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Enhanced Screening for Hepatitis D in the USA: Overcoming the Delta Blues

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Hepatitis D virus (HDV), the causative agent of delta hepatitis, is well recognized as an aggressive form of viral hepatitis, with more rapid progression to cirrhosis, and a high incidence of decompensated liver disease, hepatocellular carcinoma and liver-related death. Indeed, HDV is estimated to contribute to 1 in 6 cases of cirrhosis and 1 in 5 cases of liver cancer among persons with chronic hepatitis B globally[1]. With new therapies for HDV on the horizon[2], it is timely to look at disease burden and how effectively we are identifying HDV carriers.

The global prevalence of HDV was the focus of two recently published systematic reviews[1, 3, 4], with estimates varying from a low of 12 million to as high as 72 million persons. These widely variable results highlight the challenges of estimating the global burden of HDV infection due to the paucity of seroprevalence studies in many countries, inclusion of selective populations and use of older enzyme immunoassays that may have reduced reliability across different HDV genotypes. The seroprevalence of HDV amongst HBsAg-positive persons in the U.S. was estimated to be 5.9% (95% CI: 3.0–9.8%)[1], but the metaanalyses highlighted that U.S. data were sparse. A recent analysis of the 2011–2016 National Health and Nutrition Examination Survey (NHANES), which is representative of the noninstitutionalized U.S. civilian population, reported an anti-HDV prevalence of 42% among hepatitis B surface antigen positive carriers[5], a rate that was substantially higher that previous estimates from NHANES covering the period 1999–2012[6]. While a true increase in HDV seroprevalence in the U.S. is possible, other explanations include assay variability and differences in patient sampling. Of note, the DiaSorin anti-HDV ELISA assay has been shown to have lower specificity in comparison to the QMAX antibody capture assay[7].

Based on current epidemiologic data, the American Association for the Study of Liver Diseases (AASLD) guidance on hepatitis B recommends risk-based screening for HDV. The “at risk” groups include persons who inject drugs, persons with HIV, men who have sex with men, those at risk for sexually transmitted diseases, *and* persons who immigrated from countries of high endemicity[8]. The importance of country of origin as a risk factor for HDV

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Twitter: Delta Hepatitis: Risk based screening is a good strategy but amplified/expanded screening efforts are needed to identify the undiagnosed – particularly timely with improved screening tests and new therapies around the corner.

in the U.S. is underscored by the study from Fong and colleagues from the University of Southern California published In this issue of *Digestive Diseases and Sciences*[9]. Among 534 Mongol immigrants and their families who participated in three community screening events conducted in 2018, 9.7% were found to be HBsAg positive and among these individuals 41% were anti-HDV positive, one-third of whom were HDV RNA positive. Interestingly, no anti-HDV positive persons were identified under the age of 28 years suggesting that risk factors unique to early adulthood may contribute to HDV transmission in Mongolia. Alternatively, it may reflect implementation of universal hepatitis B vaccination program in 1991. Vaccination against HBV remains the cornerstone of preventing HDV. Thus, in the U.S., increased penetrance of HBV vaccination among adults at risk for HDV (e.g. HIV-positive, persons who inject drugs and those with sexually-transmitted diseases) would be expected to decrease HDV seroprevalence over time, as has been shown in some European countries[10]. The study from Fong and colleagues also emphasizes the importance of education and linkage to care among immigrant populations, which they provided in the context of their screening initiative.

The recommendation to screen based on country of origin was a new addition to the 2018 AASLD guidance on chronic hepatitis B and is supported by the current study[8]. It is acknowledged that not all healthcare providers will be familiar with the countries that have a high prevalence of HDV and thus unknowingly not offer screening to a foreign-born individual at risk. The AASLD guidance on screening highlights this limitation and suggests that if “uncertain”, to just proceed with screening. Additionally, it is apparent from the recent attempts to estimate global burden of HDV, that many countries lack data of sufficient quality on HDV seroprevalence, so the list of countries of high prevalence is incomplete.

Having accurate U.S. seroprevalence data is crucial in making recommendations on public health policy such as screening and improving the cascade of care for those with HDV, including access to new therapies as they become available. How are we to obtain better estimates of HDV disease burden in the U.S.? (Table) First, making HDV a Centers for Disease Control and Prevention (CDC) notifiable infection would help in evaluating trends in seroprevalence over time. Second, understanding how currently used assays perform amongst the HDV population of the U.S. is important, especially as it relates to different genotypes. Third, screening practices need to be considered. Given the challenges of using risk-based screening, universal screening of all HBsAg-positive persons may be a reasonable alternative. The European and Asian-Pacific guidelines for management of chronic hepatitis B recommend HCV and HDV in all HBsAg-positive patients. Finally, reflex testing for anti-HDV in any patient testing positive for HBsAg may be a strategy that further increases HDV screening rates, as shown in a study from the UK [11]. Collectively, high quality seroprevalence data would be an aid to understanding the relative contribution of different risk groups to total HDV disease burden and further facilitate next steps in the cascade of care.

The time is right for expanding on HDV screening efforts. New therapies, anticipated within the next few years, will likely be “game-changers” for this orphan disease. Currently, there are no approved therapies for HDV and although peginterferon is a recommended approach[8], efficacy is modest at best and tolerability a barrier to its use. Excitingly, three

new drug classes that have emerged for treatment of HDV, including viral entry inhibitors (Myrcludex), prenylation inhibitors (Lonafarnib) and virion egress inhibitors (REP-2139), appear very promising[2]. With the prospect of being able to change the course of this often devastating disease, it is imperative that healthcare providers not miss the diagnosis of HDV to limit liver-related complications and the opportunity to prevent disease through HBV vaccination.

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TABLE

Current state of HDV screening

HDV Screening Considerations	Challenges	Potential Solutions
Who is screened	Screening based on country of origin requires high quality epidemiological studies (lacking in many countries) and knowledge of these by a clinician Lack of clinician awareness of importance of HDV screening	Universal screening of all HBsAg+ persons Broader educational initiatives to bolster patient and provider awareness
Screening approaches	Anti-HDV is screening test of choice; with HDV RNA recommended if anti-HDV positive	Reflex testing for HDV in persons at time of first HBsAg-positive result may increase completeness of testing Reflex HDV RNA testing of those with anti-HDV may further identify those with active infection
Screening tests	ELISA-assays may not be equally reliable across all genotype/subtypes – more comparative work needed HDV RNA testing not validated but based on WHO standard	QMAX may offer advantages over ELISA testing; this needs to be evaluated in a large US-based cohort Studies comparing HDV RNA quantitative assays in terms of LLOQ and range would be desirable