

ABSTRACT

Chronic hepatitis B (CHB) is one of the important public health problems worldwide. Two billion people worldwide have been infected with HBV and ~ 350 million chronic carriers. Chronic HBV infection confers a significant risk of developing life-threatening complications such as cirrhosis of liver and hepatocellular carcinoma (HCC).

A positive HBsAg in the blood indicates the presence of an acute or chronic HBV infection. HBsAg becomes detectable in serum usually within 4 to 10 weeks of exposure to HBV and is generally present in serum before there is significant elevation in serum aminotransferases. If the acute infection is cleared, HBsAg will disappear within 4 to 6 months and anti-HBs is detectable in serum few weeks later. Chronic HBV infection is defined as the persistence of HBsAg beyond 6 months. During this period when HBsAg has been cleared but anti-HBs has not yet become detectable (often referred to as the “window period”), the only detectable marker of infection is the hepatitis B core IgM antibody (anti-HBc IgM). Presence of anti-HBs, with absence of HBsAg, indicates immunity to HBV infection resulting from either vaccination or resolution of a prior infection. Occasionally, both anti-HBs and HBsAg are positive in the setting of chronic infection. In this case, although the HBs antibody is present, it is unable to neutralize the HBsAg, and the host remains chronically infected.

Patients who are found to be HBsAg positive should undergo serologic and virologic work-up to fully characterize the status of the hepatitis B infection, specifically HBeAg, anti-HBe, and HBV DNA viral load. The results of these tests provide prognostic information and will guide us regarding antiviral treatment. The clinical utility of hepatitis B genotype is not yet well defined.

A liver biopsy provides useful information regarding HBV disease activity and is an important factor to decide whether to initiate antiviral therapy. Serum ALT and HBV DNA levels are, in general, good markers of disease activity; In some cases marked inflammation may be present on liver biopsy in the setting of a normal ALT and minimally elevated HBV DNA. Similarly, the liver may appear histologically normal despite a markedly elevated HBV DNA level.

Highly sensitive PCR-based quantization of HBV DNA makes it possible to precisely determine pre-treatment HBV load and monitor HBV DNA response during

treatment. HBV DNA level, HBeAg status, degree of hepatic histological activity and fibrosis, and serum transaminases are the most important parameters in determining indication, regimen, and duration of HBV treatment. Pegylated interferon (alfa-2a,2b), lamivudine, adefovir, telbivudine, entecavir and tenofovir are all approved HBV treatment and advantages and disadvantages of each agent is important in choosing the best option for each individual patient with CHB. HBV infection confers a greatly elevated risk of developing HCC, even in the absence of cirrhosis. Screening for HCC with liver ultrasound exam every 6 months in HBV-infected populations is recommended.

KEYWORDS

HBsAg, Chronic hepatitis, HCC.

1. INTRODUCTION

Chronic hepatitis B (CHB) is one of the important public health problems worldwide. Two billion people worldwide have been infected with HBV and ~ 350 million chronic carriers. Chronic HBV infection confers a significant risk of developing life-threatening complications such as cirrhosis of liver and hepatocellular carcinoma (HCC).¹

A positive HBsAg indicates the presence of an acute or chronic HBV infection. HBsAg becomes detectable in serum usually within 4 to 10 weeks of exposure to HBV and is generally present in serum before there is significant elevation in serum aminotransferases. If the acute infection is cleared, HBsAg will disappear within 4 to 6 months and anti-HBs is detectable in serum few weeks later. Chronic HBV infection is defined as the persistence of HBsAg beyond 6 months. During this period after which HBsAg has cleared but anti-HBs has not yet become detectable (often referred to as the “window period”), the only detectable marker of infection is the anti-HBc IgM.

A positive anti-HBs, in the setting of a negative HBsAg, indicates immunity to HBV infection resulting from either vaccination or resolution of a prior infection. Occasionally, both anti-HBs and HBsAg are positive in the setting of chronic infection. In this case, although the HBs antibody is present, it is unable to neutralize the HBsAg, and the host remains chronically infected.

Covalently closed circular DNA (cccDNA) plays an important role in maintaining the chronicity of this viral infection. Active viral replication and inflammation of liver can potentially lead to fibrosis, cirrhosis, end stage liver disease and HCC. Effective treatment has

been shown to stop the progression of liver disease and decrease the risk of HCC.

