

Perspective

The Hidden Epidemic of Hepatitis C Virus Infection in the United States: Occult Transmission and Burden of Disease

Society faces an immense burden of hepatitis C virus (HCV) infection-related morbidity and mortality. Transmission of HCV is ongoing, and the incidence of HCV infection has been increasing in recent years. New therapies for treating HCV infection hold considerable promise for increasing cure rates and thus reducing HCV transmission. However, many persons with HCV infection in the United States are unaware of their infection status. The Centers for Disease Control and Prevention (CDC) recently expanded its HCV testing recommendations to include 1-time HCV testing for individuals born between 1945 and 1965, a population with a 3% prevalence of infection. Linkage to care and treatment for those identified with infection through testing would have a profound impact in reducing HCV disease burden. Coordinated efforts by public health agencies, clinical care providers, laboratories, and payers are necessary to improve primary and secondary prevention of HCV disease. This article summarizes a presentation by John W. Ward, MD, at the IAS–USA live continuing medical education program held in Atlanta, Georgia, in October 2012.

The United States is reaching a crucial point in the epidemic of hepatitis C virus (HCV)-related disease. One major issue we face is the inadequate number of practitioners who are trained, equipped, and willing to take care of the large population of people who are becoming progressively ill with this chronic infection.

HCV Morbidity and Mortality: The Grim Statistics

Acute HCV infection is characterized by mild to moderate symptoms in approximately 30% to 40% of patients. Although mortality from acute HCV is rare, approximately 75% of patients with acute infection become chronically infected. Chronic HCV infection is the cause of almost all HCV-related morbidity and mortality. After 30 years of chronic HCV infection, cirrhosis occurs in 15% to 35% of patients, and of these patients, there is a 1% to 3% incidence of hepatocellular carcinoma (HCC) each year. HCV infection increases the risk for HCC 17-fold, and 31% to 61% of HCC cases have markers of HCV infection. Approximately 36%

of persons on the liver transplant waiting list have HCV-related liver disease. The lifetime risk of HCV-related death in chronic HCV infection is estimated at 37%.

Worldwide, approximately 170 million people have chronic HCV infection. Approximately 25% of persons infected with HIV also have HCV infection, with coinfection rates reported to be greater than 75% in some regions, such as China, Vietnam, and Russia. It is estimated that 2.7 million to 3.9 million people in the United States have chronic HCV infection and that more than 15,000 die each year from HCV-related disease, with mortality expected to rise in the coming years. Prevalence estimates for the United States are low, because they include only the non-institutionalized civilian population and do not account for incarcerated or homeless persons, both being populations with high prevalences of HCV infection. Age-

adjusted HCV-related mortality has been steadily increasing, with a 50% increase in rate occurring between 1999 and 2007. In 2007, HCV-related mortality exceeded HIV-related mortality, and data for 2008 indicate that the difference between the 2 rates continues to increase. More than 70% of registered deaths of HCV-infected individuals in 2007 were in those born from 1945 to 1965.

Figure 1 shows the staggering predicted future burden of HCV-related morbidity and mortality in the United States.¹ On the assumption that there are 2.7 million HCV-infected people in primary care, an estimated 1.47 million will develop cirrhosis, 350,000 will develop liver cancer, and 897,000 will die from HCV-related complications. Peaks in the prevalence of decompensated cirrhosis, HCC, and death are expected in the late 2020s and early 2030s.

HCV Transmission Continues

The HCV-related mortality trend reflects, in large part, the epidemic of HCV transmission in the years before the virus was discovered in 1989. It is

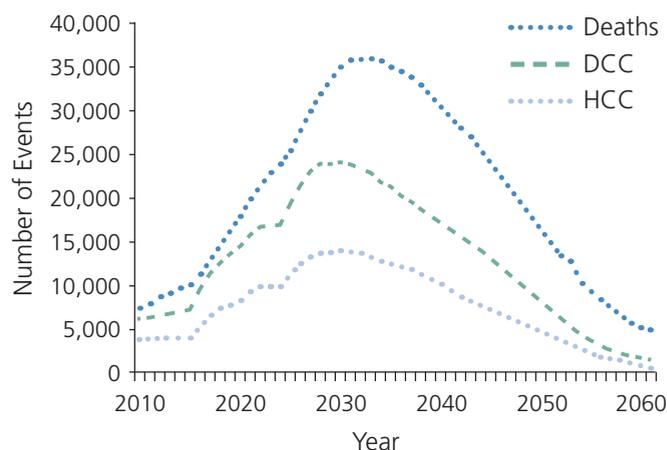


Figure 1. Future burden of hepatitis C virus (HCV)-related morbidity and mortality in the United States. DCC indicates decompensated cirrhosis; HCC, hepatocellular carcinoma. Adapted from Rein DB et al.¹

