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REVIEW ARTICLE

Chronic Hepatitis B Infection: Patient Guidance

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ABSTRACT

This patient guidance document is intended for all people at risk of or living with chronic hepatitis B (CHB) infection. Globally, CHB is one of the leading causes of cirrhosis and hepatocellular carcinoma, the most common form of liver cancer. However, less than one in five infected individuals is aware of their condition and only a small fraction of these individuals receive proper assessment and management. Safe and effective treatment is available in many countries and regions and is recommended for infected individuals who have evidence of liver damage or are at risk of complications. Several essential measures are advised for all people living with CHB, including lifestyle habits, screening for coinfection, managing comorbidities, fibrosis assessment, preventing HBV transmission, and surveillance for liver cancer. There are also recent shifts in the treatment paradigm and novel drug development. In those living with CHB, a better understanding of the disease can empower them to play an active role in management in partnership with their physicians. This guidance document has been developed in collaboration with clinicians, scientists, patients, and patient representatives to summarize updated salient knowledge to inform people at risk of or living with CHB.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; Anti-HBc, HBV core antibody; Anti-HBe, antibody to HBeAg; Anti-HBs, HBV surface antibody; ASO, Antisense oligonucleotide; AST, aspartate aminotransferase; CAM, Capsid assembly modulator; CHB, chronic hepatitis B; ETV, entecavir; GGT, gamma-glutamyl transferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LFT, liver function test; MASLD, metabolic dysfunction-associated steatotic liver disease; MTCT, mother-to-child transmission; NAs, nucleos(t)ide analogues; RNAi, RNA interference; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TLR, Toll-like receptor.

1 | Introduction

1.1 | What Is the Liver? Where Is the Liver?

The liver, the largest internal organ in the human body, is a marvel of nature with its unique spongy, reddish-brown structure. Located on the upper right side of the abdomen, just below the lungs and protected by the ribcage, it sits on the right side of the stomach and above the small intestine, roughly shaped like a cone or wedge. The liver's size varies depending on a person's height and weight. It comprises four lobes: the larger right and left lobes and two smaller ones called the caudate and quadrate lobes (Figure 1). The liver contains several essential parts, including hepatocytes (liver cells), blood vessels, capsules, and ligaments.

The liver, a powerhouse organ, performs hundreds of essential jobs to keep your body healthy. One of its primary roles is to clean your blood by removing toxins (harmful substances) and waste, which it later sends out of your body through urine and feces. The liver also breaks down old red blood cells and produces bile, a fluid that helps digest food. It processes proteins, carbohydrates, and fats so your body can use them for energy and growth. Additionally, the liver creates important proteins, such as albumin that holds fluid within the blood vessels and clotting factors that play a crucial role in the stopping of bleeding and the healing process of wounds. The liver also stores glycogen (the stored form of simple sugar) and essential vitamins for when your body needs them. Blood flows through the liver, where it is filtered and cleaned. A byproduct of this process, called bilirubin, gives urine and feces their yellow color.

Several diseases can harm the liver. Viral infections, like hepatitis A, B, C, and D are known to infect human livers and cause damage. Metabolic dysfunction, overuse of alcohol, and exposure to certain toxins and medications can also lead to liver problems like cirrhosis (severe scarring of the liver), which is the main risk factor for hepatocellular carcinoma, the most common form of liver cancer. Some liver diseases are inherited, such as hemochromatosis, which causes iron overload, and Wilson disease, which involves copper buildup. Taking care of your liver through a healthy lifestyle is not just a choice. It is a necessity for maintaining overall well-being. Protecting your liver is essential for ensuring a person's longevity.

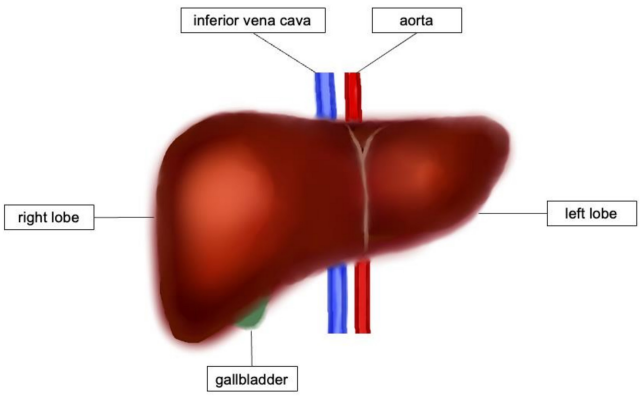

FIGURE 1 | Illustration of the basic structure of the human liver.

1.2 | What Is HBV? How Is It Transmitted?

HBV is a virus that specifically affects the liver in humans and chimpanzees, potentially causing both short-term (acute) and long-term (chronic) infections. The virus interacts with natural receptors on the liver cells that are intended for bile acid transportation. Once the virus enters the liver cell, the genetic materials of HBV that are made of DNA start to produce copies of genetic materials and synthesize viral proteins. The newly produced viral particle is then released outside of the infected liver cell to infect other cells. The viral DNA can also integrate into the human genome, which makes it difficult to eradicate the virus. HBV is most prevalent in Asia-Pacific, where 65% of global cases are found [1, 2]. It spreads primarily through contact with infected blood and bodily fluids. The most common method of transmission is from mother to child during childbirth, accounting for >90% of cases of chronic HBV infection in endemic areas like the Asia-Pacific region. HBV can also spread through sharing needles, unsterile medical procedures, or sexual contact with an infected person [3]. However, HBV cannot be transmitted through breast-feeding or social contact, such as sharing dining together, hugging or shaking hands. Because it often does not show symptoms early on, people can unknowingly carry and spread HBV. Out of 254 million people living with chronic HBV infection globally (3% prevalence), only 13% of people living with HBV are aware of the infection.

2 | Natural History of Chronic Hepatitis B Infection

The natural course of chronic infection with HBV is dynamic, ranging from asymptomatic infection or inactive phases to cases where immune responses cause hepatitis, which may progress to liver cancer or liver failure [4]. In the inactive phase, medication is usually not necessary, but in the active phase, the risk of progression to cirrhosis or liver cancer is high, making proper treatment crucial [5, 6]. Understanding the natural history of CHB is essential for grasping the disease's progression.

If you are living with CHB, your doctor may tell you that your condition goes through different phases over time. These phases reflect how active the virus is in your body and how much damage it has induced in your liver. Typically, the natural history of CHB can be categorized into five phases. The disease can evolve without following all the five phases of infection (Figure 2):

2.1 | HBeAg-Positive Chronic Infection

This phase usually follows infection acquired in infancy or early childhood when the immune response to HBV is underdeveloped. During this phase, the virus actively replicates, leading to a large amount of viral DNA in the blood (viral loads), and releases a special protein called hepatitis B e antigen (HBeAg) into the bloodstream. However, immune responses are weak, and liver inflammation (hepatitis) is minimal [7]. Because of these features, this phase is previously known as the immune tolerance phase.

