



NVHR

National Viral Hepatitis Roundtable

November 6, 2012

Robert Cosby, MD
U.S. Preventive Services Task Force
540 Gaither Road
Rockville, MD 20850

Re: USPSTF DRAFT Research Plan Screening for Hepatitis B Virus Infection in Nonpregnant Adolescents and Adults

On behalf of the approximately 200 organizations representing the chronic viral hepatitis community, the National Viral Hepatitis Roundtable (NVHR) would like to thank the United States Preventive Services Task Force (USPSTF) for the opportunity to comment and provide feedback on its draft research plan regarding the screening for hepatitis B virus infection in nonpregnant adolescents and adults. The NVHR is a coalition of public, private and voluntary organizations dedicated to reducing occurrence of infection and mortality from viral hepatitis in the U.S.

Our comments will focus on the draft research plan's proposed key questions:

- 1. What are the benefits of screening for hepatitis B virus (HBV) infection versus no screening in asymptomatic, nonpregnant adolescents and adults on morbidity, mortality, and disease transmission?***

Reducing Hepatitis and Liver Cancer Disparities: The hepatitis B virus (HBV) continues to cause significant morbidity and mortality in the United States. Chronic infection with HBV is a major risk factor for the development of end-stage liver diseases, including cirrhosis, liver failure and primary liver cancer. People who are chronically infected with HBV carry a lifetime risk of death from end-stage liver disease or primary liver cancer of between 15 and 25 percent. With more than 350 million people chronically infected worldwide, lives lost to HBV eventually could exceed 100 million. Liver cancer, the second deadliest cancer in terms of survival time, has one of the fastest growing cancer rates as measured by incidence.

Asymptomatic, and often undetectable, without screening: Nearly one-third of people who are chronically infected show no noticeable symptoms. Without diagnosis, these individuals do not receive treatment that could slow progression of the disease, and may unintentionally expose others to HBV. This makes HBV screening crucial. Screening for HBV is cost effective down to a

prevalence of 0.3 percent. Because this prevalence is less than the HBV frequency in the U.S., these parameters suggest that all adults should be screened.

Cost Efficient: When testing for infection status, all three tests should be provided: the hepatitis B surface antigen (HBsAg), the hepatitis B surface antibody (HBsAb), and the hepatitis B core antibody (HBcAb) blood tests. The latter method will ascertain more accurate infection rates by reducing false negative rates. In addition, screening would be more cost efficient if it includes all three tests since the positive core antibody tests would identify those who are already immune to the virus and do not otherwise need the vaccine.

Testing for high risk individuals has been shown to reduce morbidity and mortality from hepatitis B and provide opportunities to prevent transmission to those family member and household contacts that may have been or will be exposed to the virus. This includes immigrant populations from areas with hepatitis B endemicity greater than 2 percent.

2. *What are the harms of screening for HBV infection (e.g., labeling, anxiety, and harms of confirmatory tests, including biopsy)?*

Many individuals from high-risk communities experience stigma associated with diseases, cancers, death, and screenings. These cultural barriers prevent effective education and diagnosis. We recommend improving community-based awareness efforts and providing culturally appropriate services to overcome these obstacles.

Harm of confirmatory tests, including biopsy, could be minimal: Only 5 percent of HBV patients currently undergo liver biopsies to confirm their HBV status. Serious adverse events resulting from these liver biopsies occur in less than 1 in 1,000 patients. Death as a result of a liver biopsy occurs in less than 1 in 13,000 patients.

There are currently no evidence based studies or randomized controlled trials linking hepatitis B screening to increased harm or anxiety. The basis for many of these concerns is hypothetically true in countries where work place discrimination is prevalent against those with chronic HBV infection.

