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REVIEW

Is chronic hepatitis B being undertreated in the United States?

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SUMMARY. Chronic infection with the hepatitis B virus (HBV) is a major risk factor for development of end-stage liver disease, including cirrhosis, liver failure and primary liver cancer. There are now seven antiviral agents approved by the United States Food and Drug Administration (FDA) for the management of chronic HBV infection. Despite the fact that there are between 1.4 and 2 million chronic HBV infections in the United States, fewer than 50 000 people per year receive prescriptions for HBV antiviral medications. This report discusses possible explanations for the disparity between the number of people who are chronically infected and the number of people who receive treatment. Explanations for this incongruence include the potentially large number of infected persons who are unscreened and thus remain undiagnosed, and lack of access, including insurance, education and referral to appropriate medical care, particularly for disproportionately infected populations.

Keywords: alanine aminotransferase, Asian and Pacific Islander, barriers to health care, chronic HBV infection, HBV treatment, hepatitis B DNA, hepatitis B virus, hepatocellular carcinoma, intravenous drug user.

INTRODUCTION

Worldwide, hepatitis B is a major aetiology of primary cancer of the liver, or hepatocellular carcinoma (HCC) [1,2]. People who are chronically infected with the hepatitis B virus (HBV) carry a lifetime risk of death from end-stage liver disease or HCC of between 15% and 25% [3,4]. With more than 350 million people chronically infected worldwide, lives lost to HBV eventually could exceed 100 million.

In the United States, rates of acute HBV infection have dropped dramatically in the past decade, primarily related to universal vaccination of newborns and children [5,6]. However, high rates of chronic HBV infection still exist, particularly among high-risk adult populations [7,8]. Moreover, rates of HCC in the United States, the second deadliest cancer in terms of survival time, are one of the fastest growing cancers in incidence [9,10].

There is growing evidence that medical interventions that reduce HBV viremia by inhibiting viral replication, or that immunologically enhance the host through the action of interferons, can decrease the risk of developing HCC and end-stage liver disease and consequently improve long-term patient outcomes [11–13].

Current professional practice guidelines recommend intervention for only a subset of chronically infected individuals [13]. We note, however, that many HBV carriers whose clinical profile at the time of evaluation does not meet the current professional society guidelines for recommendation of therapy may still remain at significant lifetime risk for liver disease [14–16]. Some of these persons may later fulfil criteria for treatment. The question as to who should be treated is an ongoing question and will likely change over time as more studies identify additional risk factors and biologic markers that are associated with the subsequent development of HCC and cirrhosis. Unfortunately, we do not know at any given time, what proportion of persons in the global HBV-infected population need to be treated because of the paucity of population-based studies. Currently, treatment is limited to the sub-population of HBV carriers whose current clinical profile places them within the current guidelines, which are generally characterized as

Abbreviations: ALT, alanine aminotransferase; API, Asian and Pacific Islander; CDC, Centers for Disease Control and Prevention; CHB, chronic HBV infection; CHeCS, CDC-sponsored Chronic Hepatitis Cohort Study; FDA, Food and Drug Administration; HBeAg, hepatitis B e-antigen; HBV DNA, hepatitis B DNA; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HDV, hepatitis delta virus; HIV, human immune-deficiency virus; IDU, intravenous drug user; IOM, Institute of Medicine.

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those who present with biochemical and histological features of moderate or severe liver disease. It is possible that a large number of HBV-infected people in the United States, perhaps as many as 500 000 (25% of the higher estimate), currently fall or will fall during their lifetimes within these guidelines but are not being treated.

Based upon US Food and Drug Administration (FDA)-approved prescription information provided by Gilead Sciences, the number of people currently receiving prescription treatment for HBV in the United States is approximately 50 000, as illustrated in Fig. 1 (prescription estimates: courtesy Gilead Sciences). This means that fewer than 2.5–5% of the total chronically infected population, and, overall, possibly <10% of those who meet medical eligibility for HBV treatment in the United States, actually receive medication. There are several likely reasons as to why there is such a disparity between the number of individuals who are chronically infected with HBV and the number of people who are being treated. We will consider the possible explanations in this paper.