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estimated that some 300,000 people in the United States became infected each year during that period, primarily through injection drug use (or user, IDU) practices and transfusions before the advent of blood screening and prevention strategies. The incidence of infection has since declined to approximately 15,000 to 20,000 cases per year.

Since reaching a nadir in 2005, the incidence of HCV infection in the United States has gradually increased, with a relatively dramatic increase in 2011. Figure 2 shows the age distribution of confirmed HCV cases in Massachusetts in 2002 and 2009.² There has been a marked increase in number of infections reported in people in their 20s and early 30s since 2002, and similar findings have been reported from other states including Pennsylvania and Wisconsin. Most of these cases in younger persons involve current or past IDU. These individuals are predominantly white, equally proportioned by

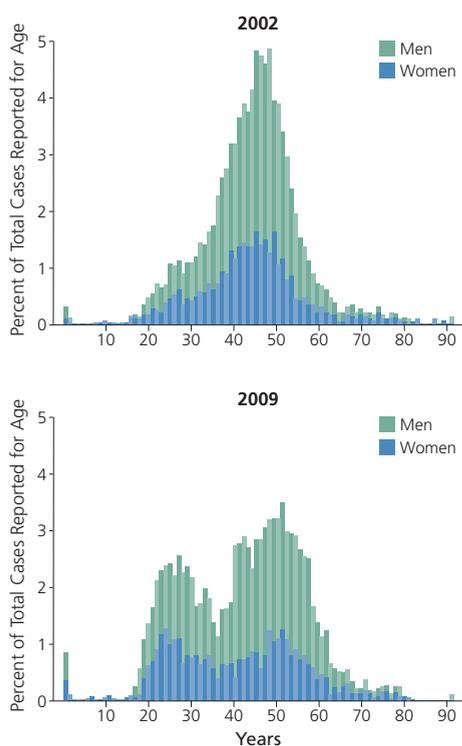


Figure 2. Age distribution of confirmed hepatitis C virus (HCV) cases in Massachusetts in 2002 (top) and 2009 (bottom). Adapted from Centers for Disease Control and Prevention.²

sex, very commonly previous users of narcotics such as oxycodone, and predominantly from suburban and rural settings—a characteristic that makes case investigation more difficult.

IDU. IDUs remain at highest risk for HCV infection. Globally, it is estimated that 64% of IDUs have HCV infection. IDU accounts for 60% to 70% of new infections in the United States and many other countries. Acquisition of HCV is fairly rapid after the start of IDU, with incidence being highest among new injectors; the estimated rate of infection within 2 years of beginning IDU is 18 to 27 per 100 person-years. Reinfection after HCV clearance is not uncommon, estimated at 1.8 to 4.7 cases per 100 person-years. The lower rate of reinfection than initial infection appears to reflect a protective effect of immune priming during initial infection.

The availability of oral direct-acting antivirals (DAAs) for HCV therapy has raised the prospect of reducing the “force” of infection by lowering the prevalence of infection in networks of those who inject drugs. Figure 3 shows projections of relative prevalence reductions based on different assumptions for numbers of infected people treated per 1000 IDU population and an assumed sustained virologic response (SVR) rate of 62.5%.³ For example, it is estimated that treating 10 HCV infections per year per 1000 IDUs with an SVR rate of 62.5% would result in a relative reduction in HCV prevalence over 10 years of 31%, 13%, and 7% assuming background prevalences of 20%, 40%, and 60%, respectively.