3. *How well do different screening strategies identify persons with HBV infection (e.g., strategies that target persons from high-prevalence countries, men who have sex with men, injection drug users, or persons based on their immunization history)?*

As one continues to use screening strategies to examine at-risk populations, including Asian Americans, Asian immigrants, African immigrants, men who have sex with men, injection drug users, persons based on their immunization history, and low-income subgroups, the association of infection status with demographic characteristics like U.S. residency, gender, age, and insurance status should also be examined, to ensure inclusion of hard to reach populations.

In addition to enrolling members of traditional at-risk groups such as Asian subgroups (Asian

Pacific Islander, Chinese, Vietnamese, and Korean), the screening strategies should be expanded to include additional understudied populations. Populations across all racial groups and some Southeast Asian groups that are at an elevated risk of the disease (e.g., Thai, Cambodian, and Hmong) are often under-reported.

Data analysis and reporting of a patient's infection or unprotected status, potential behavioral links, such as smoking and drug use, and other potential social determinants, such as income, should also be explored.

Regularly reported hepatitis infection data should be aggregated to a geographic level. This way, data can be compared across various geographic boundaries and jurisdictions without compromising the privacy protection and confidentiality of patients.

However, selective screening in and of itself is a barrier to identifying and treating infected individuals. The process takes time to complete and may lead to inaccurate assessments. Ideally, therefore, all adults should be screened.

4. *In nonpregnant adolescents and adults with no evidence of HBV immunity at screening, how effective is HBV vaccination for improving clinical outcomes?*

In the U.S., rates of acute HBV infection have dropped dramatically in the past decade, primarily due to universal vaccination of newborns and children. However, high rates of chronic HBV infection still exist, particularly among high-risk adult populations, the majority of whom are immigrants to the U.S. The Centers for Disease Control and Prevention reports the geographic distribution of chronic HBV infection in the CDC Travelers' Health Yellow Book, which reports HBsAg between 2-8%.

The 3 series HBV vaccine is extremely effective in producing long-term immunity in individuals with a normal immune system. Multiple studies have shown that in high endemicity regions, vaccine use has had a significant decrease in chronic hepatitis B and liver cancer.

5. *In nonpregnant adolescents and adults with chronic HBV infection, how effective is antiviral treatment at improving intermediate outcomes (e.g., virologic or histologic improvement or clearance of hepatitis B "e" antigen [HbeAg])?*

There are now seven antiviral agents approved by the U.S. Food and Drug Administration (FDA) for the management of chronic HBV infection. These agents are categorized as either interferon or nucleoside/nucleotide analogues.

Despite the fact that there are between 1.4 and 2 million chronic HBV infections in the U.S., fewer than 50,000 people per year receive prescriptions for HBV antiviral medications. Explanations for this incongruence include the potentially large number of infected persons who are unscreened and thus remain undiagnosed. Furthermore, it is estimated that only 40 percent of those screened in community clinics and medical offices are referred and linked to

appropriate care. A study conducted by the Hepatitis B Foundation suggests that no more than 80,000 people in the U.S. have been treated with FDA-approved medications over the past 10 years.

Current professional practice guidelines have suggested that only subsets of the chronically infected population be treated based upon disease activity, risk of disease progression, and likelihood of intervention effectiveness. Treatment is typically limited to those HBV carriers who present with biochemical and histological features of moderate or severe liver disease.

The estimates of those with HBV who would fall within the professional treatment guidelines range from 25 to 50 percent depending on the populations studied. Nevertheless, a large number of HBV-infected people in the U.S. —perhaps as many as 500,000— currently fall or will fall during their lifetimes within these guidelines, but are not being treated. Fewer than 2.5 to 5 percent of the total chronically infected population, and possibly up to 10 percent of those who meet medical eligibility for HBV treatment in the U.S., actually receive medication.

Effectiveness of Antiviral Treatment on Intermediate Outcomes

All approved treatments for the hepatitis B virus decrease HBV DNA levels. Likewise, all approved therapies have also been associated with some degree of HBeAg loss, decreases in ALT level, and improvement in liver histology.

Long term viral suppression occurs in about 55% of individuals treated with medications, though there is considerable variability to response depending on drug regimen and the host immune system. Therefore, screening and early immunization is the best way to prevent this disease.