RESULTS

Undiagnosed chronic HBV infection

The number of people that have been diagnosed with chronic HBV and are also 'aware' of their disease status is unclear. Estimates vary widely as to the percentages of those who are infected and who are aware of their disease. For example, it has been estimated that as few as 8%, and as many as 60%, of the infected population in the United States are aware of their hepatitis B status [5,17–23] (Cohen *et al.* unpublished data). One explanation for the uncertain and low diagnosis rates for chronic HBV infections in the United States is the natural history of the disease. Because most chronic HBV infections are not apparent, those infected may be unaware of their infection status, for example as many as 60% of those chronically infected report having no symptoms [5]. The absence of routine screening of high-risk populations also contributes to under-diagnosis of chronic HBV infections.

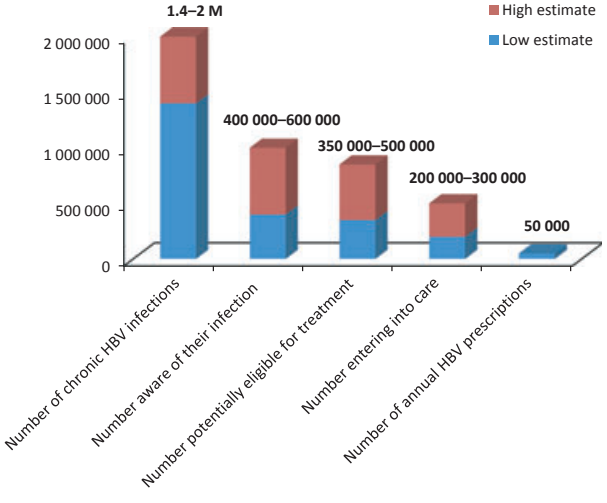

Fig. 1 Overview of chronic hepatitis B virus (HBV) infection, diagnosis and care in the United States. Gradient moves from the number of chronic infections to the number of individuals receiving treatment. Ranges are based on low (1.4 million [5], shown in blue) to high (2 million [8], shown in red) US chronic HBV infection prevalence estimates.

Self-awareness of infection status may vary greatly with risk group and even with ethnic group. Most large surveys of East Asians and others from regions of high HBV endemicity indicate that self-awareness of chronic HBV infection status prior to testing for HBV is closer to 30–40% among Asian and Pacific Islander (API) Americans [5,17–22]. Surveys in urban foreign-born API communities have indicated screening rates as low as 8% [21].

There is also little information about self-awareness of HBV status among gay men [23] and injection drug users (IDUs) [24], two other major risk groups for HBV infection. Most studies have focused on improving HBV vaccination rates rather than diagnosing infected persons. However, it appears that most HBV-infected gay men are also either unaware of their HBV status or consider themselves not at risk [23,25]. Only 2000 cases of acute HBV in IDUs are reported to the Centers for Disease Control and Prevention (CDC) each year [26], and most of these will not develop into chronic infection; this suggests that the vast majority of the estimated HBV-infected IDUs (at least 15% of the total US chronic HBV infections) are untested and unaware of their infection.

Taking these data together, a diagnosis rate of <40% and probably closer to 20–30%, rather than 60%, seems the most likely scenario in the United States. Using a compromise estimate of 30% means that of the 1.4–2 million HBV-infected individuals [5,8], an estimated 420 000–600 000 are currently aware of their infection, leaving an education, treatment and surveillance gap that could affect up to 1.4 million Americans (Fig. 1).

