INASL Position Statements on Prevention, Diagnosis and Management of Hepatitis B Virus Infection in India: The Andaman Statements

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Hepatitis B Virus (HBV) infection is one of the major causes of morbidity, mortality and healthcare expenditure in India. There are no Indian consensus guidelines on prevention, diagnosis and management of HBV infection. The Indian National Association for Study of the Liver (INASL) set up a taskforce on HBV in 2016, with a mandate to develop consensus guidelines for diagnosis and management of HBV infection, relevant to disease patterns and clinical practices in India. The taskforce first identified contentious issues on various aspects of HBV management, which were allotted to individual members of the taskforce who reviewed them in detail. A 2-day round table discussion was held on 11th and 12th February 2017 at Port Blair, Andaman & Nicobar Islands, to discuss, debate, and finalize the consensus statements. The members of the taskforce reviewed and discussed the existing literature threadbare at this meeting and formulated the 'INASL position statements' on each of the issues. The evidence and recommendations in these guidelines have been graded according to the Grading of Recommendations Assessment Development and Evaluation (GRADE) system with minor modifications. The strength of recommendations (strong: 1, weak: 2) thus reflects the quality (grade) of underlying evidence (A, B, C, D). We present here the INASL position statements on prevention, diagnosis and management of HBV in India. (J Clin Exp Hepatol 2018;8:58–80)

Hepatitis B Virus (HBV) infection is a global health problem and approximately one-third of the world's population or two billion people have been infected and carry serological evidence of past or present HBV infection. According to an estimate, in 2010, about 248 million individuals globally were chronically infected with HBV.[1] Of these approximately 15–40% will develop life-threatening liver consequences such as cirrhosis, liver failure and Hepatocellular Carcinoma (HCC), resulting in 600,000 to 1.2 million deaths per year due to HBV.[2]

In recent years many societies like European Association for the Study of the Liver (EASL),[3] American

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Abbreviations: AASLD: American Association for the Study of Liver Diseases; ADV: adefovir dipivoxil; ALT: alanine aminotransferase; Anti-HBe: antibodies to hepatitis B envelope antigen; anti-HBs: antibody to hepatitis B surface antigen; APASL: Asian Pacific Association for the Study of the Liver; ART: antiretroviral therapy; AST: aspartate aminotransferase; CBC: complete blood count; cccDNA: covalently closed circular DNA; CDC: Center for Disease Control; CHB: chronic hepatitis B; CU-HCC: Chinese University-Hepatocellular Carcinoma; DAA: direct-acting antiviral; DILI: drug induced liver injury; DNA: deoxyribonucleic acid; EASL: European Association for the Study of the Liver; eGFR: estimated glomerular filtration rate; ETV: entecavir; GAG-HCC: Guide with Age, Gender, HBV DNA, Core Promoter Mutations and Cirrhosis-Hepatocellular Carcinoma; GGT: gamma-glutamyl transferase; GRADE: Grading of Recommendations Assessment Development and Evaluation; HBeAg: hepatitis B envelope antigen; HBIG: hepatitis B immune globulin; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HDV: hepatitis D virus; HIV: human immunodeficiency virus; IFN-α: interferon alpha; INASL: Indian National Association for Study of the Liver; INR: international normalized ratio; KASL: Korean Association for the Study of the Liver; LAM: lamivudine; NA: nucleos(t)ide analogue; PAGE-B: platelets, age, gender—hepatitis B; PegIFN-α: pegylated interferon alpha; PVNR: primary virological non-response; PVR: partial virological response; RCT: randomized controlled trial; REACH-B: risk estimation for hepatocellular carcinoma in chronic hepatitis B; SOVR: sustained off-therapy virological response; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate; TDV: telbivudine; TSH: thyroid-stimulating hormone; VR: virologic response; WHO: World Health Organization
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Association for the Study of Liver Diseases (AASLD),[4] Asian Pacific Association for the Study of the Liver (APASL),[5] World Health Organization (WHO),[6] and Korean Association for the Study of the Liver (KASL)[7] have published hepatitis B guidelines. However, while these guidelines are broadly applicable, they may or may not be able to address India-specific issues relating hepatitis B. The epidemiology of HBV in India, the socio-economic and healthcare structure in India, and treatment practices in India, are different from rest of the world. Therefore, the Indian National Association for Study of the Liver (INASL) felt a need to develop 'India-specific' consensus guidelines for diagnosis and management of HBV infection. With this aim, the INASL set up a taskforce on HBV in 2016, with a mandate to develop consensus guidelines on various clinical aspects of HBV, relevant to disease patterns and clinical practices in India. These guidelines are also expected to help in developing a framework for future research on affordable management options for HBV in India. The present review summarizes the INASL consensus statements on prevention, diagnosis and management of HBV infection in India. These are the first HBV guidelines published from any society of India.

For the purpose of development of consensus statements, the taskforce identified the main contentious issues on various aspects of HBV. Members of the taskforce reviewed the existing literature, especially from India, and developed consensus statements on each of these issues. A 2-day round table discussion was held on 11th and 12th February 2017 at Port Blair, Andaman & Nicobar Islands, to discuss, debate, and finalize the consensus statements. Only those statements that were unanimously approved by the members of the taskforce were accepted. The evidence and recommendations in these statements have been graded according to the Grading of Recommendations Assessment Development and Evaluation (GRADE) system with minor modifications (Table 1). The strength of recommendations (strong: 1, weak: 2) thus reflects the quality (grade) of underlying evidence (A, B, C, D).[8] Andaman & Nicobar Islands was chosen as the venue for this meeting because these islands represent the area with one of the highest prevalence of HBV infection in India.

PHASES OF HBV INFECTION

The natural history of chronic HBV infection has been divided into distinct phases, as initially described by Chen.[9] These phases are as follows:

- Immune-tolerant phase
- Immune-active HBeAg-positive phase
- Inactive carrier phase
- HBeAg-negative immune reactivation phase, and
- HBsAg-clearance phase

These phases are of variable duration, may or may not be sequential, and not every person infected with HBV will pass through all phases.[4] These phases take into account the presence of HBeAg, HBV DNA levels, ALT values and presence or absence of liver inflammation. However, a single determination of HBV replication markers and disease activity markers does not allow an accurate classification to one of these phases. Serial monitoring of HBeAg, HBV DNA and ALT levels is required in most instances to establish the phase of infection; despite which, some subjects fall into an indeterminate gray area and management needs to be individualized.[3] Recently EASL has suggested a change in nomenclature of these phases as follows: HBeAg positive chronic infection, HBeAg positive chronic hepatitis, HBeAg negative chronic infection, HBeAg negative chronic hepatitis, and HBsAg negative chronic infection, respectively.[3] Since, the new nomenclature is easy to understand and simpler to use in dichotomizing infected individuals into those with infection (no liver inflammation or damage) and those with hepatitis (with liver inflammation and/or damage) it should be used widely. However, it may still not eliminate all gray areas as it continues to depend on ALT, which is an

Table 1 Grading of Recommendations, Assessment, Development and Evaluation (GRADE).

	Criteria
Quality of evidence	
High (A)	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate (B)	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low (C)	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low (D)	Any estimate of effect is very uncertain.
Strength of recommendations	
Strong (1)	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost.
Weak (2)	Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption.

Table 2 Phases of Chronic Hepatitis B.

Phase	Old name	New name	HBeAg	Serum HBV DNA	ALT	Liver histology
Phase I	Immune-tolerant phase	HBeAg positive chronic infection	Positive	$>10^7$ IU/ml	Normal	Minimal inflammation and fibrosis
Phase II	Immune-active HBeAg-positive phase	HBeAg positive chronic hepatitis	Positive	10^4–10^7 IU/ml	Elevated	Moderate-to severe inflammation or fibrosis
Phase III	Inactive carrier phase	HBeAg negative chronic infection	Negative	<2000 IU/ml	Normal	Minimal necroinflammation but variable fibrosis
Phase IV	HBeAg-negative immune reactivation phase	HBeAg negative chronic hepatitis	Negative	>2000 IU/ml	Elevated	Moderate-to severe inflammation or fibrosis
Phase V	HBsAg-clearance phase (also known as occult HBV infection)	HBsAg negative chronic infection	Negative	Undetectable (HBV DNA can be detectable in liver)	Normal, usually	No inflammation, minimal fibrosis. HBV DNA (cccDNA) can be detected frequently in the liver

imperfect marker of liver injury. INASL has endorsed this new nomenclature for use in India. A summary of features of all the five phases along with the new nomenclature is given in Table 2.

EPIDEMIOLOGY OF HBV IN INDIA

There is a lack of large-scale population-based studies on the prevalence of HBV in India. Most of the available data is based on blood bank and antenatal screening which has inherent biases and may not truly reflect the true national prevalence.[2] A meta-analysis of 54 studies on data of point prevalence of hepatitis B from different parts of the country, published in 2007, reported that the true prevalence in non-tribal populations is 2.4% (95% CI: 2.2–2.7%); while the true prevalence among tribal populations is 15.9% (CI: 11.4–20.4%).[10] However, a recent meta-analysis of 129 studies on 3,764,669 participants, reported that HBV prevalence estimate was 1.46% (95% CI 1.44–1.47).[1] Thus it is reasonable to conclude that the prevalence of chronic hepatitis B (CHB) in general population in India may be between 1.4% and 2.7%.

It has been estimated that only about one-third of the adult HBV infected subjects in India evolve directly from perinatal infection, while the majority (two-third) become infected during childhood or early adulthood.[11] However current knowledge of dynamics of HBV transmission is imprecise and present understanding of the role of perinatal transmission and horizontal transmission of this disease among children is based on inadequate evidence.[2] The contribution by vertical transmission may, in fact, be higher if we look at the high prevalence of HBV replicative markers in HBsAg-positive pregnant women.[12–15] More, better planned, studies are needed to definitively answer this question.

