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The dawn of a new era:
Transforming our domestic response to hepatitis B & C

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The dawn of a new era: Transforming our domestic response to hepatitis B & C

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PROGRAM OVERVIEW

Diseases associated with hepatitis B virus (HBV) and hepatitis C virus (HCV) create a considerable burden on the nation's health care system and pose many challenges in terms of effective identification, treatment, and patient management. Both chronic HBV and HCV infections are often asymptomatic, earning them reputations as silent killers. Many individuals are unaware that they are infected until they develop signs or symptoms of cirrhosis or liver cancer. As many as 2 million Americans are infected with HBV and 5 million are infected with HCV. Despite this large patient population, standards for virus prevention, screening, and clinical care are currently inadequate, resulting in a major unmet medical need.

TARGET AUDIENCE

This activity has been designed to meet the educational needs of physicians and physician assistants involved in the care of patients with chronic HBV and HCV.

EDUCATIONAL OBJECTIVES

After completing this activity, the participant should be better able to:

- Describe the need for a coordinated national response to chronic HBV and HCV
- Identify improved strategies for the screening, diagnosis, treatment, and care of people with HBV or HCV
- Outline the most recent recommendations from the Centers for Disease Control and Prevention on screening and managing HBV and HCV infections in clinical practice
- Differentiate among available therapeutic agents for HBV and HCV to optimize treatment
- Identify factors that might affect the response to treatment of infected individuals
- Describe specific treatment and management strategies in order to delay the onset of liver disease
- Identify the ethnic, racial, and socioeconomic disparities in chronic liver disease, including hepatocellular carcinoma, and screening
- Specify strategies to overcome ethnic, racial, and socioeconomic disparities in the screening and diagnosis of patients with chronic liver disease

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Introduction

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This supplement to *The Journal of Family Practice*—"*The dawn of a new era: Transforming our domestic response to hepatitis B & C*"—is based on a multistakeholder health care summit convened September 10-11, 2009, in Washington, DC, to articulate the need for a coordinated national response to the epidemic of chronic viral hepatitis. Our understanding of chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections has improved in recent years. Safe and effective vaccines for HBV as well as effective antiviral therapies for HBV and HCV infections are now available. However, current approaches to the prevention and control of chronic HBV and HCV infections have fallen short, resulting in a major public health problem. The prevalence of chronic HBV and HCV infections is expected to increase in the United States, as is the burden of hepatitis-associated cirrhosis, end-stage liver disease, and liver cancer. The time to develop new strategies to prevent, screen, and treat chronic viral hepatitis is now.

While primary care providers are often on the front lines of efforts to identify and screen patients who are at risk for HBV and HCV infections, previous attempts to increase provider knowledge and awareness about viral hepatitis and provide adequate guidance on disease prevention, screening, referral, and patient care have been insufficient. A new approach to the viral hepatitis epidemic will require a coordinated national response supported by adequate resources, as well as the commitment and involvement of health care professionals, including primary care providers, academics, researchers, government agencies, community-based organizations, private industry, advocacy groups, and policy makers at the local, state, and national levels. The call for a coordinated national response is particularly timely, given the release of the landmark report by the Institute of Medicine, *Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C*, which found that health care providers, at-risk populations, and the general public lack knowledge and awareness about chronic viral hepatitis and that inadequate federal funding is impeding national and local prevention, control, and surveillance efforts.

This supplement reviews the changing epidemiology of viral hepatitis, risk factors for infection, the natural histories of HBV and HCV infection, and the potentially devastating toll of undetected and untreated chronic infection. It discusses current screening and treatment recommendations, available therapeutic agents, factors affecting treatment response, the development of new drugs, and the pressing need

to recognize and overcome racial, ethnic, and socioeconomic disparities in chronic liver disease diagnosis and treatment. It also highlights government, community-based, and private programs that work to increase access to care for at-risk and chronically infected people and develop new strategies to transform the current infrastructure for combating HBV and HCV infections. A coordinated national response will ultimately help health care providers reduce the prevalence of chronic HBV and HCV infections, ensure the efficient delivery of care, and improve treatment outcomes for people with chronic viral hepatitis. ■

The dawn of a new era: Transforming our domestic response to hepatitis B & C

Activity 1: Overview of the viral hepatitis problem

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Chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) is the leading cause of cirrhosis of the liver and hepatocellular carcinoma (HCC) in the world. It is estimated that 800,000 to 1.4 million Americans are chronically infected with HBV and 2.7 to 3.9 million Americans are chronically infected with HCV.[1,2] However, these figures are believed to underestimate the true burden of disease in the United States.

Usual estimates of the number of infected people in the United States come largely from the serosurveillance data of the National Health and Nutrition Examination Survey (NHANES) and include only the civilian population in the United States. The survey does not include a sufficient sample of Asians, Pacific Islanders, and Alaska Natives, all of whom have a higher prevalence of chronic HBV infection, compared with the general US population.[3] It also excludes homeless, incarcerated, and institutionalized individuals, all of whom have a higher prevalence of HCV infection.[4] A more realistic estimate is that about 2 million Americans are chronically infected with HBV and that as many as 5 million are chronically infected with HCV.[3,4] Many infected individuals are asymptomatic, and many—symptomatic or not—do not seek treatment.[5]

The increasing burden of chronic HBV and HCV infections

The incidence of acute HBV infection has declined by about 80% since 1990. This decline coincided with the stepwise implementation of a nationwide vaccine strategy to eliminate HBV transmission.[6] However, the decline in acute HBV infection has not translated into diminished prevalence or burden of chronic HBV infection. HBV infection is largely a disease of immigrants—the number of people with chronic HBV infection is actually *increasing* as a result of steady immigration from areas of the world where infection is endemic, such as Asia, Africa, and Eastern Europe.[7,8]

Similarly, the incidence of acute HCV infection declined by 90% among younger individuals during this same period,[6] although the prevalence of chronic HCV infection has not changed dramatically in the recent past. Chronic infection is most prevalent among those born between 1945 and 1964—the majority of whom were infected during the 1970s and 1980s—and among certain subgroups.[2,4,9,10] As the cohort of Americans with HCV infection grows older, more of those patients are expected to develop complications of chronic HCV infection. The main source of HCV infection is

TABLE 1 Mode of transmission of HBV and HCV infections[13,14]

	HBV		HCV
	Infancy and childhood	Adulthood	
Mode of transmission	• Perinatal - Birth to an infected mother • Household	• Sexual • Injection drug use • Health care - Contact with blood, open sores - Needle sticks - Sharing razors/toothbrushes - Hemodialysis - Residents/staff of facilities for developmentally disabled individuals	• Birth to an infected mother • Patients receiving chronic hemodialysis • Injection drug use • Sexual • Recipients of blood transfusions/blood products before 1992 • Individuals with HIV
Chronic infection	Approximately 90%	Approximately 5%	75%-80%
Vaccine	Effective >90%		Not available

HBV, hepatitis B virus; HCV, hepatitis C virus.
Centers for Disease Control and Prevention. http://www.cdc.gov/hepatitis/HBV/HBVfaq.htm. Accessed December 11, 2009.
Centers for Disease Control and Prevention. http://www.cdc.gov/hepatitis/HCV/HCVfaq.htm. Accessed October 14, 2009.

injection drug use (60%). Other known sources are sexual transmission and transfusion of blood or blood products prior to 1992 (10%).[11]

Complications of chronic viral hepatitis infection

Acute HBV or HCV infection can lead to acute liver failure in rare instances (<1%). However, a more significant problem is chronic infection, which can lead to cirrhosis in about 20% to 30% of individuals, and eventually to end-stage liver disease or HCC. Many individuals are unaware that they are infected until they develop signs or symptoms of cirrhosis or liver disease. Chronic HBV infection is responsible for 3000 deaths per year in the United States, and chronic HCV infection is responsible for 12,000 deaths per year.[1] Chronic infection can thus have dire consequences: debilitating symptoms, impaired quality of life, disability, costly health care expenditures, and death.

Only a small portion of adults infected with HBV develop chronic infection. However, approximately 90% of infants who acquire HBV infection and 25% to 50% of children aged 1 to 5 years who become infected develop chronic infection.[12,13] In the case of HCV, chronic infection occurs in 75% to 85% of infected individuals[14] (**TABLE 1**).

Immunization can prevent HBV infection. For those who are already infected, antiviral treatment can suppress HBV replication, but eradication of the virus remains an elusive goal. Although a vaccine is still lacking for HCV, modern treatments are becoming more effective. Many individuals infected with HBV and HCV are asymptomatic and unaware of their infection status.[5] These individuals will not be able to benefit from modern treatments unless they are diagnosed.

HCC: The consequence of greatest concern

The most serious health consequence of chronic HCV or HBV infection is HCC. Chronic viral hepatitis is considered the primary reason for the observed tripling of HCC incidence rates in the United States from 1975 through 2005.[15]

Additionally, chronic viral hepatitis has added to the burden of the liver transplantation system in the United States, which already faces serious challenges. Recently, the United Network for Organ Sharing reported that HCV is the major indication for liver transplantation in 35.9% of individuals on the waiting list, and HBV is the underlying cause for 4.2%.[16]

Current management of chronic HBV and HCV infection: Availability of good treatments does not equal improved outcomes

Major progress has been made in the treatment of chronic HBV and HCV infections. There are 7 approved

TABLE 2 Efficacy and effectiveness of HBV and HCV interventions[19]

Efficacy	Effectiveness
Utility of a medical treatment evaluated under optimal conditions	Utility of a medical treatment in routine clinical settings (ie, real life)
Highly selected patient population	Unselected patient population
Best-trained physicians	All physicians
Academic centers of excellence	Private practice • Comparative effectiveness

HBV, hepatitis B virus; HCV, hepatitis C virus.
El-Serag HB. Presented at: The Dawn of a New Era: Transforming Our Domestic Response to Hepatitis B & C; September 10-11, 2009; Washington, DC.

therapies for chronic HBV infection, including 5 well-tolerated oral medications. In HCV clinical trials, the combination of pegylated interferon and ribavirin has produced sustained virologic response rates of 50% to 60% in patients with HCV genotype 1,[17] and higher rates in those with HCV genotypes 2 and 3.[18] Enhancing the potential benefits of these approved therapies is crucial in the quest to improve the health of patients. However, the efficacy of such treatments has not translated into effectiveness in clinical practice.[19] *Efficacy* is defined as the extent to which a specific intervention produces a beneficial effect under ideal conditions, usually clinical trials, whereas *effectiveness* is the extent to which an intervention is beneficial when deployed in a community-based practice setting[19] (**TABLE 2**).

While efficacy is largely determined by the biological effects of therapy, effectiveness takes into account external factors, such as patient characteristics, health system features, and societal influences. For example, the response to current treatments—particularly for HCV infection—is variable, depending on patient demographics (eg, African Americans have poorer responses), comorbidities, and adherence to the treatment regimen. The rates of antiviral treatment of chronic HBV and HCV infection are generally low.[20] Increasing the efficacy of treatment alone will not improve the effectiveness of hepatitis treatment; improvements in access to care and referral for, and adherence to, treatment are also crucial.

Improving outcomes for HBV infection

For HBV infection, problems exist in translating efficacy observed in clinical trials to effectiveness in clinical practice. Although oral medications with minimal side effects are available, treatment must be given for long durations (years). Many patients lack access to care and experience language and cultural barriers. Underdiagnosis and undertreatment are common. These factors must be addressed in order to increase the effectiveness of available treatments.

Improving outcomes for HCV infection

The first step in improving outcomes in HCV-infected individuals is to have clinicians appreciate the need for HCV testing. For example, HCV testing is rarely initiated in primary care clinics based on clinician-identified risk factors.[21]

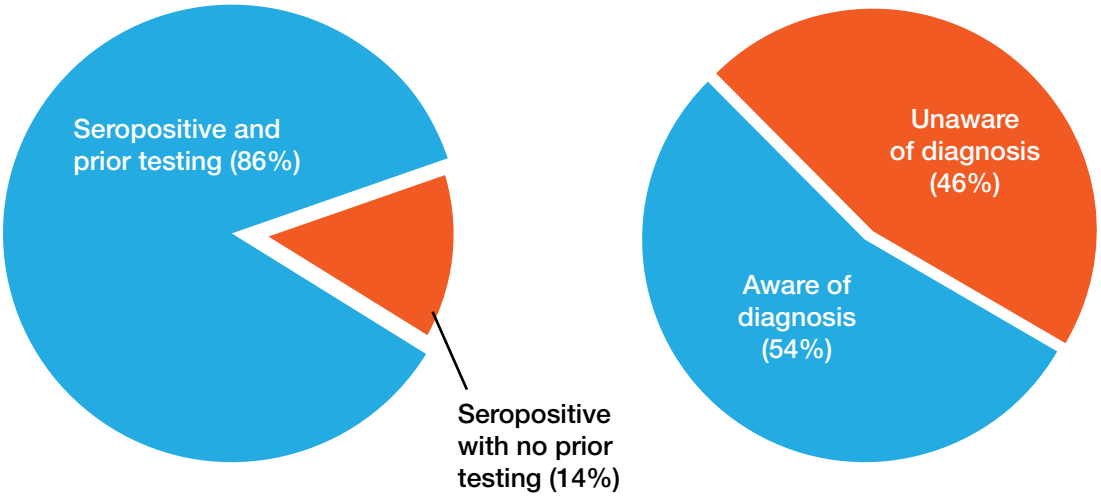
Even in populations with more equitable access to care (eg, veterans), studies have shown variations in patterns of health services/utilization. A study found that while 86% of seropositive veterans reported prior HCV testing, 46% of all seropositive veterans were unaware of their diagnosis (**FIGURE 1**).[10]

Another study involving veterans with chronic HCV infection found that only 30% to 40% of patients were deemed eligible for HCV infection treatment. Many were not considered suitable candidates due to ongoing substance abuse, comorbid medical disease, psychiatric illness, or advanced liver disease.[22]

Even when treatment is appropriate and feasible, a substantial proportion of patients do not complete therapy as a result of treatment intolerance, adverse events, or for other reasons. They may fear treatment or be in denial about their illness if they are asymptomatic. The treating clinician may lack experience, or there may be no team management for comorbidities. Legal and regulatory problems may also impede access to care (**FIGURE 2**).

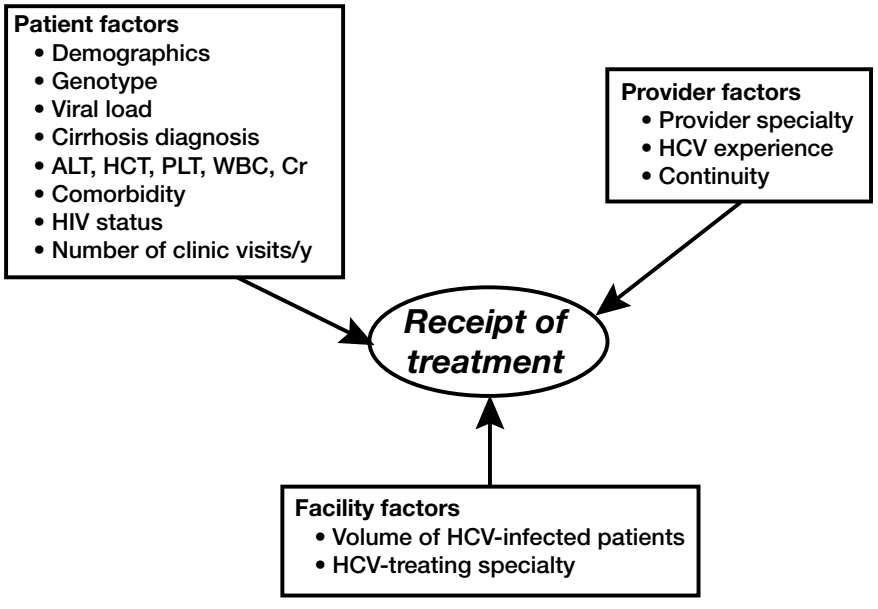
Racial, ethnic, socioeconomic, educational, and language differences can create barriers to access and to treatment success. However, if patients are optimally managed, studies suggest that HCV treatment effectiveness may be as favorable as that achieved in clinical trial populations.[23]

FIGURE 1 Estimated HCV patient status among the US veteran population



HCV, hepatitis C virus.
Adapted from Dominitz JA, et al. Hepatology. 2005;41:88-96.

FIGURE 2 Predictors of treatment outcome



ALT, alanine aminotransferase; Cr, creatinine; HCT, hematocrit; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PLT, platelet; WBC, white blood cell.
El-Serag HB. Presented at: The Dawn of a New Era: Transforming Our Domestic Response to Hepatitis B & C; September 10-11, 2009; Washington, DC.

HCC screening and impact on outcomes

The US Preventive Services Task Force, the National Comprehensive Cancer Network, and the American Cancer Society have not developed specific guidelines for HCC screening because of the lack of data from well-designed, randomized, controlled trials documenting the survival benefits of HCC surveillance. Nevertheless, one study has shown that surveillance for HCC leads to earlier

TABLE 3 HBV carriers at high risk who should be screened for HCC

Asian men ≥40 years of age
Asian women ≥50 years of age
Individuals with cirrhosis
Individuals with a family history of HCC
Africans >20 years of age
Any carrier >40 years of age with persistent or intermittent elevation of ALT levels and/or an HBV DNA level >2000 IU/mL

ALT, alanine aminotransferase; HBV, hepatitis B virus; HCC, hepatocellular carcinoma.
Adapted from Lok ASF, et al. Hepatology. 2007;45:507-539; Bruix J, et al. Hepatology. 2005;42:1208-1236.

diagnosis,[24] which is important because tumors are more amenable to curative treatment at an earlier stage of growth. One large randomized controlled trial in China demonstrated a survival benefit.[25] The American Association for the Study of Liver Diseases (AASLD) recommends an ultrasonography of the liver every 6 to 12 months for individuals deemed at high risk for developing HCC, and the monitoring of α-fetoprotein levels alone when ultrasonography is not available.[26] For HCV-infected patients, only those with cirrhosis have been shown to be at high risk for HCC, so screening may be offered. The AASLD and the Centers for Disease Control and Prevention guidelines for the management of patients with chronic HBV infection have identified HBV carriers who are at high risk and should be screened for HCC (**TABLE 3**).[27,28]

A recent study suggests that HCC screening is an uncommon practice.[29] There are also differences in terms of which patients are offered potentially curative therapy for HCC. One study suggested that "geography is destiny"—the region of the United States where health care was delivered was the greatest predictor of potentially curative treatment for HCC. Geographic variations in the extent of therapy persisted after adjusting for demographic, clinical, and tumor-related variables.[30]

Transforming our response

The early identification of HBV- and HCV-infected individuals and the prevention and treatment of chronic disease are critical for stemming later complications. Primary care providers are in a unique position to help meet this challenge, both to screen individuals at risk and to monitor those who are chronically infected so that appropriate treatment can be initiated. The primary care provider can also help patients adhere to and complete treatment. Based on the estimate of up to 7 million Americans with chronic HBV or HCV infection (which includes those individuals not counted in the NHANES studies), many patients seen in primary care settings may have viral hepatitis that requires monitoring or treatment.

Therefore, there is a need for greater awareness among primary care providers as to which subsets of their patient populations are at most risk for, or may already be infected with, HBV or HCV. Screening and treatment guidelines need to be made more user-friendly for primary care providers and other professionals. Furthermore, all health care providers should be aware of, and sensitive to, the ethnic, racial, and socioeconomic disparities that are associated with chronic HBV and HCV infections and chronic liver disease.

Management of chronic HBV and HCV infection requires a multidisciplinary approach that begins with the screening of high-risk patients. To prevent the dire consequences of liver failure and HCC, screening should be followed by the involvement of hepatologists or gastroenterologists and, when necessary, pathologists, liver transplantation programs, rehabilitation programs, and psychiatric and social services to evaluate patients and monitor their health and to treat those likely to develop progressive liver disease.

To meet these challenges, there is a need for a coordinated national response to address the issues of prevention, screening, treatment, and access to care. This response must start by raising awareness not only among health care providers and other professionals, but also among at-risk populations, the general public, and policy makers. Adequate resources must be allocated to support prevention and treatment programs, enhance patient access to treatment, encourage full utilization of available therapies, and evaluate and integrate new approaches to effective care. ■

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The dawn of a new era: Transforming our domestic response to hepatitis B & C

Activity 2: Understanding the natural history of chronic HBV and HCV infections

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The natural history of hepatitis viral infection refers to the clinical outcomes for individuals with persistent infection who do not receive antiviral treatment. Some individuals infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) will spontaneously control the initial infection, typically in the first year. Those who continue to have evidence of viral replication in the form of detectable levels of hepatitis B surface antigen (HBsAg) or HCV RNA for 6 or more months are considered to have chronic infection and are at risk for cirrhosis and liver cancer. Knowing whether a patient is at risk for these clinical outcomes determines the urgency of treatment.