2. CLINICAL PRESENTATION OF CHRONIC HBV INFECTION

According to EASL, the natural history of hepatitis B acquired early in life can be describe in 5 phases: immune tolerant phase, immune reactive HBeAg-positive phase, inactive HBV carrier state, HBeAg-negative CHB and HBsAg-negative phase.

In immune tolerant phase, patients are positive for HBeAg with high HBV DNA levels but a normal serum ALT. Liver biopsy usually shows no or minimal histological changes².

The next phase is the immune reactive HBeAg-positive phase which is characterized by positive HBeAg , relatively lower level of replication compared to the immune tolerant phase reflected by low serum HBV DNA levels, increased or fluctuating levels of aminotransferases, moderate or severe liver necroinflammation. During inactive HBV carrier state phase, there is seroconversion from HBeAg to anti-HBe, very low HBV-DNA level < 2,000 IU/ml, or undetectable serum HBV DNA and normal serum aminotransferases. Approximately 70-80% remain in inactive HBV carriers indefinitely. HBeAg-positive CHB (10-20%) may present with a high level of HBV DNA, elevated transaminases and hepatic inflammation. Inactive HBV carriers spontaneously lose HBsAg 0.5% annually. HBeAg-negative CHB seroconversion from HBeAg to anti-HBe antibodies during the immune reactive phase or may develop after years or decades of the inactive carrier state. This phase is associated with low rates of prolonged spontaneous disease remission. HBsAg-negative phase is characterized by HBsAg loss, negative HBV- DNA in serum, positive anti-HBc with or without anti-HBs in serum.³

Documentation of repeatedly normal ALT based on serial ALT measurements 3-4 months apart for at least a year is needed to determine whether a patient truly has normalization of ALT commonly referred as persistently normal ALT⁴. Spontaneous HBsAg seroclearance has been reported to occur at a rate of 0.5–1 % per year in patients with chronic HBV infection.⁵ HBsAg seroclearance is generally accompanied by undetectable serum HBV DNA, normalization of liver biochemistries, and improved liver histology.⁶ However, HCC has also been reported in a small percent of these patients, the risk being higher in those with cirrhosis, HCV coinfection, or older age at the time of HBsAg seroclearance.⁷

Chronic Hepatitis B (CHB)

Chronic hepatitis B is defined as chronic necroinflammatory disease of the liver caused by persistent infection with HBV. It can be subdivided into HBeAg-positive and HBeAg-negative chronic hepatitis B (CHB)

1. HBeAg-positive CHB

Patients with HBeAg-positive CHB present with positive HBsAg and HBeAg in serum that is

associated with active HBV replication, infectivity, and hepatic inflammation. Depending on the mode of HBV transmission, spontaneous seroconversion from HBeAg to anti-HBe is variable. Most patients underwent seroconversion remain sustained remission of HBV infection that is associated with normal transaminases and a low or undetectable level of serum HBV DNA although serum HBsAg may remain positive.

2. HBeAg-negative CHB

Patients with HBeAg-negative CHB present with positive HBsAg, but negative HBeAg in serum that is associated with active HBV replication, elevated transaminases, and hepatic inflammation. Pathologically, it is secondary to mutant viral infection in HBV pre-core or pre-core promoter region. Currently, HBeAg-negative CHB represents the most common type of CHB, particularly in European, African and Middle East countries of the Mediterranean Basin.

Chronic HBV infection and HBV cirrhosis

The annual incidence of cirrhosis has been estimated to be 2–6 % for HBeAg-positive and 8–10 % for HBeAg-negative patients. The higher rate of cirrhosis among HBeAg-negative patients is related to older age and more advanced liver disease at presentation. Among HBeAg-positive patients, the rate of cirrhosis development is higher in those who remained HBeAg positive during follow-up. Additional factors have been identified to be associated with progression to cirrhosis: habitual alcohol intake, concurrent infection with hepatitis C virus (HCV) or human immunodeficiency virus (HIV), high levels of HBV replication, and patients who had HBeAg reversion, HBV genotype (C>B).^{8,9} Coarse liver , splenomegaly, and hypoalbuminemia are indicative of cirrhosis and liver biopsy provides histological diagnosis. Patients with HBV-cirrhosis can be compensated or decompensated. The later presents with esophageal bleeding, ascites, hepatic encephalopathy, hyperbilirulinemia, and/or coagulopathy. Those with decompensated HBV cirrhosis should be referred for liver transplant evaluation.