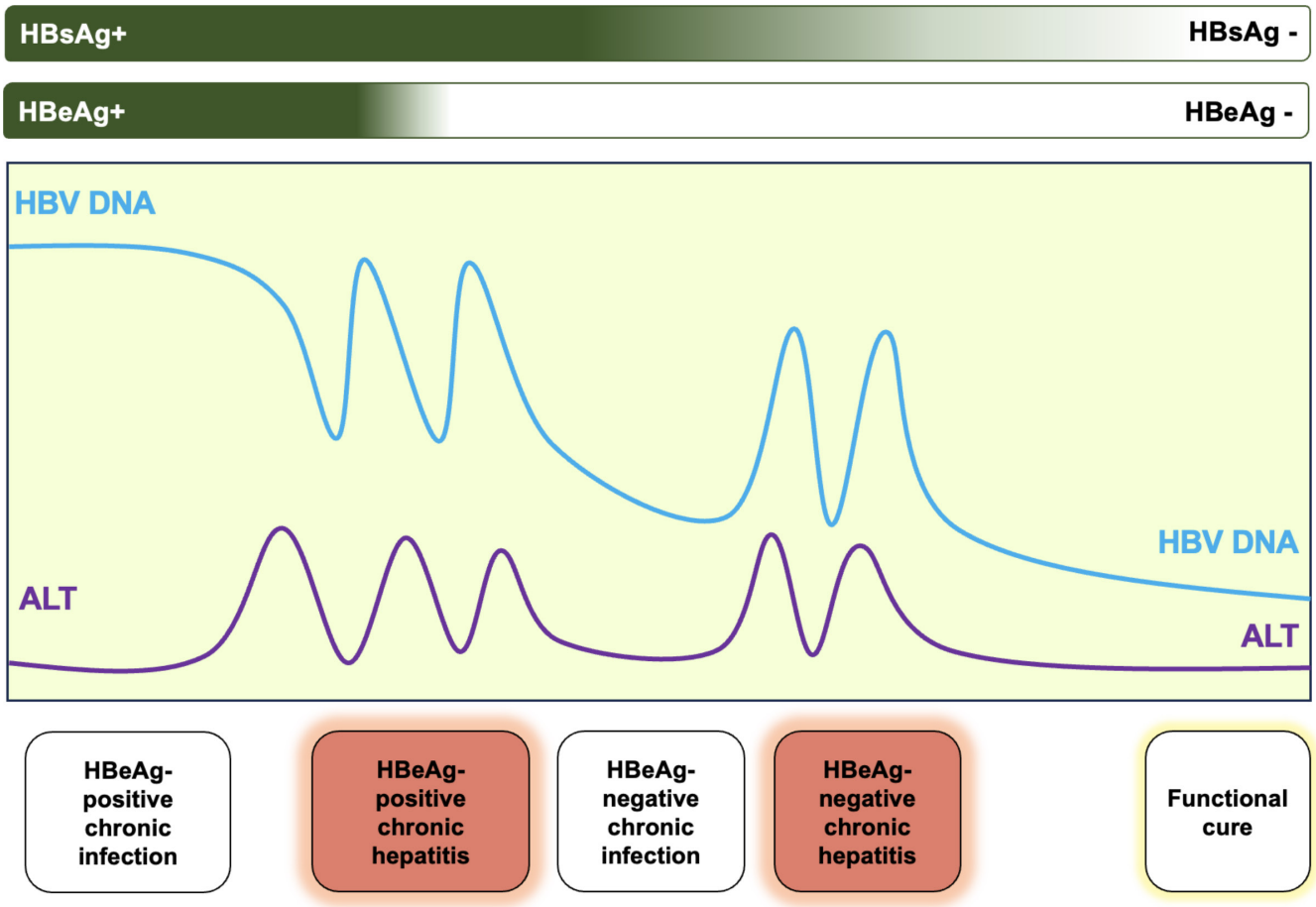

FIGURE 2 | The five disease phases of chronic hepatitis B infection. The phases highlighted in red box signify the need of antiviral treatment. Note that the final phase "Functional cure" (yellow box) is rarely achieved, with an annual rate of event being 1%–2%.

2.2 | HBeAg-Positive Chronic Hepatitis

In this phase, the immune response to HBV becomes more active, resulting in active hepatitis (inflammation of the liver). This phase is previously known as the immune clearance phase. Over time, many patients experience a process called HBeAg seroconversion, where HBeAg disappears from the blood and is replaced by an antibody against it (HBeAb or anti-HBe). The seroconversion usually signals a transition into a quieter phase of the infection [8].

2.3 | HBeAg-Negative Chronic Infection (I.E., Inactive Carrier)

Following HBeAg seroconversion, hepatitis becomes less active in most patients. In this inactive phase also known as HBeAg-negative HBV infection, viral loads are low, and hepatitis activity is often minimal with liver enzyme levels within normal ranges [9].

2.4 | HBeAg-Negative Chronic Hepatitis

Not all patients who undergo HBeAg seroconversion remain in the inactive phase. In some cases, the virus continues to replicate, and active hepatitis can persist or return. This condition carries a higher risk of serious liver complications, such as cirrhosis or liver cancer.

2.5 | Remission Phase or "Functional Cure"

In very few patients, hepatitis B surface antigen (HBsAg), a key marker of HBV infection, may disappear from the blood. Medical and scientific professionals call this phase "functional cure". The annual rate of spontaneous HBsAg clearance is very low, estimated to be about 1% [10]. For the bulk of patients who do not reach this phase, they will remain in the phases outlined in Sections 2.1–2.4 above.

Despite the disappearance of HBsAg, the virus can reactivate in certain situations, such as during chemotherapy or the use of immunosuppressive medications. Also, liver cancer can still be observed although the risk is lower compared with persistent detection of HBsAg in the blood. Therefore, careful monitoring is still important even after HBsAg disappearance.

While these phases provide a useful framework, not all patients fit neatly into them and phase transitions frequently occur [11]. Therefore, it is essential to recognize that the management of CHB should be guided by individualized assessments rather than rigid categorization.

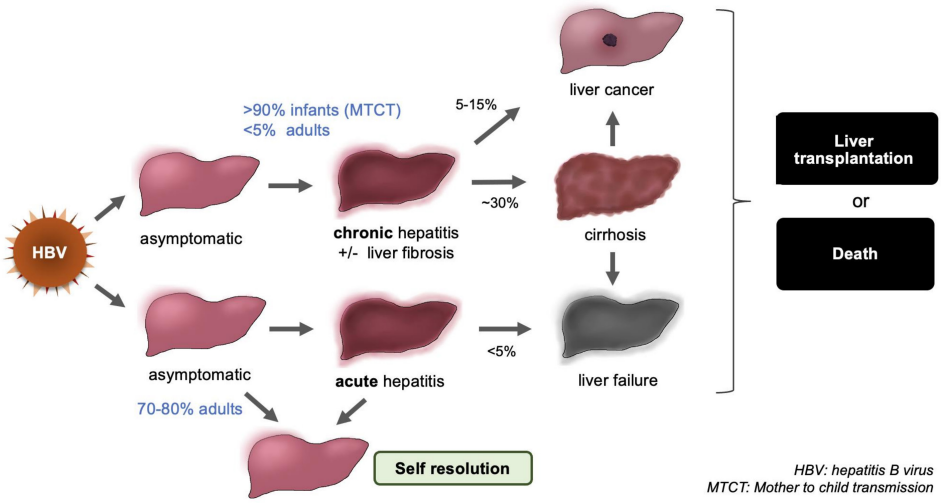

FIGURE 3 | Consequences of HBV infection.

3 | What Are the Consequences of HBV Infection?

