the benefits from recent developments in therapy for hepatitis C.

In response to the IOM's national strategy, the Department

of Health and Human Services (DHHS) has developed a road map for education and care, focusing on disparities in health literacy and access to care, to better target programs for prevention, diagnosis, and treatment of viral hepatitis (www.hhs.gov/ash/initiatives/hepatitis). If the Affordable Care Act assists patients in overcoming constraints on access to treatment for hepatitis C, the public health effect may be far more profound than that achievable with improved therapy alone.

What concrete measures might public health agencies take to improve awareness, diagnosis, and treatment of hepatitis C? Efforts to increase community awareness are enhanced by targeting high-priority populations with culturally sensitive and linguistically

of chronic hepatitis B and subsequent vaccination and treatment among Asian and Pacific Islander Americans. Of 1206 adults screened for chronic hepatitis B in its "3 For Life" pilot program, half showed no serologic evidence of immunity, and 85% of these persons were then able to be vaccinated against hepatitis B.

On a population scale, the Centers for Disease Control and Prevention has recently proposed a birth-cohort approach to screening for HCV — testing everyone born between 1945 and 1965 (an age group with increased risk of HCV exposure from the 1960s through the 1980s), rather than following the current risk-based screening recommendations (www.cdc.gov/Hepatitis/HCV/BirthCohortTesting.htm). Improved rates of re-

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appropriate educational messages. Understanding community-specific epidemiologic factors facilitates the creation of programs tailored to settings with a high prevalence of HCV infection (e.g., correctional facilities) or groups with increased risk of transmission (e.g., injection drug users) or high prevalence (e.g., migrants from Egypt and some Southeast Asian countries). A successful example of this approach is Stanford University's Jade Ribbon Campaign to increase the detection

of hepatitis C and referral to specialists for treatment depend not only on better patient awareness, but also on improved knowledge among primary care providers, which requires a greater focus on HCV in undergraduate and postgraduate continuing medical education.

Finally, if such measures successfully increase the rates of HCV detection, clinical questions remain. Do all HCV-infected persons require treatment? Many will not have progressive liver injury leading to cirrhosis, and only a

minority will have hepatocellular carcinoma. Should the decision to treat be based on the risk of progressive liver disease or cancer, or simply on the presence of the infection? Historically, histopathological evidence of inflammation or fibrosis from liver biopsy was used to identify candidates for treatment, to improve the risk–benefit ratio associated with poorly efficacious, toxic, and expensive peginterferon alfa plus ribavirin therapy. Future regimens may be more efficacious and eventually less toxic but will surely be even more expensive. What clinical variables or biomarkers are sufficiently sensitive to identify patients at low risk for complications who may not need treatment? Does a more nuanced treatment approach dilute the simple message of “detect and treat,” which resonates with many patients, clinicians, and the pharmaceutical industry?

The fragmentation and underfunding of public health services reflect a health system that’s poorly positioned to improve the awareness, prevention, diagnosis, and treatment of hepatitis C —

the necessary steps to interrupting the progress of this silent epidemic.² We are at a critical juncture, determining whether, supported by health care reform, initiatives such as those suggested by the DHHS can translate the rhetoric of health disparities into better programs and outcomes for patients with hepatitis C. If the evolution in service delivery is successful, this may be a watershed moment not only for HCV therapeutics, but also for access to hepatitis treatment, improving care for all Americans infected with HCV.

Hepatitis C offers a window into contentious issues in health care reform. How can therapy be made more accessible, and if it is more accessible, how will we as a community pay for it? At a population level, improving the diagnosis and treatment of HCV infection will be expensive but will avert much illness and death from decompensated liver cirrhosis and hepatocellular carcinoma, the prevalence of which is projected to substantially increase over the next decade, at major cost to the community.^{2,3} The

possibility of achieving future cost savings, particularly for disadvantaged groups, raises the question: can we afford not to improve the accessibility of treatment for hepatitis C?

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

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Pathological Complete Response and Accelerated Drug Approval in Early Breast Cancer

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New drugs for breast cancer have historically been approved first for patients with metastatic disease who have few remaining options for systemic treatment. Approval for an adjuvant indication occurs years later, after large, randomized trials with prolonged follow-up have been conducted in patients with

early-stage disease. Recently, neoadjuvant trials have introduced new drugs preoperatively in patients with localized breast cancer. Such treatment aims to render locally advanced cancers operable, facilitate breast-conserving surgery, and ultimately improve survival. The rate of pathological complete response

— absence of residual invasive cancer on pathological evaluation of resected breast specimens and lymph nodes after preoperative therapy — has been used as the primary end point in many neoadjuvant trials.

Promising investigational drugs should be incorporated into standard treatment for early-stage