Chronic HBV infection and HCC

The annual incidence of HCC has been estimated to be <1 % for non cirrhotic. 2-3% for chronic HBV infected patients patients with or without cirrhosis. Additional risk factors for HCC include coinfection with HCV, a family history of HCC¹⁰, habitual alcohol intake, high levels of HBV replication, HBV genotype C>B¹¹, and core promoter mutations¹², as well as obesity, diabetes, and smoking¹³.

3. INDICATIONS OF TREATMENT IN CHRONIC HBV INFECTION (FIGURES 1, 2 AND 3)

The indications for treatment are based mainly on the combination of three criteria: serum HBV DNA levels, serum ALT levels and severity of liver disease assessed by clinical evaluation, liver biopsy or noninvasive methods (fibroscan) and also taking into account age, health status,

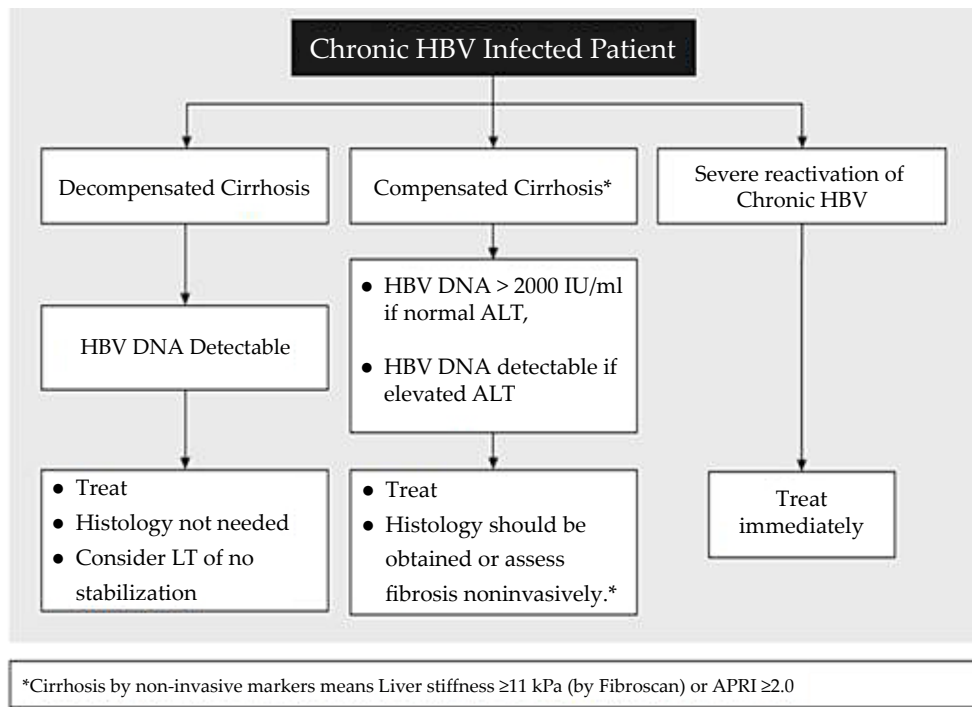


Fig. 1: Treatment indications for chronic HBV-infected patients with cirrhosis or reactivation of chronic HBV infection