HBV primarily affects the liver ("hepatotropic") and can cause acute or chronic infection. Although acute infection of HBV is mostly asymptomatic followed by self-resolution among adults (70%–80%), it can uncommonly lead to severe hepatitis or even liver failure (< 5%) (Figure 3). However, the more serious long-term consequences of HBV typically develop gradually over time from chronic infection when the host is exposed to the virus during infancy or early childhood, often without noticeable symptoms in the early stages. HBV can stay dormant in the liver cells for many years and only be detected on specific testing. Symptoms are uncommon but may include fatigue, vague abdominal discomfort and darkening of urine. The liver may insidiously become fibrotic (scarred) and finally cirrhotic (severe scarring of the liver). People with cirrhosis can be asymptomatic but can experience symptoms in more advanced stages of cirrhosis. They may be told that their "liver function tests" have abnormalities, or incidentally found to have low platelet counts or 'thrombocytopenia'. Initially, patients with cirrhosis remain "compensated", which refers to a state that there is a lot of scarring in the liver but the function of the liver is preserved. With further progression, they can develop decompensated cirrhosis, which refers to a state that the liver no longer copes with the scarring. Decompensated cirrhosis will lead to multiple complications of cirrhosis like fluid accumulation in the abdomen called "ascites", altered mental state or behavior called "hepatic encephalopathy", passage of blood in vomit or stools or "variceal bleeding". Advanced cirrhosis can also affect the kidneys leading to "hepatorenal syndrome". Patients with cirrhosis may also note weight loss especially loss of muscle called "sarcopenia", which leads to impairment in physical activity or frailty. Patients also need to be aware that the HBV virus is linked to the development of liver cancer either by the direct activity of the virus or by the path through cirrhosis (Figure 3). Liver cancer is not rare for patients with CHB, and your doctor will place you on a surveillance program if the presumed risk of liver cancer is high. Overall, 15%–40% of people with CHB will develop cirrhosis or liver cancer. As of the year 2021, it is estimated that 0.6 million people died from CHB every year around the globe.

HBV infection can also harm other parts of the body beyond the liver, such as inflammation of blood vessels (polyarthritis nodosa), and changes in blood proteins (cryoglobulinemia). Kidneys could be involved, too, with the appearance of protein in urine (membranous glomerulopathy) and potential progression to chronic kidney disease. Although these "extrahepatic" complications are not present in most patients with CHB, it is advisable to stay alert to any symptoms that could indicate their presence. Most of the complications can be ameliorated or cured with antiviral therapy.

Living with CHB can lead to undesirable psychosocial impacts, which are accentuated by the presence of advanced fibrosis, other comorbidities, and female sex [12], and on the other hand improved by viral suppression with antiviral treatment [13]. Pregnant mothers living with CHB had significantly impaired quality of life, in particular domains of "worry" and "social functioning" [14]. Internalized, social or institutional stigma was common among people living with chronic HBV, with 20% demonstrating the belief of being denied healthcare and 30% anticipating risk of workplace discrimination because of HBV [13]. Indeed, stigma and discrimination are recognized as barriers to eliminating hepatitis B virus as a public health threat by the year 2030, a goal sought by the World Health Organization. It is widely agreed by the HBV community that actions should be taken to halt stigma and discrimination associated with HBV infection through education and policy changes [15].

4 | How to Prevent Transmission of HBV?

Since the 1990s, the World Health Organization recommended all countries to implement universal infant and/or adolescent HBV vaccination. Vaccines to prevent HBV infection should be provided for all infants and people at risk of acquiring HBV (Table 1).

Recombinant DNA vaccines are purified HBsAg derived from genetically engineered yeast or mammalian cells [16]. The seroprotection rate, defined as the successful induction of protective

TABLE 1 | People at risk of HBV infection.

All infants All children and adolescent under age of 18 who have not been vaccinated Adults with any of the following risk factors: – History of sexually transmitted infections – Multiple sex partners – History of past or current hepatitis C virus infection – People incarcerated or formerly incarcerated in a jail, prison, or other detention setting – Born to HBsAg-positive mothers – Born in regions with HBV infection prevalence of 2% or more – US-born people not vaccinated as infants whose parents were born in geographic regions with HBsAg prevalence of 8% or more – People who inject drugs or have a history of injection drug use – Known human immunodeficiency virus (HIV) infection – Men who have sex with men – Household contacts or former household contacts of people with known HBV infection – History of sharing needles – Engaged in sexual contact with people with known HBV infection – On dialysis – Elevated liver enzymes	Recommendation: 1. Screen for HBV infection 2. If HBV positive: refer for thorough assessment 3. If HBV negative: provide HBV vaccination

Note: Extracted from: CDC (https://www.cdc.gov/hepatitis-b/hcp/diagnosis-testing/index.html).

antibodies in the vaccine recipient's body, of currently available single antigen vaccines is excellent, ranging from 90%–95% with three doses of vaccination. People who received the HBV vaccine have long-lasting immunological memory [17]. Although antibody levels may drop after vaccination [18, 19], HBV infection is uncommon in persons known to have responded to the primary vaccine series because of the persistence of immunological memory [20–22]. As such, a routine booster dose of the vaccine is not recommended in the general population [23]. Given the poorer response rate in immunocompromised individuals (e.g., chronic kidney disease, patients with malignancies), several modifications of the recombinant vaccines are being assessed to improve the seroprotection rates in such individuals [24, 25]. The currently available recombinant vaccines need to be administered to all newborns shortly after birth (within 24 h) and repeated dosing is necessary at 1–2 months and 6–18 months of age.

Vertical transmission from mother to child continues to be a major contributor to chronic HBV infections. The risk of transmission to newborns is highest during childbirth although transmission can occur during pregnancy. However, Cesarean section is not recommended just to prevent mother-to-child transmission (MTCT) of HBV because the mode of delivery does not change the risk of MTCT. To prevent MTCT, all pregnant mothers should be screened for HBV infection at antenatal visits at the early second trimester. If not already on treatment, mothers with very high HBV DNA or HBsAg levels in the blood should receive antiviral therapy from 24 to 28 weeks of pregnancy and continue until 12 weeks after delivery of the baby. In some parts of the world, infants born to mothers with CHB (HBsAg-positive) will also receive hepatitis B immunoglobulin whenever available, on top of the HBV vaccine.

Everyone needs to know how to stop the spread of HBV: ensuring safe sexual practices, screening of blood products, appropriate management of biomedical waste, educating about the risk of infection through needle sharing among individuals who inject drugs, and using disposable sterile needles at health care. Healthcare personnel should receive training on infection control, the use of universal precautions, and the prevention of occupational needle stick injuries to prevent the spread of the infection in healthcare facilities.

5 | How to Diagnose HBV Infection?

Blood tests are the cornerstone to diagnosing HBV infection, be it acute or chronic. These tests detect HBsAg, HBeAg, HBV surface antibody (anti-HBs), HBV core antibody (anti-HBc), antibody to HBeAg (anti-HBe), HBV DNA, and emerging biomarkers such as HBV RNA and hepatitis B core-related antigen [26].

Key Diagnostic Tests

1. *HBsAg:* This is the most abundant protein synthesized during HBV replication. Measuring HBsAg using immunoassays is essential, with a sensitivity and specificity exceeding 98%. The presence of HBsAg for more than 6 months defines chronic HBV infection [27]. Simultaneous testing for anti-HBs and anti-HBc differentiates acute, chronic, and past infections while identifying vaccinated individuals.
2. *HBeAg and HBV DNA:* Determining HBeAg status is critical to confirm the phase of infection (see Section 2). Over time, HBeAg may seroconvert to anti-HBe. The presence

of HBV DNA in the blood signifies viral replication. It also helps to determine the need of treatment (see below Section 6.2).

6 | How to Assess the Severity of Liver Disease and the Risk of Complications?

6.1 | History and Physical Examination

Following the diagnosis of CHB, the doctor will ask questions about your general health and past medical history. These would include alcohol consumption, cigarette smoking, medication history, family history of HBV infection, family history of cirrhosis or liver cancer, history of other liver diseases such as hepatitis C virus infection or steatotic liver disease (more well known to be "fatty liver"), human immunodeficiency virus infection, obesity, diabetes mellitus, metabolic syndrome, and other major medical conditions. These questions are important to identify additional risk factors for liver disease progression and to determine the management strategy. The doctor will then perform a physical examination for you to look for signs of severe liver disease.