Most HBV infections in India are due to genotypes A and D.[16–23] In two different studies from northern India, genotypes A and D were found to be equally prevalent.[16,22] However, another study from the same geographic region reported genotype D to be predominant with a low frequency of genotype A in northern Indian HBV infected patients,[21] which was similar to the HBV genotype distribution documented from western and southern parts of India.[18,23] In sharp contrast to rest of India, the eastern part of India presents an interesting epidemiologic pattern with three different HBV genotypes (genotypes A, C and D) present in comparable proportions.[2,19,20,23]

Consensus Statements

- ***The prevalence of chronic hepatitis B in general population India is between 1.4% and 2.7%. (A)***
- ***Predominant mode of transmission is horizontal, however, vertical transmission is also common in India. (B)***
- ***Most HBV infections in India are due to genotype A and D. (A)***

PREVENTION OF HBV INFECTION THROUGH VACCINATION

Recombinant hepatitis B vaccine was introduced in 1986 and has gradually replaced the plasma-derived hepatitis B vaccine.[24] The protective efficacy of hepatitis B vaccination is related to the induction of anti-HBs antibodies but also involves the induction of memory T-cells. An anti-HBs concentration of 10 mIU/ml, measured 1–3 months after administration of the last dose of the primary vaccination series is considered a reliable marker of protection against infection.[24,25] The primary 3-dose vaccine series induces protective antibody concentrations in >95% of healthy infants, children and young adults.[24,26–28]

Since 1992, WHO has recommended global vaccination against HBV, and by 2009, 177 countries had already incorporated HBV vaccination in their national immunization programs.[2] In countries that have implemented universal childhood hepatitis B immunization, this has resulted in a decline in HBV carrier rates and its long-term consequences, including HCC.[2,29]

Vaccination of infants within 24 h of birth is 90–95% effective in preventing infection with HBV as well as decreasing HBV transmission, if followed by at least two other doses. WHO recommends universal hepatitis B vaccination for all infants, and that the first dose should be given as soon as possible after birth.[6] Apart from infants, HBV vaccination is advisable for all children and adults who are not previously vaccinated.

Although knowledge about the duration of protection against infection and disease following hepatitis B vaccination is still incomplete, including knowledge on the potential role of natural sub-clinical boosting, there is no compelling evidence for recommending administering a booster dose of hepatitis B vaccine in routine immunization programmes.[24]

HBV vaccination is also recommended in people with risk factors for acquiring HBV infection, such as those who frequently require blood or blood products, dialysis patients, recipients of solid organ transplantations, injecting drug users, household and sexual contacts of people with chronic HBV infection, people with multiple sexual partners, as well as health-care workers and others who may be exposed to blood and blood products through their work.[24]

Immunosuppressive illnesses, including advanced HIV infection, chronic renal failure, chronic liver disease, coeliac disease and diabetes, are associated with reduced immunogenicity following vaccine administration. For these patients higher vaccine doses or increased number of doses are required. The anti-HBs response of such persons should be tested after they are vaccinated, and those who have not responded should be revaccinated with 1–3 additional doses.[30]

Consensus Statements

- ***Universal hepatitis B vaccination is recommended for all infants, and the first dose should be given as soon as possible after birth. (A1)***
- ***HBV vaccination is also recommended in people with risk factors for acquiring HBV infection, such as those who frequently require blood or blood products, dialysis patients, recipients of solid organ transplantations, injecting drug users, household and sexual contacts of people with chronic HBV infection, people with multiple sexual partners, as well as health-care workers and others who may be exposed to blood and blood products through their work. (A1)***
- ***HBV vaccination is advisable for all children and adults who are not previously vaccinated. (C2)***
- ***There is no evidence to support the need for a booster dose of hepatitis B vaccine. (A1)***
- ***For immunosuppressed population higher vaccine doses or increased number of doses are required. The anti-HBs response of such persons should be tested after they are vaccinated, and those who have not responded should be revaccinated with 1–3 additional doses. (B1)***

DIAGNOSIS AND INITIAL EVALUATION

Once a subject is found to be HBsAg positive, the initial evaluation should include a thorough history and physical examination, with special emphasis on possible mode of acquisition, current phase of infection and stage of disease, need for antiviral treatment, and family history of cirrhosis and liver cancer. Presence of additional risk factors for liver disease such as co-infections with other hepatitis viruses, alcohol abuse, diabetes mellitus, obesity, and metabolic syndrome, if present, should be systematically evaluated. Because tenofovir and possibly also entecavir monotherapy can cause HIV resistance mutations, all HBsAg-positive patients should be screened for HIV before these drugs are used in the treatment of HBV infection.

Laboratory tests should include assessment of liver function (AST, ALT, GGT, alkaline phosphatase, bilirubin, serum albumin, serum globulins, CBC and INR), markers of HBV replication (HBeAg, anti-HBe, HBV DNA quantitative), and tests for co-infection with HCV and HIV. Ultrasound examination of the liver is recommended in all patients. Serum HBsAg quantification can be useful, particularly in HBeAg-negative chronic HBV infection and in patients to be treated with pegylated interferon alpha (PegIFN-α).[31] HBV genotype is not necessary in the initial evaluation, although it may be useful for selecting patients to be treated with PegIFN-α, as it offers prognostic information for the probability of response to PegIFN-α therapy and the risk of HCC. In India, testing for antibodies against hepatitis A virus (anti-HAV) is not recommended.

In 2002, it was suggested that the upper limit of normal ALT should be updated to 30 U/L for men and 19 U/L for women, based on large data from Italy.[32] However, these new ALT cut-offs need to be prospectively validated in India before they can be recommended. Hence, it was decided by the INASL HBV taskforce that the upper limit of normal ALT level should be 40 U/L, as before.

If results of blood tests and ultrasonography are equivocal, a liver biopsy or non-invasive test should be performed to determine disease stage and need for antiviral treatment. Liver biopsy provides an assessment of the severity of necro-inflammation and fibrosis, rules out other causes of liver disease, and may be especially useful for persons who lack clear-cut indications for antiviral treatment.[33,34] Whereas liver biopsy is regarded as the best method to assess the severity of inflammatory activity and fibrosis, non-invasive methods to assess fibrosis severity are also useful. Among non-invasive methods, which include liver stiffness measurements and serum biomarkers of liver fibrosis, the use of transient elastography has been studied most extensively and seems to offer a higher diagnostic accuracy for the detection of advanced fibrosis, cirrhosis, and even portal hypertension.[35–38] Non-invasive methods have only moderate accuracy in identifying persons with significant fibrosis (fibrosis stage 2 or greater on the METAVIR scale), but good diagnostic accuracy in excluding advanced fibrosis and may be useful aids in

decision-making.[39,40] Intermittent exacerbations of hepatitis B may lead to overestimation of fibrosis stage by noninvasive tests, and different cutoffs for significant and advanced fibrosis depending on ALT levels have been proposed.[39]

In addition, all first-degree relatives and sexual partners of subjects with chronic HBV infection, if not previously vaccinated, should be tested for HBV and to be vaccinated if they are negative for HBsAg.

Abstinence from alcohol and smoking should be strongly recommended during initial evaluation of patients with chronic HBV infection. Barrier method of contraception is recommended to patients with HBV infection with detectable HBV DNA levels, if the partner is unvaccinated or not fully vaccinated.

Consensus Statements

- ***During initial evaluation of HBsAg positive persons, special emphasis should be on possible mode of acquisition, current phase and staging, need for antiviral treatment, presence of additional risk factors such as co-morbidities, co-infections, alcohol use, and family history of cirrhosis and liver cancer. (A1)***
- ***Laboratory tests should include assessment of liver function (AST, ALT, GGT, alkaline phosphatase, bilirubin, serum albumin, serum globulins, CBC and INR), markers of HBV replication (HBeAg, anti-HBe, quantitative HBV DNA), and tests for co-infection with HCV and HIV. An ultrasound examination of the liver is recommended in all patients. (A1)***
- ***Till more data on normal ALT levels from India are available, an ALT $\leq$40 U/L should be considered normal for Indian patients. (B1)***
- ***A liver biopsy or non-invasive test should be performed to determine disease stage and need for antiviral treatment in cases where biochemical tests and ultrasonography reveal inconclusive results. (A1)***
- ***Abstinence from alcohol and smoking should be strongly advised during initial evaluation of patients with chronic HBV infection. (A1)***
- ***Barrier method of contraception is advised to patients with HBV infection with detectable HBV DNA levels, if the partner is unvaccinated or not fully vaccinated. (A1)***
- ***Because tenofovir and possibly also entecavir monotherapy can cause HIV resistance mutations, all HBsAg-positive patients should be screened for HIV before these drugs are used in the treatment of HBV infection.***

TREATMENT GOALS

The ultimate long-term treatment goal in patients with hepatitis B is to decrease mortality rate by preventing the development of, or preventing the progression of, liver cirrhosis and/or HCC. Thus the optimal treatment result would be the loss of HBsAg and seroconversion to anti-HBs. However, this is almost impossible to achieve in patients with CHB, because intra-nuclear cccDNA persists despite treatment.[7,41] Therefore, an achievable realistic virologic goal of anti-HBV therapy is the long-term suppression of viral replication. Indices of viral replication and active hepatitis are HBV DNA level and HBeAg positivity, respectively, and patients with HBeAg-positive hepatitis B with high levels of HBV DNA have an increased risk of developing liver cirrhosis or HCC.[7,42–44] Patients with disappearance or seroconversion of HBeAg, either during natural course or by anti-viral therapy have a low risk of liver cirrhosis and HCC and so have a good prognosis.[45,46] Therefore, clearance or seroconversion of HBeAg is an important goal of antiviral treatment in patients with HBeAg-positive active hepatitis. Similarly, a decrease in the serum HBV DNA level with antiviral treatment is also very important as it results in histologic improvement, seroconversion of HBeAg, normalization of ALT levels, and thus halting the progression of hepatitis.[7,47] A decrease in HBV DNA to an undetectable level is recommended for patients on antiviral treatment, because, even in cases with HBV DNA levels of less than 10^4 copies/ml, which is considered to be inactive hepatitis, the hepatitis can still progress to liver cirrhosis and HCC.[7,48] Thus indices such as undetectable HBV DNA, loss or seroconversion of HBeAg, ALT level normalization, and histologic improvement are used to predict the treatment response and thus comprise the short-term treatment goals.[7]

