



Minority Report: ENUMERATING Treatment of Chronic HBV Infection Among Asian-American Communities

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Chronic hepatitis B virus (HBV) infection is one of the leading causes of acute and chronic liver disease globally [1]. Although its prevalence in the overall US population is decreasing as a result of the 1991 universal vaccination effort, its prevalence among populations who have origins in HBV endemic regions remains high. When accounting for individuals born in HBV endemic regions, it is estimated that there are 2.2 million people living with HBV in the USA, the majority of whom are from Asia and Africa [2]. Due to its asymptomatic nature in its early stages, two-thirds of those living with HBV are not aware of their infection [3]. Without appropriate monitoring and treatment, up to 15–25% will die prematurely from complications of cirrhosis, liver failure, or hepatocellular carcinoma [4]. As such, it is important to screen, monitor, and provide appropriate treatment to at-risk individuals.

In the USA, chronic HBV infection represents one of the most important health issues facing Asian Americans and Pacific Islanders given its high prevalence in these communities. In this issue of *Digestive Diseases and Sciences*, Lee et al. [5] published the results of the ENUMERATE study (ENtecavir Utilization, Management, and Efficacy in the United States: A MULTi-cEnter study) comparing the HBV management practices and clinical outcomes of patients chronically infected with HBV treated with entecavir in community and academic practices in a largely Asian-American patient population (83%). The study was a retrospective, multicenter cohort study of 841 subjects treated in 10 community and 16 academic practices of which 658 fit the inclusion criteria of age ≥ 18 years old, HBV

treatment naïve, duration of entecavir therapy ≥ 12 months, and had a minimum of two sets of liver function chemistries obtained after treatment initiation. Those who were co-infected with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis D virus (HDV), were pregnant or breast feeding, or had undergone solid organ transplantation were excluded. The ENUMERATE study was one of the first studies to address the issue of HBV treatment management in both academic and community settings and, perhaps more importantly, reported on the clinical outcomes in both settings. The main outcomes measured were alanine aminotransferase (ALT) normalization and HBV viral load suppression [5]. Since progression to cirrhosis, risk of decompensation, and development of hepatocellular cancer (HCC) were beyond the scope of this study, they were not reported.

Practices were also analyzed with regard to their adherence to the American Association for the Study of Liver Diseases (AASLD) 2009 HBV Practice Guidelines [6]. The AASLD guidelines recommend antiviral initiation based on a combination of hepatitis B virus e antigen (HBeAg) status, ALT level, and HBV DNA level. For HBeAg-positive patients, antiviral therapy is recommended in patients with an HBV viral load $> 20,000$ IU/mL and ALT ≥ 2 times the upper limit of normal (ULN). For HBeAg-negative patients, antiviral therapy is recommended with an HBV viral load > 2000 IU/mL and ALT ≥ 2 times the ULN, the latter defined as 30 U/L for men and 19 U/L for women.

The study found that academic practices followed the AASLD guidelines for treatment initiation 56% of the time versus 48% in community practices. Although it is not entirely surprising that academic settings have a higher rate of guideline adherence, two points deserve to be highlighted: (1) The difference in adherence to AASLD guidelines between the academic and community practices was small (56% vs 48%); and (2) the rate of non-adherence to the AASLD guidelines in academic practices was still quite high at 44%. With regard to the first point, the differences in HBV