Diagnosed, but not in care

Of those who know their status, how many are referred to and access health care, at least initially, for HBV? It appears that many, if not most, people who are aware of their infection status do not or cannot obtain appropriate follow-up care (as defined by professional practice guidelines). Research indicates that only a minority of those diagnosed as chronically infected are able to access care [27,28]. When persons are screened in hospital or as part of a targeted screening and intervention effort, up to 66% of those found to be infected are evaluated and referred to appropriate care [29,30]. However, it is estimated that only 40% of those

screened in community clinics and medical offices are referred and linked to appropriate care [29,31].

Thus, probably fewer than half of all who are diagnosed to be chronically infected with HBV are referred for appropriate care. Taking our above estimate that between 420 000 and 600 000 individuals in the United States have been diagnosed, we can estimate that approximately 200 000–300 000 have subsequently entered into care, as illustrated in Fig. 1.

Diagnosed and in care, but not receiving treatment

End-stage liver disease or HCC because of HBV does not occur in everyone with chronic HBV infection [3,4]. In most, but by no means all, chronically infected individuals, cirrhosis and HCC, when it occurs, do not appear until decades after initial infection [5]. Thus, people chronically infected with HBV are heterogeneous with respect to clinical status. Leading professional societies have suggested that only subsets of the infected population be treated, based upon disease activity, risk of disease progression and likelihood of intervention effectiveness.

For example, the American Association for the Study of Liver Disease (AASLD) practice guidelines are largely limited to those with elevated HBV DNA (viral load), elevated serum alanine aminotransferase (ALT) levels and evidence of moderate to severe inflammation or fibrosis on liver biopsy or surrogate testing, as well as those with the presence of decompensated cirrhosis [13]. Persons with a family history of HCC who have any active liver disease or an elevated HBV DNA level, and are over 40 years of age, are considered for treatment [13]. Persons co-infected with human immunedeficiency virus (HIV) should receive two antiviral drugs that cover HBV as part of their HIV treatment cocktail [13]. Finally, persons co-infected with the hepatitis C virus (HCV) who meet the same criteria for HBV treatment should be treated for both infections [13]. In addition, the prevalence of hepatitis delta virus (HDV) infection is poorly described in the United States; the HBV–HDV co-infection is associated with a high risk of developing cirrhosis and an increased rate of HCC, according to most studies [4,8,13]. Importantly, the primary treatment is interferon.

There is limited information about the proportion of chronic HBV-infected individuals who actually fall within the criteria for treatment. Community-based studies vary in their estimates of the percentages of those chronically infected who are hepatitis B e-antigen (HBeAg) positive, HBV DNA positive and have greater than normal ALT levels. The estimates of those with HBV who would fall within the professional treatment guidelines range from 25% to 50%, depending on the populations studied [15,16,32,33]. However, in many community settings, it is clear that fewer than 25% of those found to be chronically infected who are in the health care system receive any of the therapeutic drugs now approved for HBV [31,34]. This low treatment rate is supported by recent data from the CDC-sponsored Chronic Hepatitis Cohort Study (CHeCS) in which data from a cross-sectional analysis showed that only 15% (or 63 of 423) HMO-sponsored patients in 2008 received antiviral drugs for HBV (S. Holmberg, unpublished data).

Thus, as illustrated in Fig. 1, the total number of treatment-eligible individuals in the United States could be between 350 000 and 500 000, which represents 25% of the low (1.4 million) and high (2 million) US prevalence estimates. With only 50 000 current prescriptions for HBV in the United States, we have a situation where only 10–15% of potentially eligible individuals are receiving treatment. However, taking our above estimate that between 200 000 and 300 000 infected individuals enter into care, 50 000 written prescriptions indicate that once a person with HBV enters care in the United States, there is a fairly high likelihood that they will receive treatment as per the guidelines. Thus, the most important limiting step appears to be screening and identifying chronically infected individuals; the biggest barrier to treatment is proper identification of those at risk.