Consensus Statements

- ***The ultimate long-term treatment goal in patients with hepatitis B is to decrease mortality rate by preventing the development of, or preventing the progression of, liver cirrhosis and/or HCC. This may be achieved by:***
  - ***HBsAg clearance, or***
  - ***Long-term maintenance of an undetectable HBV DNA level. (A1)***
- ***The short-term treatment goals in patients with HBeAg-positive hepatitis are normalization of the ALT level, undetectable HBV DNA level, and the clearance or seroconversion of HBsAg and HBeAg. In patients with HBeAg-negative hepatitis the treatment goals are normalization of the ALT level, and an undetectable HBV DNA level. (B1)***

INDICATIONS FOR ANTIVIRAL TREATMENT

Indication for antiviral treatment is generally based on the phase of HBV infection. As mentioned before, there are five phases of chronic HBV infection. Antiviral treatment is required for phase II, immune-active HBeAg positive phase (now called as HBeAg positive chronic hepatitis) and phase IV, HBeAg negative immune reactivation phase (now called as HBeAg negative chronic hepatitis). Antiviral treatment is not needed for other phases. However, diagnosis of and differentiation between these phases may not be easy and a combination of HBV DNA levels, HBeAg status, ALT level, and liver histology may be required to diagnose these phases and guide treatment.

Serum HBV DNA level is a marker of viral replication and strongly correlates with risk of progression to cirrhosis and HCC.[43,44,49,50] Previous guidelines had chosen an arbitrary cut-off of 10^5 copies/ml or 20,000 IU/ml as an indication for antiviral treatment.[51] However, some patients with lower serum HBV DNA levels, especially those with HBeAg negative hepatitis and/or cirrhosis, frequently show progression of liver disease and hence

may need antiviral treatment. In a population-based prospective cohort study of 3582 untreated hepatitis B-infected patients established in Taiwan from 1991 to 1992[44] during a mean follow-up time of 11 years, 365 patients were newly diagnosed with cirrhosis. After adjusting for hepatitis B e-antigen status and serum alanine transaminase levels, hepatitis B viral load was the strongest predictor of progression to cirrhosis with a relative risk of more than 2.5 for HBV-DNA levels ≥2000 IU/ml. Therefore this level is widely accepted as the cut-off for indicating antiviral therapy for HBeAg negative patients.[7]

However, HBV DNA level cannot be used as the sole criteria for selection of patients for treatment. ALT activity is a crucial parameter in treatment selection and the evaluation of prognosis in patients infected with HBV. When high HBV DNA levels are associated with high ALT, indicating active necro-inflammation, antiviral treatment is indicated. Nevertheless, controversy exists and Lai et al. from USA[52] and Kumar et al. from India[53] have reported significant fibrosis and inflammation in many patients infected with HBV and persistently normal ALT levels. The second controversy relates to the cut-off of normal ALT levels. In 2002, it was suggested by investigators from Italy, that the upper limit of normal ALT should be updated to 30 U/L for men and 19 U/L for women.[32] Kumar et al.[53] from India, in their retrospective study showed that persistently normal ALT patients defined by updated criteria, the median HAI was 3 (range 1–5), median fibrosis scores was 1 (range 0–2), and distribution of fibrosis stages (0/1/2/3/4) were 35%/46%/19%/0%/0%, respectively in HBeAg negative patients. However, these new ALT cut-offs need to be prospectively validated in India before they can be recommended. Hence, it was decided by the INASL HBV taskforce to regard the upper limit of normal ALT as 40 U/L, as before.

The distinction between HBeAg negative chronic hepatitis and inactive carriers is not easy due to the fluctuating course of HBeAg-negative chronic hepatitis B.[54] Hence liver biopsy or non-invasive assessment of fibrosis is recommended in patients with HBV DNA between 2000 and 20,000 IU/ml and ALT <80 U/L. Individuals with moderate necro-inflammation or fibrosis should be offered antiviral treatment.

Patients in phase I or immune-tolerant phase (HBeAg positive chronic infection) are characterized by positive HBeAg, high viral replication, persistently normal ALT and no or minimal liver damage.[9,55] Since the risk of the progression of liver disease and the chance of a sustained response with existing anti-HBV agents are low, current guidelines do not recommend treatment but close monitoring with serial ALT and HBV DNA measurements.[3,4,7,35] However, advanced histological lesions have been reported in certain immune-tolerant patients who are usually >30–40 years old, and continued high HBV replication could increase the risk of HCC.[43,55–57] Thus, the optimal management of patients in immune-tolerant patients is often individualized according to age, which is associated with histological severity and patient outcome.[55] In particular, immunotolerant patients <30 years old can be monitored for ALT and HBV DNA, while treatment is often recommended in the few patients over 30 years.[3] A liver biopsy and/or non-invasive assessment of fibrosis may be helpful to determine the therapeutic strategy in patients above 30 years old. More studies are needed to further clarify the natural history for the optimal timing of treatment in this setting. The INASL taskforce recommended that patients in immune-tolerant phase should not be treated if aged <30 years but *may* be treated if aged >30 years.

Most guidelines agree that antiviral treatment is required for patients with cirrhosis (compensated or decompensated), acute liver failure, acute-on-chronic liver failure, and extra-hepatic manifestations of HBV regardless of ALT levels, HBeAg status or HBV DNA levels.[3–6] Antiviral treatment is also indicated in patients with family history of cirrhosis or HCC, if they have HBV DNA levels >2000 IU/ml, regardless of ALT levels or HBeAg status (Figures 1–3).

Consensus Statements

- ***Following adult patients with chronic hepatitis require antiviral treatment:***
  - ***HBeAg positive chronic hepatitis as diagnosed by:***
    - ***ALT >80 U/L, or***
    - ***If ALT 40–80 U/L and moderate necro-inflammation or fibrosis on non-invasive test for liver fibrosis or liver biopsy***
  - ***HBeAg negative chronic hepatitis as diagnosed by:***
    - ***HBV DNA >20,000 IU/ml, or***
    - ***HBV DNA >2000 IU/ml and ALT >80 U/L, or***
    - ***HBV DNA >2000 IU/ml and moderate necro-inflammation or fibrosis on non-invasive test for liver fibrosis or liver biopsy. (A1)***
- ***Following group of adult patients also require antiviral treatment:***
  - ***Patients with cirrhosis (compensated or decompensated), regardless of ALT levels, HBeAg status or HBV DNA levels***
  - ***Patients with liver failure (ALF or ACLF), regardless of ALT levels, HBeAg status or HBV DNA levels***
  - ***Patients with extra-hepatic manifestation of HBV, regardless of ALT levels, HBeAg status or HBV DNA levels***
  - ***Patients with family history of cirrhosis or HCC, with HBV DNA >2000 IU/ml, regardless of ALT levels or HBeAg status. (A1)***
- ***Patients in immune-tolerant phase (HBV DNA >20,000 IU/ml, HBeAg positive, ALT persistently normal):***
  - ***May be treated if aged >30 years***
  - ***Should not be treated if aged <30 years. (B1)***
- ***Patients in inactive carrier phase (HBeAg negative chronic infection) do not require antiviral treatment. Patients in inactive carrier phase are HBeAg negative with one of the following features:***
  - ***HBV DNA <2000 IU/ml, or***
  - ***HBV DNA 2000–20,000 IU/ml, ALT <80 U/L, and minimal inflammation and fibrosis on liver biopsy or non-invasive assessment of fibrosis. (A1)***

DRUGS USED FOR ANTIVIRAL TREATMENT

Currently, there are two main classes of antiviral drugs for treatment of chronic hepatitis B: Nucleos(t)ide Analogue

