ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Highlights From the Recent World Health Organization Guidelines for Hepatitis B Virus Infection

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G&H How much progress has been made, particularly in the United States, toward achieving the World Health Organization goal of global hepatitis B elimination by 2030?

DD Neither the United States nor the world is doing well at eliminating hepatitis B virus (HBV) infection. Globally, it is estimated that at least 246 million people are infected with hepatitis B, although I suspect that number is much higher. In the United States, the estimates range from 3 to 5 million people being infected with hepatitis B. Of those, at least half do not know they are infected, and only 10% or 15% are being treated. There are only approximately 60,000 prescriptions for HBV infection being written a year in the United States. To address that problem, the Centers for Disease Control and Prevention, and several other organizations including the US Preventive Services Task Force, recommended universal screening and vaccination for hepatitis B for people 18 years and older. It had been hoped that vaccinating infants starting in 1991 would eliminate HBV infection in the United States. However, pediatricians did not vaccinate older children at that time; they just followed the guidelines and vaccinated infants. Therefore, there are many people who are not immune to HBV infection in the United States. Universal screening and vaccination are good ideas to help eliminate HBV infection and are recommended by the World Health Organization (WHO) in countries with a prevalence of more than 2%. HBV infection needs to be diagnosed and treated, and clinical trials are currently underway for drugs that can cure this disease.

It should also be noted that some progress has been made globally in terms of infant vaccination and mother-to-child transmission, although not much. Unfortunately, in Sub-Saharan Africa, the hepatitis B vaccination rate for infants is approximately 17% at birth, even though the majority of births are attended by a health care worker. Infant vaccination for hepatitis B has been very successful in the United States starting in 1991. It is close to 100%; there is little to no risk of perinatal transmission.

G&H Why and how were updated HBV guidelines released by the WHO?

DD The WHO first released guidelines on the prevention and management of patients with chronic HBV infection in 2015, then guidelines on hepatitis B and C testing in 2017, and guidelines focusing on mother-to-child transmission of HBV infection in 2021. The goal of the 2024 guidelines was to raise awareness globally about the need for infant vaccination and universal screening for HBV infection. The WHO also added fairly aggressive treatment guidelines. A very careful and complex scientific method was used to develop these guidelines. The WHO commissioned reviews of disease-modeling surveys, which provided a key evidence base. There were 15 systematic reviews as well as research on market landscape, access, and costs; surveys and literature reviews on acceptability, values, and preferences; and modeling studies. A distinguished panel of experts formulated the recommendations, which were presented at the Asia-Pacific Association for the Study of the Liver meeting in Kyoto, Japan in March 2024.

G&H What recommendations were made regarding HBV treatment?

DD To determine treatment eligibility, the recent WHO guidelines recommend noninvasive testing or transient

elastography to evaluate the severity of any liver disease, in addition to looking at the patient's alanine aminotransferase (ALT) and HBV DNA levels and medical history such as coinfections (eg, HIV and hepatitis C) and other comorbidities (eg, diabetes, fatty liver, immune suppression, and family history of liver cancer or cirrhosis). These guidelines also recommend counseling on lifestyle (eg, alcohol, diet, and physical activity) and preparation for starting treatment such as adherence to preventative measures, screening of family household members and sexual contacts, and hepatitis B vaccination of those who are not already protected or infected. Essentially, the guidelines recommend treating all adults and adolescents aged 12 years or older, including pregnant and nonpregnant women and girls of reproductive age with any persistent, latent, or abnormal ALT level; any significant fibrosis (F2) as measured by Aspartate Aminotransferase to Platelet Ratio Index (APRI); cirrhosis (F4) regardless of HBV DNA or ALT levels; and any clinical criteria for cirrhosis. A patient is eligible for HBV treatment if their APRI score is more than 0.5 or transient elastography score is more than 7 kPa (both of which are consistent with F2); their HBV DNA level is over 2000 IU/mL and they have an elevated ALT level; or they have any of the following: coinfections (eg, HIV or hepatitis C virus), family history of liver cancer or cirrhosis, immune suppression, comorbidities (eg, diabetes), and extrahepatic manifestations, regardless of their HBV DNA or ALT levels. In the absence of access to the patient's HBV DNA level, persistently abnormal ALT levels alone, which can be measured by assays, can be used to determine treatment eligibility. HBV DNA testing is not available in many resource-limited countries.

