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.

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Responding to Hepatitis C through the Criminal Justice System

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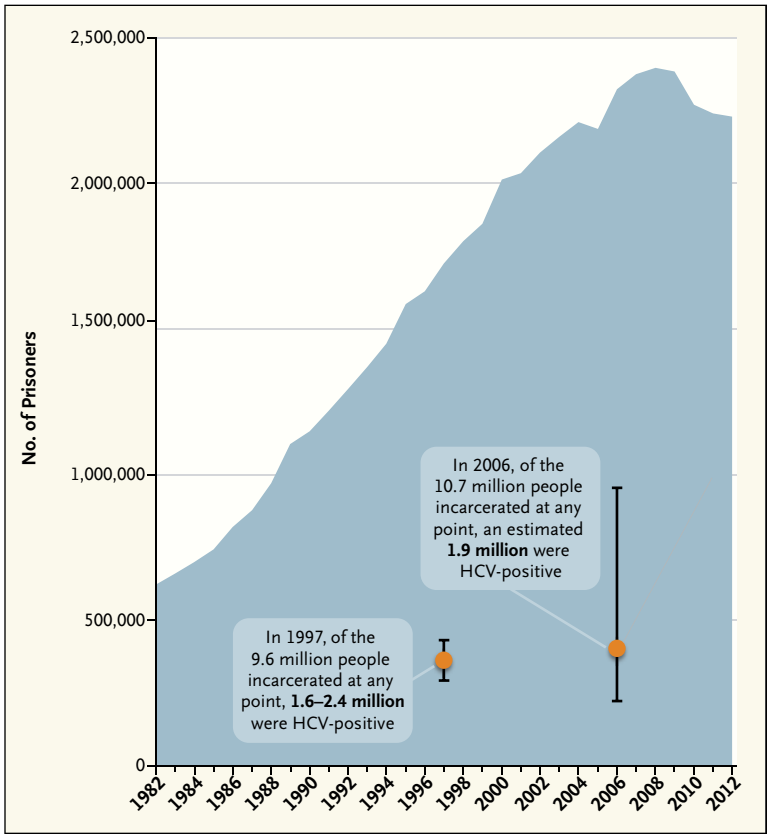
Related articles, pp. 1879 and 1889

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



Census of Federal and State Prisons and Local Jails, 1982–2012, with Estimated Prevalence of HCV, 1997 and 2006.

Data are from the Bureau of Justice Statistics; Hammett et al., AJPH 2002; and Varan et al.[4] Rates vary between federal and state prisons, among states, and between jails and prisons. Point estimates and I bars refer to the number of people in prison on any given day.

their status — there is a lag time of several decades between infection with HCV and development of clinically significant disease. Thus, in the absence of large-scale efforts at diagnosis and treatment, the burden of HCV-associated disease is expected to increase dramatically in the near future, and more than 1 million people are expected to die from HCV by 2060.[2]

The first treatments for HCV were approved in the early 1990s, and treatments have steadily improved in both efficacy and side-effect profile. In December 2013, the first non–interferon-based, all-oral regimen for the treatment of HCV was approved by the Food and Drug Administration (FDA). This short-course (12-week) regimen with an acceptable side-effect profile is likely to be the first of many and represents a triumph of medical science over disease, with high (approximately 90%) cure rates. Yet a single treatment course costs approximately $84,000 per person for the one new medication (sofosbuvir) alone.

Most HCV infection in the United States is the result of past use of injection drugs. Our four-decade "war on drugs" has led to the highest per capita incarceration rate in the world,[3] and as a result, most Americans who inject drugs have been incarcerated at some point in their lives. It is therefore not surprising that the prevalence of HCV infection in the criminal justice population has reached epidemic proportions (see graph). One in six prisoners is infected.[4] With more than 10 million Americans cycling in and out of prisons and jails each year, including nearly one of every three HCV-infected Americans, the criminal justice system may be the best place to efficiently identify and cure the greatest number of HCV-infected people. From a public health standpoint, the high concentration of patients with a curable contagious disease living in correctional institutions presents a critical opportunity to have a substantial effect on this epidemic. And with the burden of disease expected to grow, the sooner we treat and cure large numbers of people, the better. But correctional-system health care is often dissociated from community health care, and standards of care in prisons and jails are often vague and rarely uniform.

In 1976, the U.S. Supreme Court ruled (in *Estelle v. Gamble*) that failure to provide the community standard of care for prisoners amounts to cruel and unusual punishment and is therefore prohibited by the Eighth Amendment of the Constitution. Subsequent litigation and threats of litigation led to dramatic improvements in the quality and quantity of health care delivered to prisoners. Although it is substantially limited by the 1996 Prison Litigation Reform Act, litigation remains the primary force driving the reform of prisoner health care to meet basic community standards of care — but "community-standard" health care is a relatively low bar to clear. And when it comes to managing HCV infec-

tion in correctional settings, as a matter of public health and public policy, care aimed only at meeting a minimal constitutional standard represents a missed opportunity.

Newer HCV treatments have dramatically changed the community standard of care, raising many questions that need to be addressed to develop a rational, uniform public health strategy. For example, is there a cost limit to the care provided to prisoners? The courts have consistently upheld the need for other sorts of treatments regardless of cost. But the courts have not been challenged by costs of this magnitude for so many patients. If we estimate that 17% of people incarcerated today have HCV and aim to treat them all, the cost will be $33 billion. If we treat even half the people with HCV who pass through corrections facilities in a year, the cost will be $76 billion.