Natural history of chronic HBV infection

HBV is transmitted by percutaneous or permucosal exposure to infectious blood or body fluids. HBV is approximately 100 times more infectious than human immunodeficiency virus (HIV) and 10 times more infectious than HCV.[1,2] Acute HBV infection develops in approximately 30% to 50% of adults at the time of initial infection and is characterized by anorexia, nausea, vomiting, and jaundice. The risk of progression varies with age, with the highest rate occurring among infants and young children (25%-90%) and lowest rate occurring among adolescents and adults (<5%). The majority of individuals with chronic HBV infection are asymptomatic, and one-third have no evidence of liver disease. The remainder have chronic hepatitis that can lead to cirrhosis and hepatocellular carcinoma (HCC). Rates of progression to cirrhosis and/or HCC vary according to a number of host, viral, and environmental factors.

The clinical course of chronic HBV infection has several phases that are defined by patterns of HBV DNA levels, biomarkers, and liver enzyme concentrations. The 3 main phases of chronic HBV infection are: immune tolerant, immune active, and inactive.[3] Some experts also include a resolution and a reactivation phase (**TABLE 1**).[4] All of the phases are marked by the continued presence of HBsAg, except for the resolution phase.[3,4]

The natural history of chronic HBV infection depends on when infection first occurred (**FIGURE 1**). Individuals infected as infants (typically from maternal-fetal transmission) nearly always develop chronic infection. The immune tolerant phase is usually clinically silent for years or even decades. Viral replication is active in this phase because HBsAg and high levels of HBV DNA are detectable in the blood. However, liver enzymes such as alanine aminotransferase (ALT) and aspartate aminotransferase are often

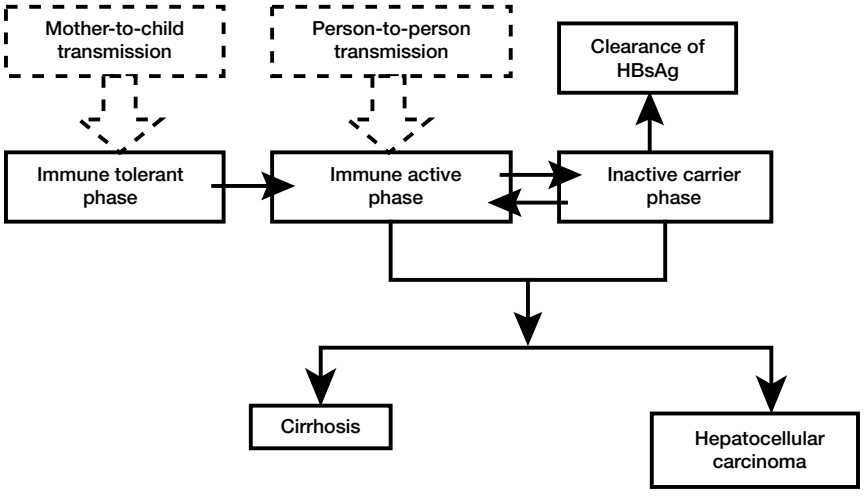
TABLE 1 Phases of chronic HBV infection

Phase	ALT levels	Liver histology	HBV DNA/HBeAg levels
Immune tolerant phase[a]	Normal or minimally elevated	Active or inactive minimal inflammation or fibrosis	• >20,000 IU/mL, HBeAg+
Immune active phase[a]	Elevated	Active: Liver biopsy shows chronic hepatitis	• >20,000 IU/mL while HBeAg+ • >2000 IU/mL after loss of HBeAg and development of antibody to HBeAg
Inactive phase[a]	Persistently normal	Inactive: Liver biopsy shows variable, usually minimal fibrosis	• <2000 IU/mL, HBeAg–
Resolution[b]	Normal	Inactive: Scant fibrosis	• No detectable serum HBV DNA (low levels might be detectable in the liver) • HBeAg– and HBsAg–
Reactivation phase[b]	Elevated, often fluctuating levels	Active: Liver biopsy showing variable amounts of fibrosis	• Moderate, often fluctuating levels >2000 IU/mL

ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

[a]McMahon BJ, et al. Hepatology. 2009;49(5 suppl):S45-S55.
[b]Keeffe EB, et al. Clin Gastroenterol Hepatol. 2008;6:1315-1341.

FIGURE 1 Natural history of chronic HBV infection



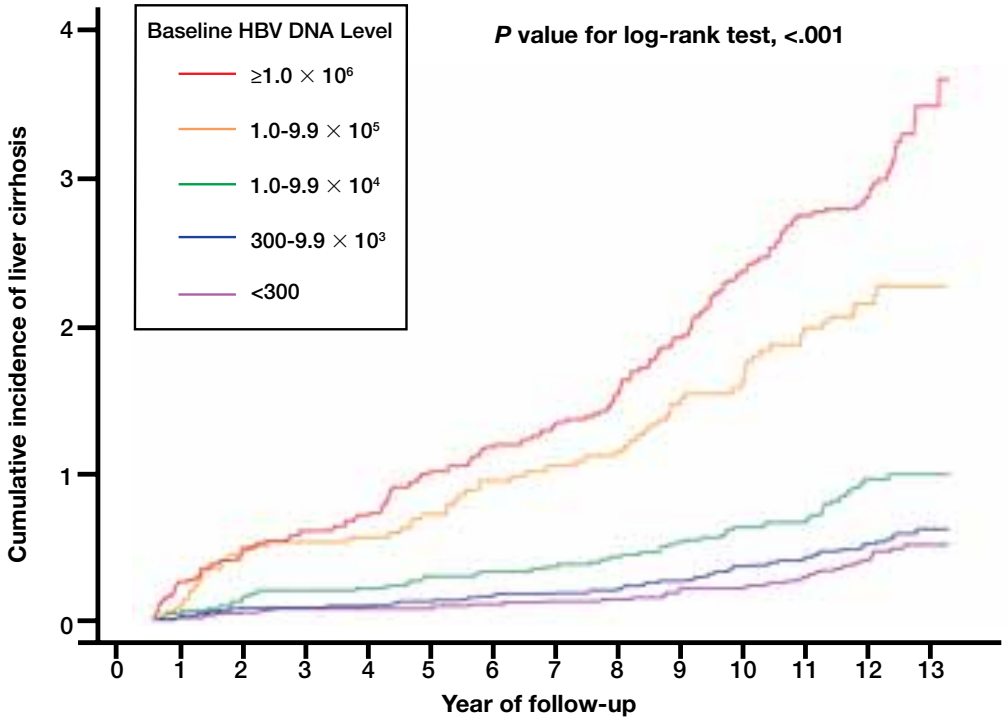
HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

Sorrell MF, et al. Ann Intern Med. 2009;150:104-110. © 2009 by American College of Physicians—Journals. Reproduced with permission.

not elevated, most likely because there is little cellular immunity attempting to clear the infection. This immune tolerant phase eventually progresses to an immune active phase, heralded by evidence of liver inflammation and elevations in liver enzymes.[5]

HBV infection takes a substantially different course in individuals infected for the first time as adults. Most individuals who acquire HBV infection as adults sponta-

FIGURE 2 Cumulative incidence of liver cirrhosis



HBV, hepatitis B virus.

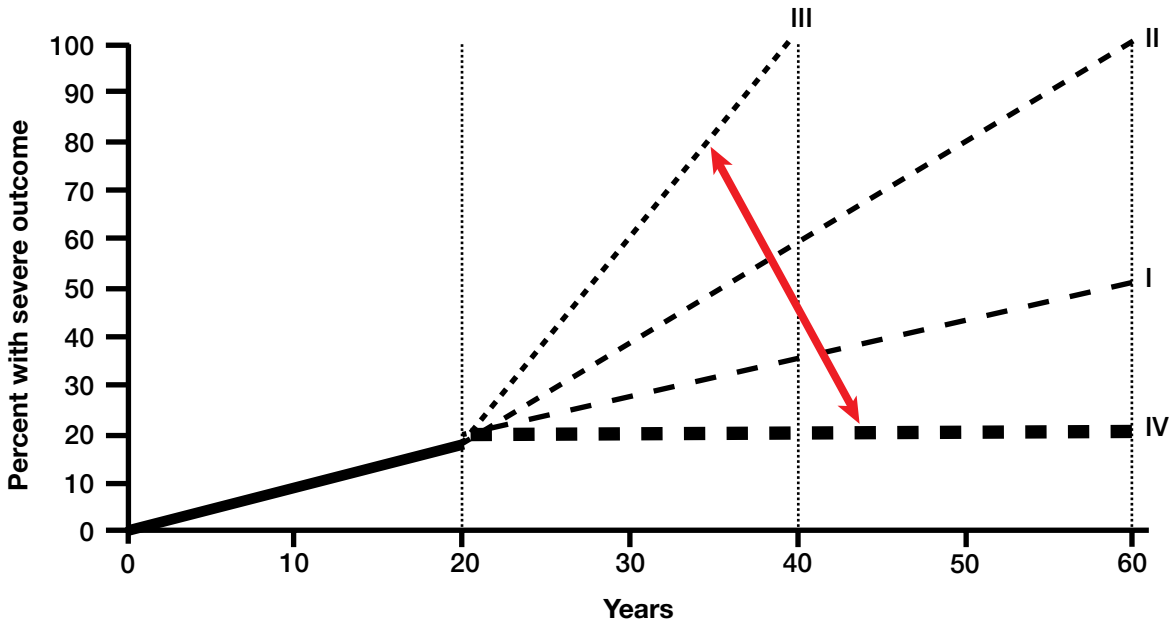
neously clear it.[5,6] In those who progress to chronic HBV infection, the initial phase is typically immune active; the liver is injured by inflammation (necroinflammation) and develops scarring that can progress to cirrhosis.

Hepatitis B e antigen (HBeAg) status has been used to classify the natural history of infection. HBeAg is detected in the immune active phase and, accordingly, has been used as a correlate of high replication and infectivity. If HBeAg is spontaneously cleared, an antibody to HBeAg (anti-HBe) can be detected. This event corresponds with a lower HBV DNA level and lower risk of HCC and cirrhosis. However, transitions occur between these phases, and while about three-fourths of HBeAg–positive adults will seroconvert (ie, become HBeAg-negative and anti-HBe–positive), a proportion will revert to HBeAg-positive status.[7,8]

In the natural course of HBV infection, transitions occur between phases.[5] Individuals in the immune active phase often clear much of the infection and move to the inactive phase. In the latter phase, liver enzymes are normal and HBV DNA levels are less than 2000 IU/mL, but HBsAg remains detectable. Individuals can then either revert to a clinically (and immunologically) active phase while they remain HBeAg-negative or clear HBsAg from their blood completely. When complete HBsAg clearance occurs, the infection will remain controlled or dormant unless it is reactivated by immunosuppression from other diseases or use of drugs such as rituximab or cancer chemotherapy.[3,5,9]

The majority of liver damage occurs during the immune active phase, and the longer an individual remains in this phase, the greater the risk of developing cirrhosis or HCC. Certain factors appear to influence the risk of developing cirrhosis, including older age, presence of HBeAg, HBV genotype C, excessive alcohol consumption, and coinfection with HIV, HCV, or hepatitis D virus.[5,10] Elevated HBV DNA levels have also been identified as a risk factor for the development of cirrhosis.[3,11]

FIGURE 3 Projected outcomes in chronic HCV infection[a]



[a]Curve I: Observed outcomes at 20 years will continue on the same trajectory over ensuing decades.

Curves II and III: Assume acceleration of fibrosis; thus, every HCV-infected individual would develop a severe outcome if he or she does not die of another illness in the 40 to 60 years from the onset of infection.

Curve IV: Individuals who have not progressed in 20 years will not suffer deleterious outcomes.

HCV, hepatitis C virus.

Alter HJ, Seeff L. Recovery, persistence and sequelae in HCV infection: a perspective on long-term outcome. Semin Liver Dis. 2000;20:17-35. Reprinted with permission.

Chronic HBV infection can progress to HCC. Risk factors include male gender, older age, family history of HCC, alcohol consumption, HBV genotype C, seropositivity for HBsAg, seropositivity for HBeAg, presence of cirrhosis, and high serum HBV DNA levels.[3,12] In the large, prospective Risk Evaluation Viral Load Elevation and Associated Liver Disease (REVEAL) study, an elevated serum HBV DNA level (≥10,000 copies/mL) was a strong risk predictor of HCC, independent of HBeAg status, ALT level, and liver cirrhosis.[12] Investigators found that for all participants, the adjusted hazard ratio (HR) of developing HCC was 1.1 for those with serum HBV DNA levels of 300 to 9999 copies/mL (P=.86) and 6.1 for those with HBV DNA levels ≥1 million copies/mL (P<.001). Risk began to increase significantly at HBV DNA levels of 10,000 to 99,999 copies/mL (HR, 2.3; P=.02) relative to patients with HBV DNA levels <300 copies/mL.[12] In an analysis of the REVEAL cohort involving 3582 patients, the development of cirrhosis was highly dependent on baseline HBV DNA levels, increasing from 4.5% among patients with HBV DNA levels <300 copies/mL to 36% among those with ≥1 million copies/mL (**FIGURE 2**).[11]

Natural history of chronic HCV infection

Since Dr Harvey Alter first characterized HCV, its natural history has been controversial owing to the great heterogeneity of this virus and the many cofactors that can influence its course and progression.[13] Our understanding of the natural history of HCV infection is still evolving.

The natural history of HCV infection involves 2 major clinical transitions: spontaneous resolution vs viral persistence and asymptomatic viral persistence vs cirrhosis. Spontaneous resolution is highly variable and occurs in approximately 10% to 60% of individuals, typically in the first 6 to 12 months of infection. This occurs more frequently in women than in men, and more frequently in

whites than in African Americans.[13,14] Chronic infection develops in 75% to 85% of individuals infected as older adults (>45 years) and 50% to 60% of those infected as adolescents or younger adults.[1,15] The majority of individuals with chronic HCV infection are asymptomatic, and approximately 30% have no evidence of liver disease. The risk for progression to cirrhosis also varies by age at infection, from 10% to 20% after 20 years of infection among those infected as older adults to <5% among individuals infected as adolescents or younger adults.[1] In addition, those without HBV infection, HIV infection, other forms of immunosuppression, or excess alcohol consumption are more likely to recover from acute HCV infection than are those who are immunocompromised or those who abuse alcohol. Complete recovery also occurs more often in individuals with particular polymorphisms in human leukocyte antigen genes and genes involved in interferon lambda production.[16,17]

The best way to determine if an individual has chronic vs resolved HCV infection is to test for both HCV-specific antibodies and for HCV RNA.[18] Individuals with spontaneous resolution of HCV infection have only HCV antibodies in their blood, while those with chronic HCV have both HCV antibodies and viral RNA. Repeated detection of HCV RNA at 6-month intervals provides strong evidence of chronic HCV infection.

Individuals who do not achieve spontaneous recovery develop chronic infection. During the first few decades after becoming infected, the majority of individuals lack clinical manifestations of HCV infection. However, some will undergo the transition to liver failure or HCC. In a recent Markov simulation of chronic HCV infection, progression from cirrhosis to HCC occurred in approximately 18% of patients after 20 years of exposure.[19] An earlier study found a slightly lower risk, with 7% of patients progressing to HCC in 5 years and 18% experiencing decompensation (ie, liver failure).[20]

Progression is neither linear nor inevitable; in the initial 2 to 3 decades postexposure, 80% of HCV-infected patients will be asymptomatic and suffer no complications. Various projected long-term outcomes are shown in **FIGURE 3**. In the absence of treatment, the natural history of HCV infection may lie between curves I and IV. In other words, about 30% of patients will experience a severe outcome after 60 years of infection.[15]

Complications of chronic HCV infection

Laboratory clues that cirrhosis is advancing (rather than compensated) are a low serum albumin concentration, low blood platelet count, high serum creatinine level, and high total bilirubin level. These laboratory and clinical findings are used in various systems (such as the Model for End-Stage Liver Disease and Child-Pugh score) to stage cirrhosis and anticipate the need for liver transplantation.

In addition to laboratory findings, there are confounding factors that influence the rate at which chronic HCV infection progresses to cirrhosis and liver failure. The course of chronic HCV infection has been shown to be influenced by age at infection, gender, and coinfection. Rapid progression of liver fibrosis has occurred in individuals who are coinfected with HBV or HIV.[21] In one study of people with chronic HCV infection, cirrhosis developed in 37% of HIV-positive individuals after 20 years and in 69% after 25 years, compared with 10% in HIV-negative individuals at either time point.[22] Excessive alcohol intake (>60 g/d for men and >40 g/d for women) has been associated with a 2- to 3-fold greater risk of cirrhosis and decompensated liver disease and more rapid development of cirrhosis, with 58% of excessive drinkers becoming cirrhotic by the second decade vs 10% of nondrinkers.[23] Evidence suggests that nonalcoholic steatohepatitis (NASH), a severe form of fatty liver disease, may impact the disease course as well. Fibrosis was seen at a median duration of infection of 23 years in 54% of HCV-positive patients with NASH, in 32% with steatosis (fat only, with no associated inflammation), and in 16% with chronic HCV alone.[24] Males also appear to be at increased risk for fibrosis.

In individuals with chronic HCV infection, HCC rarely occurs unless there is significant liver fibrosis, defined as either cirrhosis or bridging fibrosis. The factors associated with the development of HCC in this population are essentially the same as those associated with the development of cirrhosis. Unlike chronic HBV infection, there does not appear to be a strong association between the HCV RNA level and the development of cirrhosis or HCC. ■

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The dawn of a new era: Transforming our domestic response to hepatitis B & C

Activity 3: Transforming strategies for the prevention of chronic HBV and HCV infections

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DISCLOSURES

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Hepatitis B virus (HBV) infection is a global burden. According to the World Health Organization's 2008 update, approximately 2 billion people worldwide have been infected with the virus; 350 million are living with chronic infection; and at least 600,000 die each year from active disease or its complications.[1] The statistics for hepatitis C virus (HCV) infection are equally somber, with an estimated 170 million people believed to be infected worldwide.[2] In the United States, strategies for the prevention and treatment of these infections need to be advanced and implemented on a national level, as the consequences of disease progression remain serious.

HBV infection

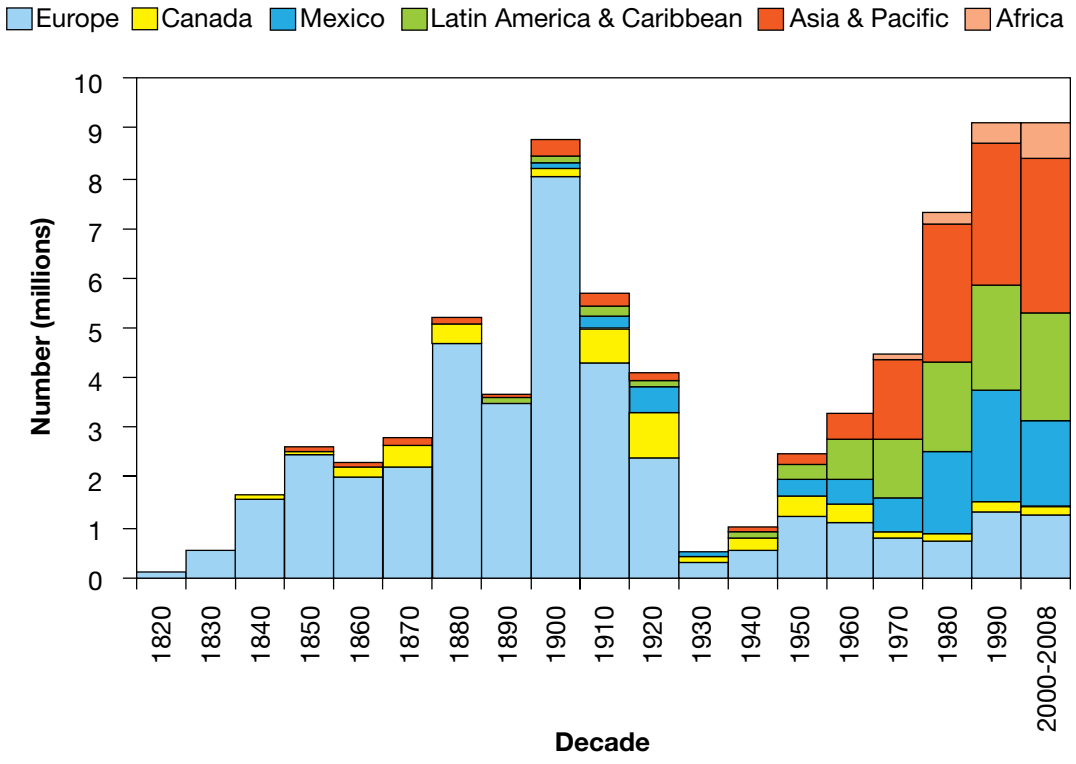
The global burden of HBV infection has critical implications for the United States, as immigration from moderately and highly endemic regions is increasing. From 2000 to 2007, a total of 6.2 million legal permanent residents entered the United States.[3] Immigration from endemic areas, particularly Asia, the Pacific Islands, and sub-Saharan Africa, has increased dramatically since the 1960s (**FIGURE 1**).[4] A recent study based on US Census Bureau data suggests that the number of foreign-born individuals living with chronic HBV infection in the United States may be higher than previously thought, ranging from 850,000 to 2.2 million, with >50% from Asia, 13% to 15% from Africa, and 9% to 18% from Central America. Corresponding HBV prevalence rates for foreign-born individuals range from 4.8% to 10.6% among Asians, 7.8% to 16.8% among Africans, and 0.4% to 2.5% among Central Americans.[5]

Owing to an effective national immunization program in the United States, the majority (47%-70%) of people with chronic HBV infection are now foreign-born.[6] Since most HBV transmission occurs at birth or in early childhood, immigrants from endemic regions tend to arrive in the United States already chronically infected.