Diagnosed and previously treated

Another possible explanation for the current low level of HBV treatment is that a large number of the 1.4–2 million chronically infected individuals might have already been treated, resulting in either benefit or lack of efficacy. However, this is unlikely because preliminary findings from a study conducted by the Hepatitis B Foundation suggest that no more than 80 000 people in the United States have been treated with FDA-approved medications over the past 10 years (T. Block *et al.,* work in progress). Thus, prior treatment can account for only a small proportion of the current putative undertreatment, or treatment disparity, as only a very small percentage of people in the United States have received treatment in the past for chronic HBV infection.

DISCUSSION

There is a clear disparity between the number of people in the United States who have chronic hepatitis B infection and the number who receive treatment. This disparity remains largely unexplored, and the ideas expressed in this report, while speculative and based on limited information, point to the need for universal screening of populations at high risk for HBV infection, identified by CDC guidelines, as well as further research and interventions targeted at developing effective methods of ensuring that chronically infected individuals receive regular monitoring of their infection and be treated if and when appropriate.

As stated in the recent US National Academies of Sciences Institute of Medicine (IOM) report on Hepatitis and Liver Cancer [35], chronic HBV infection remains an

under-diagnosed disease in the United States. To improve diagnosis rates in high-risk groups, the CDC issued expanded HBV screening guidelines in September 2008 [5]. However, it is not known how well these guidelines have been translated into practice by physicians. There are also a number of personal and environmental barriers that contribute to low screening rates, especially in foreign-born and first generation API populations. Personal barriers can include lack of information or misinformation about the disease; cultural beliefs regarding physician usage when not feeling ill; and fear of stigmatization and discrimination by family, friends and community members [19,28,36]. HBV knowledge deficits have been reported in API communities, regarding transmission, prevention, diagnosis and treatment outcomes of HBV [20,21,28,37]. Personal factors are a primary contributory barrier to screening and diagnosis, which can be overcome: studies have shown that people in at-risk populations who have more accurate knowledge about HBV are the most likely to be screened for their HBV status [20,21].

Environmental barriers to HBV diagnosis, particularly in high-risk ethnic immigrant populations, include lack of access to routine, ongoing medical care because of lack of insurance or being under-insured and difficulty navigating the US health care system [27,29,35]. Data indicate that some groups of foreign-born APIs have high rates of non-insurance, resulting in postponement of seeking care and difficulty obtaining care [38,39]. APIs also report lower use of most health care services including cancer screenings and are less likely to have a source of ongoing health care, representing barriers that are exacerbated by limited English proficiency [39,40]. With up to 70% of chronic HBV infections occurring in foreign-born individuals [5], one can estimate that up to 500 000 chronically infected individuals in the United States have no health insurance (e.g. 400 000 foreign-born and 100 000 US-born), which can be a reason for lack of diagnosis, as well as lack of treatment. Equally important are provider-related barriers: providers are often unaware of the risk groups that should be screened for HBV, or there is a communication breakdown with high-risk individuals that stems from language and cultural barriers, especially with foreign-born persons from endemic regions [37,41–43].

Personal and environmental barriers can help to explain why over 1 million chronically HBV-infected individuals in the United States remain undiagnosed, and why many of those who have been diagnosed still do not receive care and treatment. Research to reduce barriers and improve access to diagnosis and care for infected individuals in the United States is necessary if the gaps are to be overcome. Public education and awareness campaigns need to play an important role in promoting HBV screening and vaccination to high-risk communities. There are a number of culturally and linguistically appropriate programs that have had some success in improving HBV-related knowledge, as well as screening rates [27,44–46]. With more recent public attention paid to viral hepatitis, as well as the 2010 IOM report [35], it is hoped that additional funding will be made available to support a national, comprehensive educational campaign that will reduce HBV-associated stigma and significantly improve rates of screening and linkage to care. It is also important to note that continued efforts to educate providers must coincide with any public awareness campaign to help overcome provider-related barriers to HBV screening, including lack of knowledge [41,47,48].