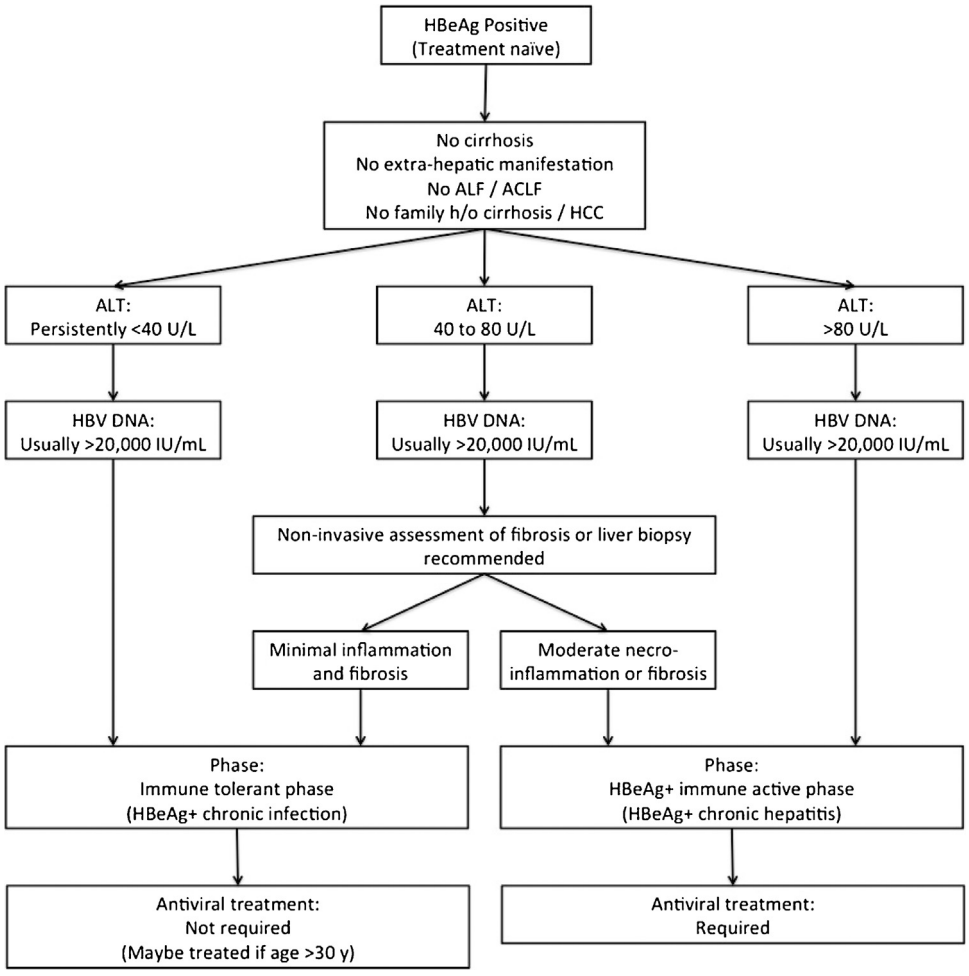

Figure 1 Algorithm for management of HBeAg positive treatment naïve patients.

(NA) and pegylated interferon alpha (PegIFN-α). The NAs that have been approved for HBV treatment are Lamivudine (LAM), Adefovir Dipivoxil (ADV), Entecavir (ETV), Telbivudine (TBV), Tenofovir Disoproxil Fumarate (TDF) and Tenofovir Alafenamide (TAF)[3]. Although all NAs act on HBV polymerase, their mechanism of action differs: ADV inhibits the priming of reverse transcription; LAM and TDF/TAF inhibit the synthesis of the viral (−) strand DNA; and ETV inhibits three major stages of HBV replication.[6] The NAs can be classified into those associated with low barrier against HBV resistance (LAM, ADV, TBV) and those with high barrier to HBV resistance (ETV, TDF, TAF). Because of risk of development of resistant HBV strains, only NAs with high barrier to HBV resistance (ETV, TDF, TAF) are recommended. ETV, TDF, and TAF are safe drugs with no major safety concerns.[58–60] However, TDF is preferred in pregnant women or women of childbearing age.[61] Renal and bone density monitoring may be required with the use of TDF owing to the risk of renal impairment and osteoporosis, especially in those with prior renal impairment, osteoporosis, or advanced age.[62]

IFN-α has been used for over 30 years. Its pegylated form (PegIFN-α) has improved pharmacokinetics, prolonged half-life, and superior efficacy.[60] PegIFN-α is more effective for HBeAg positive patients who have high pretreatment ALT, lower HBV DNA level and genotype A (vs. genotype D), as well as those with favorable viral predictors, such as pre-core stop codon or basal core promoter mutants infections in Asian patients and wild-type virus in Caucasian patients.[63] The main advantages of PegIFN-α over NAs are the absence of resistance and achievement of higher rates of HBeAg and HBsAg loss. However, the disadvantages of PegIFN-α are low efficacy (less than 50% of persons treated will respond), high cost, administration by injection and frequent adverse effects, and numerous contra-indications, which precludes its use in majority, particularly in resource-limited settings. Relative and absolute contraindications to PegIFN-α include the presence of decompensated cirrhosis and hypersplenism, thyroid disease, autoimmune diseases, severe coronary artery disease, renal transplant recipients, pregnancy, seizure disorder, psychiatric illness, concomitant use of

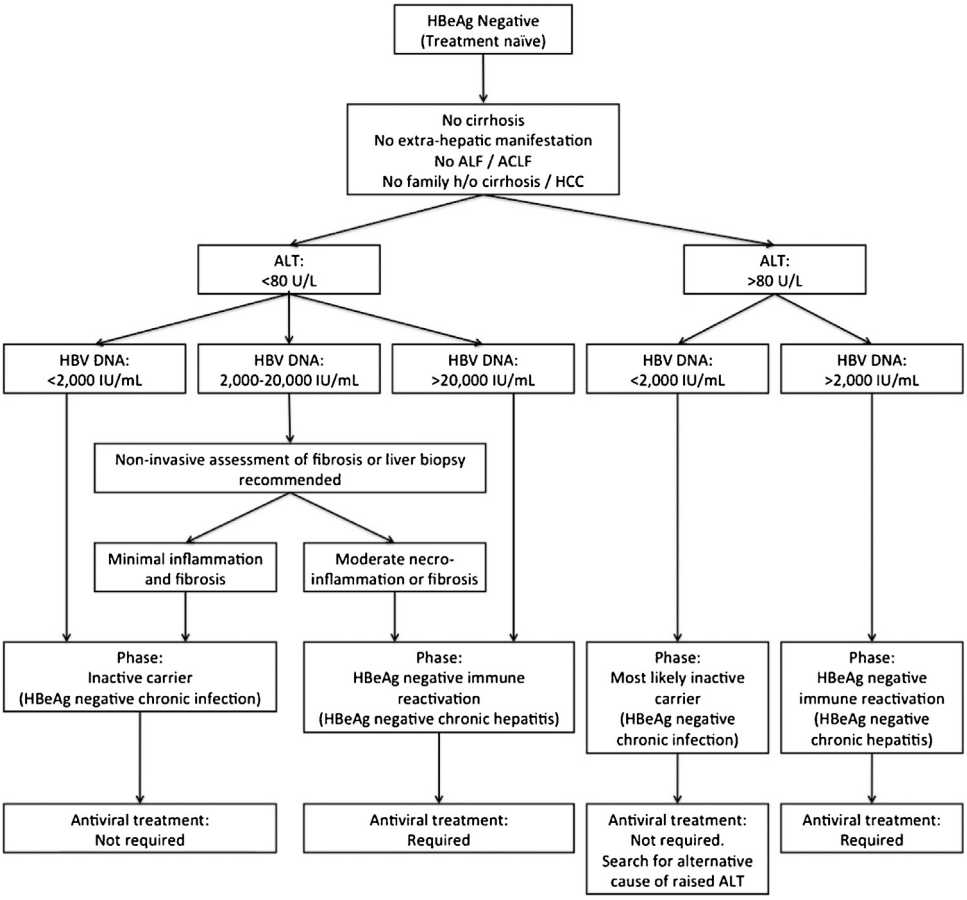

Figure 2 Algorithm for management of HBeAg negative treatment naïve patients.

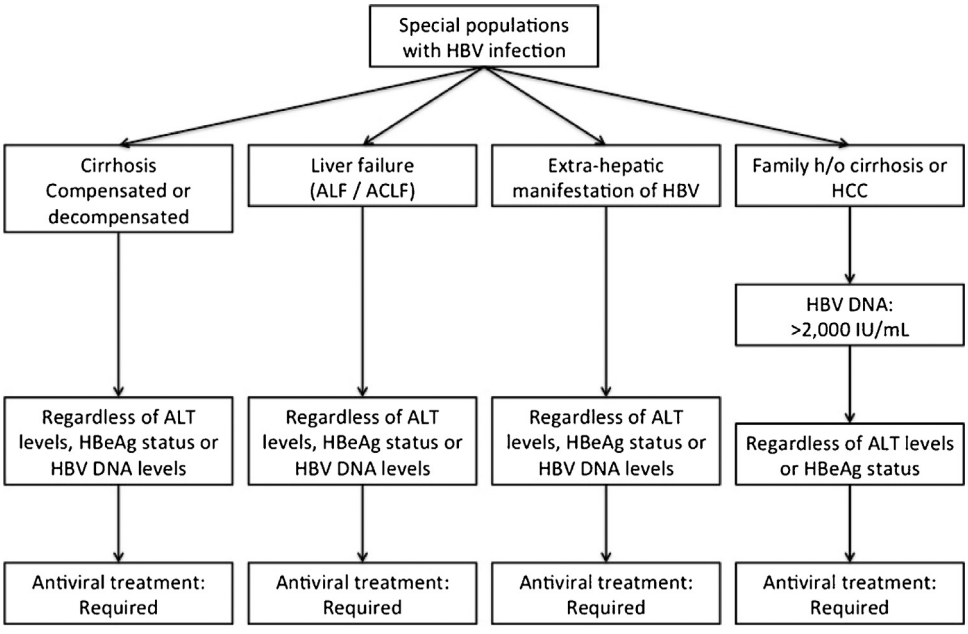

Figure 3 Algorithm for management of patients with cirrhosis, liver failure, extra-hepatic manifestations of HBV, and family history of cirrhosis or HCC.

certain drugs, retinopathy, thrombocytopenia and leucopenia.[6]

Although two randomized controlled trials[64,65] have shown a higher percentage of complete HBV DNA suppression with NA combination therapy in HBeAg-positive patients with high baseline viral load, the differences in terms of on-treatment HBV DNA levels and clinical/serological endpoints observed with both strategies are not strong enough to recommend ab initio combination for this group of patients.[3] Similarly the combination of PegIFN-α and NAs has not yielded higher rates of off-treatment serological or virological responses and is not recommended.[4,66]