Prevention strategies for HBV infection

Since 1991, the prevention framework of the Centers for Disease Control and Prevention (CDC) has resulted in an overall reduction in the incidence of acute HBV infection by approximately 80% due to widespread vaccination. Among children younger than 15 years of age, incidence has decreased by 98%, from 1.2 cases per 100,000 people in 1990 to .02 cases per 100,000 people in 2007.[7]

FIGURE 1 Immigration patterns



Adapted from data in 2008 Yearbook of Immigration Statistics. Washington, DC: Office of Immigration Statistics; 2009.

Nevertheless, the immigration of people already infected with HBV adds to the burden of disease in the United States. Global vaccine programs are expanding, but these programs are new and coverage is variable. Therefore, more emphasis needs to be placed on referring chronically infected individuals for care and treatment and screening people born in endemic regions. Those at risk (ie, men who have sex with men [MSM] and injection drug users [IDUs]) for chronic HBV infection should also be screened.[6] Implementation of screening will require educating health care providers (including primary care physicians) and the public—especially those individuals at highest risk for infection—about HBV infection. To ensure the success of this approach, particularly within immigrant populations, barriers to effective care must be addressed, including differences in culture and customs, language, and access to health care.

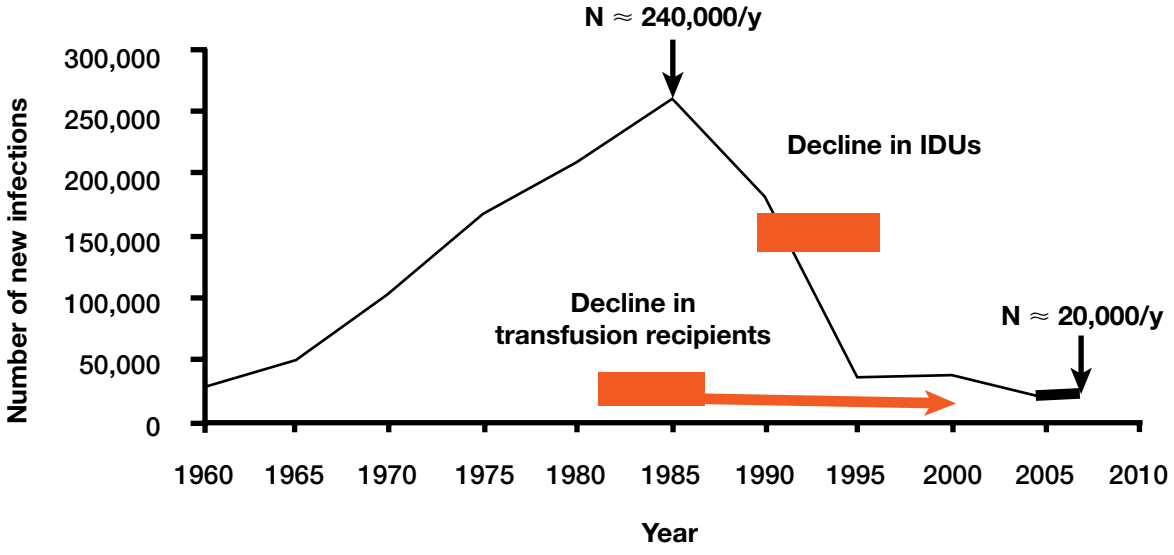
HCV infection

The number of people in the United States chronically infected with HCV is estimated to be approximately 5 million. This includes 3.2 million (95% confidence interval [CI], 2.7-3.9) in the noninstitutionalized civilian population and 634,000 to 1.2 million incarcerated or homeless individuals.[8-10]

In the noninstitutionalized civilian population, HCV infection is most prevalent among those born between 1945 and 1964.[9] HCV prevalence is high among certain subgroups, especially non-Hispanic black males aged 40 to 49 years (13.6%) and Mexican American males aged 50 to 59 years (10%).[9] The prevalence of HCV infection is also high among human immunodeficiency virus (HIV)–infected people.[11] In the US Veterans Affairs hospital population, the HCV prevalence is 5.4% overall, but is much higher among Vietnam-era veterans (11.0%) and among those with annual household incomes below $10,000 (17.1%).[12]

The strongest predictors for HCV infection are high-risk exposures that are well recognized: injection drug use; blood or blood product transfusion; organ or tissue transplantation from HCV-infected donors; occupational and other blood exposure in health care settings; birth to an

FIGURE 2 Estimated incidence of acute HCV infection, United States, 1960-2007



HCV, hepatitis C virus; IDUs, injection drug users.

Adapted from data in Armstrong GL, et al. Hepatology. 2000;31:777-782; Alter MJ, et al. Hepatology. 1997;26:62S-65S.

infected mother; sex with an infected partner; and having multiple sex partners.

Injection drug use poses the highest risk

Injection drug use is the primary mode of transmission of HCV, accounting for approximately 50% of reported cases of acute infection in the United States.[7] In one study, syringe sharing was associated with a 3-fold higher risk of HCV infection, as was sharing drug preparation equipment (ie, cookers or cotton).[13]

Even rare or sporadic injection drug use significantly increases the risk for HCV infection. In one study, the prevalence of HCV among college and university students who reported daily, regular, or sporadic drug use was 29% compared with 9% among those who reported injecting drugs once or twice. In contrast, only 0.5% of those who reported no history of injection drug use were HCV-positive.[14] Among those with a history of injecting drugs for at least 5 years, HCV prevalence reaches nearly 90%.[9] The magnitude of injection drug use related to HCV infection is of great concern because approximately 3.4 million Americans, or 1.5% of the population, report having ever injected drugs. The highest reported frequency of injection drug use is among individuals aged 35 to 59 years, which is also the cohort with the highest prevalence of HCV.

Recent studies suggest that the incidence of HCV infection is declining among IDUs in some areas. An analysis of 4 studies of Seattle-area IDUs found that the prevalence of HCV infection among individuals aged 18 to 30 years dropped from 68% to 32% between 1994 and 2004. There were also increases in self-reported needle exchange, condom use, and HBV vaccination.[15]

A San Francisco study found that young IDUs who stopped injecting during the study effectively eliminated their risk for HCV infection. Those who continued to inject were most at risk for HCV infection when they borrowed needles from an HCV-infected person (sex partner or other), pooled money to buy drugs (which indicated they were in injecting partnerships), or exchanged sex for money.[16] A prospective study from Vancouver found seroconversion among IDUs aged 24 years and younger to be associated with obtaining help to inject drugs, twice daily injection of cocaine, and sex trade work.[17] Young or recent users represent an important subgroup to target for harm reduction methods that aim to prevent infection.

TABLE Selected Medicare quality indicators

If:	Then:
Positive HCV antibody test	• RNA test
Any positive HCV test	• Hepatitis A vaccination • Hepatitis B vaccination
Positive RNA test	• Antiviral treatment
HCV treatment	• Genotype test pretreatment • Viral load test pretreatment • Viral load test at week 12

HCV, hepatitis C virus.

Kanwal F, et al. Hepatology. 2008;48:358A.

Emerging HCV transmission patterns

Health care–associated HCV infections occur in the settings of chronic hemodialysis, surgery, endoscopy, inpatient wards, and pain management or oncology clinics. A review published in 2009 reported 33 outbreaks in nonhospital health care settings over the past decade, including outpatient clinics, hemodialysis centers, and long-term care facilities, with 448 people acquiring HCV or HBV infections. In each setting, the putative mechanism was patient-to-patient transmission through failure of health care personnel to adhere to fundamental principles of infection control.[18] Transmission of HCV has also occurred in abdominal organ transplantation centers.[19]

Clusters of transmission among HIV-positive MSM have recently been reported in the United States, Western Europe, and Australia. These are associated with unsafe sex between people who deny being IDUs. Approximately 5% of acute HCV infections in the United States occur among MSM; half of these individuals also report being IDUs. The overall prevalence in this subgroup has not increased and remains no higher than the prevalence among heterosexual men, indicating that newly acquired HCV infections are not yet widespread in this population. Regardless, the potential emergence of HCV infection among HIV-infected MSM warrants careful monitoring and further investigation.

Advances and challenges in preventing and treating HCV infection

Great strides have been made in the past 2 decades in the prevention and treatment of acute HCV infections (**FIGURE 2**). Transfusion-associated infections have been virtually eliminated. There has been a dramatic reduction in infections associated with IDUs owing in part to education about unsafe injection practices and the establishment of needle exchange programs in some cities. Moreover, therapies for chronic HCV have improved greatly, and promising compounds are currently in development. The incidence of HCV infection, however, continues to be high among new IDUs. Among young IDUs, the annual observed incidence of HCV infection is 33.4% (95% CI, 28.0-39.9).[20]

Screening for HCV

The current recommendations for identifying HCV infection call for routine testing of those at highest risk (see Activity 4, page S29). While some health care professionals advocate for more widespread screening of the general population, others suggest that to optimize the available resources, screening should be narrowed to target those most likely to be infected. Most HCV-positive individuals can be identified by the presence of 2 or 3 major characteristics, such as having a history of injection drug use, receiving a blood transfusion before 1992, and having abnormal alanine aminotransferase levels,[9,21] assuming that such histories are ascertained or available.

Ensuring that patients receive quality care

For the management of both HBV and HCV infections, quality measurements need to be instituted and attained. Where possible, areas of improvement should be identi-

Panel discussion

Chris Taylor: What actions do you consider most important for us as a society, and as clinicians and frontline providers, to prevent new hepatitis C virus (HCV) infections?

Corinna Dan: We need to do a better job of identifying risk factors in the community. There are missed opportunities to initiate programs that will put prevention in the forefront within our community health centers.

Martha Saly: We need a stronger political will to prevent viral hepatitis, and we need a national strategy that is supported by the federal government. We also need to encourage individuals who self-identify with risk factors to test for the disease.

Lorren Sandt: The federal ban on syringe exchange should be lifted.

Tracy Swan: Syringe exchange is crucial. Let's make it very simple for injection drug users to reduce their HCV risk. We need vending machines, and pharmacy sales to make it simple. We're also seeing outbreaks of sexually transmitted HCV among human immunodeficiency virus (HIV)-positive men who have sex with men. We need to highlight these new outbreaks and provide information on risk reduction.

Joan M. Block: We should adopt a policy of zero tolerance against hepatitis B virus (HBV). The problem is, many people are unwilling to admit risk factors or are unclear about what they are. We need to expand the current immunization guidelines to encourage all adults to be vaccinated. HBV screening should become a part of routine care independent of perceived risk. Finally, we should test and vaccinate the family and social contacts of infected people.

Denton Chase: We need to encourage a national policy and to construct a national awareness campaign.

Chris Taylor: How can we slow the progression of disease in chronically infected persons whose acute infection was not diagnosed and managed?

Corinna Dan: Only 1 in 4 people with HCV and 1 in 2 with HBV have been diagnosed, so most of those infected are at risk for complications. We need to train providers in primary care settings and community health centers to test for HBV and HCV, and to deliver the messages about these diseases.

Martha Saly: Every community center has participated in quality-improvement collaboratives for diabetes, hypertension, even HIV. Why not for viral hepatitis? We need to advocate for the expansion of Medicare to cover all underinsured persons who cannot afford to get the care they need for HBV and HCV.

Joan M. Block: The key to preventing disease progression is to improve access to care.

Denton Chase: Many patients already in our system have tested positive and have since been lost or are not being followed. If we can demonstrate success in truly managing our already diagnosed chronic patients over time, it will ensure that we can better serve all of the newly diagnosed patients that our other efforts are geared towards.

Tracy Swan: For HCV, encourage treatment and drug development. There is an incredibly robust drug pipeline right now for HCV. With new drugs the paradigm will shift. What is less likely to shift is the difficulty in getting treatment for certain groups of patients (eg, HCV-infected persons with comorbidities and individuals still actively using drugs). We must address the psychosocial issues that make treatment difficult and develop a good infrastructure to allow delivery of care. Community-based organizations and peer support that is cost-effective can make this happen.

Chris Taylor: How do we take action on the things we have learned at this forum? How do you see the future of advocacy and policy implementation?

Tracy Swan: While we scale up access to care and treatment, we should not ignore the need to advocate for a more coordinated research agenda for both HBV and HCV.

Denton Chase: Industry and the community should come together to put the resources and money behind the things we all agree can start to make a difference, such as a national awareness campaign on liver cancer.

Joan M. Block: We need to appoint spokespeople. Let's foster relationships with "congressional champions" who understand the problem and are working to find the funds for the Centers for Disease Control and Prevention and other federal agencies to address this problem.

Corinna Dan: We need to rethink how we address hepatitis by calling our legislators and directing them to the National Viral Hepatitis Roundtable Web site, where they can access policy materials. Our representatives need to hear that people in their districts are dying.

DISCLAIMER

The opinions expressed in the panel discussion are those of the participants. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

fied and factors modified to improve the level of care. Interventions should be developed that take advantage of medical registries, quality improvement collaboratives, clinical reminders, templates, and other measures. Moreover, primary care providers should be trained not only to identify risk factors and screen patients appropriately, but also to effectively treat these infections.

Use of quality indicators

The US Department of Health and Human Services Centers for Medicare and Medicaid Services has identified chronic HCV infection as one of the priority areas for quality measurement. HCV-specific quality indicators (QIs) include confirmation of HCV viremia, hepatitis A and HBV vaccinations, alcohol use counseling, genotype and viral load testing before treatment, antiviral treatment, viral load testing at treatment week 12, and contraception counseling (**TABLE**).[22]

Several studies have found significant variations in QI scores across different measurements in various settings and among various patient populations. Quality improvement collaboratives involving multiple practices and hospitals should lead to better QI scores and improved patient care. The focus on quality measurement, coordination of care, and assessment of results should also be included in the training of gastroenterologists and hepatologists. ■

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The dawn of a new era: Transforming our domestic response to hepatitis B & C

Activity 4: Recommendations for prevention, screening, and diagnosis of HBV and HCV infections

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Dr Dienstag reports the following: Consultant: Abbott Molecular, Boehringer Ingelheim, Bristol-Myers Squibb, Genzyme, Human Genome Sciences, Medtronic, Schering-Plough Research Institute. Grant/Research Support: NIDDK, Vertex. Ownership Interest: Options: Achillion, Metabasis, Nucleonics

Dr Liang and Dr So have no real or apparent conflicts of interest to report.

Early identification of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections enables clinicians to initiate appropriate care in order to prevent or delay the consequences of these infections. Primary care providers often lack specific guidance on the screening and management of viral hepatitis. The Centers for Disease Control and Prevention (CDC) and medical societies have an important role to play in formulating and disseminating up-to-date and accurate guidance for clinicians on the prevention, identification, and control of viral hepatitis.

CDC testing and public health management: Recommendations for HBV infection

The CDC released comprehensive HBV testing recommendations in 2008 to address the expanding need to identify and treat individuals with chronic HBV infection.[1] As the incidence of acute HBV infection has decreased, the interest in identifying chronically infected individuals has grown. Furthermore, improved treatments for chronic HBV infection are now available, and these increase the value of testing for infection.[2] The CDC based the screening recommendations on the prevalence of HBV infection in certain subgroups.[2] As shown in **TABLE 1**, chronic HBV infection is relatively uncommon in the general population, but occurs at a higher frequency in those with risk factors for transmission.[1]

The 2008 CDC recommendations for identification of chronic HBV infection are summarized in **TABLE 2**.[1,3]

Recommended laboratory tests for chronic HBV infection in different patient populations, such as foreign-born individuals or pregnant women, are shown in **TABLE 3**.[4]

Positive identification of chronic HBV infection also requires a public health response. Household contact, needle-sharing, and sexual partners of hepatitis B surface antigen (HBsAg)–positive patients should be identified, tested, vaccinated, and referred for medical care as needed.[1] Clinicians should educate their HBsAg-positive patients about the disease, including how to prevent transmission to others and how to manage their own long-term health. Education must be culturally sensitive and accompanied by additional counseling when necessary. Evaluation of all patients by a clinician experienced in management of chronic liver disease is necessary to prevent or manage the serious liver complica-

TABLE 1 Estimated prevalence of HBV by subgroup[a]

	Chronic HBV infection[b] (%)	Ever infected with HBV[c] (%)
General population	0.3	4.8
Subgroup		
HIV-positive people	4-17	24-76
IDUs	3-6	20-70
MSM	1-3	10-40
Sexual contacts of HBsAg+ people	3.5-9	25-59
Household contacts of people with chronic HBV infection	3-20	15-60

HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HIV, human immunodeficiency virus; IDUs, injection drug users; MSM, men who have sex with men.
[a]Derived from data for 1999-2002.
[b]HBsAg-positive.
[c]Antibody to hepatitis B core antigen–positive; includes people with resolved and chronic infections.
Weinbaum CM, et al. MMWR Recomm Rep. 2008;57:(RR-8):12.

TABLE 2 Recommended populations for screening for chronic HBV

CDC recommendations for hepatitis B screening before 2008:
• All pregnant women
• Infants born to HBsAg+ mothers
• Household contacts and sex partners of HBV-infected persons
• People born in countries with HBsAg prevalence of >8%[a]
• People who are the source of blood or body fluid exposures that might warrant postexposure prophylaxis (eg, needle stick injury to a health care worker or sexual assault)
• People infected with HIV
• Hemodialysis patients
Expansion of CDC recommendations in 2008:
• People born in geographic regions with HBsAg prevalence of ≥2%[b]
• People not vaccinated as infants whose parents were born in regions with high HBsAg prevalence
• People with behavioral exposures to HBV (IDU, MSM)
• People needing immunosuppressive therapy
• People with elevated ALT/AST of unknown etiology

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CDC, Centers for Disease Control and Prevention; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HIV, human immunodeficiency virus; IDU, injection drug user; MSM, men who have sex with men.
[a]Africa, Southeast Asia, the Middle East (except Israel), South and Western Pacific islands, the interior Amazon River basin, Haiti, and the Dominican Republic.
[b]South, Central, and Southwest Asia; Israel; Japan; Eastern and Southern Europe; Russia; areas surrounding the Amazon River basin; Honduras; and Guatemala.
Weinbaum CM, et al. MMWR. 2008;57:(RR-8):10-11; CDC Health Information for International Travel 2010.

tions associated with viral hepatitis. Clinicians should report all HBsAg-positive laboratory results to local or state health departments.[1]

CDC testing and public health management recommendations for HCV infection

The CDC last published recommendations for HCV

TABLE 3 Recommended laboratory tests for chronic HBV

Appropriate candidates to test	Recommendation
• People born in geographic regions with high and intermediate HBV endemicity (≥2%) • Unvaccinated persons born in the US to parents born in geographic regions with high HBV endemicity (≥8%)	Test for HBsAg
IDUs, MSM	Test for HBsAg and anti-HBc or anti-HBs
Immunocompromised patients	Test for all serologic markers (HBsAg, anti-HBc, anti-HBs)
Hemodialysis patients	Test for all serologic markers (HBsAg, anti-HBc, anti-HBs); test vaccine nonresponders monthly for HBsAg
Pregnant women	Test for HBsAg during each pregnancy
Infants born to HBsAg+ mothers	Test for HBsAg and anti-HBs at 1 to 2 months following completion of 3 vaccine doses
Contacts of HBsAg+ persons (household, needle-sharing, or sex partner)	Test for HBsAg, and anti-HBc or anti-HBs
HIV-positive people	Test for HBsAg, and anti-HBc or anti-HBs
Blood, organ, plasma, semen, and tissue donors	Test for HBsAg, anti-HBc, and HBV-DNA, as required
People with elevated ALT or AST levels of unknown etiology	Test for HBsAg
People who are sources of blood or body fluid exposures that might warrant postexposure prophylaxis	Test for HBsAg

ALT, alanine aminotransferase; AST, aspartate aminotransferase; anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to hepatitis B surface antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HIV, human immunodeficiency virus; IDUs, injection drug users; MSM, men who have sex with men.