Health care–associated transmission. Health care–associated transmission remains an important cause of HCV infection in the United States and globally, estimated to account for 40% of HCV infections worldwide. In countries with high prevalence of chronic HCV infection (ie, >3%), including Egypt, Pakistan, and Mongolia, it is the major transmission mode. In these locales, injections are common and injection practices are difficult to change. In the United States and other countries with low prevalence, health

care–associated transmission continues to cause outbreaks. In the United States, 1 to 2 outbreaks are reported every month, typically from outpatient settings such as dialysis, pain management, and oncology clinics. A recent study has shown that exposure to a health care setting is an independent risk factor for acquisition of HCV in people aged 55 years and older in the United States,⁴ suggesting that there are ongoing sporadic transmissions that are not revealed in the context of outbreaks.

Other modes of transmission. HCV can also be transmitted through blood contamination of shared devices for nasal insufflation of cocaine. Estimates of HCV-seropositive status among non-IDUs range from 0% to 17%.⁵ Mother-to-child transmission from HCV-infected mother to infant occurs in approximately 4% of births and in 25% of births in which the mother is coinfecting with HCV and HIV. There is no current recommendation to screen mothers for HCV, because there is no protective intervention that can interrupt transmission.

Heterosexual transmission accounts for 14% of reported cases of acute

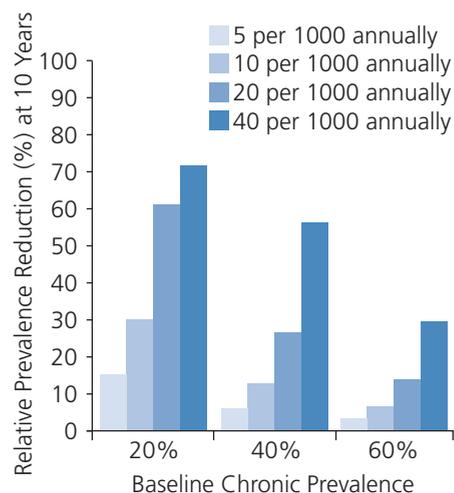


Figure 3. Estimated 10-year relative reduction in hepatitis C virus (HCV) prevalence among injection drug users (IDUs) according to number of HCV-infected IDUs treated annually with assumed sustained virologic response rate of 62.5%. Adapted from Martin et al.³

HCV infection in the United States,⁶ although transmission has been found to be rare among long-term HCV-serodiscordant couples. HCV infection incidence is high among HIV-infected men who have sex with men (MSM), estimated at 6.08 cases per 1000 person-years.⁷ Household contacts of infected persons are at 2-fold increased risk of infection as a result of incidental blood exposure from such items as toothbrushes and razors. Approximately 3% of acute HCV-infection cases in the United States occur in health care workers as a result of occupational exposure.⁶

HCV Screening

Since 1998, CDC has recommended HCV screening based on risk factors, including any history of injecting illegal drugs; receipt of clotting factors before 1987; receipt of blood or organ transplants before July 1992; history of chronic dialysis; evidence of liver disease (eg, persistently abnormal levels of alanine aminotransferase); and having HIV infection. Children born to HCV-infected mothers also are at risk, along with health-care, emergency medical, and public safety workers with needlestick, sharp, or mucosal exposure to HCV-positive blood.

Risk-based strategies to reduce transmission continue to be important, and attempts to refine such strategies are in progress. Some issues being considered include how often IDUs should be tested to detect recent or recurrent infection, and whether sexual contacts of HIV-infected MSM should be screened. However, risk-based strategies are insufficient to satisfactorily identify all HCV-infected persons and thereby potentially reduce transmission. Inherent barriers to a risk-based approach to testing include limitations in physician knowledge and experience, patient concerns about stigma, and poor patient recall of long-past risk behaviors. Further, individuals may not be aware that they are at risk of exposure to HCV in medical or other settings. Overall, it has been estimated that 45% to 85% of HCV-infected persons in the United States are unaware of their infection status.⁸⁻¹⁰

One striking example of the inadequacy of risk-based testing is provided by a study in 170 HCV-infected people identified through the 2001-2008 National Health and Nutrition Examination Survey (NHANES). Of these persons, 51% were unaware of their infection status prior to being tested in the survey. Among those who were aware of their infection status before the survey, the reasons for prior HCV testing were routine physical or blood test in 46%, symptoms of hepatitis in 16%, blood donation in 10%, and HCV risk factors in 4%.¹¹

The Good News and the Bad News: HCV Can Be Cured, But Most Infected Patients Are Not in Care

The advent of DAAs brings promise of increasing cure rates with shorter treatment durations and reduced rates of serious adverse events in HCV-infected patients. Regimens consisting of all oral agents have been found to produce high clearance rates, sometimes exceeding 90%, with 12 weeks of treatment, and more than 20 investigational drugs currently are in phase II or III trials. However, the benefits of such improved treatment in reducing the burden of HCV disease cannot be realized if infected persons are not brought into care. Testing is the link

that will identify infected people. Extra effort will be needed to bring infected persons into care.