6.2 | Blood Tests

Usually, additional blood tests will be arranged to assess the severity of liver disease and to predict the risk of cirrhosis and liver cancer:

1. *Liver function test (LFT, also known as liver panel or liver enzymes):* This refers to a series of biochemical measurements including aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), bilirubin, and albumin. Moreover, renal function test, clotting profile, and complete blood count are also frequently ordered. These tests are interpreted altogether rather than in isolation to assess the degree of liver inflammation, functional impairment of the liver, and presence of portal hypertension. For instance, a constellation of reduced platelet count, reduced albumin level, elevated bilirubin, and prolonged prothrombin time signals progression to decompensated cirrhosis.
2. *Alpha-fetoprotein*: This is known as a cancer marker for liver cancer, the most common form of liver cancer. If the anticipated risk of liver cancer is substantial, your care provider may order this test for you and repeat it every 6 months for cancer surveillance. However, the marker is not 100% accurate, where false positive results and false negative results are often observed. Therefore, it should be interpreted carefully and you should consult your doctor if in doubt.
3. *Co-infection with hepatitis C virus, hepatitis D virus, and human immunodeficiency virus:* These viral infections are associated with worse prognosis in CHB infection and therefore are routinely checked at diagnosis.
4. *Quantitative HBsAg:* This measures the level of HBsAg protein in the blood, which is different from the qualitative test (yes or no) used for diagnosis of HBV infection. HBsAg levels can help to predict the response to treatment and the chance of achieving functional cure spontaneously or following treatment interruption.

Because levels of ALT and HBV DNA fluctuate over time, a one-off measurement is not sufficient. Serial measurements of laboratory tests are often required (for instance, every 3–6 months for ≥ 1 year) to more thoroughly assess the risk profile.

6.3 | Fibrosis Assessment

For fibrosis evaluation, imaging studies and non-invasive tools such as vibration-controlled transient elastography (e.g., FibroScan) or scoring systems calculated from routine blood tests such as FIB-4 (calculated from ALT, AST, age, platelet count) are sometimes used [28, 29]. A liver biopsy is not universally performed for all patients with CHB but remains an option for complex cases or in special circumstances, for example, enrolment in a drug trial.

The availability of these tests may vary depending on the healthcare setting. Your doctor will choose the most appropriate tools based on accessibility and your specific clinical needs.

7 | General Advice Following Diagnosis of CHB

Apart from receiving regular blood tests and ultrasound scans, and attending medical appointments, you should also pay attention to the following aspects related to your daily living.

7.1 | Dietary Advice

You should avoid eating undercooked seafood or animal parts especially internal organs for their known risks of causing acute viral hepatitis A or E. At least one-third of people with chronic hepatitis B infection also have coexisting metabolic dysfunction-associated steatotic liver disease (MASLD), more commonly known as "fatty liver disease" [30]. MASLD more commonly affects overweight or people with diabetes. Although it is difficult to conclude the effect of coexisting MASLD on the risk of liver cancer in the context of CHB, MASLD per se is a risk factor for liver cancer, and concomitant MASLD and CHB may exacerbate the risks of liver cancer [31]. Therefore, it is prudent for you to maintain a healthy diet to prevent the onset or worsening of MASLD. The Mediterranean diet is rich in plant-based foods (fruits and vegetables, whole grains, nuts and legumes), healthy fats (olive oil instead of animal fat, lean meats, less red meat), and less sweets/added sugars. This type of diet is known to reduce the risk of liver fat accumulation and inflammation in the liver, thereby reducing the risk of MASLD.

7.2 | Lifestyle and Habits

Physical exercise reduces liver fat, inflammation, and potentially reverses fibrosis. It also improves your fitness, prevents muscle wasting, and lowers the risk of death. Ideally, physical exercise should be conducted 3–5 days per week. Moderate (e.g.,

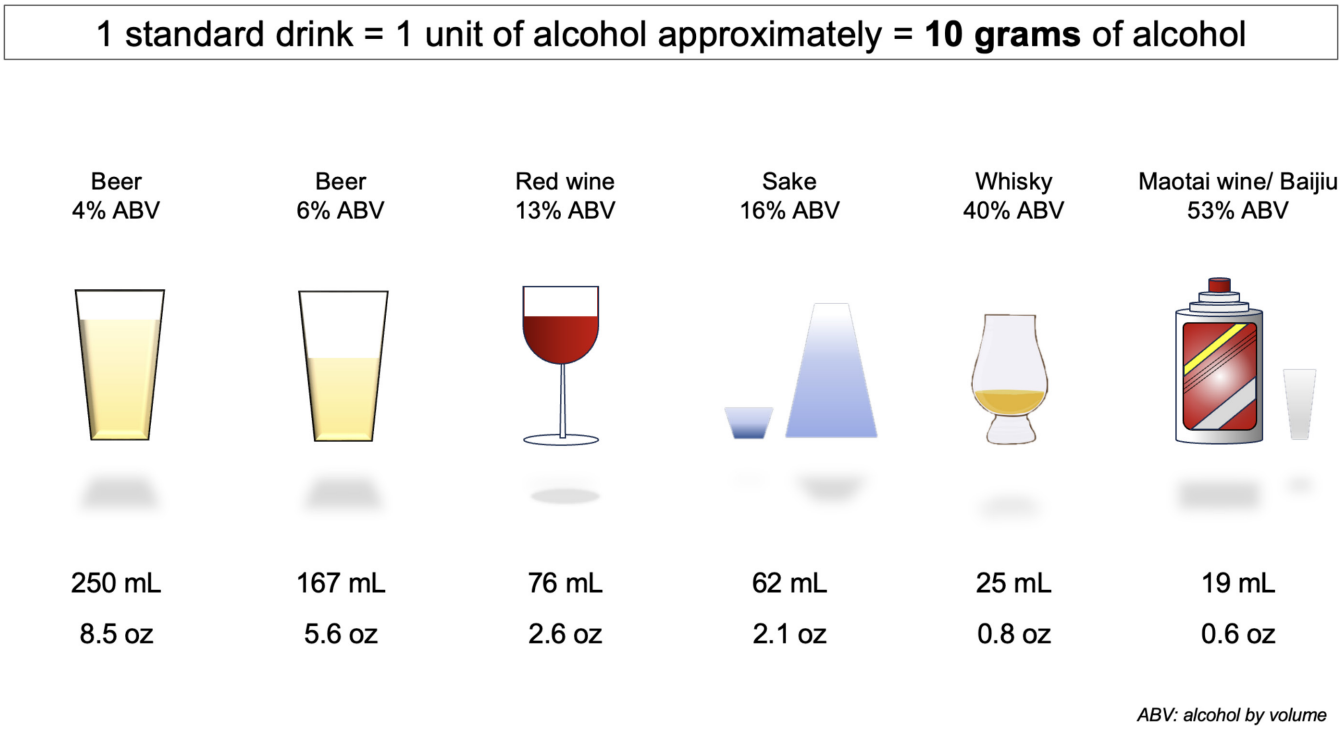

FIGURE 4 | Examples of one unit of alcohol.

brisk walking) to vigorous intensity (e.g., running) is necessary to impact liver health. You should aim for at least 150 minutes of moderate aerobic activity or 75 minutes of vigorous activity per week.

Cigarette smoking should be avoided, for its effects in delaying the chance of reaching viral quiescence [32], worsening the risk of liver fibrosis progression and liver cancer [33, 34]. In contrast, moderate coffee consumption may protect against the development of liver cancer in people living with CHB [35, 36]. Drinking excessive alcohol can exacerbate the risk of liver fibrosis and liver cancer [37], and therefore should be avoided. Men should limit alcohol intake to no more than 2 units per day, while women should not exceed 1 unit per day. Examples of one unit of alcohol include the following: 250 mL of beer with 4% alcohol, 76 mL of wine with 13% alcohol, or 25 mL of whisky with 40% alcohol (Figure 4).