Centers for Disease Control and Prevention. Recommendations for routine testing and follow-up for chronic hepatitis B (HBV) infection. http://www.cdc.gov/hepatitis/HBV/PDFs/ChronicHepBTestingFlwUp.pdf. Accessed October 7, 2009.

prevention and control in 1998.[5] The recommendations, shown in **TABLE 4**, are based on the risk of infection associated with certain behaviors or medical history and the need for exposure management. Routine testing is not currently recommended for health care, emergency, and public safety workers; pregnant women; household (nonsexual) contacts of HCV-positive individuals; or the general population. Recommended tests for chronic HCV are shown in **TABLE 5**.[5]

The CDC is currently drafting new recommendations for HCV testing to incorporate the evolving epidemiology of HCV as well as the development of rapid tests for HCV.[2] Although the prevalence rate of HCV infection in the general population is estimated to be approximately 1.6% (**TABLE 6**), most (66%-69%) infected individuals were born between 1945 and 1964. These individuals are now reaching the age when liver complications associated with chronic HCV infection are becoming evident.[6,7] In addition, the prevalence of HCV infection is markedly elevated among injection drug users, despite the fact that 80% of infected individuals have not recently injected drugs.[6] Recent data suggest that new HCV infections may be expanding in this population, particularly among younger users.[6]

The CDC is also comparing the current model of risk-based screening with other strategies, including enhanced risk screening in urban public clinics and birth year–based testing in public clinic and managed care settings.[2] In addition, the CDC is evaluating the cost-effectiveness of testing in various settings, including drug treatment centers, prisons, sexually transmitted disease clinics, and primary care clinics. Rapid HCV tests are currently undergoing validation and field testing for possible inclusion in the revised recommendations.[2] An important feature of

TABLE 4 Recommended populations for HCV testing

People who ever injected illegal drugs, including those who injected once or a few times many years ago and do not consider themselves drug users
People with selected medical conditions, including those: • who received clotting factor concentrates produced before 1987 • who were ever on chronic (long-term) hemodialysis • with persistently abnormal levels
Prior recipients of transfusions or organ transplants, including those: • who were notified that they received blood from a donor who later tested positive for HCV infection • who received a transfusion of blood or blood components before July 1992 • who received an organ transplant before July 1992
Health care, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCV+ blood
Children born to HCV+ women

ALT, alanine aminotransferase; HCV, hepatitis C virus.

Centers for Disease Control and Prevention. MMWR. 1998;47(RR-19):21.

the new HCV recommendations is that they will address issues concerning the link to medical care following testing.

Professional medical societies: Current guidelines and policies for screening and management of HBV and HCV infections

Medical societies can play an active and vital role in transforming the national response to viral hepatitis by providing high-quality, relevant guidelines. Clinical guidance is most beneficial when it is effectively disseminated, effectively implemented, and has widespread support by peers or sources trusted by physicians.[8] However, current guidelines and policies on HBV and HCV screening and management vary greatly between primary care and specialist medical societies or are nonexistent.

HBV and HCV guidelines from key societies

American Academy of Family Physicians (AAFP). The AAFP recommends HBV screening for pregnant women.[9] The AAFP found insufficient evidence to recommend for or against routine HCV screening for adults at high risk for infection.

American Academy of Pediatrics (AAP). The AAP endorses the immunization recommendations made by the CDC for HBV.[10]

American Association for the Study of Liver Diseases (AASLD). The AASLD recommends HBV screening for high-risk populations and immunization according to the CDC recommendations for all unvaccinated adults.[11] The AASLD also provides guidance on the management of patients with chronic HBV infection.[11] The AASLD recommends HCV screening for high-risk populations and counseling for those infected to prevent transmission.[12] In addition, the AASLD recommends HCV genotyping for treatment planning and provides guidance for caring for patients throughout treatment.[12]

American College of Obstetricians and Gynecologists (ACOG). ACOG recommends serologic testing of all pregnant women for HBsAg, but not for HCV infection. Additional recommendations include HBV immunization of HBsAg-negative women who have risk factors, household contacts, and sexual partners of women with chronic HBV, as well as all newborns.[13]

American College of Occupational and Environmental Medicine (ACOEM). The ACOEM recommends HBV immunization of health care workers and provides guidance for management of occupational exposures to HBV and HCV.[14]

American College of Physicians (ACP). The ACP refers members to the US Preventive Services Task Force (USP-

TABLE 5 Recommended laboratory tests for chronic HCV

Test	Application
Hepatitis C antibody by EIA	Screening for past or present HCV infection
RIBA for HCV antibody to specific HCV antigens, or the signal-to-cutoff ratio specific to the EIA	Confirmation of positive EIA
PCR for HCV RNA	Medical evaluation and management

EIA, enzyme immunoassay; HCV, hepatitis C virus; PCR, polymerase chain reaction; RIBA, recombinant immunoblot assay.

Centers for Disease Control and Prevention. MMWR. 1998;47(RR-19):11.

TABLE 6 Estimated prevalence of HCV subgroup

Characteristic	Prevalence of antibody to HCV % (95% CI)
General population	1.6 (1.3-1.9)
Injection drug user	57.5 (44.1-69.9)
Blood transfusion before 1992 (ages 20-59y)	5.8 (3.7-9.0)
HIV-positive (ages 18-49y)	13.8 (5.3-31.3)
Dialysis patients	7.8
Number of lifetime sex partners:	
0-1	0.5 (0.2-1.4)
2-9	1.1 (0.5-2.1)
10-19	2.6 (1.5-4.6)
20-49	7.5 (5.3-10.6)
50+	12.0 (8.5-16.7)

CI, confidence interval; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

Data from Armstrong GL, et al. Ann Intern Med. 2006;144:706-707; Finelli L, et al. Semin Dial. 2005;18:57.

STF) for guidance on HBV and HCV screening.[15,16] The USPSTF recommends HBV screening for all pregnant women, but is against routine HBV screening for the general population.[16] For adult HBV immunizations, the ACP refers members to the CDC adult vaccination schedule.[17,18]

American College of Preventive Medicine (ACPM). For HBV, the ACPM refers physicians to the USPSTF guidelines.[19] For HCV, the ACPM recommends screening for high-risk populations.[20]

American Gastroenterological Association (AGA). For HCV, the AGA recommends screening for high-risk groups.[21] The AGA also provides guidance for HCV treatment.[21]

American Society for Reproductive Medicine (ASRM). The ASRM recommends that high-risk individuals seeking fertility therapy be offered testing for HBsAg and HCV. In addition, ASRM recommends testing semen donors, HBV vaccination of seronegative partners of HBV-infected partners, and counseling women who are HCV-positive about the risk of transmitting HCV to the fetus. For HCV, the ASRM recommends vaccination for HBV and hepatitis A virus, and the referral of all HCV-positive and HBsAg-positive patients for evaluation of possible liver disease.[22]

Infectious Diseases Society of America (IDSA). For both HBV and HCV, the IDSA refers members to published AASLD guidelines.[23] ■

Panel Discussion

Samuel So: Data from surveys indicate that clear guidance on viral hepatitis screening, diagnosis, and treatment is lacking for primary care providers. Educational initiatives are greatly needed for both hepatitis C virus (HCV) and hepatitis B virus (HBV).

William B. Baine: The US Preventive Services Task Force (USPSTF) last made pronouncements on HCV screening in 2004, which included a recommendation against screening healthy people in the general population and a statement that the evidence was insufficient to determine whether there were benefits to screening high-risk populations. The HCV recommendations are due to be revised; however, several issues need to be considered before the next revision. First, evidence is needed to demonstrate the net benefit of HCV screening in the aggregate for those groups targeted for screening, not just in the fraction of infected persons destined to develop decompensated cirrhosis or hepatocellular carcinoma. Second, data are needed that document the full spectrum of morbidity and mortality attributable to HCV infection across all organ systems, and not just in the liver alone. Finally, screening recommendations should not be made on the basis of oversimplified or naive models of cost-effectiveness that promise cost savings if severe complications and death are averted. We should not be ashamed of spending money to save lives—lives and health are worth saving for their own sake.

Jake Liang: Beyond increasing primary care provider awareness and knowledge of viral hepatitis, the need for an effective public education program is critical. It can be done, as evidenced by the informational campaign for the 2009 H1N1 influenza virus. In addition to basic information about the screening, management, and prevention of serious complications, the residual shame and stigma surrounding HBV and HCV infections must be addressed.

Cindy Weinbaum: The Centers for Disease Control and Prevention (CDC) 2008 HBV screening guidelines include a recommendation to test people who had been vaccinated after exposure to HBV and therefore have a risk of actually being positive for chronic HBV.

Marion G. Peters: How do we solve the problem of time constraints in primary care?

Litjen Tan: Getting the attention of primary care providers and demonstrating to them why screening for chronic HBV and HCV infections should be a high priority is a major challenge. Most clinicians tell me that in the absence of any kind of HBV or HCV screening, they have no time to talk to patients about tobacco cessation, obesity management, or exercise, while still addressing the main reason for their visit. Most adult treatment is based on acute care management and not prevention. Formulating recommendations and guidelines in a way that supports third-party reimbursement for the physician who implements the recommendations would be a good first step.

Jules L. Dienstag: The American Gastrointestinal Association (AGA) and the American Association for the Study of Liver Diseases (AASLD) made clear recommendations for HCV screening that may be useful in discussions with insurance companies or legislators. From the perspective of the hepatology and gastroenterology fields, chronic HCV is a progressive infection that can result in severe complications. Treatments are available that can reduce the morbidity and mortality of this liver infection; therefore, recommendations for the screening of high-risk populations are endorsed and likely to reduce the clinical impact of chronic HCV infection. Both the AGA and the AASLD disagree strongly with the USPSTF, which did not recommend screening for HCV infection.

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The opinions expressed in the panel discussion are those of the participants. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

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The dawn of a new era: Transforming our domestic response to hepatitis B & C

Activity 5: Achieving health equity to eliminate racial, ethnic, and socioeconomic disparities in HBV- and HCV-associated liver disease

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DISCLOSURES

Dr El-Serag, Dr McGlynn, Dr Graham, and Dr So have no real or apparent conflicts of interest to report.

Dr Howell reports the following: Consultant: Abbott, Roche Pharmaceuticals, Vertex Pharmaceuticals. Speakers Bureau: Vertex Pharmaceuticals

Mr Fang, Ms Anderson, and Ms Thiel have no real or apparent conflicts of interest to report.

Despite the overall success in the fight against viral hepatitis, there remain racial, ethnic, and socioeconomic disparities in the incidence and prevalence of acute and chronic viral hepatitis, the outcomes of chronic viral hepatitis, and health care access and quality. Numerous federal and community initiatives are aimed at overcoming these discrepancies.

Disparities in disease outcomes and treatment of viral hepatitis

Minority populations in the United States are disproportionately affected by acute and chronic viral hepatitis.[1] For example, African Americans bear a disproportionate burden of new hepatitis B virus (HBV) infections, with an incidence of 2.2 cases/100,000 population in 2007. This is higher than all other racial and ethnic groups.[2] The prevalence of HBV infection among African Americans is also higher than among whites, while the prevalence of hepatitis C virus (HCV) infection is higher among African Americans than among non-Hispanic whites and Mexican Americans.[3]

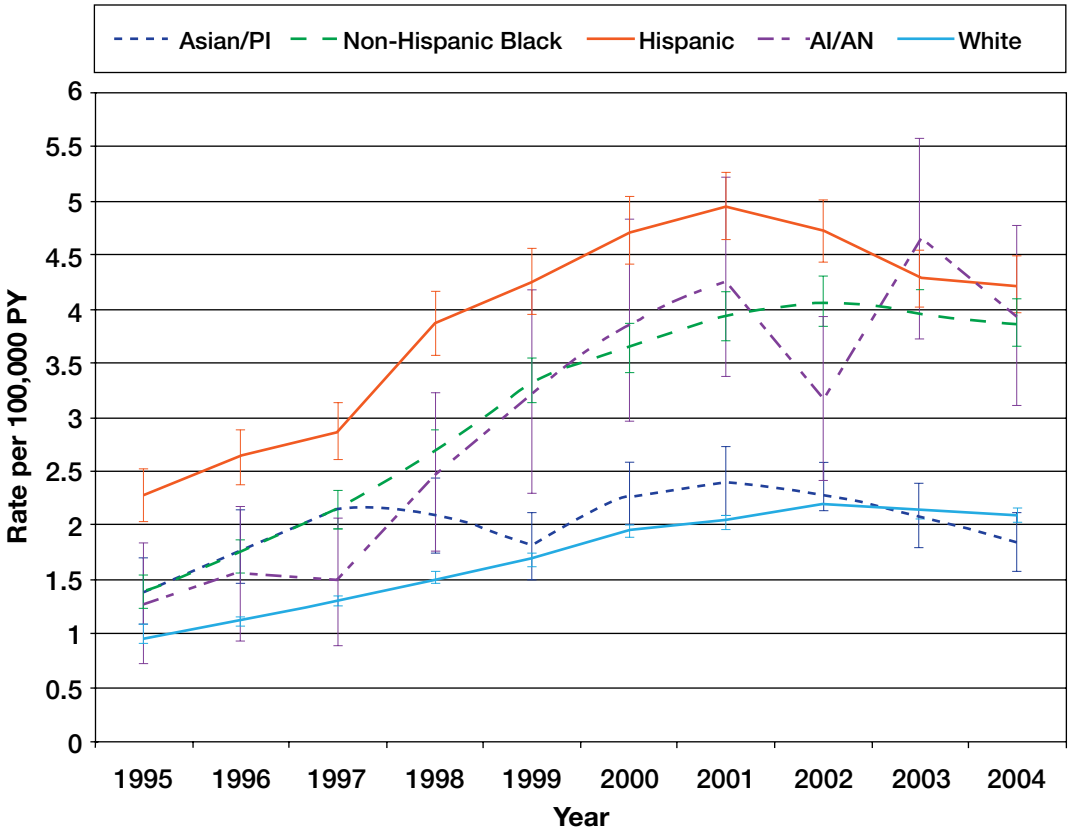
Of the roughly 4 million noninstitutionalized/nonhomeless Americans infected with HCV, 920,000 are African American,[3] accounting for 23% of the disease burden, while representing approximately 13% of the population. There is less information available regarding incidence and prevalence of viral hepatitis among Hispanic Americans, but 260,000 Mexican Americans are infected with HCV, accounting for about 6% of the disease burden.[3] The strongest risk factor for HCV infection is injection drug use.[3]

Outcomes

Although mortality rates from chronic liver disease and cirrhosis have declined since 1985, they remain the ninth leading cause of death in the United States. The highest mortality rate from liver disease resulting from all causes occurs in American Indians and Alaska Natives (22.6/100,000), followed by Hispanics (13.9/100,000), white non-Hispanics (9.2/100,000), African Americans (7.7/100,000), and Asians or Pacific Islanders (3.6/100,000).[4] Regardless of racial or ethnic group, mortality rates from chronic liver disease are twice as high among males than among females.[4]

Chronic HCV. A study of HCV mortality (ie, deaths related to HCV as a contributing or underlying cause) found that the overall mortality rate among HCV-infected individuals more than doubled from 1995 to 2004,

FIGURE 1 **Annual age-adjusted HCV mortality rates and 95% confidence intervals by race/ethnicity, 1995-2004**



AI/AN, American Indian/Alaska Native; HCV, hepatitis C virus; PI, Pacific Islander; PY, per year.

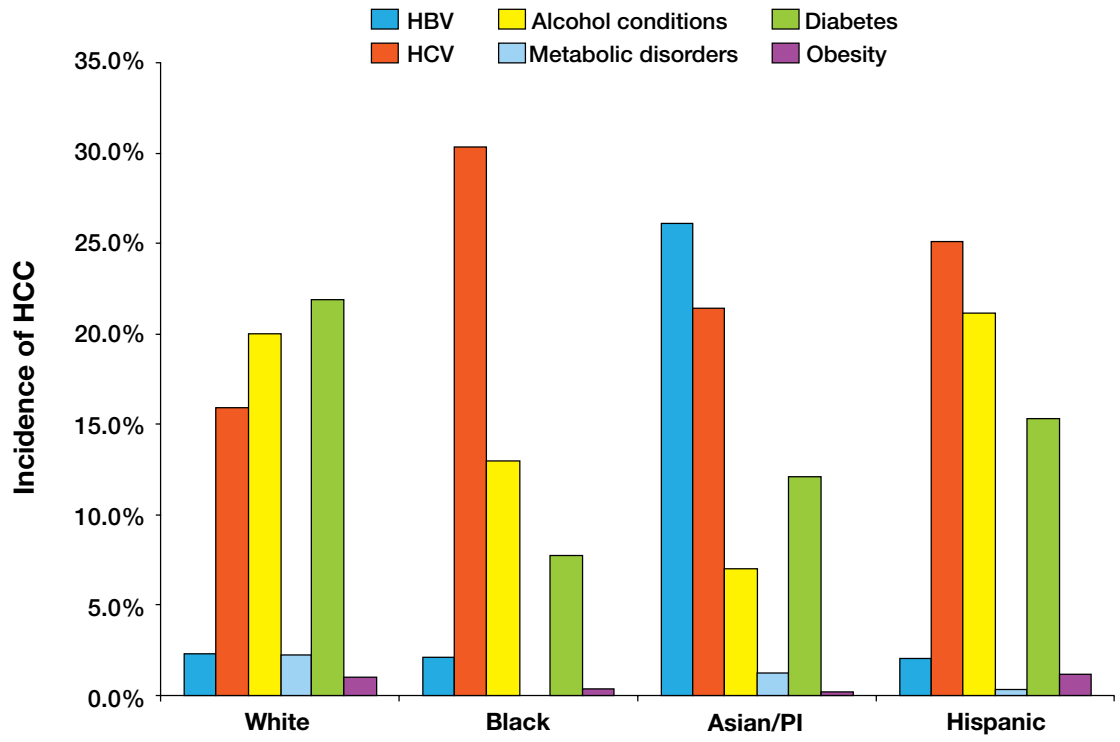
Wise M, et al. Hepatology. 2008;474:1133. Reprinted with permission.

and that the greatest increases in mortality occurred among non-Hispanic blacks and American Indians/Alaska Natives (**FIGURE 1**).[5]

Hepatocellular carcinoma (HCC). Cirrhosis, chronic HBV infection, and HCV-related cirrhosis are the major risk factors for the development of HCC, the most common type of liver cancer.[6] Incidence rates of HCC have tripled from 1975 to 2005, with marked recent increases among middle-aged African American males, Hispanic males, and white non-Hispanic males.[7,8] Asians/Pacific Islanders had a higher incidence rate and mortality rate than other racial and ethnic groups but experienced a smaller annual percent change in HCC incidence rates, compared with other racial ethnic groups.[8] Moreover, while Asians and Pacific Islanders make up approximately 5% of the total population, this group accounts for 24% of all HCC cases in the United States.[9]

There is considerable variability in the etiology of HCC among different racial and ethnic groups. In a study of the Medicare population, the dominant risk factor for HCC for Asians was HBV infection, for African Americans it was HCV infection, and for non-Hispanic whites it was diabetes mellitus.[9] With the exception of Asians, alcohol-related conditions were the second leading factor (**FIGURE 2**). Attributable risks may explain about two-thirds of HCC cases, but this proportion varies by race and ethnicity. Almost half of the cases of HCC occurring among African Americans and about

FIGURE 2 Attributable risks of HCC factors by racial/ethnic group: SEER-Medicare, 1991-2005



HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; SEER, Surveillance, Epidemiology, and End Results Program.

McGlynn, KA. Presented at: The Dawn of a New Era: Transforming Our Domestic Response to Hepatitis B&C; September 10-11, 2009; Washington, DC.

one-third found among Asians are not explained by known risk factors.

Health care access and quality

Disparities in health care access and quality based on race, ethnicity, and socioeconomic status persist[10] and have been documented for African Americans and Hispanics, compared with non-Hispanic whites.[11]

Hepatitis treatment. African Americans infected with HCV genotype 1 are less likely to receive treatment than their white counterparts.[12] Disparities in the evaluation and management of HCV infection based on race are independent of the health care system and payer status.[12,13] For example, African Americans and whites evaluated at Veterans Affairs Medical Centers were equally likely to be referred for HCV treatment and to have biopsies, but African Americans were less likely to actually receive treatment.[14] Nontreatment was also associated with increasing age, alcohol dependence, drug use, and medical and psychiatric comorbid illness.