To increase identification of HCV-infected individuals in the United States, the first step CDC recommends is to implement a 1-time test for all persons born between 1945 and 1965. This birth cohort has an infection prevalence of 3%, approximately 5 times greater than the prevalence among other adults. An evidence-based review of the strategy of testing this population and linking infected people to care indicates that treatment-related clearance of infection would reduce the risk of HCC by 70% and lower the risk of all-cause mortality by 50%. The NHANES survey mentioned above found that 50% to 60% of HCV-infected persons had at least 2 alcoholic drinks per day. A clinician-directed intervention on alcohol use as part of the care of infected patients identified through 1-time testing was estimated to decrease alcohol use by more than 38% over 1 year of follow-up. Harms of the 1-time testing strategy would include exposure to HCV treatment that is not effective and potentially serious but reversible adverse events.

The potential health impact of this birth cohort strategy is summarized in Table 1.¹² The model initially included only the impact of effective treatment with peginterferon alfa and ribavirin,

Table 1. Estimated Health Impact of Testing the 1945 to 1965 Birth Cohort for Hepatitis C Virus (HCV)

Outcome	Birth Cohort Testing With Therapy	
	Peginterferon alfa/ribavirin	Peginterferon alfa/ribavirin with telaprevir
Additional identified cases	809,000	809,000
Cirrhosis cases averted	138,000	203,000
Decompensated cirrhosis cases averted	50,000	74,000
Hepatocellular carcinoma cases averted	32,000	47,000
Transplants averted	11,000	15,000
Deaths from HCV averted	82,000	121,000
Medical costs averted	\$1.5 billion	\$2.5 billion
Costs per QALY gained	\$15,700	\$35,000

QALY indicates quality-adjusted life-year. Adapted from Rein DB et al.¹²

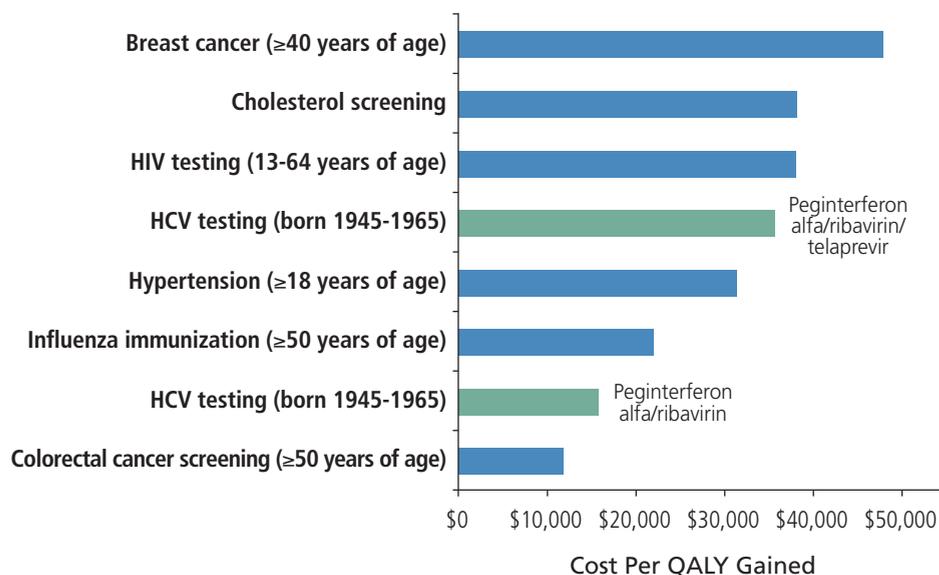


Figure 4. Comparison of cost-effectiveness of hepatitis C virus (HCV) strategy compared with other routine preventive services. QALY indicates quality-adjusted life-year. Adapted from <http://www.prevent.org/National-Commission-on-Prevention-Priorities/Rankings-of-Preventive-Services-for-the-US-Population.aspx>. Accessed December 4, 2012.