While those with inactive disease still are at risk for HCC, albeit at a much lower rate, better methods and markers not only identifying those who are at risk for developing HCC or reactivating back to the immune active phase and markers for diagnosing HCC early are needed. There is a need for future research to focus on the development of new classifications of medicines to be used alone or in combination with the nucleoside analogues that will offer more potent suppression of HBV DNA and decrease the risk of resistance.

While advocating for increased screening and linkage to care, we must think about the ability of the health care system to effectively manage up to 1.4 million newly diagnosed chronically infected individuals. 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 treating end-stage liver disease [49–56]. This has been shown many times over for both screening and management of other chronic illnesses, such as diabetes, hypertension and HIV infection [57–59]. Screening and medical management of chronic HBV infection affords significant health benefits to infected individuals and can be accomplished in a cost-effective manner. In 2007, Hutton *et al.* [49] showed that active screening and linkage to care efforts for API populations had an incremental cost-effectiveness ratio of $36 088 per QALY gained compared with voluntary screening practices. In 2008, Spackman and Veenstra [50] showed that treatment with currently approved therapies resulted in clinical benefit for HBeAg+ patients and was cost-effective compared with no treatment. Their findings were consistent with previous studies, as well [51,53,55]. Most recently, Armbruster and Brandeau [56] developed a model leveraging disease prevalence with screening and contact tracing rates to optimize cost-effective strategies for controlling HBV. This model can be used as a template for future large-scale HBV screening and linkage to care efforts in the United States.

CONCLUSION

In summary, the data indicate that probably 4–5% of chronic HBV patients are screened, get into care, receive

treatment and then are 'successfully' treated or remain in treatment (Fig. 1). Even using the most conservative estimates, it appears that there are more than 300 000, and possibly 500 000, people in the United States with chronic HBV infections who may fall within the treatment guidelines. With only 50 000 people treated, however, the largest barriers to care are most likely at the level of patient awareness, diagnosis and access to care. These appear to be the 'slow' steps in the process; once a patient is diagnosed and able to access caregivers, they appear to have a fairly good chance of receiving appropriate treatment. The gaps between diagnosis and treatment can be explained by a number of existing barriers, including lack of patient awareness of their risk factors (e.g. belong to a high-risk ethnic group), lack of provider knowledge of which groups to screen and treat, lack of insurance or under-insured and high costs of ongoing treatment, fear of long-term medication and side-effects, reluctance to take long-term medication when a patient feels healthy and lack of knowledge among physicians about when to prescribe medication and whom to treat [28,37] (Cohen *et al.*, unpublished data).

Although some ambiguities remain regarding the precise fraction of those infected who receive care, it seems clear that the percentage of chronic hepatitis B patients in the United States that have been diagnosed and receive antiviral therapy is in the single digits. Unfortunately, there is a lack of published data regarding screening, referral and treatment rates for chronic HBV infection in the United States. Thus, while our proposed estimates rely upon limited data and assumptions, the overwhelming body of evidence suggests that only a minority of chronic HBV-infected patients in the United States are being diagnosed and receiving appropriate treatment. As chronic HBV infection and primary liver cancer rates in the United States continue to rise, research and intervention efforts that explore and reduce barriers to care and improve rates of diagnosis, management and treatment are necessary to reduce the morbidity and mortality associated with this serious liver infection in the United States.

STATEMENT OF INTERESTS

Chari Cohen has served as an advisory board member for Gilead Sciences, Inc. and Bristol-Myers Squibb. Chari Cohen owns stocks and shares in Gilead Sciences, Inc. and Bristol-Myers Squibb. Carol Brosgart was an employee of Gilead Sciences, Inc. from June 1998 through July 1, 2009. Carol Brosgart owns stocks and shares in Gilead Sciences, Inc. Robert Gish has served as a speaker and consultant for Bristol-Myers Squibb, Gilead Sciences, Inc. and Roche, and all payments are made to a research and educational fund at California Pacific Medical Center.

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There are no funding interests to disclose for this manuscript.

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