HCC and liver transplantation. African Americans have a more advanced HCC tumor stage at diagnosis and are less likely to receive local or surgical therapy than whites, even when the tumor is localized to the liver.[15] Researchers have also cited a large number of disparities in access to and outcomes of liver transplantation between African Americans and whites. African Americans are underrepresented on the United Network for Organ Sharing liver transplantation waiting list.[16] When they are listed, African Americans have more advanced disease than whites, suggesting a delay in referral.[16,17] In addition, African Americans are less likely to receive live-donor transplantation, have a lower survival rate after transplantation, and experience a higher rate of graft loss.[18] More studies are needed to evaluate medical center and geographic effects on racial and ethnic variation in survival, graft failure, and quality of life. Racial and ethnic variation in posttransplant outcomes may

be related in part to differences in immunosuppression pharmacokinetics and adherence.[19]

At-risk populations

There are insufficient data to fully explain the racial and ethnic disparities in hepatitis infection and outcomes. It is clear that many interrelated factors are involved. One reason for the racial disparity in HBV disease is high rates of exposure and low rates of immunization among African Americans at high risk. Thus, while universal vaccination of children and adolescents is closing the HBV gap between African Americans and other racial and ethnic groups, current immunization strategies have not sufficiently penetrated the populations at highest risk,[20] which include injection drug users.

Similarly, the risk of HBV (and HCV) infection is high among the incarcerated. African Americans and Hispanics are overrepresented in the incarcerated population.[21] Young adults (25-45 years old) who have been incarcerated or who engage in high-risk behavior are the cohort that needs to receive HBV vaccination.[22] Socioeconomic status also impacts the epidemiology of viral hepatitis. Lower income levels have been associated with a greater likelihood of infection with HBV or HCV.[23]

There are also differences in the natural history of chronic hepatitis and the efficacy of therapy among minorities. For example, Hispanics have a higher frequency of cirrhosis than African Americans and trend toward more cirrhosis than non-Hispanic whites.[24] The need for more effective HCV treatments is pressing, especially in minority populations, because the response to combination therapy of pegylated interferon and ribavirin (standard therapy for HCV infection) is lower for African Americans and Hispanics compared with non-Hispanic whites.[25,26] Also, African Americans and Hispanics are underrepresented in clinical trials for novel antiviral therapies.

Eliminating disparities

Disparities in morbidity and mortality associated with HBV and HCV infections according to race, ethnicity, and socioeconomic status must be recognized by primary care providers. Government and community initiatives are also crucial for overcoming these disparities. While the following discussion focuses on HBV infection, the need to address HCV infection is no less important. Screening of individuals at risk for HCV infection, followed by evaluation of and care for those infected, is the central secondary prevention strategy for HCV infection.

Government initiatives

Federal agencies are working to address the disproportionate burden of viral hepatitis, liver disease, and liver cancer among patient subgroups. The Office of Minority Health (OMH) advises the Office of the Secretary of the US Department of Health and Human Services and the Office of Public Health and Science on public health program activities that affect minority populations. In addition to racial and ethnic minorities, the OMH serves a broad cross section of underserved populations, including those with limited English proficiency.

In 2007, the Centers for Disease Control and Prevention (CDC), in collaboration with state and local health agencies, launched the Adult Hepatitis B Vaccination Initiative. The initiative targets high-risk individuals and vaccination clinics in high-risk areas and supports increased education of health care providers.[20]

Community initiatives

Community HBV initiatives play an important role in increasing grassroots and health care provider awareness of HBV disease by offering the opportunity for screening, vaccination, and referral for care. They also play an important role in advocacy at the local, state, and national levels.

Within the Asian/Pacific Islander communities, several initiatives have demonstrated success in increasing HBV awareness, screening, diagnosis, and treatment, in addition to effecting change at the legislative level.

The Jade Ribbon Campaign. The Jade Ribbon Campaign, launched in 2001 by the Asian Liver Center (ALC) at Stanford University, is a culturally and linguistically targeted awareness campaign that unites health care providers, community organizations, policy makers, and the media. From 2001 to 2006, 3163 Asian/Pacific Islander adults were screened at community centers for hepatitis B surface antigen (HBsAg) and its antibody (anti-HBs).[27] Of the 8.9% who were HBsAg-positive, two-thirds were unaware of their infection. Of those who said that they had been vaccinated, 5.2% were HBsAg-positive.[27] The efficacy of the Jade Ribbon Campaign was studied in a group of 476 Chinese Americans who attended a 5-hour screening and education event. Even though 80% of the participants reported attaining a col-

Panel Discussion

Ted Fang: Asian Americans are the fastest growing ethnic population in America. A large proportion has college degrees and high incomes, and entrepreneurship is high. These are going to be the future donors and future voters, and our elected officials and industry need to know about it. These are also the future patients who are going to buy drugs. Insurance companies need to know about this because Asian Americans are their future customers as well. Two-thirds of the Asian American population were born or were raised in the United States. Most of our advertising campaign is in English but with Asian images.

Thelma King Thiel: I focus on the education component. There needs to be a coordinated effort to discourage behavioral choices that can lead to disease. Our teachers and parents don't know how to teach kids to adopt healthy behaviors. The problem with hepatitis is that most people don't know they have it. We need to motivate patients to assess their own risk behaviors to see the need for screening. The Hepatitis Foundation has tried to fill the gaps by going out to the gatekeepers—nurses, nurse practitioners, and other health care providers who work on the front lines. We give them simple, easy, quick messages and communication techniques to engage patients to participate in their own care. We also have 14 educational DVDs—our most recent one for adolescents won an Emmy. Teachers love it. But we have a long way to go to beef up our education in this country.

Janelle Anderson: At the National Task Force on Hepatitis B for Asians and Pacific Islanders, we currently have 133 public, private, and nonprofit organizations as members. Our website is www.hepbtaskforce.org. Our mission has expanded from promoting hepatitis B vaccination to children to both screening and vaccination of a broader target age group. We have a monthly conference call and daily e-mail and Web site updates where our members share their resources and educational materials, which are available on our Web site in 6 languages.

Kenneth Lin, Agency for Healthcare Research and Quality: Dr So, you mentioned several screening programs in the Asian immigrant community. How did you prepare for all the patients you were inevitably going to find? How did you prepare to ramp up the management capabilities of those communities?

Samuel So: We lined up access to low-cost or free vaccination sites. For the San Francisco Hep B Free campaign, even the private hospitals are willing to participate in indigent care. Indigent patients are also referred to the San Francisco Department of Public Health clinic. I always suggest to any groups that do community-based screening programs to arrange these details before they commence; otherwise, the public will be frustrated. We ask those people who have insurance to see their doctors.

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lege degree or higher, 45% reported that the Jade Ribbon Campaign was their only source for learning about HBV disease.[28] Although 86% had health insurance and 74% had a regular physician, 71% of attendees said that their physicians had never spoken to them about HBV.[28] A 1-year follow-up survey of 309 of the 476 participants showed that two-thirds of HBsAg–positive individuals had received care for chronic HBV or were screened for liver cancer, and 78% heeded the recommendation to have family members tested.[28]

The Hepatitis B Initiative. The Hepatitis B Initiative is an outreach program that has partnered with 9 Asian churches in the Baltimore and Washington, DC, metropolitan areas to provide faith-based HBV education, testing, and vaccination. As part of the program, 1775 people were tested for HBsAg and anti-HBs from 2003 to 2006; of those, 2% were found to be HBsAg–positive, and 61% were unprotected. Of those unprotected, 79% completed the 3-shot HBV vaccine.[29]

San Francisco Hep B Free. San Francisco Hep B Free is the nation's first citywide campaign to test Asian/Pacific Islander adults for HBV infection and offer vaccination. During its first 18 months, approximately 3000 people were screened, and 663 health care providers attended continuing medical education courses.[30]

Asian American Hepatitis B Program/BFreeNYC. New York City funded the Asian American Hepatitis B Program, which provided $9 million in grants over 3 years. Among 925 new participants screened during a 6-month period, 14.8% were HBsAg-positive.[31] The program was

expanded and renamed BFreeNYC to serve other populations at risk for HBV, including recent immigrants from Eastern Europe, Africa, the Caribbean, and Latin America. Since 2004, the program has screened over 8000 people and vaccinated approximately 2000.

3 For Life. Community outreach programs do not have to be free to be effective. A fee-for-service, community-based pilot program (a partnership between the ALC, the San Francisco Department of Public Health, and a community YMCA) called 3 For Life targeted Chinese Americans and attracted 1206 participants. Of unprotected adults, 85% were vaccinated as a result of the program.[32] ■

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The dawn of a new era: Transforming our domestic response to hepatitis B & C

Activity 6: Reports from today's health care environment on the implementation of screening, diagnosis, and treatment recommendations

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Examining the prevention and control of chronic viral hepatitis in different health care settings—including the Veterans Health Administration (VHA), the correctional system, the managed care setting of the Kaiser Permanente (KP) system, and primary care settings—can help identify the most effective strategies to prevent hepatitis B virus (HBV) and hepatitis C virus (HCV) transmission, increase the rate of early diagnosis, and enhance acceptance of and adherence to treatment.

The VHA

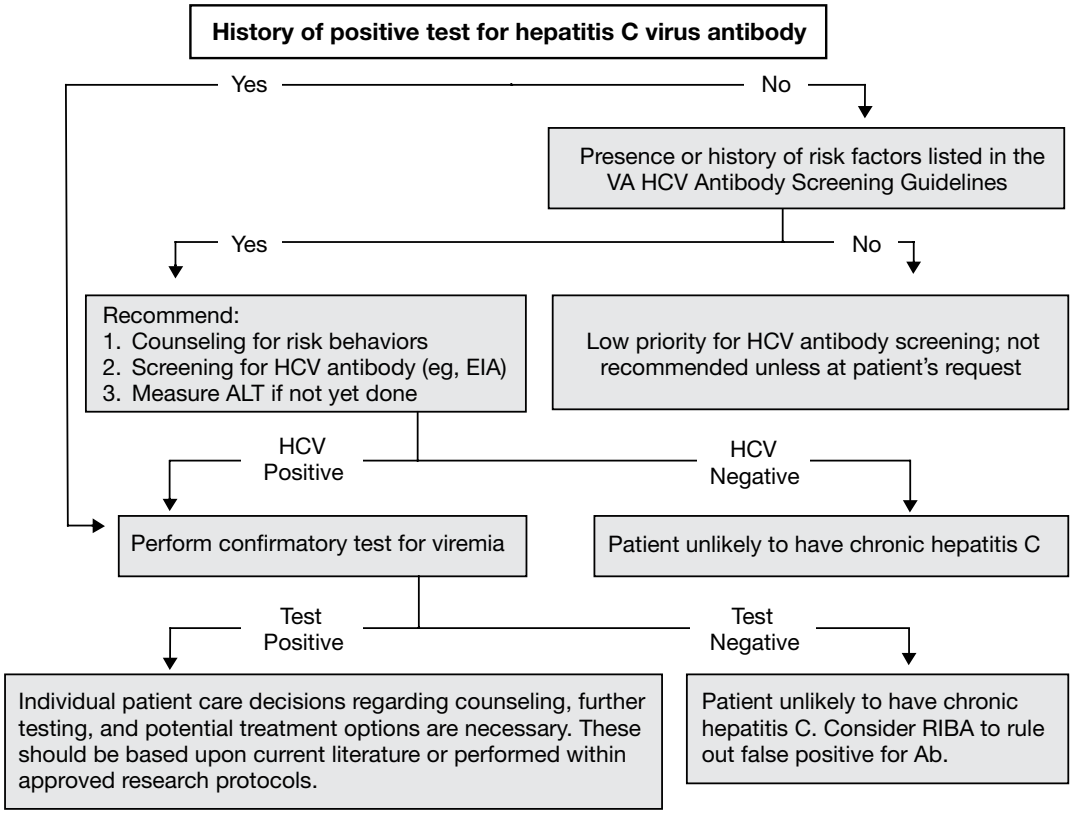
As the largest provider of medical care to individuals infected with HCV, the VHA serves as a valuable source of information about the epidemiology of HCV infection and the implementation of screening, diagnosis, and treatment for HCV, as well as the overall status of HCV care in the United States. The VHA recognized the significance of HCV infection in veterans early on. In 1999, the VHA conducted a day-long, nationwide HCV surveillance in which more than 26,000 veterans were tested, of whom 6.6% were positive for the HCV antibody.[1] In 2005, a study found a prevalence of 5.4% in a cluster sample of VHA medical center users, with the higher rates among Vietnam-era veterans.[2]

The current VHA policy for HCV testing is universal clinical screening, in which every patient is questioned about risk factors related to HCV infection (**FIGURE 1**).[3]

The criteria for screening veterans for HCV infection are a patient's desire for testing or the presence of one or more of the following: being a Vietnam-era veteran, receiving a blood transfusion before 1992, past or present injection drug use, immoderate use of alcohol, tattoo or repeated body piercings, history of intranasal cocaine use, history of hemodialysis, blood exposure on skin/mucous membranes, history of multiple sex partners, an unexplained elevation in levels of aspartate aminotransferases, or unexplained liver disease.

In 2001, the Hepatitis C Clinical Case Registry (CCR: HCV) was created through the Center for Quality Management. The registry monitors patient outcomes, trends in response to treatment, trends in toxicity, resource utilization, and verification of workload for reimbursement. Among patients in the CCR: HCV in care from 1998 to 2007, 190,608 (59.9%) had laboratory evidence of chronic HCV infection.[4]

FIGURE 1 Hepatitis C virus antibody screening flow chart



Ab, antibody; ALT, alanine aminotransferase; EIA, enzyme immunoassay; HCV, hepatitis C virus; RIBA, recombinant immunoblot assay; VA, Veterans Affairs.

US Department of Veterans Affairs. www.hepatitis.va.gov/vahep?page=prtop02-ct-chart. Accessed January 25, 2010.

In 2008, 147,352 veterans had chronic HCV infection documented by HCV viremia, a number that has remained relatively constant since 2004. Twenty-one percent of the veterans with HCV viremia were found to have ever received antiviral medication.[5]

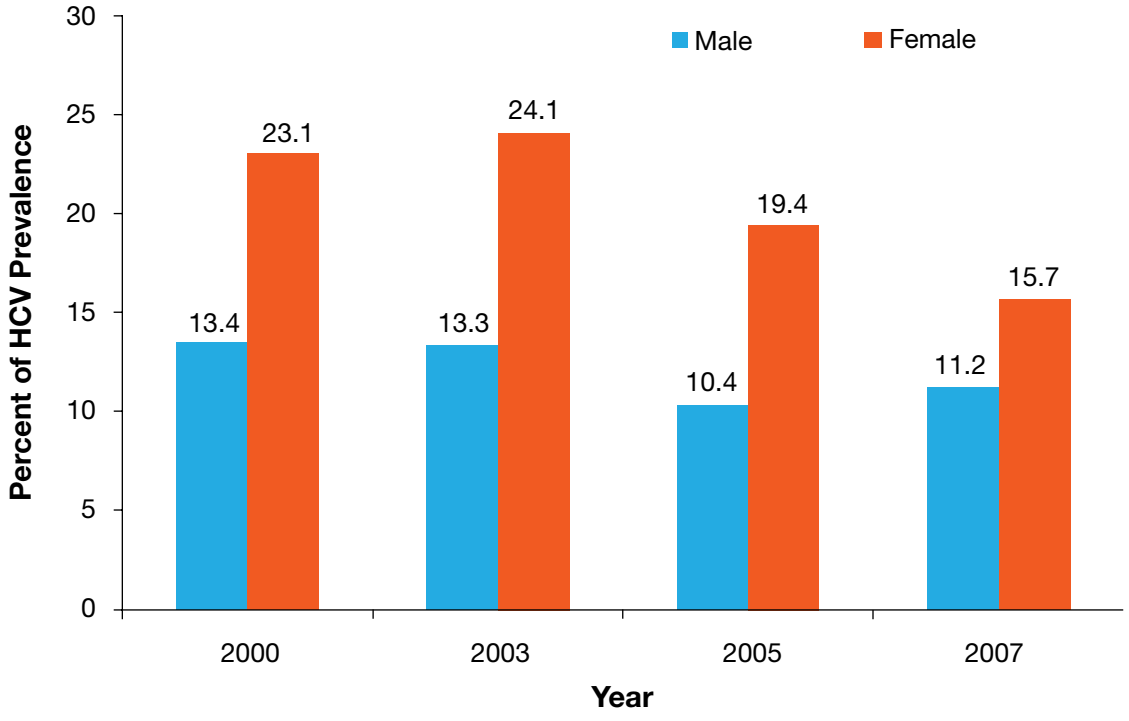
Data from 2000 to 2007 reveal that treatment of 5944 patients infected with HCV genotypes 1, 2, or 3 with pegylated interferon and ribavirin resulted in sustained virologic response (SVR) rates of 20% for genotype 1, 52% for genotype 2, and 43% for genotype 3.[6] These rates of response are substantially lower than those reported in clinical trials.

The prevalence of cirrhosis and hepatocellular carcinoma (HCC) among veterans with HCV viremia in VHA care is substantial. Of the 147,352 veterans with HCV viremia in VHA care in 2008, 19,012 (13%) were ever diagnosed with cirrhosis and 2174 (1.5%) were ever diagnosed with HCC. In 2008, there were 5967 deaths among veterans with HCV viremia.[5]

Practice patterns

A 2007 Web-based survey of 268 VHA care providers revealed that one-on-one educational counseling (49%) and referral to a formal HCV group education clinic (36%) were the most frequent means of educating newly diagnosed patients.[7] The survey also assessed the practices of 141 lead clinicians with respect to confirmatory testing of a positive HCV antibody test result and found that HCV polymerase chain reaction (PCR) was run automatically by the laboratory only 36% of the time. However, in 48% of cases, the provider was required to order HCV PCR separately, often resulting in delays in diagnosis.[7] These data should strengthen the case for a policy of

FIGURE 2 HCV seroprevalence among incoming inmates entering NYS DOCS: 2000 through 2007



HCV, hepatitis C virus; NYS DOCS, New York State Department of Correctional Services.

New York State Department of Health and New York State Department of Correctional Services. Surveys of HIV and HCV seroprevalence among inmates entering New York State correctional system: 2000-2007 (unpublished).

reflex confirmatory testing to improve the timeliness of diagnosis.

The future of HCV care at the VHA

The VHA anticipates an increasing demand for treatment as:

- patients become aware of improvements in anti-HCV treatments
- pressure increases to address comorbidities (eg, alcohol use, substance abuse, obesity, and psychiatric disease) as treatment barriers
- the number of veterans who require care for HCV-related liver disease increases along with an expanding need for specialty service care (eg, transplantation and interventional radiologists)
- improved clinical surveillance for sequelae of end-stage liver disease becomes more available, and the need to develop innovative models for health care delivery becomes more evident

Prevention and control of viral hepatitis in correctional settings

Most inmates eventually reside in communities upon their releases. Correctional institutions' staffs and visitors move between correctional facilities and social service settings outside of the correctional system. This is of major concern because viral hepatitis is more prevalent among inmates than in the general population. The Centers for Disease Control and Prevention (CDC) estimates that, among inmates, 1.0% to 3.7% have chronic HBV infection and 12% to 35% have chronic HCV infection.[8] The correctional system offers key opportunities to prevent, screen for, and treat hepatitis infections, although these are often limited by suboptimal funding and other barriers. Access to medically necessary health care in correctional settings is a constitutional right, and the standards for health services provided there are evolving, just as they are in the larger community.

HBV and correctional settings

Nearly 40% of people with acute HBV have a history of incarceration. In one study, only 12% of prison entrants had serologic evidence of HBV immunity.[9] The relatively low rate of vaccination occurs despite inmates' acceptance of HBV vaccination.[10] According to a Department of Justice report, in 2000 about two-thirds of state prison facilities had programs to vaccinate inmates for HBV, although these were mostly in targeted groups and limited by funding resources.[11] HBV vaccination is not economical in correctional settings, but it is economical in the overall health care system.[12]

HCV and correctional settings

Approximately one-third of all HCV-infected people pass through correctional facilities annually.[13] Many correctional systems have developed protocols for the identification and treatment of inmates with HCV infection. In 2000, nearly 80% of state adult correctional facilities reported testing for HCV (in targeted groups of inmates), and nearly 70% reported having a policy to treat inmates for HCV infection.[11] As with HBV programs, funding and the logistics of incarceration limit the availability of comprehensive screening and treatment programs for incarcerated individuals.[13,14]

In most prison systems, treatment is only initiated if the expected length of stay is long enough to complete treatment. To overcome this barrier to treatment, the New York State Hepatitis C Continuity Program was established to provide continuity of care beyond release. In New York, HCV seroprevalence among incoming inmates has remained stable since 2000 and is declining among women over this time period (**FIGURE 2**).

Screening for HCV infection is targeted at those inmates with risk factors. Treatment is usually by protocol; as of August 2009, 2849 inmates in New York state correctional facilities had been treated for HCV infection.[15] Under the program, treatment can be initiated when medically indicated irrespective of the time remaining until a prisoner's release date.[16] Inmates who initiate HCV treatment prior to release receive timely referral to appropriate clinics for continuation of treatment.