In addition, because more than 95% of prisoners are eventually released, most HCV-related illness will occur in the community. Should everyone be screened and treated? That approach makes sense in incarcerated populations, given the low cost of screening and the high prevalence. Even screening without treatment, particularly for populations in jail for short periods, could have a substantial effect on the trajectory of disease, especially if it were accompanied by enrollment in insurance coverage made available under the Affordable Care Act.[5]

Late-stage disease, for which treatment is more urgent, is relatively easy to detect clinically, since it is associated with decreased platelet counts and albumin levels. Staging of the disease is imperfect, however, so the best community standard of care would include treating earlier-stage disease as well. But since the cost savings associated with treating earlier disease are likely to be realized after a prisoner has been released, there is a strong financial disincentive for correctional systems to diagnose and treat early HCV disease.

Stemming the epidemic of HCV-related disease requires a national strategy that addresses these questions and a clear approach to screening, diagnosing, and when appropriate, treating and curing people both in the community and in correctional facilities. Early detection and treatment in correctional settings has the potential to prevent future need for treatment, which, along with its attendant costs, would occur predominantly in the community; it could also prevent ongoing viral spread. The past several decades of mass incarceration in the United States have unintentionally provided a public health opportunity for diagnosing and treating HCV. If we are serious about addressing the HCV epidemic, we believe the correctional health care infrastructure must play a major role, and a new approach that focuses on aggressive and comprehensive early diagnosis, evaluation, and treatment is a critical next step.

As we develop a plan of action, we can draw on lessons learned in the early years of HIV diagnosis and treatment in the correctional setting. Correctional facilities faced similar cost and treatment challenges in responding to the HIV epidemic, which was even more complicated because it required long-term treatment with ongoing monitoring. Given the high efficacy but also high costs of new HCV therapies, we would be wise to apply some of the lessons learned from the HIV epidemic. In that case, the Ryan White Care Act resulted in a surge in resources for combating HIV, including funding for medications and a nationwide network of clinicians. Since people whose HCV infection is eradicated can be reinfected if they are exposed again, we will also need to provide comprehensive ongoing addiction-treatment services both during patients' incarceration and after their release.

Although the history of medical care in U.S. correctional facilities has been a story of struggling to meet minimum standards of care, moving beyond those standards in the case of HCV would benefit everyone. A new standard of correctional health care should be expected in response to epidemics — a standard that necessitates deploying external emergency funding to optimize both correctional and community-based treatment. The high up-front costs of early diagnosis and treatment in the correctional setting are justifiable for the same reasons they are justifiable in the community: earlier diagnosis and treatment of HCV are cost-effective in the long run. Seizing this opportunity for timely care will require leaders to consider the criminal justice system as part of the fabric of U.S. health care. In taking this step, we can help to change the perception of the HCV epidemic in the criminal justice system, transforming it from a legal liability to a critical opportunity to change the course of HCV in the United States.

Dr. Rich reports receiving an honorarium for participation in a Gilead Clinical Care advisory board meeting in 2012.

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HISTORY OF MEDICINE

The Biology and Genetics of Obesity — A Century of Inquiries

Chin Jou, Ph.D.

Related article, p. 1909

The obese lack willpower; they overeat and underexercise — or so believe a majority of Americans. A 2012 online poll of 1143 adults conducted by Reuters and the market research firm Ipsos found that 61% of U.S. adults believed that "personal choices about eating and exercise" were responsible for the obesity epidemic.[1] A majority of Americans, it seems, remain unaware of or unconvinced by scientific research suggesting that "personal choices" may not account for all cases of obesity.

Yet for more than a century, physicians have been proposing that some cases of obesity are a function of innate biologic mechanisms or heredity. In 1907, the German pathologist Carl von Noorden delineated two types of obesity: exogenous and endogenous (1953; see box for historical *Journal* articles cited). Exogenous obesity, which accounted for most cases, was the consequence of external culprits — namely, food consumption in excess of energy expenditure. But some people had endogenous obesity, caused by hypometabolism or other thyroid disorders.

Some early-20th-century doctors bluntly dismissed the idea of endogenous obesity. George Van Ness Dearborn, a neuropsychiatrist who had been on the faculty at Harvard and Tufts, declared in 1917 that "the great and culpable majority of the obese achieve their uncomplimentary fatness."[2] Nonetheless, a survey of medical journal articles on obesity in the 1910s and 1920s reveals that even physicians who might have shared Dearborn's sentiments conceded that dietary excess and lack of exercise could not account for all cases of overweight. And although the hypometabolic thesis had fallen out of favor by 1930, when more accurate calculations of body-surface area indicated that the metabolic rates of the obese were normal, researchers in the second half of the 20th century continued to make the case that some people were predisposed to obesity.

In the 1950s, for instance, the work of Rockefeller University's Jules Hirsch showed that for obese people, long-term weight loss is a lifelong struggle. Hirsch found that although obese subjects could shed a substantial amount of weight through drastic calorie restriction, their metabolic rates would dip in response to calorie reductions. This effect meant, for example, that if an obese woman dropped down from 200 lb to 130 lb, she would have to consume fewer calories to remain at 130 lb than would a 130-lb counterpart whose weight had always held steady. The previously obese woman, then, required more "willpower" to maintain her reduced weight than someone who had never been obese. Decades later, in 1995, Hirsch and his former Rockefeller colleagues Rudolph Leibel and Michael Rosenbaum observed that just as the metabolism of subjects who had lost 10% of their body weight decelerated, the metabolism of those who had gained 10% of their body weight revved up (1995). These findings suggested that the body has built-in mechanisms that resist attempts to resize it for the long term.

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