Consensus Statements

- ***Following drugs should be used for treatment:***
  - ***Tenofovir Disoproxil Fumarate (TDF), Tenofovir Alafenamide (TAF), Entecavir (ETV), and Pegylated Interferon alpha (PegIFN-α). (A1)***
- ***All the drugs should be used as monotherapy. Combination therapy or sequential therapy of NA and PegIFN-α is not recommended at present. (B1)***
- ***Following drugs should not be used for treatment:***
  - ***Lamivudine, adefovir, and telbivudine. (A1)***
- ***In patients with cirrhosis:***
  - ***Oral antiviral therapy with tenofovir or entecavir is preferred. (A1)***
  - ***PegIFN-α may be used with careful monitoring of liver function and side effects in patients with compensated liver cirrhosis with preserved liver function. (B2)***
  - ***The use of PegIFN-α is contraindicated in patients with decompensated cirrhosis due to the risk of serious complications, such as hepatic failure. (A1)***

MONITORING OF PATIENTS CURRENTLY NOT ON ANTIVIRALS

Patients who are not candidates for antiviral therapy need periodic monitoring of their disease status. The monitoring should be with serum ALT and HBV DNA levels. If indicated non-invasive assessment of liver fibrosis should also be done. It is desirable that patients with HBV DNA >2000 IU/ml should have ALT determinations at least every 3–6 months, HBV DNA determinations every 6–12 months and assessment of liver fibrosis every 12 months.[3] Patients with HBV DNA <2000 IU/ml should have ALT determinations every 6–12 months and periodical HBV DNA and liver fibrosis assessments, perhaps every 2–3 years.[3]

Consensus Statements

- ***Patients who do not fulfill any of the above treatment indications should be followed as follows:***
  - ***Patients with HBV DNA >2000 IU/ml: should have ALT determinations at least every 3–6 months, HBV DNA determinations every 6–12 months and assessment of liver fibrosis every 12 months.***
  - ***Patients with HBV DNA <2000 IU/ml: should have ALT determinations every 6–12 months and periodical HBV DNA and liver fibrosis assessments, every 2–3 years. (B1)***

MONITORING OF PATIENTS ON ANTIVIRAL TREATMENT

During antiviral therapy, close monitoring for side effects of each drug is mandatory.

Monitoring of drug compliance of patient is of paramount importance, especially with long-term NA treatment. In a recently published systematic review[67] the mean adherence to various NA regimens was reported in three studies and varied from 81 to 99%.[68–70] The proportion of patients with perfect adherence was also reported in three studies and varied from 66% to 92%.[69,71,72] Poor adherence to antiviral treatment may lead to increased risk of drug resistance and treatment failure. Virological response is better in adherent patients compared to non-adherence patients.[67,69–71,73]

The optimal timing and frequency of monitoring of serological and biochemical markers (HBeAg and anti-HBe, serum ALT and HBV DNA) to assess treatment response and alterations in disease phases on treatment are not well established.[6]

It is recommended that ALT and HBV DNA levels should be monitored every 3–6 months, HBeAg/anti-HBe every 6 months, and HBsAg levels every 6–12 months for patients on NA therapy. Renal function, including estimated Glomerular Filtration Rate (eGFR), and serum phosphate levels should be monitored if TDF is used or when patients are at risk of renal disease treated with any NA 3–6 monthly. Patients on TDF at risk of development and/or with underlying renal or bone disease should be considered for switching to ETV or TAF.

Since PegIFN-α has many side effects, patients treated with it should receive frequent blood counts especially during the early stage of treatment. They should be monitored with periodic assessments of CBC, ALT, TSH, HBeAg, anti-HBe, serum HBV DNA and HBsAg levels. It is recommended that HBV DNA levels should be monitored every 12 weeks, HBeAg/anti-HBe every 24 weeks, and HBsAg levels every 24 weeks during treatment. After the end of treatment, levels of ALT and HBV DNA should be monitored monthly for the first 3 months to detect early relapse, and then every 3 months in the first year after therapy.

HCC surveillance is mandatory for all patients with cirrhosis as well as those with medium or high baseline HCC risk scores, i.e., at the onset of therapy. Several scoring systems have been developed to predict the risk of HBV-related HCC based on some of the known HCC risk factors, e.g., REACH-B score,[74] CU-HCC score,[75] GAG-HCC score,[76] and PAGE-B score.[77] None of these scores have been validated in Indian patients. Of these, the simplest to use is CU-HCC score,[75] which uses five parameters: age, albumin, bilirubin, HBV DNA, and presence or absence of cirrhosis (Table 3). INASL recommends the use of this score in Indian patients until a score validated in Indian patients is published.

Table 3 CU-HCC Risk Score.

Factor	Score
Age, years	
>50	+3
≤50	0
Albumin, g/L	
≤35	+20
>35	0
Bilirubin, mg/dl	
>1.1	+1.5
≤1.1	0
HBV DNA, IU/ml	
<2000	0
2000–20,000	+1
>20,000	+4
Cirrhosis	
Yes	+15
No	0

Score <5 low risk, 5–19 medium risk, ≥20 high risk.

Although studies have also shown a good overall safety profile for NAs, adverse drug reactions have been reported in patients with advanced cirrhosis. These include a broad spectrum of drug-induced injuries, including lactic acidosis, myalgia, neuropathy, azotemia, hypophosphatemia, muscular weakness, and pancreatitis, as well as immune-mediated responses (i.e., allergic reactions).[78] Hence, patients with decompensated cirrhosis receiving NAs should be closely monitored for tolerability of the drugs and the development of rare side effects like lactic acidosis or kidney dysfunction.

Consensus Statements

- *During antiviral therapy, close monitoring for side effects of each drug is mandatory. (A1)*
- *Monitoring of drug compliance of patient is of paramount importance as poor adherence to antiviral treatment may lead to increased risk of drug resistance and treatment failure. (B1)*
- *All patients treated with NA:*
  - *Should be followed with periodical assessment of ALT and serum HBV DNA. (A1)*
  - *Following patients should undergo periodical renal monitoring at least including eGFR and serum phosphate levels:*
    - *Patients at risk of renal disease treated with any NA*
    - *All patients regardless of renal risk treated with TDF*
  - *Patients on TDF at risk of development and/or with underlying renal or bone disease should be considered for a switch to ETV or TAF.*
- *All patients treated with PegIFN-α*
  - *Should be monitored with periodic assessment of CBC, ALT, TSH, HBeAg, anti-HBe, serum HBV DNA and HBsAg levels. (A1)*
- *HCC surveillance is mandatory for all patients with cirrhosis as well as those with medium or high HCC risk scores at the onset of therapy. (B1)*
- *Patients of decompensated cirrhosis should be closely monitored for tolerability of the drugs and the development of rare side effects like lactic acidosis or kidney dysfunction. (B1)*

TREATMENT RESPONSE

Definitions of various terms used for response and non-response on HBV treatment are given in Table 4.

In spite of treatment with NA with high genetic barrier to resistance (TDF, TAF, or ETV), not all persons achieve viral suppression even after 96 weeks of therapy. Among those treated with entecavir, 70–83% of HBeAg positive persons and 91–98% of HBeAg negative persons achieve viral suppression; while those treated with tenofovir, viral

Table 4 Definitions of Treatment Response and Non-Response.

Terminology	Definition
Virologic Response (VR)	Decrease in serum HBV DNA to less than 2000 IU/ml after 6 months of therapy
Complete Virologic Response (CVR)	Decrease in serum HBV DNA to an undetectable level
Partial Virologic Response (PVR)	Decrease in HBV DNA of more than 1 $\log_{10}$ IU/ml but detectable HBV DNA after at least 12 months of therapy in compliant patients
Primary Virologic Non-Response (PVNR)	Less than one $\log_{10}$ decrease of HBV DNA after 3 months of therapy
Sustained Off-therapy Virologic Response (SOVR)	Serum HBV DNA levels <2000 IU/ml for at least 12 months after the end of therapy
Virologic breakthrough	Increase in HBV DNA level of more than 1 $\log_{10}$ IU/ml compared to the nadir (lowest value) level on-therapy
Biochemical response	Normalization of ALT levels based on the traditional ULN (40 IU/ml).
Biochemical breakthrough	Increase in serum ALT level after ALT normalization on antiviral therapy
Histological response	Decrease in necroinflammatory activity (by ≥2 points in histologic activity index or Ishak's system) without worsening in fibrosis compared to pretreatment histological findings
Serologic response for HBeAg	HBeAg loss and HBeAg seroconversion
Serologic response for HBsAg	HBsAg loss and HBsAg seroconversion

suppression rates were 76% for HBeAg-positive persons and 90% for HBeAg negative persons.[64,79–81] Treatment failure is considered when there is Primary Virological Non-Response (PVNR), Partial Virological Response (PVR) or virological breakthrough. Before switching to other forms of therapy, it is essential to check for compliance in patients with treatment failure when using ETV or TDF, which have high barrier to resistance.[60] Poor compliance is now the main cause of PVNR.