Sleep hygiene should be maintained, as fragmented sleep or short sleep duration has been linked to insulin resistance, a key factor in the pathogenesis of MASLD, and increased pro-inflammatory cytokine levels that underlie disease progression in MASLD [38]. The sleep duration should be no less than 7 hours per day [39].

7.3 | Vaccination

The European and American guidelines recommend all patients diagnosed with CHB to receive vaccination against hepatitis A virus if not already immune. There are currently no vaccines available for hepatitis C or D virus. For hepatitis E virus, a three-dose vaccine administered by intramuscular injection is licensed for use in China and Pakistan but has not been submitted for pre-qualification at the World Health Organization [40].

7.4 | Concomitant Medical Conditions

If you also have Type 2 diabetes mellitus, which is a known risk factor for liver cancer even in the non-HBV infected population [41, 42], it is critical for you to make efforts and work closely with your family doctor or endocrinologist to improve the control of sugar, for the fact that poor glycemic control can further increase the risk of liver cancer [34]. If you are also taking a cholesterol-lowering drug class called statins, you should continue taking them as statins may reduce the risk of liver cancer, and will not have a negative impact on CHB, unless your doctor advises you to stop them [43].

7.5 | Complementary and Alternative Medicine

Non-prescription treatments, such as herbal medicine, nutrient supplements, traditional Chinese medicine, or home remedies, are usually not recommended because of unproven effects and potential risks of liver damage. Always consult your doctor before using any nonprescription remedies.

7.6 | Family and Social Activities

It is useful to remember that HBV is seldom transmitted via sharing of food or usual social interactions. HBV is transmitted by body fluid. Spouse and household contacts of people living

with HBV should be screened for HBV infection by blood test. If they are uninfected, they should be vaccinated against HBV if they have not already done so. Personal items especially toothbrushes and shaves should not be shared. Otherwise, normal social interaction such as dining together, hugging, or shaking hands will not lead to transmission of the virus.

8 | How to Treat CHB?

8.1 | What Treatments Are Currently Available

Currently, there are two options available for the treatment of CHB, which can be classified into injectable pegylated-interferon alpha (peginterferon) and oral nucleos(t)ide analogues (NAs) [5, 44, 45]. Peginterferon treatment induces immune control over HBV and has a finite duration of 48 weeks with subcutaneous injection once per week. It has a variable response pattern of HBV suppression but in general has a higher chance than oral NAs of achieving functional cure, which confers a significant risk reduction in disease progression and liver cancer [46, 47]. Nonetheless, peginterferon treatment has side effects such as causing flu-like symptoms after drug administration, reduction in blood cell counts, disruption of thyroid function, etc., and cannot be used in patients with advanced liver cirrhosis and pregnancy [45]. Some countries no longer stock peginterferon for the treatment of CHB. On the other hand, the first-line NAs of choice are entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF). NAs are taken orally every day [5, 44, 45]. They have excellent efficacy (close to 100%) in suppressing HBV activity [48–50]. They are also much more well-tolerated compared with peginterferon.

8.2 | What Can They Do to My Liver?

By suppressing the activity of HBV thus resolving inflammation in the liver, the HBV DNA copies will drop rapidly within a few months, with normalization of ALT expected in those who started off with abnormal ALT. Antiviral treatment can reverse liver fibrosis and even cirrhosis [51]. Antiviral treatment has been consistently shown to reduce the risk of disease progression, and complications of cirrhosis and liver cancer [52, 53].

8.3 | Why Do I Need to Take the Drug on a Long-Term Basis?

In contrast to peginterferon, NA treatments are in general initiated for long-term or even indefinite treatment to maintain HBV suppression as there is a chance of rebound of viral activity and liver inflammation or even leading to liver failure if the NA is stopped prematurely [54]. Stopping NA treatment can be possible if a functional cure of CHB is achieved, albeit rare (around 1%–5% up to 10 years) [55], or in some other special circumstances where HBV activity is dormant after years of NA treatment. However, this should be well assessed and counseled by doctors specialized in HBV care before making the decision to stop NAs as the safety of stopping the treatment varies across individuals with different statuses of CHB [54] (also see Section 11 below).

8.4 | What if I Missed the Dose?

While the risk of missing a dose or two of NAs is low and there is no need to take double doses at the next drug administration, it is advised that individuals taking NAs should adhere to the treatment to avoid the risk of HBV reactivation. ETV should be taken on an empty stomach (at least 2 h after a meal and 2 h before the next meal), while TDF or TAF is best taken with a meal.

8.5 | Are There Any Side Effects That I Should Be Aware of?

Despite being a long-term treatment, all first-line NAs have minimal to no risk of drug resistance (1.2% in 5 years for ETV; negligible for TDF or TAF) [50, 56]. They do not have significant drug–drug interactions with most of the commonly used drugs. Consistent data also have confirmed excellent safety profiles regarding the three first-line NAs. For instance, ETV only rarely leads to acid–alkali imbalance in blood for individuals with advanced liver disease and is safe in the vast majority of patients [57]. TDF may lead to loss in bone mineral density increasing the risk of bone fracture, and decline in kidney function, in a small proportion of patients [58]. These bone and kidney side effects, if present, can be potentially reversed through switching to TAF, which has a superior safety profile compared with TDF in terms of bone and kidney safety signals [59]. All first-line NAs have a very low rate of virological resistance if they are taken according to the prescription. Conclusively, despite being a long-term treatment with a relatively lower chance of functional cure, the minimal side effects, oral administration, and consistent efficacy in sustaining viral suppression made NAs the more preferred CHB treatment worldwide.

9 | When Should I Consider Treatment?

9.1 | Goal of Therapy

The goal of therapy for CHB is to prevent progression of hepatitis, advanced fibrosis or cirrhosis, decompensation, or liver cancer. Your doctor will discuss the treatment goals with you and recommend the management based on your disease profile and personal preferences.

Ideally, antiviral therapy would completely remove the virus from your body. However, this is currently not possible because some of the virus stays hidden in the liver cells for life. Instead, current treatments aim to stop the virus from multiplying, lower the virus levels in your blood to undetectable amounts, and bring your liver enzyme levels back to normal.

A main parameter to be considered by your doctor is ALT, an enzyme test, which is a part of your LFT panel (see Section 6.2). An elevated ALT level is a marker of liver inflammation. The other parameters to be considered include viral markers such as HBeAg and HBV DNA level, evidence of liver damage (e.g., significant liver fibrosis), or risk of liver complications (e.g., family history of liver cancer).