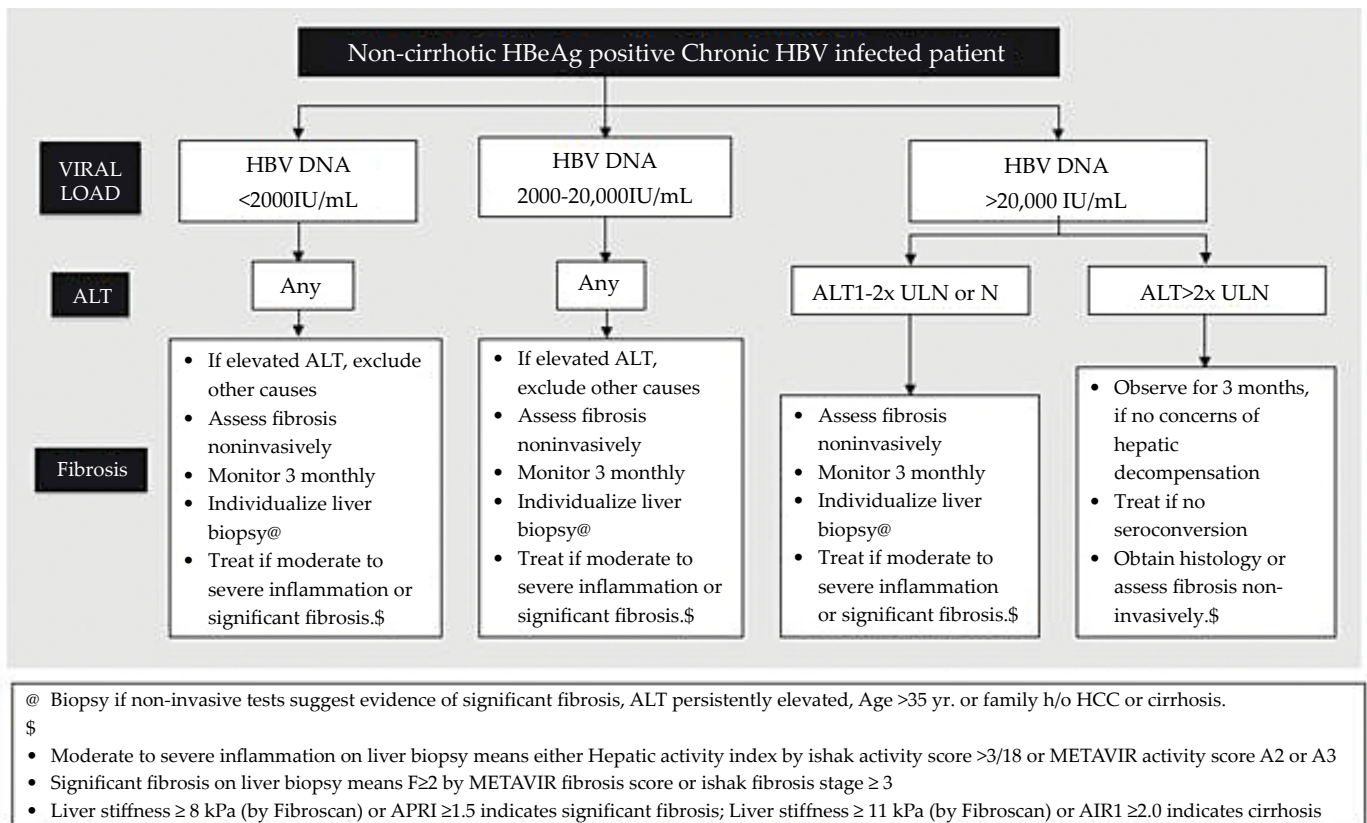


Fig. 2: Treatment indications for noncirrhotic HBeAg-positive chronic HBV-infected patients

family history of HCC or cirrhosis and extrahepatic manifestations.

- Decompensated cirrhosis and detectable HBV DNA, treatment with NA(s)^{14,15} and they should be considered for liver transplantation at the same time.

- Compensated cirrhosis and HBV DNA level 2000 IU/ml even with normal ALT. Liver biopsy is recommended, but noninvasive assessment of fibrosis is another option.
- Severe reactivation of chronic HBV infection.
- Treatment may be started in pre-cirrhotic chronic