Needs in the correctional setting

The provision of HBV vaccine for all who desire it would be wise but requires funding. Most vaccine registries are developed for children and do not allow for the inclusion of adults. However, an adult vaccine registry would ensure that inmates receive the complete series. Screening for HBV and HCV infections in correctional facilities is also needed, although identifying a greater number of infected prisoners will result in an increase in the number of inmates who will require treatment and a corresponding need for more funding. In addition, collaboration between correctional facilities and public health departments can facilitate prevention education, HBV immunization, treatment for HBV and HCV infections, and continuity of care upon discharge.

Lessons from a managed care population: Experience from KP of Northern California

The Northern California KP Medical Care Program is an integrated health care delivery system with 3.2 million members and, except for extremes of income, is representative of the total area's population. The KP Viral Hepatitis Registry includes the records from 1995 to the present of all patients with chronic HBV and HCV infections. The registry database is updated early each calendar year to include data from the prior year. Current (year 2008) data include 14,763 patients with chronic HBV infection and 19,829 who are infected with chronic HCV, most of whom have at least 5 years of membership in the KP health plan. Based on identified cases, the age-adjusted prevalence of HCV infection in adult health plan members is 0.7%; however, this percentage is considered an underestimate, based on the National Health and Nutrition Examination Survey, which would suggest that perhaps 20,000 additional, yet unidentified, cases of HCV infection exist among the KP membership. As a result, KP is currently assessing the feasibility of improvements in risk assessment and birth cohort–based screening for HCV infection.[17]

The race and ethnicity distribution of HBV and HCV infections within KP has been analyzed: Asians/Pacific Islanders represent over 80% of the cases of HBV infection, while non-Hispanic whites represent the majority (59%) of those infected with HCV, followed by Hispanic (16%), African American (14%), and Asian/Pacific Islander (8%) populations. The peak age of KP patients with HCV infection is between 50 and 60 years, whereas patients infected with HBV have a much wider age distribution.[17]

Achieving SVR is key in treating HCV infection

Among patients with HCV currently in the KP health

Panel Discussion

Audience question: Dr Manos, you touched on treatment variability in your cohort patients that ranged from 13% to 35%. What has your health care system done to address treatment variability?

M. Michele Manos: We have convened a group of expert health care providers in an effort to build consensus about how to eliminate treatment disparities between facilities.

Audience question: Have any of you collected information specifically on treatment according to socioeconomic status, beyond the indigent, for example, those at 200% or 400% of the federal poverty level who do not qualify for Medicaid? The treatment of viral hepatitis can be thought of as even more complicated than heart surgery—from diagnostics to long-term treatment and extensive follow-up—and is fraught with hurdles for patients, including such things as scheduling time for numerous health care visits, finding transportation, and the ability to schedule child care.

Son T. Do: We found that socioeconomic factors, for which we have only surrogate indicators, actually did *not* correlate with discontinuation and response.

Ronald O. Valdiserri: We do not have those data available at the Veterans Health Administration (VHA), but you raise an important point. It reminds me of discussions of withholding highly active antiretroviral therapy from injection drug users because they did not have the support systems. The positive point is that if health care systems are configured to address those patient needs, then any patient population that qualifies from a medical perspective should be able to get that care.

Audience question: Dr Manos, you mentioned that Kaiser Permanente (KP) is doing cost studies on hepatitis C virus (HCV). Is that also the case with hepatitis B virus (HBV)?

M. Michele Manos: Awareness has been raised partly because of our involvement with the Hep B Free program. We are planning outcomes studies for HBV. They are challenging because we do not have a cutpoint at the end of treatment to examine outcomes. One of the areas that is evident, though, is the need for better screening. We also need to do a better job in the community of interpreting laboratory results for HBV screening. We have been working with facilities that have a large number of HBV patients, and the registry has been providing them with tracking databases, which may help us move toward an automated system for caring for our HBV patients.

W. Ray Kim: Are you using nurse practitioners and physician assistants in the screening process or for patient education?

M. Michele Manos: We certainly use a lot of other providers in the HCV world, and many of the clinicians who are interested in HBV have put forward some proposals to start using such a system with ancillary providers.

W. Ray Kim: I was impressed that there were 140,000 patients being treated in the VHA system. I know that there are not that many hepatologists in the VHA system to take care of all of them.

Ronald O. Valdiserri: No, there are not. There is a broad array of health care providers taking care of patients with chronic HCV, including midlevel clinicians and advanced practice–level nurses. Large Veterans Administration medical centers on the West Coast or the East Coast essentially have most of what they need at hand. We are a national system and the challenge at hand is to cover the entire continental United States, including the veterans who live in rural areas where few, if any, specialty providers exist. One model that we are exploring for rural patients includes telehealth.

Lester Wright: We have the same issues in corrections. We expect our primary care providers to use a primary care guideline and manage most of the care with consultation. We do use telehealth for many of the consultations. It is a challenge to devise models of care delivery that recognize that primary care providers cannot have everything placed on their shoulders. I think that the midlevel provider who is available to troubleshoot the patients who are on interferon therapy is most important.

W. Ray Kim: In those KP facilities with low HCV treatment rates, did you identify any correlates?

M. Michele Manos: The facilities that excel in screening seem to excel in all areas, both for HCV and HBV. Some of our most successful and most experienced HCV treaters are clinical pharmacists. We also have several internal medicine doctors who, working with the gastrointestinal (GI) department, have chosen to do HCV treatment exclusively, and they are some of our most successful providers. I attribute it to the fact that so many of the issues with HCV treatment are medical in nature and not GI in nature.

DISCLAIMER

The opinions expressed in the panel discussion are those of the participants. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

plan, 21% have been treated (ranging from 13% to 35% among various Northern California KP medical service areas). Premature discontinuation or noncompliance with therapy (21% overall; 27% in patients with genotype 1) and modest rates of SVR (50%) are areas for continued research and quality improvement efforts. The negative factors in adherence to therapy for HCV infection are African American or Hispanic race/ethnicity, presence of cirrhosis, diabetes, and HCV genotype 1. Negative factors for SVR are African American or Hispanic race/ethnicity, presence of cirrhosis, a baseline HCV RNA in excess of 500,000 IU/mL, depression at baseline, and HCV genotype 1.[17]

Data from 2500 patients treated for HCV infection indicate that patients who achieved SVR had significant reductions in the incidence of HCC, decompensated cirrhosis, liver grafts, and hospitalization for liver disease, compared with those who did not achieve SVR, and death due to liver disease. The incidence of diabetes, hospitalization for nonhepatic problems, and death due to such conditions was also significantly reduced. These findings point to the substantial long-term benefits of successfully treating HCV infection.[17]

Primary care: Implementing HBV screening and treatment in the real world

Nationwide, there is a significant gap between the number of Americans infected with HBV and the number of Americans who have been diagnosed or are receiving treatment.

Populations to be screened for HBV are encountered in internal medicine, family, pediatric, and obstetric/gynecology practices. The majority of clinician-patient encounters are driven by a problem or illness, with little time given to discuss screening. Most patients visiting a practice are first approached by office staff assistants; therefore, medical assistants and nurses should be convinced of the necessity to screen for HBV infection.[18]

Screening rates in clinicians' offices vary widely, ranging from none to almost all patients, even in patient populations that have a high prevalence of HBV infection. In addition, provider screening for HBV infection differs by patient ethnicity. In an academic general internal medicine practice at the University of California, San Francisco, the screening rate was as high as 72% for Southeastern Asians and Pacific Islanders and as low as 21% for non-Hispanic whites.[19] Chinese patients were more likely than other ethnicities to be screened, especially if the clinician spoke Chinese.[19] Screening was also a function of the duration of the physician-patient relationship. Significant inroads have not been made into screening the indigent, the young and healthy, and uninsured patient populations.

Implementing HBV screening in clinical practice can be a significant responsibility for both primary care providers and subspecialists. Reasons for not screening for HBV infection include a lack of understanding about the natural history and consequences of chronic HBV infection, unfamiliarity with blood tests needed for screening, and skepticism about the benefits of treatment, as well as difficulty in following changes in recommendations for screening. The CDC recommendation for screening at-risk populations is extensive and was further expanded in 2008[20]; primary care providers may perceive this list as daunting (see Activity 4, page S29). Ultimately, time is perceived as the largest obstacle by primary care providers. Nearly half of all physician practices in the United States are solo practices or group practices of up to 5 clinicians, and these types of practices typically have fewer resources available to screen patients.

Steps to increase screening and treatment of HBV

The importance of involving nurses and office assistants in screening has been discussed. A reminder system for HBV screening would help physicians to screen their patients more often. This system may come in the form of a master sheet reminder of all disease-specific screening tests recommended, to which HBV can be added. Institution of electronic health records with a reminder prompt may also prove useful. Knowing the proper billing codes for screening may also increase screening rates.

Other suggested strategies to promote compliance with HBV screening guidelines in primary care settings include increased clinician education; using insurance mandates or pay-for-performance screening targets; providing clear and strong governmental and medical society recommendations; and offering education and support to empower patients. ■

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The dawn of a new era: Transforming our domestic response to hepatitis B and C

Activity 7: Entering the new era of therapy for HBV and HCV infections

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Treatment of HBV infection

There are 7 approved medications for chronic hepatitis B virus (HBV) infection: 5 oral nucleoside/nucleotide analogues (lamivudine, entecavir, telbivudine, adefovir, and tenofovir) and 2 injectable therapies (interferon alfa-2b and pegylated interferon alfa-2a).[1,2] The non-approved drugs—pegylated interferon alfa-2b, emtricitabine, and a combination of emtricitabine and tenofovir—have also been used to treat chronic HBV infection. Treatment with the interferons is limited to one year; treatment with oral medications is usually long-term or indefinite. Other drug characteristics are summarized in **TABLE 1**.[3] Guidelines are available from the American Association for the Study of Liver Diseases (AASLD)[2] and an expert panel of hepatologists,[1] with reviews of each drug, recommendations on selecting therapies for individual patients, and a treatment algorithm for monitoring treatment response and adjusting medications as needed.

The ultimate goal of antiviral therapy for chronic HBV infection is to prevent progression to advanced liver disease (ie, cirrhosis and liver failure), hepatocellular carcinoma (HCC), and death; however, long-term studies to demonstrate such benefits are not available.[4] Changes in virologic, biochemical, and histologic parameters are used to predict clinical benefit.[4] Parameters used to assess treatment response include normalization of serum alanine aminotransferase (ALT) levels, improvement in liver histology, decrease in serum HBV DNA level, and loss of hepatitis B e antigen (HBeAg).[2]

Drug resistance is a concern with some oral agents. Resistance to HBV therapies can lead to loss of initial HBV DNA response, reversion of histologic improvement, increase in ALT levels, and progressive liver disease.[2] However, rescue therapy with a non–cross-resistant oral agent is almost always successful.[3] Among the approved therapies for HBV, lamivudine is associated with the highest rates of drug resistance in treatment-naive patients, while entecavir and tenofovir are associated with the lowest rates of drug resistance.[2]

Patient selection

Currently, patients with chronic HBV infection are selected for treatment based on HBV DNA levels, ALT levels, and the extent of liver disease. Patients are typically treated if they are HBeAg-positive and have ALT levels >2 times the upper limit of normal (ULN), or have moderate to severe hepatic fibrosis and HBV DNA levels >20,000 IU/mL. Patients

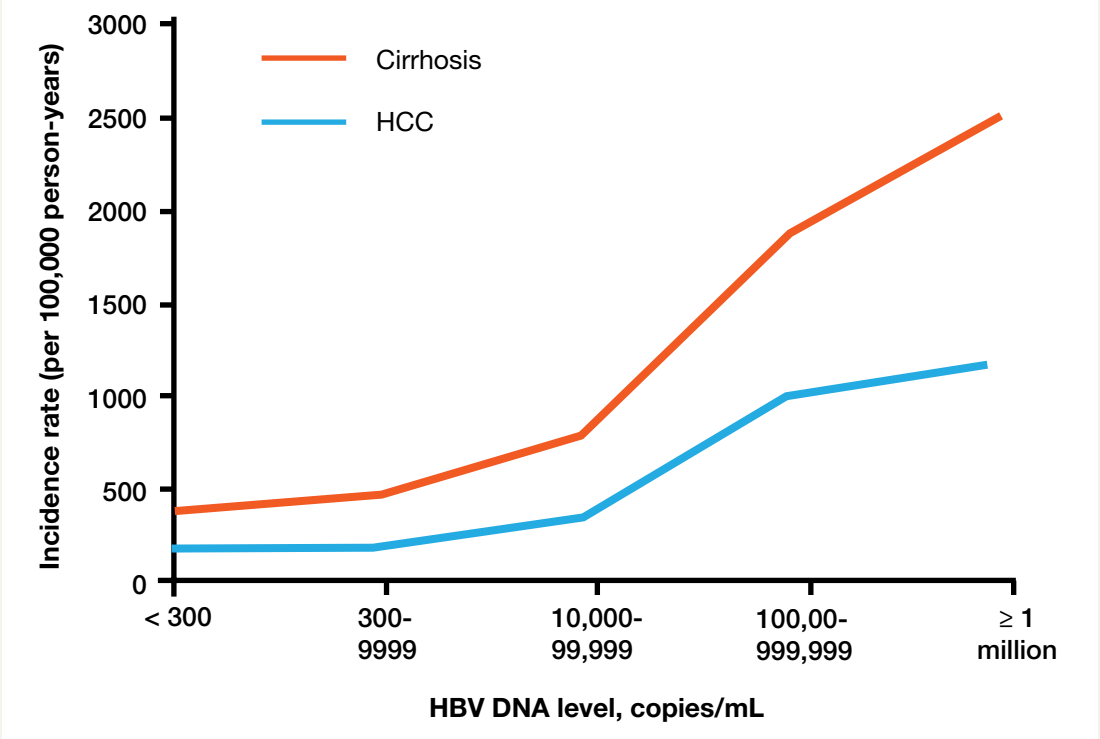
TABLE 1 **Characteristics of pegylated interferon and nucleoside/nucleotide analogues used for the treatment of chronic hepatitis B infection**

Characteristics	Pegylated interferon	Oral agents
Administration	Subcutaneous injection, once weekly	Oral, once daily
Duration	1 year	Indefinite in <80%
Tolerability (side effects)	Poor (fatigue, flu-like symptoms, anxiety, depression)	Excellent
Maximum $\log_{10}$ HBV DNA suppression	4.5	6.9
1-year HBeAg seroconversion (>1 year)	~30%	~20% (30%-50%)
HBsAg loss year 1 (year 2)	3%-4%	0%-3% (3%-5%)
Resistance	None	LAM > TBV, ADV > ETV, TDF

ADV, adefovir; ETV, entecavir; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LAM, lamivudine; TBV, telbivudine; TDF, tenofovir.

Adapted from Dienstag JL. Hepatology. 2009;49:(5 suppl) S112-S121.

FIGURE **Incidence of HCC and liver cirrhosis in the REVEAL study cohort**



HBV, hepatitis B virus; HCC, hepatocellular carcinoma; REVEAL, Risk Evaluation Viral Load Elevation and Associated Liver Disease study.

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who are HBeAg-negative are usually treated if they have HBV DNA levels >20,000 IU/mL and ALT levels >2 times ULN. Patients who are HBeAg-negative and have HBV DNA levels between 2000 to 20,000 IU/mL may be considered for a liver biopsy, and those with moderate to severe hepatic inflammation or significant fibrosis may

TABLE 2 **AASLD recommendations for selecting chronic HCV patients for therapy**

Characteristics of patients for whom therapy is widely accepted	• Age >18 and HCV RNA-positive in serum, and • Chronic hepatitis with significant fibrosis (bridging fibrosis or higher) on biopsy, and • Compensated liver disease, and • Acceptable laboratory and hematological indices (hemoglobin 13 g/dL for men, 12 for women; neutrophils >1500/mm^3; creatinine <1.5 mg/dL), and • Willing to be treated and to adhere to treatment requirements, and No contraindications
Characteristics of patients needing individualized treatment	• Prior treatment failed (nonresponder or relapsed) with either interferon + ribavirin or pegylated interferon monotherapy • Current users of illicit drugs or alcohol who are willing to participate in a substance abuse program • No fibrosis or mild fibrosis on biopsy • Acute hepatitis C • Coinfection with HIV • <18 years of age • Chronic renal disease • Decompensated cirrhosis • Liver transplant recipients
Characteristics of patients for whom therapy is contraindicated	• Major uncontrolled depressive illness • Renal, heart, or lung transplant • Autoimmune hepatitis or other autoimmune condition known to be exacerbated by pegylated interferon and ribavirin • Untreated thyroid disease • Severe concomitant medical illness (eg, severe hypertension, heart failure, poorly controlled diabetes) • Pregnant or unwilling to use adequate contraception • <2 years of age • Known hypersensitivity to drugs used to treat HCV

AASLD, American Association for the Study of Liver Diseases; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

Ghany MG, et al. Hepatology. 2009;49:1335-1374.

be considered for treatment. Patients who need immunosuppressive therapy or are coinfected with human immunodeficiency virus (HIV) or hepatitis C virus (HCV) are treated.[2,4]

The dependence on ALT levels as an indicator of the need for treatment has been called into question because significant fibrosis and inflammation can occur in patients with chronic HBV infection despite persistently normal ALT levels.[5] Although not universally accepted, some recent studies suggest that the ULN for ALT levels should be reduced to 30 U/L for men and 19 U/L for women.[2] In addition, HBV carriers with limited access to health care may not be treated.[6] Decisions on whether to treat pregnant women should be made by assessing the stage of liver disease and the potential benefit to the mother vs the potential risk to the fetus.[1]

Determining the risk of liver disease

Predicting a patient's risk of disease progression can be challenging and relies primarily on biological markers.

Elevated ALT levels have been shown to be associated with an increased risk for serious hepatic complications, such as cirrhosis and HCC.[7] In addition, an elevated viral load increases the risk of advanced liver disease; the large-scale, prospective Risk Evaluation Viral Load Elevation and Associated Liver Disease (REVEAL) study found that the risk of progression to cirrhosis or HCC for individuals with chronic HBV infection significantly increased with persistently higher levels of HBV DNA (**FIGURE**).[8-10]

Treatment of HCV infection

Treatment options for HCV infection have evolved since the mid-1980s, when patients were treated with interferon before the identification of the virus.[11] With the introduction of ribavirin in the 1990s and the more recent advent of pegylated interferon, HCV treatment entered a refinement phase, with increased focus on optimal dosing, viral kinetics, and treatment of nonresponders and other challenging populations. A new phase is now beginning with the development of *s*pecifically *t*argeted *a*ntiviral *t*herapy for H*C*V, also known by the acronym STAT-C. In current clinical practice, as with chronic HBV infection, appropriate patient selection is a cornerstone of HCV treatment.

Patient selection

Both the AASLD and the American Gastroenterological Association (AGA) have recommendations on patient selection for treatment. The AASLD 2009 guidelines are based on available clinical trial evidence; however, clinician judgment is also critical (**TABLE 2**).[12] According to the AGA position statement, treatment for previously untreated patients is indicated for those with circulating HCV RNA, elevated ALT levels, evidence of moderate to severe hepatitis grade and stage, and compensated liver disease.[13]

Impact of comorbidities on the management and prognosis of chronic liver disease

Comorbid medical and psychiatric conditions are common in patients with chronic HCV infection.[14,15] Certain comorbidities, such as alcohol and substance abuse, metabolic syndrome, HIV infection, and psychiatric disorders can adversely affect disease outcomes.[16]

Alcohol consumption. Alcohol consumption increases the risk of death and cirrhosis in chronic HCV infection.[17] Alcohol use lowers the probability of achieving a sustained viral response; however, intervention strategies for alcohol can improve antiviral treatment response rates.[18] In addition to alcohol, steatosis and metabolic syndrome reduce response to antiviral treatment, most likely by accelerating fibrosis.[19-21] Substance abuse, however, may have no detrimental effect on the probability of completing interferon therapy and achieving a treatment response, provided patients receive adequate supervision and support.[22]

HCV/HIV coinfection. Patients with both HCV and HIV have a more rapid course of liver injury, and many are dying prematurely of liver disease despite having well-controlled HIV.[23,24] The prevalence of HCV in HIV-infected individuals is not equally distributed among risk groups: HIV-infected patients with a history of injection drug use are more likely to be coinfected with HCV than those who contracted HIV via sexual transmission.[25,26]

Patients coinfected with HCV and HIV can be effectively treated with interferon and ribavirin, with a sustained viral response of 30% to 40% in those infected with HCV genotype 1.[27,28] In a recent study of HIV/HCV-coinfected patients, treatment with interferon and ribavirin for 24 weeks led to an undetectable level of HCV RNA in 31% of the patients. In addition, during a mean follow-up of approximately 21 months, responders had a significantly lower rate of death and long-term liver complications compared with nonresponders.[29]

Despite the availability of effective treatment, treatment rates remain unacceptably low for patients coinfected with HIV and HCV. In a study at an urban HIV treatment center, only 33% (277/845) of patients coinfected with HCV and HIV were referred for HCV care, and only two-thirds (185) of those kept their first appointment.[30] Ultimately only 29 of the original 845 patients received HCV treatment, and less than 1% (6) of the full cohort achieved a sustained virologic response.