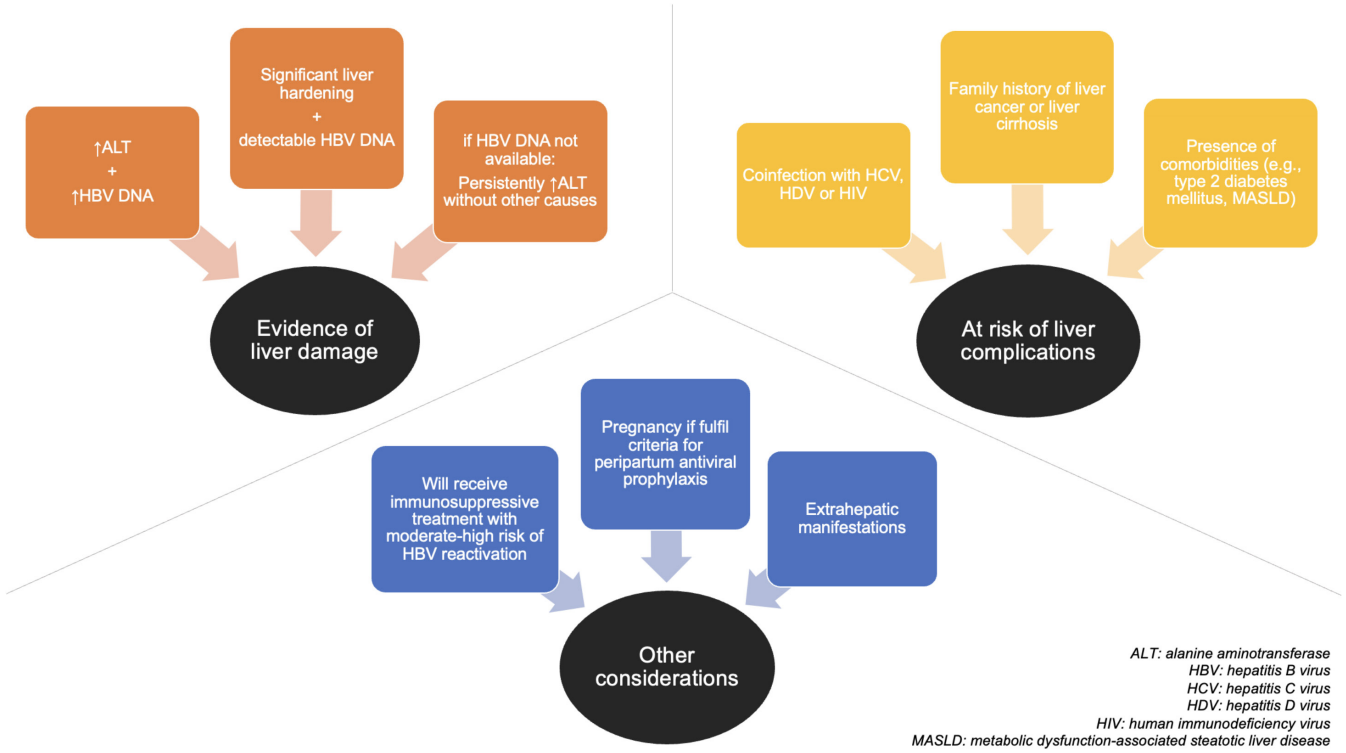

FIGURE 5 | Treatment indications: when antiviral treatment for CHB should be considered.

9.2 | Treatment Indications in Chronic Hepatitis B in the General Setting

Your doctor will assess carefully the stage of the disease and may decide to treat you for HBV infection in certain situations (Figure 5), such as:

i. Immune-active chronic hepatitis B (HBeAg negative or HBeAg positive)
   - Immune-active CHB, determined by elevated ALT or inflammation and hardening of the liver, with an elevated HBV DNA.

ii. Significant liver hardening with detectable serum HBV DNA.

iii. In healthcare settings where HBV DNA measurement is not routinely available: persistently abnormal ALT without other causes

iv. Co-infection with hepatitis C virus, hepatitis D virus, or human immunodeficiency virus

v. Family history of cirrhosis or liver cancer

If you do not meet the treatment criteria, then your physician may monitor your ALT and HBV DNA levels instead. According to current guidelines, some patients are clear candidates for treatment. However, for others, the decision is more complex. This is often the case when ALT levels are not raised but HBV DNA is > 2000 IU/mL. If ALT is raised but HBV DNA is below 2000 IU/mL, it is important to rule out other reasons for the ALT elevation, such as alcohol use or MASLD.

In cases that are not as straightforward, the doctor may decide based on their professional judgment. In some situations, a liver biopsy can help guide the decision. Treatment is typically started if the biopsy shows at least moderate liver damage or significant inflammation, without additional factors that contribute to liver damage other than HBV.

9.3 | Preventing Reactivation in Immunosuppressed Patients

If you are receiving immunosuppression such as systemic steroids or agents like rituximab, scheduled to undergo organ transplantation, or are receiving cytotoxic chemotherapy, then antiviral prophylaxis is often indicated to prevent a complication known as *HBV reactivation*. The diagnostic criteria for HBV reactivation include the following: (i) a rise in HBV DNA compared with baseline (or an absolute level of HBV DNA when a baseline is unavailable) or (ii) reverse seroconversion (seroreversion) from HBsAg negative to HBsAg positive for HBsAg-negative patients. Following HBV reactivation, a *hepatitis flare* demonstrated by ALT elevation can occur. Severe hepatitis flare can lead to *liver failure* when there is impaired synthetic function of the liver (total bilirubin > 3 mg/dL [i.e., 51.3 μmol/L] or international normalized ratio > 1.5), presence of ascites, or encephalopathy.

Before starting the immunosuppressive therapy, your doctor will order blood tests for HBsAg, and sometimes anti-HBc is also checked to look for hidden HBV infection ("occult" HBV). HBV reactivation has been frequently reported, most commonly in HBsAg-positive patients who received cytotoxic or antirheumatic therapies. However, patients with "occult" HBV are not immune from the risk of HBV reactivation, such as those who will receive B cell depletion therapy like rituximab or will undergo hematopoietic stem cell transplant.

Antiviral prophylaxis is indicated in patients at high risk of reactivation. Patients at moderate risk of HBV reactivation might be started on antiviral treatment or have their blood tests closely monitored. Patients at low risk of HBV reactivation do not require antiviral prophylaxis.

9.4 | Preventing MTCT

One of the key measures of preventing HBV transmission involves universal neonate vaccination with HBV vaccine. Recombinant HBV vaccine is safe in pregnancy and is recommended in women who are not immune to HBV.

If HBV infection (HBsAg positive status) is detected for the first time during pregnancy, women should be linked to care for additional tests. If the mother meets standard eligibility criteria (see Section 9.2), antiviral therapy should be started as usual. In pregnant women already on therapy, TDF should be continued while ETV or other drugs should be switched to TDF. TAF has not been evaluated in large scale in pregnancy in CHB population, although data in pregnant mothers with human immunodeficiency virus infection suggest its safety. In women who are not eligible for therapy per standard criteria, a decision should be made regarding antiviral prophylaxis to prevent mother to child transmission (see Section 4). Treatment decision in pregnancy is taken depending on the maternal HBV DNA at the second trimester, where a cut-off of 200 000 IU/mL is adopted. In regions where HBV DNA is not routinely available, HBeAg or quantitative HBsAg can be used as an alternative to guide peri-partum antiviral prophylaxis [60, 61], or simply treat all HBsAg-positive pregnant women [61]. Breast-feeding is not contraindicated in HBsAg-positive patients or those taking TDF either for treatment or prophylaxis to prevent MTCT.

HBV-infected pregnant women who are not on antiviral therapy as well as those who stop antiviral at or early after delivery should be monitored closely for up to 6 months after delivery for hepatitis flares and seroconversion. Long-term follow-up should be continued to assess the need for future therapy. Partners of women with HBV infection should be assessed for HBV infection as well. If they are found to be HBV positive, they should undergo thorough evaluation. If they are not HBV carriers, they should receive HBV vaccine if they do not have anti-HBs in the blood.

10 | What Else Do I Need to Do After Starting Treatment?

10.1 | Monitoring of Treatment Efficacy

After commencing antiviral therapy, you will still require ongoing monitoring. This should occur at least on a six-monthly basis but may be more frequent if there are abnormalities in your investigations.

Regular on-treatment blood tests are required to ensure that your HBV is adequately controlled by antiviral therapy as evidenced by normal LFTs and undetectable or very low HBV DNA levels in your blood. Reasons for abnormal LFTs in a patient with suppressed HBV DNA include coinfection with other viruses affecting the liver (e.g., hepatitis C virus) or other concurrent liver diseases (e.g., MASLD, alcohol-associated liver disease, or drug-induced liver injury). It is important that these LFT abnormalities are investigated, diagnosed, and treated appropriately. Otherwise, if there is ongoing liver inflammation from other conditions, progression of fibrosis and/or development of cirrhosis can still occur even if your HBV is under control. This should be monitored using noninvasive tests of liver fibrosis as discussed above.