6. In nonpregnant adolescents and adults with chronic HBV infection, how effective is antiviral treatment at improving health outcomes?

The major goals of anti-HBV therapy are to prevent the development of progressive liver disease, specifically cirrhosis and liver failure, and prevent the development of liver cancer and subsequent death. This is why most published reports of anti-HBV therapy use changes in short-term virologic, biochemical, and histological parameters to infer the likelihood of long-term benefit. There are studies which conclusively show short term response to therapy including reversal of fibrosis with treatment.

7. In nonpregnant adolescents and adults with chronic HBV infection, how effective is behavioral counseling in reducing transmission and improving health outcomes?

Appropriate counseling of those patients with chronic hepatitis infection to change behavior can limit progression of the disease, thereby reducing the cost of management to society. It is important to recognize that many primary and secondary prevention activities (such as those targeting healthy eating, physical activity, smoking, alcohol use, immunizations, etc.) are

particularly beneficial to those already have suffered from chronic viral hepatitis and other chronic diseases.

For those found to be infected, referral networks that are capable of providing culturally and linguistically appropriate follow-up counseling and care should be established.

However, in the U.S., over 50% of those with chronic hepatitis B are among Asian Americans and immigrants, who have acquired disease via vertical transmission during the birthing process and therefore, behavioral risk factors for HBV are not helpful.

8. *What are the harms associated with antiviral treatment for HBV infection?*

Each HBV treatment has unique advantages and risks associated with the administration of the drug. The use of interferon treatments is associated with systematic side effects, such as headache, nausea, flu-like symptoms, depression, and some hematologic abnormalities. Long-term use of nucleoside and nucleotide treatments can result in the development of resistance, and is also associated with renal toxicity, muscle weakness or pain, and mitochondrial toxicity.

There have only been five cases of life threatening drug toxicity seen in worldwide literature for patients undergoing entecavir treatment. Every year, only 1 percent of patients using the antiviral medication Tenofovir experience bone or renal events.

9. *Do improvements in intermediate outcomes improve final health outcomes?*

Although available randomized, controlled trials show encouraging short-term results—demonstrating the favorable effect of treatment on such intermediate markers of disease as HBV DNA level, liver enzyme tests, and liver histology—limited rigorous evidence exists demonstrating the effect of these therapies on important long-term clinical outcomes, such as the development of liver cancer or a reduction in deaths, since the interval from chronic hepatitis B to cirrhosis and/or liver cancer may require long term follow up before these can be adequately assessed.

Certainly, we understand the pathophysiology of disease progression, the oncogenic potential of hepatitis B surface antigen and the associated hepatocellular carcinoma prevalence among those infected with hepatitis B.

Conclusion

While increasing HBV screening rates and providing long-term medical management for those found to be infected might appear to be burdensome to the health care system, research and experience show that early identification and appropriate disease management of HBV are cost-effective when compared to the financial and quality of life costs of morbidity and mortality associated with HBV, such as treating end-stage liver disease. Additionally, the availability of an effective vaccine should provide us with an opportunity to eradicate this disease among all populations.

Screening and medical management of chronic HBV infection affords significant health benefits to infected individuals and can be accomplished in a cost-effective manner. But with only 50,000 people being treated for HBV, significant barriers to care remain at various levels, including patient education and awareness, provider awareness and diagnostic capabilities, and access to care.

The NVHR thanks the USPSTF for the opportunity to comment and provide feedback on its draft research plan regarding screening for hepatitis B virus infection in nonpregnant adolescents and adults. We hope the USPSTF will take our comments into consideration. Should you have specific questions or wish to discuss our comments, please feel free to contact Martha Saly, Director of the NVHR, at 707-242-3333 or mbsaly@nvhr.org.

Sincerely,

A handwritten signature in cursive script that reads "Martha Saly". The signature is written in black ink on a light-colored background.

Martha Saly, Director
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