Psychiatric comorbidities. Psychiatric comorbidities occur in many HCV-infected patients[31]; a survey of a Veterans Affairs population found that one-third of all patients with chronic HCV infection had an active psychiatric disorder.[15] However, coexistence of depression and other psychiatric comorbidities does not preclude successful treatment. A study of patients infected with HCV with a comorbid psychiatric or substance disorder found that implementing an integrated care model with access to mental health professionals led to rates of antiviral

therapy recommendation and initiation similar to those of patients without psychiatric or substance disorders.[31]

Recent research

Treatment responses are mainly defined by the results of HCV RNA tests. The optimal response is a sustained virologic response. Other patterns include relapse, partial response, and nonresponse. Recent research is aimed at improving patters of response.

Pegylated interferon for chronic HCV infection. Pegylated interferon alfa-2b or pegylated interferon alfa-2a in combination with ribavirin is the standard treatment for HCV infection, achieving response rates of 40% to 60% for patients with HCV genotype 1,[32] and higher rates for those with HCV genotypes 2 and 3.[33] The 2 forms of pegylated interferon (plus ribavirin) were recently compared in the IDEAL study, which was a 3-arm trial conducted with patients with chronic HCV genotype 1. The IDEAL study assessed the effects of standard dose (1.5 µg/kg/wk) and low-dose (1.0 µg/kg/wk) pegylated interferon alfa-2b combined with weight-based ribavirin and pegylated interferon alfa-2a (180 µg/wk) plus ribavirin.[34,35] The IDEAL results demonstrated that sustained virologic response was comparable among the 3 treatment groups and between the 2 pegylated interferon alfa-2b doses. Patients taking pegylated interferon alfa-2a had a higher end-of-treatment response rate, but they were also more likely to experience relapse; therefore, the sustained virologic response rates were similar for both treatments.

Genetic polymorphism increases response rate. Another important recent finding arising from the IDEAL study is the identification of a genetic polymorphism that is associated with a 2-fold increase in sustained virologic response to treatment.[35] More than one-third of all patients do not respond adequately to therapy, and those that do are more likely to be of European rather than African ancestry.[32,35] The recently identified polymorphism occurs at a much greater frequency in European than African populations and may therefore explain approximately half of the difference in response rates to HCV therapy observed between African Americans and patients of European ancestry.

Viral kinetics indicate probability of sustained virologic response. Viral kinetics play an important role in treatment duration. Emerging evidence suggests that patients infected with HCV genotypes 2 and 3 who achieve a rapid virologic response by week 4 of therapy can have their treatment period truncated to 12 to 16 weeks, rather than the standard 24 weeks, with no reduction in efficacy.[36] In addition, data suggest that patients with a <2-log reduction in HCV RNA levels by week 12 of treatment are unlikely to attain a sustained virologic response, and discontinuation of therapy may be considered to avoid subjecting these patients to unnecessary therapy.[36] However, evidence suggests that patients with genotype 1 and a slow response can benefit from retreatment with the same or different pegylated interferon and extending treatment times to 72 weeks.[37] Patients who relapse were more likely to respond to retreatment compared with those who did not respond

Panel Discussion

Marion G. Peters: Do you foresee any problems with cross-resistance between antiviral drugs for human immunodeficiency virus (HIV) and specifically targeted antiviral therapy for hep C (STAT-C) drugs for hepatitis C virus (HCV)?

Jeffrey S. Murray: We have seen no evidence to indicate there will be cross-resistance between currently available HIV and STAT-C drugs. However, the potential exists for newer drugs that are still in development.

Marion G. Peters: If a patient treated for chronic HCV achieves a sustained virologic response, are they still at risk for liver cancer?

Ira M. Jacobson: Yes, unfortunately, in clinical practice we are seeing patients with advanced fibrosis or cirrhosis who have a sustained virologic response to antiviral therapy develop liver cancer. These patients need to be monitored for hepatocellular carcinoma (HCC), even when they have a sustained virologic response.

Marion G. Peters: From the perspective of the Veterans Administration, what is needed to improve the effectiveness of viral hepatitis care?

David B. Ross: We need to do a better job of communicating the importance of recognition and diagnosis of viral hepatitis. Ideally, primary care physicians would respond to a positive test for HBV or HCV with the same sense of urgency as they would to a patient with a blood pressure reading of 220/120 mm Hg. In addition, we need a fully integrated system of care with access to all medical and psychiatric services needed after testing. Electronic medical records and software that facilitates continuity of care and patient follow-up are also needed.

DISCLAIMER

The opinions expressed in the panel discussion are those of the participants. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

to initial pegylated interferon therapy. Patients with less fibrosis, a lower baseline viral load, and genotype 2 or 3 were also more likely to respond to retreatment.[38] Treatment with consensus interferon, a synthetic form of interferon, in combination with ribavirin is effective for some nonresponders, particularly those who do not have cirrhosis.[32] Maintenance therapy with pegylated interferon does not appear to have any benefit on long-term hepatitic complications for initial nonresponders.[39]

Specifically targeted antiviral therapy for HCV (STAT-C). Several recent clinical trials suggest that the protease inhibitors telaprevir and boceprevir in combination with pegylated interferon and ribavirin may lead to an improved response.[40-42] A nucleoside polymerase inhibitor (R7128) and nonnucleoside polymerase inhibitor (filibuvir) also demonstrated efficacy against HCV in preliminary trials.[11,43] A phase 1 trial recently showed that a combination of a protease inhibitor and nucleoside polymerase inhibitor without pegylated interferon was safe and effective in reducing viral load in previously untreated patients with HCV genotype 1.[44]

Several challenges to effectively treating HCV still remain. Baseline predictors of response need to be defined to aid in patient selection and duration of therapy. The potential for development of resistance with different therapies must be determined. The viral kinetics of new therapies must be described. And finally, markers of complete viral eradication must be found.

The role of governmental agencies in HBV and HCV research and treatment development

NIH clinical research programs for viral hepatitis

The National Institutes of Health (NIH) is composed of individual institutes, offices, and centers that engage in clinical research programs for a diverse range of medical conditions, including chronic viral hepatitis.[45] In addition to supporting hepatitis clinical programs, the NIH has produced several reports and plans for addressing viral hepatitis, such as the Trans-NIH Action Plan for Liver Disease Research,[46] The Burden of Digestive Diseases in the United States (2008),[47] and the National Commission on Digestive Diseases: Opportunities and Challenges in Digestive Diseases Research.[48] In 2008, the NIH provided $93 million for HCV research and $53 million for HBV research, with similar funding levels for 2009-2010.[49]

Role of the FDA in clinical trials and drug development

As mentioned, several different classes of HCV drugs are now in clinical trials. In order to promote and encourage efficient and appropriate use of resources, the FDA identifies outstanding research needs for treating HBV infection and defines principles for new drug development for HCV infection. From a regulatory perspective, new HBV drug development should target relationships between surrogate end points and clinical outcomes, and timing and duration of therapy.[50] As determined by the FDA, the principles for HCV drug development include prescribing treatment options and minimizing emergence of resistance; defining optimal dose and treatment duration; including relevant populations in early phase trials; studying combinations of investigational agents; and developing regimens for patients who currently have no treatment options.[50]

Economic issues in the treatment of chronic HBV and HCV infections

Hepatitis B and C are associated with substantial morbidity, mortality, and direct and indirect costs. The estimated cost for hospitalizations related to HBV infection in 2006 was more than $1 billion,[51] and the direct medical costs for HCV infections are estimated to amount to $10 billion between 2010 and 2019.[52] There is increasing pressure for all treatments, including those for viral hepatitis, to demonstrate cost-effectiveness in addition to therapeutic benefits.[53,54]

To help policy makers in governmental organizations appropriately plan for viral hepatitis, collaboration between clinicians and all others with a financial stake in fighting this disease is needed to provide accurate assessments of the value of viral hepatitis treatments. In addition to HBV and HCV clinical studies, cost-effectiveness analyses are needed to translate health outcomes into health economic metrics. ■

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The dawn of a new era: Transforming our domestic response to hepatitis B and C

Activity 8: Transforming strategies to provide access to care

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A comprehensive response to viral hepatitis must address barriers to prevention and care in uninsured, underinsured, and medically underserved populations. Strategies to improve access to care include development and funding of community health care centers, recognition of and outreach to disenfranchised patient populations, and the expansion of the Ryan White Care Act and Medicaid.

Chronic hepatitis B infection: Gaps in care and potential solutions

The disease burden of chronic hepatitis B virus (HBV) infection is substantial and disproportionately affects immigrant populations. There are many challenges to ensuring access to medical care for foreign-born populations. A review of the success of one community health care center serving an immigrant population with a high prevalence of HBV infection can provide insights into strategies that may be applicable to other areas of the nation.

The Charles B. Wang Community Health Center (CBWCHC) is a federally qualified health center (FQHC) that provides services to medically underserved, non–English-speaking, low-income populations in New York City with 2 sites: one in Chinatown (Manhattan) and the other in Flushing (Queens). In 2000, in New York City, approximately 44% or 2.7 million of all adults were foreign-born, and 21% of those individuals were Asian.[1] The Chinese are the largest Asian group in New York, accounting for 45% of the city's Asian population. Approximately 60% of the Chinese in New York have limited English language proficiency, and 20% live below the poverty line.[2] In 2008, the CBWCHC provided care for 36,000 patients; 72% of these patients had some form of government-provided insurance, 23% had no insurance, and 5% had commercial insurance.[3]

Importance of partnerships, integrated care, and other tools

The CBWCHC works with multiple partners, including government agencies, nongovernmental organizations, and industry, to provide affordable routine screening tests and vaccinations (**TABLE**). HBV testing and care is done routinely for CBWCHC patients and through community outreach programs. In the 2 largest screening programs, between 2004 and 2008, approximately 22% of the almost 4000 individuals tested were hepatitis B surface antigen (HBsAg)–positive. Further analysis of

TABLE HBV screening and vaccination program and partners at Charles B. Wang Community Health Center in New York City

Program	Partners	Years of program	Total patients screened
Community-based screening	Chinese American Medical Society, Chinese American Independent Practice Association, Oxford, GlaxoSmithKline, New York City Department of Health and Mental Hygiene (NYC DOHMH)	2000-2002	1600
Asian American Hepatitis B Program (AAHBP)	New York City Council, New York University (NYU), NYC DOHMH, New York City Health and Hospitals Corporation	2004-2008	3000
Hepatitis B family (HBV household contacts)	Robin Hood Foundation, NYC DOHMH	2006-2008	1200
Perinatal household contacts	NYC DOHMH	2008-current	170
B Free NYC	Gilead, Bristol-Myers Squibb, NYU	2009-current	700 (goal)
Total			6670

HBV, hepatitis B virus.

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those individuals who reported that this was their first time being tested resulted in an HBsAg-positive rate of 14%, reflecting a potential bias of screening programs because they attract individuals who have previously tested positive for HBV. Almost one-third of those screened (28%) were found to have no evidence of immunity to HBV, indicating there is still a need to screen and vaccinate in this community. In the largest screening program where follow-up care was provided for those who were HBsAg-positive, 62% accessed follow-up care, which was provided at no charge, and 19% of those eventually began antiviral therapy. In addition, approximately 73% of the patients who were offered vaccination in the 2 largest screening programs completed the recommended 3 doses.[3]

This low follow-up rate for services available at no cost led CBWCHC to work to enhance its delivery of care and to improve outcomes by adopting the chronic care model.[4] The goals of using this integrated approach in the management of chronic HBV infection are to improve interaction among the patient, his or her family, and the practice team; to help patients develop the confidence and skills needed to manage their condition; and to ensure better compliance with visits, adherence with antiviral regimens, and prevention and early detection of cirrhosis and hepatocellular carcinoma.

To further improve clinical decision making and continuity of care, the center uses tools such as an HBV disease registry, HBV history forms, and flow sheets in electronic format as well as a patient self-tracker that serves as an education tool and a portable medical record. The CBWCHC also negotiates its own rates with radiology services and laboratories, offers sliding scale fees as well as free services, utilizes pharmaceutical assistance plans, provides for referrals, and facilitates access to specialists outside the center.

Approximately 98% of all patients are served in a language other than English, including Mandarin, Cantonese, Fujianese, Korean, and Vietnamese. In addition, providers are aware of potential barriers to care, such

as their patients' use of complementary and alternative medicine, including herbal medications, and their health beliefs.

Targeting pregnant women to reduce perinatal transmission

In 2006 and 2007, approximately 20% of CBWCHC's pregnant patients were HBsAg-positive, and many were diagnosed for the first time. Pregnancy is an opportune time to educate patients about HBV so they can be encouraged to establish regular HBV care, and screening of household contacts can be made available to them. CBWCHC coordinates care among its internal medicine, women's health, and pediatric specialties to monitor HBV-infected pregnant women during and after their pregnancy and ensure appropriate vaccination and testing of their infants. Collaborating with the hospitals where CBWCHC patients deliver has been crucial, ensuring that their HBV status is known at the time of delivery so that hepatitis B immune globulin can be provided within 12 hours for infants of HBsAg-positive mothers.

Closing the gaps in HBV infection care

Based on the experience at CBWCHC, suggestions for closing the gaps in care for HBV infection across the nation include increasing health insurance coverage by allowing subsidies for up to 400% of the federal poverty level, expanding Medicaid by removing the 5-year residency requirement, disallowing the exclusion of treating preexisting conditions, and extending Medicare Part D medication coverage. In addition, care can be improved by using a chronic care model as described above, accessing enhanced health informatics, and providing culturally appropriate care. Finally, funding is required for comparative effectiveness research on health disparities, increased grants for communities with disparities, and increased resources for Federally Qualified Health Centers and clinician training.[3]

Chronic hepatitis C virus infection: Gaps in care and potential solutions

Chronic hepatitis C virus (HCV) infection disproportionately affects the disenfranchised. Those who inject illicit drugs are overwhelmingly affected, with HCV prevalence levels as high as 80% to 90% among long-term injectors and incidence rates of new infection of 10% to 40% per year among young injectors.[5,6] Incarcerated and homeless populations have prevalence rates far above the national average, as do people with severe mental illness or other medical or behavioral conditions, and disadvantaged ethnic minorities.[7] In a nationally representative sample of noninstitutionalized, housed people, for example, 14% of African American men aged 40 to 49 years were infected.[8] A staggering 39.8 million people in the United States lived below the poverty line in 2008—3 million more than in 2007—including 23% of Latinos, 25% of African Americans, and nearly 1 in 5 children of all nationalities.[9] Americans living in poverty have a 9-fold increased prevalence of HCV infection.[8] All these groups are disproportionately uninsured, underinsured, and underserved, and will likely continue to be so even if the US Congress passes health care reform. Yet these are the groups most in need of comprehensive prevention and treatment services. Measures to close existing gaps must be implemented if we wish to contain the morbidity and mortality associated with HCV.

The rate of new HCV infections among those who inject illicit drugs represents a dramatic decline from the 1980s, when as many as 80% of such people were infected within the first year of drug use.[10] This underscores the effectiveness of interventions implemented to prevent HIV transmission in this population—community-based outreach and education, HIV counseling and testing, syringe exchange and syringe access programs, and increased availability of substance use treatment—for preventing HCV transmission as well. Yet many communities continue to lack these basic interventions.[11] Even surveillance activities undercount those at highest risk for hepatitis C disease if special attention is not focused on the disenfranchised (eg, homeless or incarcerated individuals).[12] Estimates of the incidence rate count new infections only in people who feel well most days and visit their doctors when they do not, an uncommon scenario among those most at risk for infection with HCV.[6,13] Accurate surveillance of conditions that disproportionately affect disenfranchised populations must specifically target these groups.

Closing the gaps in hepatitis C care requires an integrated approach to providing multidisciplinary services, including continuing primary care, specialty care (eg, human immunodeficiency virus [HIV] and hepatol-

Panel Discussion

Edward Chow: One way to help close the gaps in access to care is to develop community-based health plans. In San Francisco, our Chinese Community Health Plan (CCHP) provides medical preventive services, including hepatitis B virus (HBV) testing and vaccination. CCHP has supported the efforts of San Francisco Hep B Free in bringing individuals in for both testing and treatment.

Educating local policy makers about hepatitis also produces results. Mayor Gavin Newsom issued an executive order on September 9, 2009, stating that written educational materials on the importance of HBV screening and vaccination must be provided to all people registering for a marriage license in San Francisco. The goal is to bring people into testing, preventive services, or treatment earlier, and ultimately to improve the overall health of the city, state, and nation.

Ira Jacobson: Why isn't hepatitis C virus (HCV) as heavily funded as HIV, and what steps are needed to increase resources for HCV?

Brian Edlin: One reason, at least in part, is the success of advocacy campaigns and the community involvement associated with HIV/AIDS. We can use the response to AIDS as a blueprint for how to formulate a response to HBV and HCV. Clearly, for viral hepatitis, we need to increase advocacy and community involvement as well as communication and collaboration with policy makers on a national level. Health care reform that would provide universal coverage is also needed.

I**ra Jacobson:** Would there be any additional value to increased surveillance for HCV and the gathering of demographic data?

Brian Edlin: Increased surveillance is a very sensible idea; however, adding demographic data to the current surveillance systems we have will not provide information on those individuals missed by the system. Entire segments of the HCV population will continue to be missed unless surveillance efforts specifically target disenfranchised populations.

Norma Harris (Division of Viral Hepatitis, Centers for Disease Control [CDC], Atlanta): Currently, the viral hepatitis surveillance efforts by the CDC are done on a small budget, and we need increased funding to expand surveillance. Few sites have the resources to do adequate case surveillance, let alone surveillance for chronic HCV in special, hidden populations. One measure the CDC Division of Viral Hepatitis has taken for special populations, such as injection drug users, high-risk heterosexuals, and men who have sex with men, is to partner with the Division of HIV/AIDS Prevention, which has a national HIV behavioral surveillance system with approximately 24 participating sites.

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ogy), mental health services, substance abuse services, social services, and case management. Further research is necessary to develop optimal methods for delivering these services. Indeed, the Institute of Medicine, in its 2009 report, identified the development of optimal treatment strategies for HCV infection in at-risk populations such as African Americans and injection drug users as one of the nation's top research priorities.[14]

Surveillance and treatment of acute HCV infection may offer an effective approach to interrupting HCV transmission.[6] Regular screening of high-risk individuals such as those who inject illicit drugs would identify new infections during the acute phase, when treatment is twice as effective as during chronic infection. This approach would prevent chronic infection and avert secondary transmission. The incarcerated population offers an unparalleled opportunity to screen for, treat, and prevent HCV infection (see Activity 6, page S43).[15]

The Ryan White CARE Act

In considering how to meet HCV prevention and treatment needs, it is not necessary to reinvent the wheel. Since 1991, the Ryan White CARE (Comprehensive AIDS Resources Emergency) Act (RWCA) has provided federal funding for comprehensive primary and specialty medical care for patients living with HIV/AIDS.[16] This program funds integrated, multidisciplinary care, including mental health services, substance use treatment, case management, and other essential social services. Unlike Medicaid, it funds prevention services such as testing and risk reduction counseling, and health care provider education and training to improve the quality of care. Funded programs are designed locally by grantees.

Initiatives target special populations, such as women, children, youth, and ethnic minorities. The program is successful in reaching those most in need: 72% of clients are below the poverty line. This effective program costs $2.1 billion annually,[16] a minor proportion of the total $2.5 trillion annual health care expenditure.

Although 4 times as many people in the United States are living with HCV as with HIV, antiviral treatment for HCV, in contrast to HIV, usually lasts only a year or less and is curative in half of those treated. Providing HCV prevention and care services to all those in need is neither impossible nor impractical. The RWCA should be expanded to cover HCV prevention and care.

Medicaid hepatitis expansion project

Medicaid eligibility for adults is severely limited and, with few exceptions, adults without children or disabilities are excluded from coverage, no matter how low their income. Low-income adults without insurance coverage are more than twice as likely as those with Medicaid coverage to forego medical care when they need it because of cost.[17] Delays in treatment can have serious consequences for those with viral hepatitis. Opening Medicaid enrollment to adults with chronic HBV or HCV infections would allow these individuals to seek treatment earlier, which may reduce the risk of progression to advanced liver disease.

Medicaid overview

Medicaid is the nation's largest health care program, with an estimated 68 million people enrolled in 2009.[18] Medicaid provides coverage for 34 million children (26%) and coverage for 41% of all births. Approximately 10 million Americans with disabilities are covered by Medicaid, including 44% of people with HIV or AIDS and 60% of those living in nursing homes.