because that therapy was the only US Food and Drug Administration (FDA)-approved treatment at the time the analysis was started. Modeling that included the effect of the DAA telaprevir was subsequently performed when the drug was approved for use in combination with peginterferon alfa and ribavirin. As shown, it is estimated that full implementation of the strategy could identify 809,000 additional cases of HCV infection. Treatment that included telaprevir could avoid 203,000 cases of cirrhosis, 74,000 cases of decompensated cirrhosis, 47% of cases of HCC, 15,000 liver transplants, and 121,000 deaths. HCV infection is associated with substantial financial costs, with patients having 3-fold more disability days (1.36 vs 0.34 days) than other employees¹³ and much higher annual health care costs (\$21,000 vs \$5500 for others).¹⁴ With implementation of the birth cohort strategy, a total of \$2.5 billion in medical costs could be averted. The costs per quality-adjusted life-year (QALY) gained are estimated to be \$15,700 with peginterferon alfa and ribavirin treatment, and \$35,700 with treatment including telaprevir. These estimates compare well with estimates for other interventions considered to be good medical practice in the

United States (Figure 4).

Based on such analyses, CDC has added a new recommendation to the existing risk-based testing recommendations, as follows:

- Adults born during 1945 through 1965 should receive 1-time testing for HCV without prior ascertainment of HCV risk factor (*strong recommendation, moderate quality of evidence*).
- All persons with identified HCV infection should receive a brief alcohol screening and intervention as appropriate, followed by referral to appropriate care and treatment services for HCV infection and related conditions as indicated (*strong recommendation, moderate quality of evidence*).

Control and Elimination of HCV Transmission and Disease

HCV presents numerous epidemiologic challenges. HCV transmission continues to occur, with incidence appearing to be increasing in some US populations, such as young people living in the Northeast and Midwest,

and perhaps the Appalachian region. The burden of chronic infection and related disease is large, with the large population of people living with HCV becoming increasingly ill with HCV-related liver disease. At a time when anti-HCV therapy is improving, many if not most persons living with HCV infection remain undiagnosed and unaware of their infection status.

HCV infection is a health disparity for persons born during 1945 through 1965. The fact that most of the infected individuals in this cohort do not know their infection status provides a strong motivation for implementation of the CDC recommendations regarding testing and linkage to care. The goal is the control and eventual elimination of HCV transmission and disease. Achieving this goal requires comprehensive strategies to prevent transmission and to prevent consequences of chronic infection. Risk-based prevention strategies are necessary to detect and prevent new infections, whereas 1-time testing for the 1945-to-1965 birth cohort reduces morbidity and mortality among those infected.

New HCV therapies also promise to be powerful prevention tools in reducing transmission of new infections and the consequences of chronic HCV infection. However, HCV testing and linkage to care must improve if the health gains that are anticipated with the new therapies are to be realized. To achieve our goals, collaborations are essential among public health agencies, clinical care providers, laboratories, and payers to improve HCV testing, prevention, care, and treatment. 

Presented by Dr Ward in October 2012. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Ward in March 2013.

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Cases on the Web



NEW Preventing Anal Cancer in HIV-Infected Men and Women

Timothy Wilkin, MD, MPH

CME Credit Available: 1.50 AMA PRA Category 1 Credits™

Level: Advanced

Anal cancer is an increasingly common cancer among HIV-infected adults. High-grade anal intraepithelial neoplasia, for which there are several treatment options, can be diagnosed using anal cytology and high-resolution anoscopy with biopsies.

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Daniel K. Shirley, MD, and Robert J. Kaner, MD

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Smoking prevalence is increased in the HIV-infected population, and studies suggest an increased susceptibility to chronic obstructive pulmonary disease (COPD) in this group. HIV primary care practitioners must be knowledgeable about diagnosis and management of COPD.

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Aracelis D. Fernandez, MD, and Stephen Stafford, BA

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Management of Chronic Hepatitis C Virus Infection in Advanced Liver Disease

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