Virological breakthrough in compliant patients is mainly related to the development of HBV drug resistance.[3] The incidence of virological breakthrough depends on the NA's genetic barrier to resistance profile. Treatment adaptation should be performed as soon as viral breakthrough is identified and confirmed to prevent a further increase in viral load, subsequent ALT elevation and progression of liver disease including the risk of liver failure.[3,82,83] For patients treated with a drug with a high genetic barrier to resistance, treatment could either be switched to another drug with a high genetic barrier to resistance or be continued with monitoring for a Virologic Response (VR) at 3–6-months intervals. For patients treated with a drug with a low genetic barrier to resistance, treatment should be switched to a drug with a higher genetic barrier to resistance.[3,7,82,83]

Consensus Statements

- ***Treatment failure is considered when there is PVNR, PVR or virological breakthrough. (A1)***
- ***Compliance to therapy should be checked in all cases of treatment failure. (A1)***
- ***Treatment adaptation should be performed as soon as treatment failure under NAs is confirmed and should be based on NAs cross-resistance data:***
  - ***For patients treated with a drug with a high genetic barrier to resistance, treatment could either be switched to another drug with a high genetic barrier to resistance or be continued with monitoring for a VR at 3–6-months intervals. (C1)***
  - ***For patients treated with a drug with a low genetic barrier to resistance, treatment should be switched to a drug with a higher genetic barrier to resistance. (B1)***
- ***An antiviral resistance test should be performed when virologic breakthrough occurs, especially in cases with good compliance. (A1)***
- ***Rescue antiviral therapy should be started as soon as possible upon emergence of resistant variants, especially when viral breakthrough is detected and genotypic resistance is confirmed. (A1)***

PREDICTORS OF PEGIFN-α RESPONSE AND STOPPING RULES

In HBeAg-positive CHB patients, pretreatment predictors of response to PegIFN-α are low viral load, high serum ALT levels (above 2–5 times ULN), HBV genotype and high activity scores on liver biopsy. HBV genotypes A and B have been shown to be associated with higher rates of HBeAg seroconversion and HBsAg loss than genotypes C and D. In HBeAg-negative CHB patients, high baseline ALT, low baseline HBV DNA, younger age, female gender and HBV genotype were independent predictors of response to PegIFN-α therapy but the negative and positive predictive values of these variables are low. Patients with genotypes B or C had a better chance of response than genotype D patients.

The most important on-treatment predictor of response to PegIFN-α is serum HBsAg level.[3,84,85] In HBeAg-positive CHB patients, a decline of HBsAg levels below 1500 IU/ml at 12 weeks is a reasonable predictor of HBeAg seroconversion, while HBsAg levels >20,000 IU/ml for HBV genotype B and C or no decline of HBsAg levels for HBV genotype A and D are associated with a very low probability of subsequent HBeAg seroconversion.[85] At week 24 HBsAg levels >20,000 IU/ml predict no response regardless of genotype. In HBeAg-negative CHB patients, a combination of a lack of decrease in HBsAg levels and <2 $\log_{10}$ IU/ml decline in HBV DNA at 12 weeks of PegIFN-α predicts no response, especially in genotype D patients (Table 5).[3,86]

Consensus Statements

- ***In HBeAg-positive CHB patients:***
  - ***At 12 weeks of PegIFN-α therapy:***

HBsAg levels >20,000 IU/ml for genotype B and C, or no decline of HBsAg levels for genotype A and D, are associated with a very low probability of subsequent HBeAg seroconversion and can be used as PegIFN-α stopping rules. (B2)

  - ***At 24 weeks of PegIFN-α therapy:***
    - ***HBsAg levels >20,000 IU/ml for any genotype, is associated with a very low probability of subsequent HBeAg seroconversion and can be used as PegIFN-α stopping rules. (B2)***
- ***In HBeAg-negative CHB patients:***
  - ***At 12 weeks of PegIFN-α therapy:***
    - ***No decrease in HBsAg levels and <2 $\log_{10}$ IU/ml reduction in serum HBV DNA levels predicts no response and should be used as PegIFN-α stopping rules. (B1)***

CESSATION OF ANTIVIRAL TREATMENT

PegIFN-α treatment has a finite duration. In most studies PegIFN-α has been used for 48 weeks, which is considered

Table 5 Predictors of PegIFN-α Response.

HBeAg status	Factors
HBeAg positive	Low viral load High serum ALT HBV genotype (A & B > C & D) High activity score on liver biopsy On treatment HBsAg levels
HBeAg negative	Low viral load High serum ALT HBV genotype (B & C > D) Younger age Female gender On treatment HBsAg levels

to be the preferred duration. A 6-month course of PegIFN-α and/or a lower dose are inferior to the recommended 48 weeks course. The 48-week treatment duration yields HBeAg seroconversion rates of 20–31% and sustained off-treatment HBV DNA suppression <2000 IU/ml in about 65% of persons who achieve HBeAg to anti-HBe seroconversion.[4,87,88]

For HBeAg-positive patients although the ideal goal of treatment is to achieve HBsAg loss, this is rarely observed after NA therapy. Hence the primary endpoint when treating patients with HBeAg-positive hepatitis with NA is to achieve HBeAg seroconversion. Thus in HBeAg positive patients, the NA treatment may be discontinued at least 12 months after serum HBV DNA is undetectable and HBeAg seroclearance or seroconversion is attained.[7] Undetectable serum HBV DNA and HBeAg seroconversion are strongly correlated with favorable biochemical and histologic responses.[89] According to the existing data, the weighted probability of durable HBeAg seroconversion was 91.9% and 88.0% at 12 and 24 months, respectively, after NA discontinuation and virological remission defined as HBV DNA <2000–20,000 IU/ml was maintained in about 50% of such patients at 3 years after cessation of NAs.[3,90]

For HBeAg-negative patients the optimal treatment duration for NA therapy is unknown. Hence, the treatment cessation should be individualized according to the clinical treatment response and the baseline severity of the liver disease.[7] In these patients if long-term (>3 years) virological suppression is achieved and close post-NA monitoring can be guaranteed the NA therapy can be discontinued. Recent studies have suggested that discontinuation of NAs might be feasible in patients who achieve undetectable serum HBV DNA level on three separate occasions 6 months apart.[5] The duration for which HBV DNA is undetectable on therapy is an important factor affecting the probability of off-NA virological remission off-treatment.[90] Hence, a cut-off of 3-years for undetectable HBV DNA on treatment seems to be a reasonable period before NA discontinuation is attempted. According to a recent meta-analysis, durable virological remission, defined as HBV DNA <2000–20,000 IU/ml, were 43.7%, 31.3%, and 30.1% at 12, 24, and 36 months, respectively, after NA discontinuation if they have remained for more than two years on virological remission during therapy.[90]

Since overt hepatitis flares and life-threatening episodes of hepatic decompensation have been occasionally reported in patients with pre-existing cirrhosis who discontinue NAs, treatment discontinuation is currently discouraged in patients with cirrhosis.[3,91]

Consensus Statements

- ***PegIFN-α the treatment should be stopped at 48 weeks or at 12 or 24 weeks, if stopping rules are met. (A1)***
- ***In patients receiving NA, the treatment should be stopped if:***
  - ***HBsAg loss is achieved, with or without anti-HBs seroconversion***
  - ***For HBeAg-positive patients at least 12 months after serum HBV DNA is undetectable and HBeAg seroclearance or seroconversion is attained.***
  - ***For HBeAg-negative patients if long-term (>3 years) virological suppression is achieved and close post-NA monitoring can be guaranteed. (B1)***
- ***Antiviral treatment should not be stopped in cirrhotics. (A1)***

MONITORING AFTER CESSATION OF ANTIVIRAL TREATMENT

After stopping antiviral treatment, the response to antiviral persists in some patients, while others relapse. These relapsers may face a deterioration of their liver function. Therefore, regular monitoring is needed to check for the durability of the treatment response, relapse, and liver function.[7]

During the first year after the cessation of antiviral treatment, liver function should be monitored and serum HBV DNA should be measured every 3 months, while HBeAg and anti-HBe that should be checked at 6-month intervals. Beyond 1 year after the cessation of antiviral treatment, liver function and serum HBV DNA should be tested every 6 months to detect viral relapse.

As mentioned previously, HCC surveillance is mandatory for all patients with cirrhosis as well as those with moderate or high HCC risk scores even after cessation of antiviral treatment.

Consensus Statements

- ***During the first year after the cessation of antiviral treatment, liver function should be monitored and serum HBV DNA should be measured every 3 months, and HBeAg and anti-HBe should be checked at 6-month intervals. (B1)***
- ***Beyond 1 year after the cessation of antiviral treatment, liver function and serum HBV DNA should be tested every 6 months to detect viral relapse. (C1)***
- ***HCC surveillance is mandatory for all patients with cirrhosis as well as those with moderate or high HCC risk scores even after stoppage of antiviral treatment. (A1)***

PREVENTION OF HBV RECURRENCE AFTER LIVER TRANSPLANTATION

Recurrent HBV infection following liver transplantation was a major risk before the advent of NA therapy.[92] Therefore, all potential liver transplantation candidates should receive NA therapy with the aim of achieving an undetectable HBV DNA level at the time of transplantation.

Following liver transplantation, NA therapy in combination with hepatitis B immune globulin (HBIG) reduces the risk of graft infection to <5%.[3,92] The aim of this combination treatment was to achieve an anti-HBs level of >50–100 IU/L. Low-dose HBIG in combination with an antiviral or conversion to antiviral monotherapy after a short-term HBIG combination therapy have been studied,

to reduce the cost of HBIG plus NA regimens, especially in patients who have achieved HBV DNA negative status at liver transplantation.[93]

Thus it is recommended that patients who are at a high risk for HBV recurrence, namely those who are HBV DNA positive at the time of liver transplantation, who are HBeAg-positive, have HCC, and HDV or HIV co-infected should receive lifelong combination therapy with NA plus HBIG. Patients with a low risk of recurrence can discontinue HBIG but need continued mono-prophylaxis with a potent NA. In selected patients HBIG-free regimen from start may also be considered.[92–95]

HBsAg-negative patients receiving livers from donors with evidence of past HBV infection (anti-HBc positive) are at risk of HBV infection due to immunosuppression, and therefore, should receive antiviral prophylaxis with a NA indefinitely.[96]

Consensus Statements

- ***Pre-transplant therapy with a NA is recommended for all HBsAg-positive patients undergoing liver transplantation to achieve the lowest possible level of HBV DNA (preferably undetectable HBV DNA level) before transplantation. (A1)***
- ***Patients who are at a high risk for HBV recurrence, namely those who are HBV DNA positive at the time of liver transplantation, who are HBeAg-positive, have HCC, and HDV or HIV co-infected should receive lifelong combination therapy with NA plus HBIG. (B1)***
- ***Patients with a low risk of recurrence can discontinue HBIG but need continued mono-prophylaxis with a potent NA. In selected patients HBIG-free regimen from start may also be considered. (B2)***
- ***HBsAg-negative patients receiving livers from donors with evidence of past HBV infection (anti-HBc positive) are at risk of HBV infection and should receive antiviral prophylaxis with a NA indefinitely. (B1)***

HIV CO-INFECTED PATIENTS

The incidences of cirrhosis and HCC are reportedly higher in patients with HBV/HIV co-infection than in those with HBV monoinfection.[97,98] Therefore, European and American guidelines on the management of HIV infected patients recommend the initiation of ART in HIV/HBV co-infected patients irrespective of CD4 cell count.[99,100] ART should include either TDF or TAF, which have antiviral activity against HIV and HBV. Entecavir or tenofovir monotherapy should never be used in patients with HBV/HIV co-infection due to the development of resistant HIV. When ART regimens need alterations, antiviral agents that are effective against HBV should be included to avoid HBV reactivation. Stopping TDF- or TAF-containing ART should be avoided in persons with HIV/HBV co-infection because of the high risk of severe hepatitis flares and decompensation following HBV reactivation hepatitis.