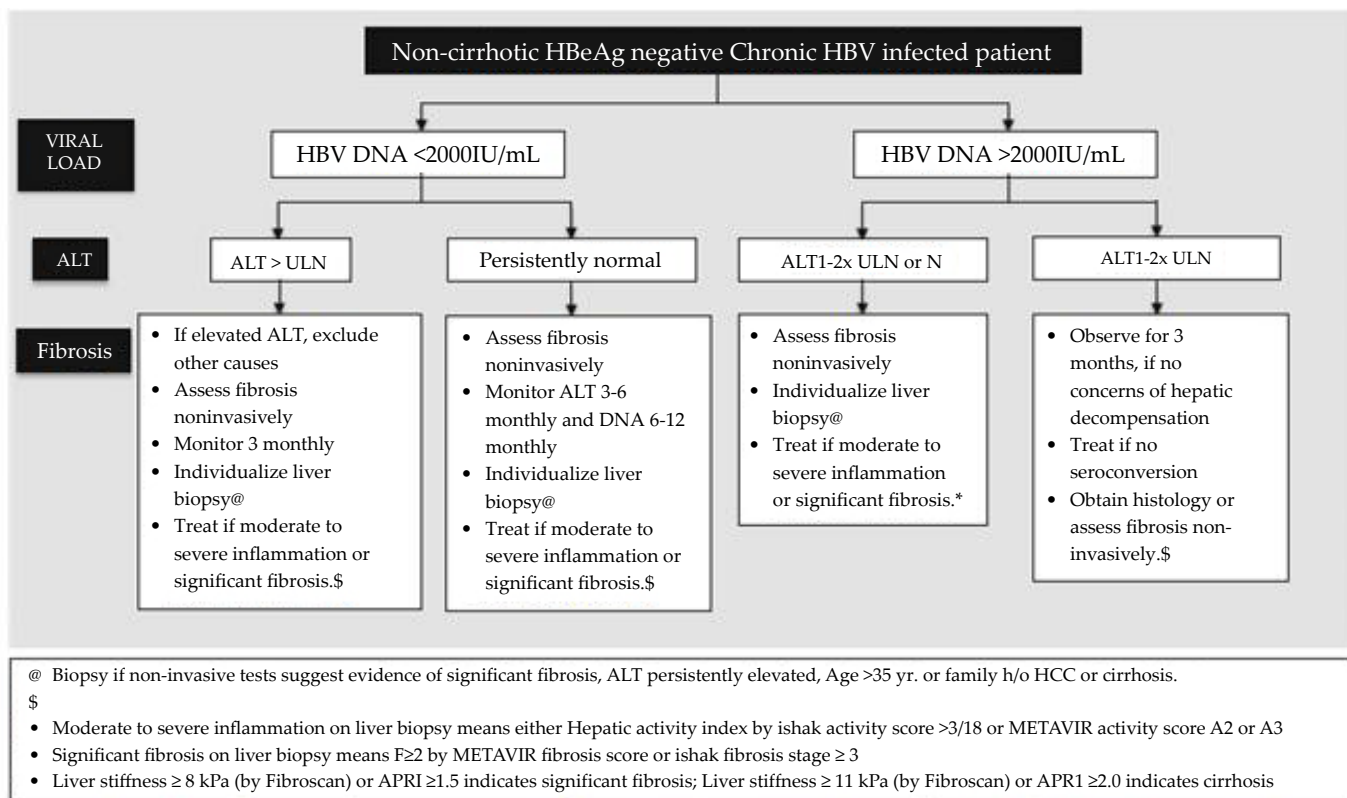


Fig. 3: Treatment indications for noncirrhotic HBeAg-negative chronic HBV-infected patients

HBV infected patients with persistently elevated ALT levels 2 times the upper limit of normal (ULN) (at least 1 month between observations) and HBV DNA level 20,000 IU/ml if HBeAg positive and 2000 IU/ml if HBeAg negative. In such patients, liver biopsy or noninvasive method may be used for the estimation of the extent of fibrosis is useful in patients who start treatment.

4. CURRENT AVAILABLE THERAPY

Anti-HBV treatments are either immuno- modulators or oral nucleos(t)ide analogs (NA). Immuno-modulators available in most countries are the conventional IFN, PEG-IFN- α 2a and PEG-IFN- α 2b. Oral NA consist of the first generation drugs lamivudine and adefovir, and the newer generations entecavir, telbivudine and tenofovir.

IFN based therapy is given for a finite duration. Although IFN-based therapy is associated with more side effects compared to NA, it has a higher likelihood of sustained off-treatment response. In HBeAg-negative patients, young age, female, high serum ALT levels, low serum HBV DNA were associated with a higher chance of achieving sustained response with PEG-IFN therapy¹⁵.