Rarely, HBV develops resistance to antiviral therapy, which is heralded by new elevation of or failure to suppress your HBV DNA level, followed by elevated ALT levels. The risk of this is very low with current first-line NAs, which is estimated to be 1.2% at 5 years for ETV and virtually no clinical resistance reported to date for tenofovir [62]. However, the rate of ETV resistance is increased (51% at 5 years) if you were previously treated with older generation NAs (e.g., lamivudine) [62]. If your virus develops resistance to the prescribed antiviral therapy, a switch to another drug is usually required. It is important to note that persistent nonadherence to your prescribed antiviral therapy (beyond the occasional missed dose) will also cause elevations in your HBV DNA level.

10.2 | Monitoring for Treatment Adverse Events

Your doctor will monitor your renal function since both HBV itself and certain NAs (i.e., TDF) can cause renal impairment [58, 63]. Since NAs are cleared from your body by the kidneys, your antiviral therapy dose may need to be adjusted (reduced) if you have moderate to severe renal impairment [58].

Both HBV itself and TDF can result in loss of bone mineral density and consequently an increased risk of osteoporosis and fractures [58, 64]. Thus, people at risk of bone loss will require regular screening with a bone mineral density scan.

10.3 | Monitoring for Liver-Related Complications

If you have cirrhosis, you may need further interventions such as a gastroscopy to check for large veins (varices) in your esophagus or stomach, nutritional supplementation, and/or nonselective beta-blockers to reduce your risk of worsening cirrhosis (decompensation) and bleeding from varices.

As aforementioned, HBV is a carcinogen that can cause liver cancer development even in the absence of cirrhosis. Although

TABLE 2 | CHB populations with sufficient risk to warrant liver cancer surveillance.

Patients with CHB infection and cirrhosis
Patients with CHB infection without cirrhosis: • Asian men older than 40 years • Asian women older than 50 years • Sub-Saharan Africans older than 20 years • Family history of liver cancer

antiviral therapy significantly reduces the risk of liver cancer, it does not abolish it [53, 65]. Thus, patients at high risk of liver cancer regardless of antiviral therapy (Table 2) still need to undergo 6-monthly surveillance most commonly with liver ultrasound and blood tests for alpha feto-protein, which is used as a tumor marker for liver cancer. Detection of a solid lesion or poor visualization of the liver on surveillance ultrasound usually necessitates further investigation with a computed tomography scan, magnetic resonance imaging scan, or earlier follow-up ultrasound. Liver cancer surveillance has been shown to improve survival by diagnosing liver cancer at an earlier (curable) stage, yet its overall uptake and adherence remain poor in many countries [66]. It is estimated that more than 80% of patients did not receive biannual ultrasound scans for liver cancer surveillance [67]. This is the main reason for the delayed diagnosis of liver cancer—more than 50% of liver cancer was diagnosed at an advanced stage.

Regular follow-up with your doctor also provides you with opportunities to discuss the possibility of stopping antiviral therapy or being involved in upcoming clinical trials of new agents against HBV (discussed below).

Therefore, for all the above reasons, it is important to continue seeing your hepatitis B doctor beyond renewing your prescription.

11 | Can I Stop Antiviral Treatment?

If you are taking medications for HBV, you might wonder whether treatment has to be lifelong or if there is a point when stopping is possible. The most critical thing to remember is to never stop your hepatitis B medications without first consulting your physician. Stopping treatment is a major decision that requires careful consideration and planning [68]. Without proper preparation and monitoring, stopping treatment could reactivate the virus, causing liver damage with potentially serious consequences [69].

11.1 | Why Is Hepatitis B Treatment Typically Long-Term Without a Fixed Duration?

Currently available medications for CHB, particularly oral antiviral drugs, are highly effective at suppressing the virus, reducing liver inflammation, slowing or preventing liver scarring, and lowering the risk of liver cancer. However, these medications do not eliminate the virus from the body. When treatment stops, the virus often becomes active again, causing injuries to the liver. For most patients, staying on medication is the safest way to maintain control over the infection and protect the liver from damage [44, 45].

11.2 | When Might Stopping Treatment Be Considered?

Deciding to stop hepatitis B treatment requires consultation with a specialist experienced in managing CHB. Several factors have to be checked when planning to stop treatment (Table 3) [70]. You should have been on treatment for a prolonged period (typically 3 years or longer) and the virus should have been "sleeping" (HBeAg negative and HBV DNA undetectable on repeated blood tests) for several years (at least more than one). Your overall health is good with a fully functioning liver. Moreover, you are willing and able to commit yourself to intensive follow-up with frequent blood tests (usually monthly in the first several months following treatment cessation) [71]. Finally, you should recognize symptoms of severe hepatitis flares, such as loss of appetite (anorexia), tea-colored urine, or yellowing of the eyes (jaundice), and have no difficulty in seeking medical care promptly.

TABLE 3 | Checklist for planning to stop treatment for chronic hepatitis B.

Item	Requirement
✓ Prolonged duration of antiviral treatment	You should have received antiviral therapy for at least 3 years or longer.
✓ Potent and sustained viral suppression	HBeAg is negative and HBV DNA undetectable in your blood for at least 1 year.
✓ Favorable results of predictive biomarkers	Generally safer with lower HBsAg titer (e.g., < 100 IU/mL); HBsAg negativity is the ideal scenario.
✓ A well-functioning liver and good overall health	Your liver is not severely scarred (cirrhotic) and the evaluations of its functions are all normal.
✓ Commitment to intensive follow-up care	You'll have to be closely monitored with frequent blood tests (typically monthly in the first year).
✓ Awareness of potentially serious consequences	You are aware of symptoms suggesting severe hepatitis and ready to seek medical care promptly.

11.3 | What Tests May Help Predict if It Is Safe to Stop Treatment?

You will need several tests to assess whether you are a good candidate for stopping treatment. Blood tests to check for viral activities, including HBeAg, HBV DNA, and HBsAg (ideally quantitative measurements), are essential. You should not stop taking medications with positive HBeAg or detectable HBV DNA in the blood. A lower titer of serum HBsAg (e.g., < 100 IU/mL) helps predict a safer treatment cessation [72]. It is generally safe to stop treatment after HBsAg becomes negative, especially if you continue therapy for an additional year after achieving this milestone [73]. You also need to ascertain your liver is healthy enough, requiring blood tests such as platelet count and LFT. Besides, it is crucial to know if your liver is significantly scarred because the risk of complications from treatment withdrawal increases when the liver is severely scarred (cirrhotic) [74].

12 | Are There New Treatments Available? Should I Consider Joining Clinical Trials?

The landscape of pharmacotherapy for CHB is evolving rapidly. Because current therapies rarely cure HBV infection, ongoing research is focused on developing treatments that offer higher rates of *functional cure*, defined as sustained loss of HBsAg and unquantifiable HBV DNA in the blood [75, 76]. An alternative endpoint is called "partial cure", which is defined as sustained HBsAg level below 100 IU/mL and unquantifiable HBV DNA in the blood at 24 weeks off-treatment [76]. Some investigational efforts even aim for complete eradication of the virus from the liver, although this approach remains in its infancy with limited human data.

12.1 | Types of Novel Therapies

These novel therapies can be classified by their principal mechanisms of action into antiviral agents and immunomodulators [77]. The former directly targets the virus, disrupting its lifecycle and reducing viral products, whereas the latter aims to restore immune control over the virus by enhancing the patient's immune response. Several new classes of CHB treatments are currently under investigation in both preclinical and clinical trials [78]. Here, we will highlight those in the more advanced stage of clinical development, that is, Phase II or III (Table 4), including the following.