Current Medicaid eligibility is based on patient categories and low-income criteria. The primary categories include low-income parents and their children and individuals with disabilities. There are only 3 conditions that allow exceptions for childless and nondisabled adults: breast and cervical cancer, tuberculosis, and pregnancy. Therefore, nondisabled adults without children who have viral hepatitis have no disease-specific pathway to Medicaid coverage. Although states may apply for waivers to allow coverage of nondisabled, childless adults, the state must demonstrate that the waiver does not add more cost to the Medicaid program, ie, that it shows budget neutrality within a 5-year time frame.

Policy makers should consider expanding Medicaid to provide care for childless adults with chronic HBV infection. This could be achieved by allowing coverage to be based on income alone (eg, up to at least 100% of the poverty level), eliminating the need for waivers or demonstration of budget neutrality, and adopting federal legislation to allow states to implement disease-specific viral hepatitis coverage.[18] As the burden of chronic HCV and HBV infection is only expected to grow in the coming years, adjustment of the Medicaid system to provide care for the uninsured is imperative. ■

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The dawn of a new era: Transforming our domestic response to hepatitis B & C

Activity 9: Transforming the current infrastructure for combating HBV and HCV infections

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The approach to controlling and preventing hepatitis B virus (HBV) and hepatitis C virus (HCV) infections adopted by the US Centers for Disease Control and Prevention (CDC) has evolved to address emerging transmission patterns and to halt or reverse expected increases in morbidity, mortality, and related health costs. The CDC aims to eliminate HBV transmission by using safe and effective vaccines and to minimize HCV transmission and mortality. The Ryan White HIV/AIDS Program offers viral hepatitis screening, vaccination, and treatment for low-income individuals with human immunodeficiency virus (HIV), although there are challenges in terms of funding, sufficient provider knowledge, and patient education.[1]

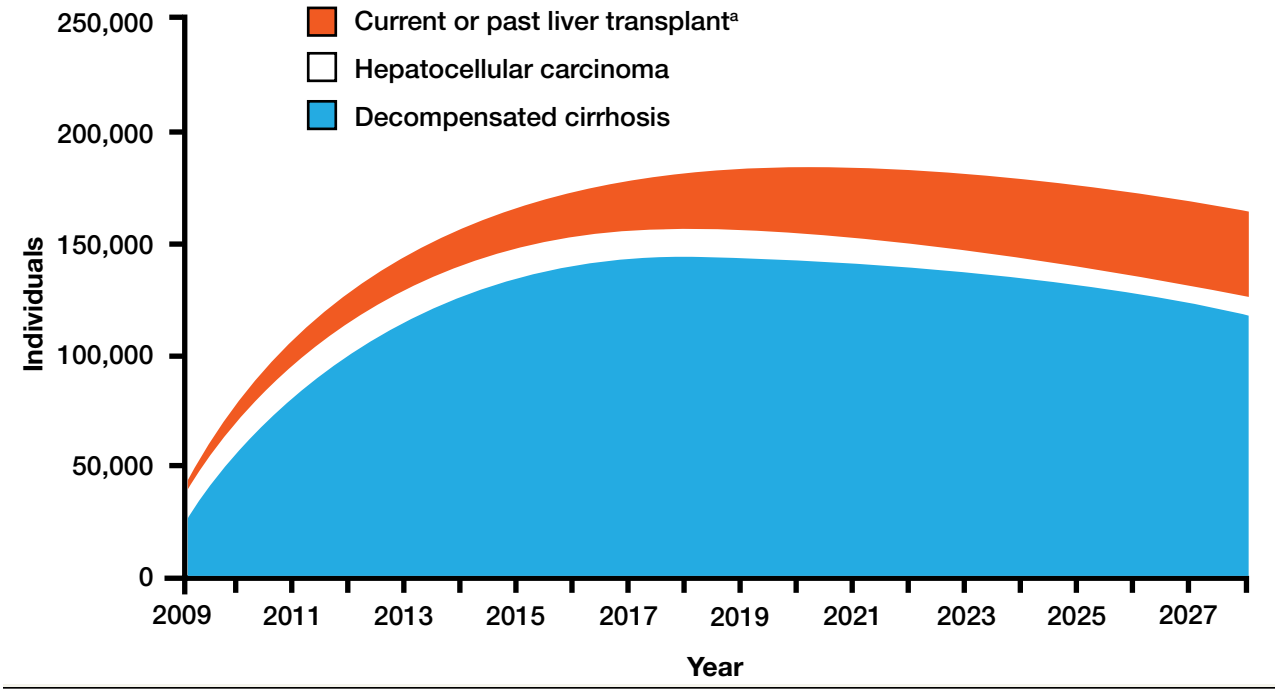
Modernizing the CDC's approach

Epidemiologic imperatives for modernizing the CDC's approach to preventing chronic viral hepatitis are numerous.[2] Because millions of Americans are currently living with chronic viral hepatitis, the burden of disease is large.[3] Increased immigration and an aging population have highlighted the disproportionate burden for certain segments of society, including African Americans, Asian/Pacific Islanders, Hispanics with known risk factors, and baby boomers (those born between 1945 and 1964), for whom adverse outcomes and costs associated with chronic viral hepatitis are projected to increase.

Between 12,000 and 15,000 deaths per year are attributed to these infections; many infected individuals are unaware of their status, which points to missed opportunities to prevent related morbidity and mortality. For example, in the absence of effective prevention and treatment strategies, one model projects that, in the coming decades, the number of patients with HCV-associated morbidity will greatly increase **(FIGURE 1)**.[4]

The CDC has identified 6 components that are crucial to modernizing its efforts to eliminate HBV transmission, decrease the incidence of HCV infection, and improve health outcomes for those infected with chronic viral hepatitis: (1) an improved and sound evidence base for prevention; (2) accurate acute and chronic disease surveillance; (3) public health policies implemented by both public and private providers; (4) effective delivery of proven interventions; (5) education to prepare communities to accept prevention services; and (6) resources to support the public health response.[2] These goals will be accomplished by committing resources to develop each component in the approach and by forging partnerships with other stakeholders.

FIGURE 1 Projected increase in HCV-related morbidity through 2027



[a]Liver transplants include both HCV-related transplants that occur during the year and survivors of such transplants since 2009.

Pyenson B, Fitch K, Iwasaki K. Consequences of hepatitis C virus (HCV): costs of a baby boomer epidemic of liver disease. Pyenson B. Milliman Inc, 2009. www.milliman.com/expertise/healthcare/publications/rr/consequences-hepatitis-c-virus-RR05-15-09.php. Accessed December 11, 2009.

Evidence base for prevention

Research to improve screening for viral hepatitis is the first priority, as screening efforts to date have not been fully effective. The CDC is currently evaluating new testing technologies such as point-of-care HCV tests and optimal strategies for reaching target populations. For example, screening based on year of birth might be an effective strategy to reach the baby boomer cohort. Research to guide efforts to increase awareness is needed both for providers and the general public, particularly in communities with health disparities related to chronic viral hepatitis.

Program research is needed to identify the best practices to assist communities seeking to implement prevention programs, including programs for people recently arrived from high-prevalence regions. In addition to screening, prevention programs include vaccination, case management, and referral for care. The Division of Viral Hepatitis at the CDC is charged with developing immunization policies that will complement screening efforts. Evidence-based policies are needed to address specific patient situations, including whether individuals vaccinated as infants require booster doses in later life and whether older adults in institutional settings who may be at risk for HBV should be vaccinated.

Tracking emerging patterns of transmission is imperative to developing the evidence base for prevention. The most recent trends indicate that HBV and HCV transmission is occurring in health care settings, through sexual exposure for those who are positive for HIV, and among injection drug users.

Accurate disease surveillance

The CDC is taking steps to improve the quality of outbreak detection as well as to develop reliable chronic HBV and HCV disease reporting systems and registries. Tracking HIV coinfection and the incidence of liver cancer among patients is also being addressed. Case reporting must be coordinated with prevention programs at state and local health departments because the surveillance data must inform and guide local actions.

To improve monitoring of health care disparities, the CDC supports the Racial and Ethnic Approaches to Community Health (REACH) survey to track viral

hepatitis–related risk factors and use of preventive services within 28 African American, Hispanic, Asian, and American Indian/Alaska Native communities. Data will be collected between 2009 and 2013, including data specific to HBV infection.[5,6] REACH will also gather information from 22 action communities and 18 centers of excellence to implement and evaluate successful practice-based and evidence-based programs designed to help eliminate health care disparities.

The CDC will also improve monitoring of viral hepatitis prevalence and receipt of viral hepatitis prevention services through the National HIV Behavioral Surveillance System (NHBS). Started in 2003, the NHBS collects data from high-risk adults (ie, injection drug users, men who have sex with men, and heterosexual adults in high-prevalence areas) in 25 US cities.[7] The CDC has also started an observational cohort study of individuals undergoing treatment for viral hepatitis to monitor delivery of clinical prevention services.

Broadly implemented public health policies

The CDC has issued recommendations to guide the implementation of education, screening, and referral programs for chronic viral hepatitis. The compiling of evidence to guide the US Preventive Services Task Force in assessing prevention policies is under way. The findings of the CDC-commissioned review of viral hepatitis prevention by the Institute of Medicine (IOM) were issued in early January 2010.[8] Another CDC goal is to work more closely with the Centers for Medicare and Medicaid Services and insurers to promote routine delivery of viral hepatitis services.

Effective delivery of proven interventions

CDC support of state and local prevention capacity includes 55 CDC adult viral hepatitis prevention coordinators.[9] However, these coordinators lack the resources to implement education, testing, and referral programs and do not have funds for developing new prevention tools. The CDC currently provides little funding for chronic viral hepatitis screening. Although HIV, viral hepatitis, and sexually transmitted disease prevention programs must be integrated, hepatitis services cannot simply be added to HIV programs. The field of viral hepatitis is its own discipline, and delivery of successful interventions requires knowledge and skills to address these infections together with HIV infection and sexually transmitted diseases.

Current vaccination programs provide a robust opportunity to extend vaccinations and provide additional screening and referral services. For example, an estimated 24,000 HBV-infected mothers give birth annually, and the CDC recommends they be referred for care.[10] One longstanding recommendation is that all family members of HBV-infected mothers be screened and vaccinated. However, the means to implement these recommendations are limited. Additional work with other organizations and partners must also be initiated in order to deliver prevention programs to injection drug users.

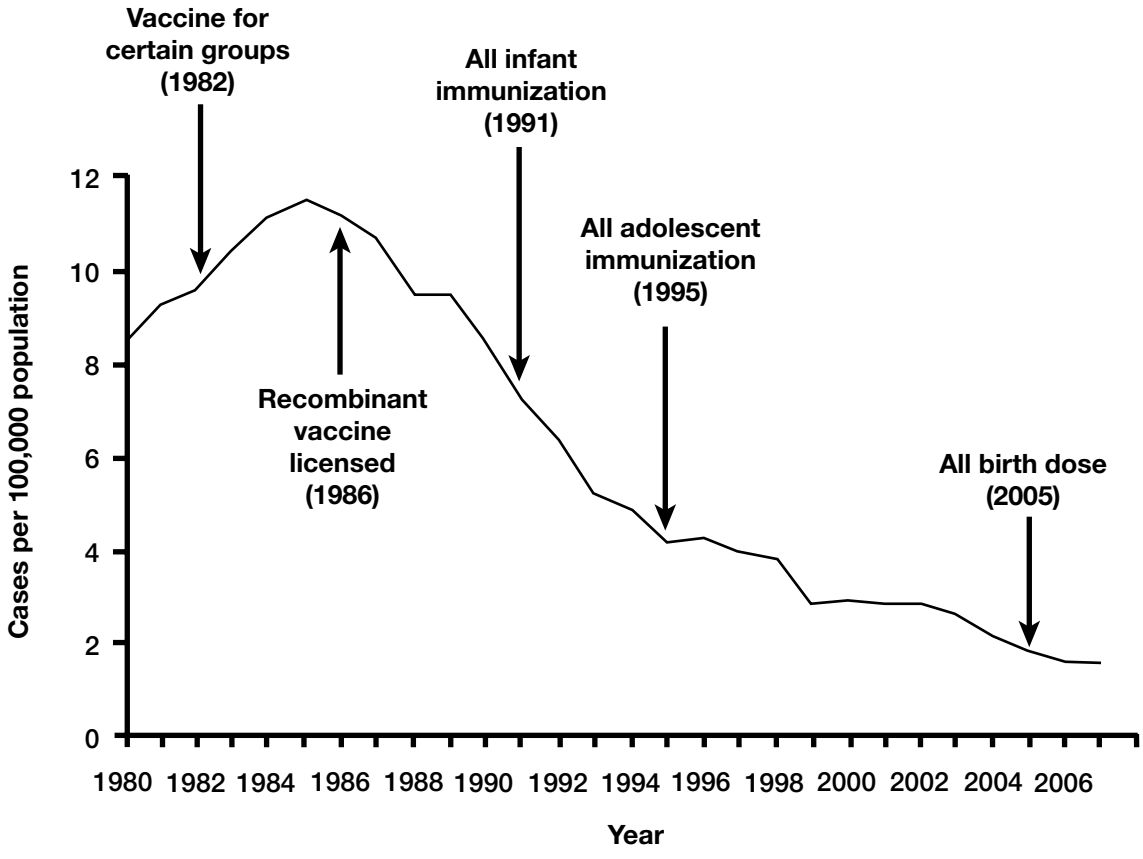
Preparing communities to accept prevention services

A primary goal is to increase general awareness of viral hepatitis in ways that will benefit patients in terms of how they access prevention and care. New ways of presenting evidence-based HBV and HCV information to the general public should be sought, such as positioning hepatitis prevention and screening as cancer prevention tools in public awareness campaigns.

Building awareness and cooperation among community-based organizations is important. By engaging diverse community groups that are closest to the public they serve, education and information can be more effectively targeted to the social and cultural norms in each community. Targeted efforts are essential for convincing community members to accept the services that will be most useful for preventing viral transmission in their local area. Community-based organizations can also be the primary resources for distributing toolkits and offering prevention expertise that can address health care disparities.

The stakeholders in hepatitis prevention also include groups such as AARP (formerly the American Association of Retired Persons), which represents a demographic group with a high prevalence of HCV infection. Such organizations can help amplify the importance of hepatitis prevention and screening to the public and to policy makers. Efforts to develop partnerships with the American Diabetes Association offer another prevention opportunity, given the association between HCV and diabetes and the documented outbreaks of HBV among residents in long-term care with diabetes.[11,12] On a smaller scale, academic centers and individual businesses can be engaged to deliver prevention services to students and employees.

FIGURE 2 Decline in estimated new cases of HBV infection with hepatitis B vaccination



Ward J. Presented at: The Dawn of a New Era: Transforming Our Domestic Response to Hepatitis B & C; September 10-11, 2009; Washington, DC. Adapted from CDC. Hepatitis B FAQs for health professionals. www.cdc.gov/hepatitis/HBV/HBVfaq.htm.

Resources to support the public health response

Hepatitis B. All of these CDC goals require substantial investment. Large investments in public health make a substantial difference in attaining public health goals. Following the issuance of a recommendation for universal vaccination of infants in 1991, HBV infection rates have fallen dramatically.[13] Tracking the incidence of acute HBV infection after various interventions made possible by large financial support illustrates the effectiveness of intervention **(FIGURE 2).**

Hepatitis C: Creating an HCV safety net within the Ryan White Program

The structure of the well-established Ryan White Program, administered by the Department of Health and Human Services Health Resources and Services Administration (HRSA), presents another opportunity to decrease the incidence of HCV and improve care for coinfected individuals.[14] This $2 billion federal program, begun in 1991, provides funds directly to states, cities, and community-based organizations to provide care for the uninsured and underinsured population with HIV. Although clinicians working within the Ryan White Program have successfully incorporated HBV detection and prevention, similar success in decreasing HCV infections in this patient population has not been observed.

Because HCV coinfection is common among patients with HIV,[15] breaking down specific barriers within the Ryan White Program may help decrease the burden of hepatitis C disease. Possible targets for action include improving clinician knowledge and expertise related to HCV treatment, providing funds for HCV test-

ing and counseling, and improving HCV-related quality measures required for organizations to receive Ryan White Program funding.[14]

A central tenet of the program, and one often cited as the reason for its success, has been that grantees have control over expenditures. Needs assessments and priorities are developed at the local level, and patients infected with HIV are required to participate in the planning process. The Ryan White Program funds medical care considered critical to local needs, including substance abuse treatment, mental health and legal services, transportation to the clinic, child care during appointments, as well as intensive case management and medical care. Funding of such support services can serve as a model for future efforts to serve those with HCV, including homeless veterans.

Why is HCV capacity-building needed? The HIV/AIDS Bureau recognizes that 15% to 30% of patients with HIV are coinfected with HCV,[16] that liver disease is a major cause of death in this population,[17] and that the rate of liver disease in HIV-HCV coinfected patients is increasing.[18] The Ryan White Program presents an ideal setting for multidisciplinary, community-based, intensive case management with integrated care; thus, it emphasizes providing technical assistance and planning at the state and local level to foster access to HCV treatment within the context of HIV care. However, these efforts have not been successful at increasing access to treatment.

Barriers to HCV care within the Ryan White Program. A number of barriers to HCV care within the Ryan White Program have been identified, including a lack of HCV treatment knowledge by providers and a lack of skill to deliver treatment. Providers' attitudes toward HCV treatment goals represent another barrier because some clinicians do not consider the response rates achievable with current treatments (approximately 30%-40% in HIV-HCV coinfected patients with HCV genotype 1) to be successful treatment for their patients. Further, community health centers have voiced concerns about the costs of genotype testing and other expenses that would be involved if HCV treatment were added to HIV care. Access to specialty HCV care, including biopsies, has been a challenge despite clinics being permitted to use Ryan White Program funds for specialty care access. Locating appropriate specialty providers in the community who are willing to also provide assistance has proven difficult for some centers.

Patients' attitudes are a barrier because many patients have multiple HIV comorbidities and believe that HCV carries an additional stigma. Patients often also fear biopsy procedures, and HCV treatment can have side effects that lead to high rates of discontinuation. For practitioners, coinfection with HIV complicates the care of patients with hepatitis.

HCV care supported by the Ryan White Program. Ryan White Program funds can be used to provide patient counseling, laboratory monitoring, HCV treatment, and medical visits to primary care and subspecialty providers. Many Ryan White centers provide part-time integrated HCV care, in that they work with HIV patients who are about to start HCV treatment or who are already receiving it.

Currently, 29 AIDS Drug Assistance Programs (ADAPs) pay for HCV treatment (interferon and ribavirin),[19] and another 13 consider those treatments to be part of the ADAP services even though medications are obtained through the drug manufacturer's access program. Many Ryan White centers and other ADAPs believe that an expansion of services to include HCV treatment would be a strain on their budgets, yet ADAPs that cover HCV treatment spend less than 0.23% of available funds for these medications.

Ryan White Program funding can also be used to build HCV capacity through provider education offered by the AIDS Education and Training Centers and through funding of additional technical assistance needed to accommodate the additional needs of those with HIV-HCV coinfection.

Current data and ongoing efforts. Despite having an ideal setting through which to provide HCV care and treatment, and despite providers dedicated to helping these disenfranchised patients, the Ryan White Program has failed to adequately integrate HCV treatment. In 2006, approximately 91% of patients with HIV treated within Ryan White centers underwent HCV antibody testing, yet only 6841 patients were treated for HCV in Ryan White clinical programs, representing the estimated 2% of patients with HIV in those programs who were thought to be infected with HCV.

To facilitate increased HCV care and treatment in the Ryan White Program, beginning in 2010, the HIV/AIDS bureau is developing a technical assistance tool that will highlight various models of HCV care integration used by Ryan White Program grantees that have had success in treating these patients. Some of the sug-

gested models will involve Ryan White Program primary care providers being responsible for increasing the center's capacity for HCV care, and other models will illustrate how to enlist assistance from hepatitis specialists, when financially feasible.

One key component of integrating HCV care into Ryan White centers will be to develop effective patient support groups for coinfected patients to empower them to agree to HCV care and, once they receive care, to support them during treatment. Other components addressed in the technical assistance tool will include the type of leadership a center should have in place for successfully integrating HCV care, and the type of HCV treatment funding a center should arrange.

Using a pilot approach, approximately 12 Ryan White centers will have the opportunity to receive up to $100,000 in 2010 to integrate HCV care into their HIV primary care settings using the key factors identified in the technical assistance tool being developed. If successful, additional funding for HCV care may be expanded to additional Ryan White centers.

Within the HRSA, the Office of Minority Health and Health Disparities is also working with the CDC and primary care associations to create linkages between health departments and community health centers. These agencies are working toward increased HCV and tuberculosis prevention, detection, and treatment. The National Association of Community Health Centers is also attempting to integrate HCV care into primary care settings. Two successful programs that the association has highlighted were modeled on the Ryan White Program approach to HIV, illustrating the opportunity that the Ryan White Act presents for promoting HCV care among the disenfranchised. ■

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