As a potent immune modulator, IFN has both direct and indirect anti-HBV effect although its precise mechanisms remain to be defined. IFN is the first FDA approved agent for HBV infection.

The course of IFN treatment is 48 weeks that offers a small, but certain opportunity of HBsAg clearance. Reactivation of HBV infection occurs in approximately 10-15% of patients who responded to treatment, most commonly

within a year after discontinuing IFN treatment. IFN is administrated by subcutaneous injection, associated with side effects and represents an expensive treatment regimen.

Lamivudine (LAM)

As a nucleoside analogue, LAM inhibits HBV DNA replication by suppressing HBV DNA . LAM represents a safe, cost-effective, and convenient HBV treatment regimen, but it does not result in HBsAg clearance and treatment duration is not for definite period. Risk of resistance is very high. Dose is 100mg daily.

Adefovir (ADV) Dipivoxil

Adefovir dipivoxil is a prodrug of ADV and a nucleotide analogue of adenosine monophosphate that inhibits HBV DNA replication by suppressing HBV DNA polymerase. Dose is 10mg daily.

Entecavir

Entecavir, a carbocyclic analogue of 2-deoxyguanosine, inhibits HBV replication at three different steps: the priming of HBV DNA polymerase, the reverse transcription of the negative strand HBVDNA from the pregenomic RNA, and the synthesis of the positive strand HBVDNA. The approved dose of entecavir for nucleoside-naive patients is 0.5 mg daily orally and for lamivudine-refractory/resistant patients is 1.0 mg daily orally. Doses should be adjusted for patients with estimated creatinine clearance ≤ 50 mL/min.

Telbivudine/LdT

Telbivudine is an L-nucleoside analogue with potent

202 antiviral activity against HBV. Recommended dose is 600 mg daily in empty stomach.

Tenofovir

Tenofovir disoproxil fumarate is a nucleotide analogue that was first approved for the treatment of HIV infection as Viread (tenofovir only) or Truvada (tenofovir plus emtricitabine as a single pill) and was approved for the treatment of chronic hepatitis B in 2008. Daily dose is 300 mg in empty stomach.

5. GOALS OF HBV TREATMENT

The goal of therapy for CHB is to improve quality of life and survival by preventing progression of the disease to cirrhosis, decompensated cirrhosis, end-stage liver disease, HCC and death. This goal can be achieved if HBV replication can be suppressed in a sustained manner. Then, the accompanying reduction in histological activity of CHB decrease the risk of cirrhosis and the risk of HCC,¹⁶. However, chronic HBV infection can not be completely eradicated due to the persistence of covalently closed circular DNA (cccDNA) in the nucleus of infected hepatocytes, which may explain HBV reactivation^{17,18,19}. Moreover, the HBV genome integrates into the host genome and might favour oncogenesis and the development of HCC.²⁰⁻²²

6. PREDICTORS OF HBV TREATMENT RESPONSE

Clinical, biochemical, and virological predictive factors to HBV treatment response is important for planning and monitoring HBV treatment. A low level of pre-treatment serum HBV DNA, high levels of ALT and histological activity, a history of adulthood HBV infection, and non-Asian ethnic origin have been associated with higher sustained response rates to IFN treatment¹⁵.

7. ON-TREATMENT MONITORING AND DURATION OF THERAPY

- During NA therapy, HBeAg, anti-HBe (in patients with HBeAg-positive) and ALT should be monitored every 3 months.
- The HBV DNA level should be measured at month 3 and 6 of therapy and then every 3–6 months if agents with a low genetic barrier.
- Renal function and bone profile should be monitored at least every 3 months if TDF or ADV is used and muscle symptoms and muscle weakness should be monitored during telbivudine therapy.
- Duration of therapy with IFN is 48 weeks and unknown for NAs. But treatment with NAs can be stopped in HBeAg positive CHB after at least 1 year, preferably after 3 years of additional therapy after HBeAg seroconversion with undetectable HBV DNA by PCR and persistently normal ALT levels and HBeAg negative CHB and after HBsAg loss following either anti-HBs seroconversion or at least 12 months of a post-HBsAg clearance consolidation period or after treatment for at least

2 years with undetectable HBV DNA documented on three separate occasions, 6 months apart²³.

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