12.1.1 | Antisense Oligonucleotide (ASO) and RNA Interference (RNAi)

Both ASOs and RNAi therapies work by silencing viral genes, thereby reducing the production of viral proteins including HBsAg. RNAi therapies such as xalnesiran, JNJ-3989, and VIR-2218 [79–81], and ASOs like bepirovirsen have been tested in large, multicenter clinical trials [82]. Preliminary results suggest that these agents may be effective in lowering HBsAg levels, with a minority of patients achieving a functional cure [83]. However, the decline in HBsAg levels often plateaus after a few months, and HBsAg levels frequently rebound after treatment cessation, indicating the need for combination strategies to achieve sustained responses.

12.1.2 | Capsid Assembly Modulator (CAM)

CAMs work by disrupting the formation of the HBV capsid, which is a protein layer that contains the viral DNA, thereby

TABLE 4 | Novel treatments currently in phase II or III clinical trials for chronic hepatitis B.

Class	Example agents	Mechanism of action	Development stage
Antisense oligonucleotides (ASOs)	Bepirovirsen	Targets viral RNA for degradation, reducing HBsAg levels and inhibiting viral protein synthesis.	Phase II/III
RNA interference (RNAi)	Xalnesiran, JNJ-3989*, VIR-2218, AB-729	Silences viral RNA, reducing the production of HBsAg and other viral proteins.	Phase II/III
Capsid assembly modulators (CAMs)	Vebicorvir*, ABI-H3733*, ALG-000184	Disrupts capsid formation, preventing viral replication and reducing replenishment of HBV cccDNA.	Phase II
Entry inhibitors	Bulevirtide	Blocks viral entry into liver cells by inhibiting the NTCP receptor, preventing new infections of hepatocytes.	Phase II for HBV; conditionally approved for HDV in Europe
Toll-Like receptor (TLR) agonists	Ruzotolimod, selgantolimod	Activates innate immune pathways to stimulate natural killer cells and T cells, enhancing antiviral immune responses.	Phase II
Therapeutic vaccines	VTP-300, VBI-2601	Stimulates adaptive immune responses to target HBV-infected cells and promote HBsAg clearance.	Phase II
Immune checkpoint inhibitors	ASC22 (Envafolimab)	Blocks the PD-1/PD-L1 pathway to reverse immune exhaustion and boost HBV-specific T cell responses.	Phase II

*development has been discontinued.

inhibiting viral replication. CAMs may also prevent the replenishment of cccDNA, the key reservoir of HBV. This class of investigational agents, such as vebicorvir and ABI-H3733 [84, 85], has shown limited efficacy in achieving functional cure on its own and the development has been terminated.

12.1.3 | Entry Inhibitors

Entry inhibitors, such as bulevirtide (also known as myrcludex B), block the virus from entering liver cells by inhibiting the receptor that HBV uses to enter hepatocytes [86]. This drug has received conditional approval for use in Europe for patients with HBV and hepatitis D virus coinfection. While monotherapy with entry inhibitors has been shown to have a limited impact on HBsAg levels, they may offer greater benefit as part of combination regimens.

12.1.4 | Toll-Like Receptor (TLR) Agonists

By binding to TLR, these agents activate innate immune responses, the first-line defense against pathogens such as HBV. Agents such as ruzotolimod and selgantolimod [87, 88], which are TLR7 and TLR8 agonists, respectively, generally do not directly lower HBsAg levels and are being explored in combination with antivirals to achieve more durable HBsAg loss.

12.1.5 | Therapeutic Vaccines

Unlike preventive vaccines that aim to protect uninfected individuals from contracting HBV, therapeutic vaccines are designed to stimulate an immune response in patients infected with HBV. The goal of these vaccines is to restore or enhance the responses specifically against HBV, which are often weak or in CHB. Currently, these agents, such as VTP-300 and VBI-2601 [89], have shown limited efficacy in achieving a functional cure and therefore they are being tested in combination with other therapies.

12.1.6 | Immune Checkpoint Inhibitors

These agents aim to reverse immune dysfunction, a state in which T cells lose their ability to effectively target HBV-infected cells, by blocking inhibitory pathways that suppress T-cell function. While immune checkpoint inhibitors have been widely used to treat cancers, their application in CHB is still in early stages [90]. Because of concerns about immune-related adverse events, these agents are carefully tested in selected patients, typically at low doses.

While most trials evaluate the rate of functional cure as an important endpoint, some trials also look at the rate of partial cure, and/or the proportion of participants who can reach a predefined "NA cessation criteria" and may follow with stopping the NA under strict monitoring conditions. Post-NA cessation hepatitis flare and liver failure have been reported in a trial participant who was assigned to the placebo arm with NA followed by NA cessation [91]. While this is extremely uncommon, a high level of vigilance is essential to resume antiviral therapy in a timely manner in patients with rapidly rising DNA and/or ALT, or demonstrating signs of liver decompensation (see Section 11 above).

12.2 | Considerations for Joining a Clinical Trial

Joining a clinical trial offers an opportunity to access cutting-edge treatments for CHB. However, it is important to understand that clinical trials are designed to test new treatments with the primary goal of collecting data on their effects. While your safety is the top priority, with trials conducted under strict ethical guidelines and overseen by regulatory bodies, there is still a risk of experiencing adverse reactions to the investigational drug. Moreover, there is no guarantee that the experimental treatment will provide better outcomes than existing standard therapies.

You may want to join a clinical trial if current treatments are not achieving your desired results, you are interested in trying new therapies, you are willing to commit to the trial requirements, and, most importantly, you have discussed the potential risks and benefits with your doctor. Always talk to your doctor to see if a clinical trial is a good fit for your treatment goals and overall health.

When considering a specific clinical trial, it is important to be well-informed and prepared. Start by understanding the trial's purpose and goals, and make sure you know how the experimental treatment differs from standard therapy. Discuss your responsibilities as a participant, including the time commitment, required visits, tests, and procedures. Be aware of potential risks and ask how side effects will be monitored and managed. If the trial includes a placebo group, ask about your chances of receiving the actual treatment and what happens if you are assigned to the placebo. Practical considerations such as travel requirements, costs, and specific restrictions (such as the avoidance of pregnancy) should also be assessed before making a decision. Being informed and maintaining open communication with your healthcare team will help you make the best decision for yourself and ensure a positive experience in the trial.

13 | Summary

CHB is a common viral infection that may have severe consequences but is highly treatable. Vaccination and medications, where appropriate, for pregnant mothers living with CHB, are highly effective at preventing transmission to newborns. Antiviral medications are recommended in certain situations and are highly effective at suppressing the virus and preventing complications such as liver cancer and liver hardening. Monitoring for the development of liver cancer when appropriate, with ultrasound scans and blood tests is helpful to detect cancer early. Better treatments for CHB may be available in the next few years.

Disclosure

This guidance document is intended for all people at risk of or living with chronic hepatitis B virus (HBV) infection. Chronic hepatitis

B (CHB) is a lifelong infection and can lead to potentially serious consequences. You need to develop a thorough understanding of the condition to develop the appropriate attitude and partner with your healthcare professional in tackling this illness. This guidance document will assist you in reaching these goals. It has been developed by clinicians, scientists, patients, and patient representatives and is based on current scientific recommendations. It is not intended to replace the advice and arrangements made by your medical team but to empower you to make informed decisions. Importantly, every person has a different risk profile regarding the risk of HBV infection and the risk of liver complications from CHB. You should always consult your physician for personalized advice under the framework of standard recommendations.

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Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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