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management between practice settings may have been minimal since the physicians who participated in this study were all part of the Asian Health Foundation, a nonprofit organization of leading medical experts dedicated to improving the health of Asian Americans and Pacific Islanders. Due to its focus and interest in HBV, membership in the group likely increases awareness of HBV treatment guidelines compared with clinicians at large. With respect to the second point of the 44% non-adherence rate to the AASLD guidelines, given that the overwhelming percentage of patients in the study were of Asian heritage, it is possible that the clinicians used practice guidelines other than the AASLD guidelines such as the Asian-American HBV guideline by Tong et al. [7] published in 2011. The Asian-American HBV guideline recommends treatment initiation for patients with HBV viral load > 2000 IU/mL and ALT “above normal” regardless of HBeAg status. ALT ULN in this case varies by clinical laboratory, differing from the AASLD’s definition of 30 U/L for men and 19 U/L for women (recently changed to 35 U/L and 25 U/L, respectively). Furthermore, patients with albumin < 3.5 g/dL, platelet count < 130,000 mm³ [3], or the presence of the basal core promoter (BCP) mutation should also be initiated on treatment, regardless of ALT level [7]. Forty-two percent of the patients in this study had ALT < 2 times ULN at treatment initiation which could be explained in part by providers following practice guidelines other than those published by the AASLD. It would be helpful in future studies to qualitatively evaluate the reasons for deviation from the AASLD guidelines.

The ENUMERATE study only looked at patients for whom entecavir therapy was initiated and thus did not include either patients who may have benefited from antiviral therapy based on the AASLD guidelines but were not treated, or patients who received antiviral treatment other than entecavir. Understanding the barriers to starting antiviral therapy in untreated patients who meet criteria for treatment initiation could have positive public health consequences and is central to reducing the burden of disease.

The study found that patients who were initiated on treatment in the community setting were more likely to self-discontinue treatment than those in academic practices—51% and 29%, respectively. The reasons for this higher discontinuation rate are unclear and were stated to be beyond the scope of this study. Nevertheless, issues such as health literacy, mistrust of the health system, religious beliefs, language barriers, and financial barriers including lack of insurance coverage may have contributed. Since Asians, Africans, and other populations are heterogeneous, these factors, along with other factors pertaining to different countries of origin, deserve to be studied in greater detail in future studies.

Qualitative data with regard to the reason for discontinuation would be helpful to guide future management, as premature cessation or interruption of antiviral therapy robs

patients of the potential long-term benefits of antiviral suppression and is associated with a small risk of HBV flare which can precipitate liver failure, and when frequent can be associated with antiviral resistance [8]. Furthermore, it is unclear what comprises the “community setting.” Most clinicians assume the community setting in this case includes private practices, private specialty clinics, community hospitals, as well as community health centers. As these settings have vastly different characteristics and patient demographics, it would be helpful to compare HBV management and clinical outcome among these different community settings in future studies. For example, in the community health center setting, barriers to care include provider shortages and lack of capacity, mitigated, however, by the unique capabilities of community centers to provide for the needs of underserved populations with resources such as financial navigators and language interpretation services, [9, 10] resources that may increase medication adherence rates as they improve patient education and may help address financial barriers to treatment.

Interestingly, despite differences in medication adherence and deviation from the AASLD guidelines, the response to entecavir therapy, measured as HBeAg seroconversion and HBsAg loss, was similar in both settings. Academic practices had a higher rate of HBV viral suppression, whereas community practices had a higher rate of ALT normalization. A dual diagnosis of concomitant liver disease, such as fatty liver, was not recorded for this study and could explain the difference in rates of ALT normalization.

Overall, this study was able to describe the “real-world” management of HBV treatment in a largely Asian-American population and was able to provide objective data with regard to treatment outcome for a disease that disproportionately affects the rapidly growing Asian-American, Pacific Islander, and African communities in the USA. The patients treated in this study were treated by Asian-American providers who have a specialized clinical focus in HBV. As such, it likely represents a “best-case” scenario in describing HBV practice patterns in the USA. In future studies, including a wider range of providers will improve identification of potential gaps in care.

Finally, although there have been many qualitative studies reporting barriers to screening for viral hepatitis, this is the first quantitative study looking at HBV management practices for patients with HBV in different settings. A qualitative study will increase the understanding of the barriers to care and guide future funding and public health or outreach initiatives. Moreover, including data for patients with HBV who are not receiving treatment will also increase understanding of guideline adherence in different practice settings since the decision to initiate versus delay treatment is the principal purpose of many HBV practice guidelines. The management of chronic HBV is complex. By better

understanding the reasons for treatment initiation, adherence, and discontinuation, patient care will improve.

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