Drug toxicity (renal, bone, liver) should be closely monitored during ART. Since TDF maybe associated with greater nephrotoxicity and bone mineral density loss, regimens containing TAF are also being investigated. A recent study showed that in HIV/HBV co-infected patients with a stable suppression of HIV and HBV DNA, switching ART from a TDF- to a TAF-containing regimen maintained HIV and HBV suppression in majority of patients, with improved eGFR and bone density parameters.[101]

All HBsAg-positive patients should be screened for HIV before TDF, TAF and possibly also ETV are used in the treatment of HBV infection because these drugs can cause HIV resistance mutations.

Consensus Statements

- ***All HIV-positive patients with HBV co-infection should start Antiretroviral Therapy (ART) irrespective of CD4 cell count. (B1)***
- ***HIV-HBV co-infected patients should be treated with a TDF- or TAF-based ART regimen. (A/B1)***

HDV CO-INFECTED PATIENTS

It is estimated that ~20 million people are infected with HDV worldwide, particularly in Mediterranean countries, central Africa, Middle East, and South America. However, it is very uncommon in India.[102,103] HDV infection is more prevalent in Mediterranean countries, Central Africa, Middle East, and South America. The incidences of cirrhosis and HCC are higher in patients with HBV/HDV coinfection than in those with HBV monoinfection.[104,105] HDV infection can be diagnosed by detecting anti-HDV antibody or HDV RNA in the serum or by detecting HDV antigen in liver tissue by immunohistochemistry. The treatment goals are to inhibit HDV replication, normalize ALT, and improve histology findings.

IFN-α (conventional or pegylated) is the only drug that can inhibit HDV replication. PegIFN-α for at least 48 weeks is the current treatment of choice in HDV-HBV co-infected patients with compensated liver disease.[7] If well tolerated PegIFN-α treatment can be continued until week 48 irrespective of on-treatment response pattern. Treatment response can be evaluated by measuring the serum HDV RNA level at week 24. PegIFN-α showed HDV RNA negativity rates of 17–43% at 6 months after the end of 48 or 72 weeks of treatment.[106–108] In patients with decompensated liver disease, PegIFN-α should not be used and these patients should be evaluated for liver transplantation.

Neither NAs nor ribavirin showed significant effects on HDV RNA levels in patients with HDV infection.[3] Although HDV is often the predominant virus in this co-infection, considerable fluctuating activity of HBV and HDV or both viruses, including alternating predominance can be seen during the natural history of this chronic co-infection.[3] NA treatment is recommended for those patients with HBV DNA levels being persistently above 2000 IU/ml, and might be considered in order to block residual HBV replication in those with advanced liver disease.

Consensus Statements

- *PegIFN-α for at least 48 weeks is the current treatment of choice in HDV-HBV co-infected patients with compensated liver disease. (A1)*
- *In HDV-HBV co-infected patients with ongoing HBV DNA replication, NA therapy should be considered. (B1)*
- *PegIFN-α treatment can be continued until week 48 irrespective of on-treatment response pattern if well tolerated. (B2)*

HCV CO-INFECTED PATIENTS

In India, in patients with CHB the HCV prevalence rate is expected to be the same as HCV prevalence rate in general population, which is between 0.5% and 1.5%.[109]

In patients with chronic HBV infection, the HCV co-infection increases the risk of severe or fulminant infection, accelerates the liver disease progression, and increases the risk of cirrhosis and HCC.[3,110–112] It is necessary to determine which virus is dominant by means of serologic or virology tests and it has been observed that in HCV-HBV co-infected patients, the HBV DNA level is often low or undetectable, although it may fluctuate widely, and HCV is usually the main driver of chronic hepatitis activity.[3]

When HCV is replicating and causes liver disease, it should be treated following the same rules as applied to HCV mono-infected patients. Sustained virological response rates for HCV in HBV and HCV co-infected patients are comparable with those in HCV mono-infected patients.[113,114] However, treatment of HCV with direct-acting antivirals (DAAs) may cause reactivation of HBV, during or after HCV clearance.[115] HCV-HBV co-infected patients undergoing DAA therapy and also fulfilling the standard criteria for HBV treatment should receive concurrent NA treatment. HCV-HBV co-infected patients undergoing DAA therapy but not fulfilling the HBV treatment criteria should be considered for concomitant NA prophylaxis until week 12 post-DAA, and monitored closely. HBsAg-negative, anti-HBc positive patients undergoing DAA should be monitored and tested for HBV reactivation in case of ALT elevation.[3,7,113,114]

Consensus Statements

- *Treatment of HCV with DAAs may cause reactivation of HBV. Patients fulfilling the standard criteria for HBV treatment should receive NA treatment. (B1)*
- *HBsAg-positive patients undergoing DAA therapy but not fulfilling the HBV treatment criteria should be considered for concomitant NA prophylaxis until week 12 after DAA, and monitored closely. (B2)*
- *HBsAg-negative, anti-HBc positive patients undergoing DAA should be monitored and tested for HBV reactivation in case of ALT elevation. (B1)*

ACUTE HEPATITIS B, ACUTE LIVER FAILURE, SEVERE ACUTE REACTIVATION, ACUTE ON CHRONIC LIVER FAILURE

Acute HBV infection in more than 95% of adults will recover clinically and virologically including seroconversion to anti-HBs without antiviral therapy. The HBV chronicity rates in adults following an episode of acute HBV infection is <5%. In about 1% adults acute hepatitis B may result into severe or fulminant course leading to acute liver failure.[116]

In uncomplicated acute hepatitis B, antiviral therapy is not indicated.[117] The main treatment goal in patients with acute hepatitis B is preventing the risk of acute liver failure. Typically patients with 'severe acute hepatitis B' have a protracted severe disease characterized by bilirubin >5 mg/dl plus INR >1.5, for >4 weeks.[118] Although randomized controlled trials are lacking, several cohort studies indicate that the early antiviral therapy with highly potent NAs in patients with severe acute hepatitis B can prevent progression to acute liver failure and subsequently liver transplantation or mortality.[119,120]

In India, one of the important differential diagnoses of acute hepatitis B is spontaneous reactivation of CHB. Although, differentiating reactivation from acute hepatitis B is difficult, usually the former will have more severe jaundice, higher INR, more protracted course, higher HBV DNA levels, a low titer of anti HBc IgM (<1:1000), and higher risk of developing liver failure.[121] Thus patients with reactivation more often mimic those of severe acute hepatitis B (bilirubin >5 mg/dl plus INR >1.5, for >4 weeks) and thus merit treatment with NAs.

Patients with acute liver failure or acute-on-chronic liver failure due to HBV should immediately be started with NA, and should be considered for liver transplantation.[122]

Consensus Statements

- *Most adults with uncomplicated acute HBV hepatitis do not require antiviral treatment because they will fully recover spontaneously. (B1)*
- *Patients with protracted severe disease (bilirubin >5 mg/dl plus INR >1.5, for >4 weeks) have either 'severe acute hepatitis B' or severe acute reactivation of CHB. These patients are at risk of liver failure (ALF or ACLF) and thus merit antiviral treatment with NA. (C1)*
- *Patients with acute liver failure or acute-on-chronic liver failure due to HBV should immediately be started with NA, and should be considered for liver transplantation. (A1)*

CHILDREN

In children the treatment decision should be individualized taking into consideration factors like age, phase of infection, HBeAg status, ALT level, liver biopsy findings, and family history of HBV-associated cirrhosis or HCC.[7] Generally the threshold for starting antiviral treatment in children is higher than in adults. However, if treatment is indicated the treatment window should not be missed because cirrhosis can occur in their 20s and HCC later in life.

Most children remain in the immune-tolerant phase until late childhood or adolescence, however, some children progress to the immune-active phase. Even in the immune-active phase (with increased ALT levels and histologic findings of liver inflammation and fibrosis) these

children are usually asymptomatic. Antiviral therapy is not indicated for children in immune-tolerant phase (HBeAg positive, HBV DNA >20,000 IU/ml, normal ALT). Even in immune active phase, a conservative approach to antiviral treatment is warranted because the course of the disease is generally mild.[123] HBeAg-positive children should be considered for antiviral treatment when their serum ALT levels are above 2×ULN for at least 6 months and their HBV DNA levels are above 20,000 IU/ml.[124] Acute elevation of liver enzymes with an ALT level of >5×ULN may be followed by spontaneous HBeAg seroconversion. It is therefore reasonable to delay treatment for an observation period of at least 3 months if there is no concern regarding hepatic decompensation.

HBeAg-negative children should be considered for antiviral treatment if the HBV DNA level >2000 IU/ml, and when the AST or ALT level is >2×ULN or liver biopsy shows moderate-to-severe necro-inflammation or periportal fibrosis. Children with cirrhosis should receive antiviral treatment regardless of HBeAg status and ALT level.