As for treatment itself, the recent guidelines recommend tenofovir disoproxil fumarate (TDF) or entecavir as preferred regimens, and, if there is no access to TDF monotherapy, TDF plus lamivudine or TDF plus emtricitabine as alternative regimens. The guidelines also recommend entecavir or tenofovir alafenamide fumarate (TAF) for people with osteoporosis and/or impaired kidney function as well as children or adolescents.

Importantly, during treatment, the guidelines recommend hepatocellular carcinoma surveillance via ultrasound and alpha-fetoprotein every 6 months (particularly in people with cirrhosis or a family history of liver cancer or cirrhosis) as well as evaluation of HBV treatment response every 12 months, adherence at each visit, noninvasive testing via APRI or transient elastography if available, and monitoring of ALT and HBV DNA levels as well as renal function, as indicated with TDF or entecavir, both of which have to be dose-modified.

In these guidelines, the WHO expanded treatment criteria and was more aggressive about treating HBV infection since it can be very contagious, not just mother-to-child but person-to-person via almost any body fluid, tears, saliva, nasal secretions, and so on. The 2024 guidelines differ from older ones, which recommended only treating patients older than 30 years and those with persistently abnormal ALT levels. There is hope that following the new guidelines will help bring HBV infection under control throughout the world, including in the United States. Expanding the treatment base will hopefully help prevent transmission as well as prevent liver cancer, along with increasing the treatment of HBV infection.

G&H Could you discuss the recommendations involving pregnant patients and mother-to-child transmission?

DD The new WHO guidelines are clear about treating mothers with HBV DNA levels over 200,000 IU/mL, at least in the third trimester, if not before, to prevent mother-to-child transmission. According to the guidelines, all pregnant women in the third trimester who have HBV DNA levels of 200,000 IU/mL or more should be treated with TAF or TDF. Immediate infant vaccination is also recommended and, if possible, administration of hepatitis B immunoglobulin upon the first immediate vaccination. There has been good adherence to this practice in the developed world, but little in Sub-Saharan Africa because of cost. However, a recent article in the *Journal of the American Medical Association* by Dr Calvin Pan and colleagues showed that treating pregnant patients in the last trimester can avoid the need for hepatitis B immunoglobulin at the time of birth and allow providers to continue with just the normal hepatitis B vaccine regimen.

G&H How do the recent WHO guidelines seek to improve HBV diagnostics?

DD These guidelines recommend, when available, that hepatitis B surface antigen (HBsAg) screening be accompanied by reflex HBV DNA testing, which is a new recommendation. HBV DNA point-of-care testing would provide almost instantaneous results for quantitative HBV DNA reading at the point of care, similar to testing for blood glucose (although not quite that fast). Such testing makes diagnosis easier so patients do not have to wait days to weeks for results and also improves linkage to care.

The WHO guidelines also now recommend that all patients who are positive for HBsAg be tested for delta hepatitis antibody. This recommendation is for all HBsAg-positive patients because it is difficult to establish risk factors for delta hepatitis and treatment is becoming available in many parts of the world with the drug

bulevirtide, which will hopefully be approved in the United States next year.

G&H How aware are US providers of the recently updated WHO guidelines?

DD I do not think most US providers are aware of these guidelines. Unfortunately, the WHO lost some credibility during the COVID-19 epidemic. There have been some rumors that new US society guidelines on HBV treatment might be coming out, but one of the last things I heard was there would not be new guidelines until new treatments are available. I think these updated WHO guidelines should be broadly adopted in the United States, and providers should be made aware of them so that more people can be screened and treated for HBV infection. The updated WHO guidelines are much more aggressive than the guidelines we currently have from the American Association for the Study of Liver Diseases, which are older. By some estimates, we are only treating 10% or 15% of the people who are actually infected with hepatitis B. That is not going to be much help in preventing disease progression, transmission, and liver cancer. Treatment needs to be expanded.

Disclosures

Dr Dieterich has served as a consultant/advisor and independent contractor to, and has received research support; consulting fees; honoraria for lectures, papers, and teaching; and compensation for service on advisory boards from, Gilead, Intercept, and AbbVie.

Suggested Reading

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