PegIFN-α, ETV and TDF have been found to be as safe and effective in children, as in adults.[3,125–128] Entecavir is considered the first-line therapy in children older than 2 years and tenofovir in those older than 12 years (Table 6).[7]

Consensus Statements

- ***In children, antiviral treatment should be considered for following patients:***
  - ***HBeAg-positive children with an HBV DNA level >20,000 IU/ml, when the ALT level is >80 U/L,***
  - ***HBeAg-negative children with an HBV DNA level >2000 IU/ml,***
    - ***when the ALT level is >80 U/L, or***
    - ***when liver biopsy shows moderate-to-severe necro-inflammation or periportal fibrosis***
  - ***Children with cirrhosis. (B1)***
- ***Antiviral therapy is not indicated for children in immune-tolerant phase (HBeAg positive, HBV DNA >20,000 IU/ml, normal ALT). (A1)***
- ***In children or adolescents who meet treatment criteria, ETV, TDF, TAF, and PegIFN-α can be used. (B2)***

HEALTHCARE WORKERS

It is recommended that unvaccinated or incompletely vaccinated healthcare workers with reasonably anticipated risk for blood or body fluid exposure should receive hepatitis B vaccination.[129] It is also recommended that vaccinated healthcare workers receive post-vaccination serologic testing (antibody to hepatitis B surface antigen [anti-HBs]) 1–2 months after the final dose of vaccine is administered.[129]

EASL and Center for Disease Control (CDC), recommends that HBV infection alone should not disqualify infected persons from the practice or study of surgery, dentistry, medicine, or allied health fields.[3,130]

Since, percutaneous injuries sustained by HBV positive healthcare personnel during certain surgical, obstetrical, and dental procedures provide a potential route of HBV transmission to patients, healthcare workers require antiviral therapy, even if they do not fulfill the typical indications for treatment, to reduce direct transmission to patients.[131] EASL recommends that healthcare workers, including surgeons, gynecologists and dentists, who are HBsAg-positive with HBV DNA >200 IU/ml may be treated with a potent NA to reduce levels of HBV DNA ideally to undetectable or at least to <200 IU/ml before resuming exposure prone procedures.

Consensus Statements

- ***Unvaccinated or incompletely vaccinated healthcare workers with reasonably anticipated risk for blood or body fluid exposure should receive hepatitis B vaccination. (A1)***
- ***Vaccinated healthcare workers should receive post-vaccination serologic testing (anti-HBs) 1–2 months after the final dose of vaccine is administered. (B1)***
- ***HBV infection alone should not disqualify infected persons from the practice or study of surgery, dentistry, medicine, or allied health fields. (C1)***
- ***Healthcare workers performing exposure prone procedures with serum HBV DNA >200 IU/ml may be treated with NA to reduce transmission risk to patients. (B2)***

PREGNANCY

Before Pregnancy

All HBV positive women of childbearing age should be counseled about implications of pregnancy, the risk of mother-to-child transmission of HBV, and safety of HBV drugs during pregnancy and lactation.

A CHB woman of childbearing age, who plans pregnancy in the near future, should be treated with antiviral agents that belong to pregnancy category B drugs, or be

Table 6 Antiviral Treatment Indications in Children.

Cirrhosis	HBV DNA	HBeAg status	ALT	Liver biopsy	Treatment advice
No	>20,000	Positive	Normal	Not required	No treatment
No	>20,000	Positive	>80	Not required	Treat
No	>2000	Negative	>80	Not required	Treat
No	>2000	Negative	<80	Consider	Treat if moderate necro-inflammation or fibrosis Wait if absent
Yes	Detectable	Any	Any	Not required	Treat

advised to delay therapy until the child is born. TDF and telbivudine belong to pregnancy category B, of which TDF should be preferred, because it has a better resistance profile and more extensive safety data in pregnant HBV positive women.[3,132–134] Entecavir, adefovir and lamivudine belong to pregnancy category C drugs and should not be used.[135] The other option is the use of PegIFN-α, which has an advantage of finite duration of therapy. However, due to risk of fetal malformations, PegIFN-α treatment is contraindicated during pregnancy, and hence it should always be recommended only in combination with contraception.[7]

During Pregnancy

Screening for HBsAg in the first trimester of pregnancy is strongly recommended.[14] If the pregnant woman is already on NA therapy, TDF should be continued while ETV or other NA should be switched to TDF, and continued throughout pregnancy. If HBV infection is newly diagnosed during pregnancy, the treatment indication should be evaluated and antiviral treatment with TDF should be started if she has advanced fibrosis or cirrhosis.

If the woman does not have advanced fibrosis or cirrhosis, the main goal is the prevention of mother-to-child transmission, which is considered to occur mainly at delivery, and causes the majority of chronic HBV infection in babies. The mainstay of treatment is a combination of HBIG and vaccination given within 12 h of birth. This prophylaxis reduces the rate of perinatal transmission from >90% to <10%.[3,7] HBIG and vaccine failures occur almost exclusively in women with high HBV DNA levels (>200,000 IU/ml) and/or HBsAg level above 4–4.5 log 10 IU/ml.[134,136–138] LAM, TBV or TDF prophylaxis has been used in this setting during the last trimester of pregnancy starting at week 24–28 of gestation. Of them, TDF is the preferred agent due to its characteristics mentioned previously. In a randomized study in pregnant HBsAg-positive women with high HBV DNA levels (>200,000 IU/ml), the rate of mother to child HBV transmission at post-partum week 28 was 0% in those treated with TDF compared to 7% in the placebo control group per protocol analysis having a similar safety profile.[134]

After Delivery

Ninety percent of infants infected as a neonate progress to chronic infection; thus HBV prophylaxis at birth is of paramount importance. A recent meta-analysis of randomized controlled trials of hepatitis B vaccine administered at birth found that immunized infants born to mothers infected with hepatitis B were 3.5 times less likely to become infected with HBV (relative risk, 0.28; 95% confidence interval, 0.20–0.40).[139] Further, providing HBIG in addition to HBV vaccine to newborns within 12 h of birth can prevent 90–95% of cases of perinatal infection.[15] Thus newborns of HBV-infected mothers should receive HBIG and hepatitis B vaccine at delivery and complete the recommended vaccination series.[7]

If the mother is on NA therapy given as prophylaxis, i.e., only for the prevention of perinatal transmission, its duration is not well defined (stopping at delivery or within the 12 weeks after delivery). The safety of NA therapy during lactation is uncertain. HBsAg can be detected in breast milk, but breastfeeding may not be considered a contraindication in HBsAg-positive mothers. In women treated with TDF, tenofovir concentrations in breast milk have been reported but its oral bioavailability is limited and thus infants are exposed to only small concentrations. Thus breastfeeding is not contraindicated in HBsAg-positive untreated women or women on TDF treatment.

Consensus Statements

- ***All HBV positive women of childbearing age should be counseled about implications of pregnancy, the risk of mother-to-child transmission of HBV, and safety of HBV drugs during pregnancy and lactation. (A1)***
- ***A CHB woman of childbearing age, who plans pregnancy in the near future, should be treated with antiviral agents that belong to pregnancy category B drugs (preferably TDF), or be advised to delay therapy until the child is born. (B2)***
- ***PegIFN-α has an advantage in female patients who are planning pregnancy due to its finite treatment duration. (C1) However, the side effects pertaining to fetal malformations make PegIFN-α treatment contraindicated during pregnancy, and it should be recommended only in combination with contraception. (A1)***
- ***Screening for HBsAg in the first trimester of pregnancy is strongly recommended. (A1)***
- ***In pregnant women already on NA therapy, TDF should be continued while ETV or other NA should be switched to TDF. (B1)***
- ***In all pregnant women with high HBV DNA levels (>200,000 IU/ml) or HBsAg levels >4 log_{10} IU/ml, antiviral prophylaxis with TDF should start at week 24–28 of gestation and continue for up to 12 weeks after delivery. (A1)***
- ***Newborns of HBV-infected mothers should receive HBIG and hepatitis B vaccine at delivery and complete the recommended vaccination series. (A1)***
- ***Breastfeeding is not contraindicated in HBsAg-positive untreated women or on TDF-based treatment or prophylaxis. (C2)***

PATIENTS UNDERGOING IMMUNOSUPPRESSIVE THERAPY OR CHEMOTHERAPY

Impaired host immunity due to chemotherapy or immunosuppressive treatment increases the risk of HBV reactivation, however, its exact incidence is unclear. The reactivation can be in the form of exacerbation of chronic HBV infection, or in the form of relapse of past HBV infection. Therefore, it is recommended to screen for HBsAg and IgG anti-HBc prior to initiation of immunosuppressive treatment or chemotherapy. If either is positive, serum HBV DNA should be tested. Exacerbation of chronic HBV infection is defined ≥2 log_{10} increase of HBV DNA level from the baseline level or a new appearance of

HBV DNA to a level of ≥100 IU/ml. Relapse of past HBV infection is defined among HBsAg negative, IgG anti-HBc positive and HBV DNA negative patients as reappearance of HBsAg or detectable HBV DNA.[7] The diagnosis of HBV reactivation requires the exclusion of other conditions such as chemotherapy drug induced liver injury (DILI), liver metastases, and other types of viral hepatitis. Many patients with HBV reactivation are asymptomatic, but the clinical course varies widely from jaundice to decompensation or even death.[7,140–143]

The risk of HBV reactivation can be higher if rituximab is given alone or in combination with steroids.[3] According to a meta-analysis a rituximab-containing regimen increased the risk of HBV reactivation among HBsAg-positive and HBsAg-negative/anti-HBc-positive lymphoma patients (relative risk 2.14, 95% CI 1.42–3.22, $P = 0.0003$).[144]

Patients without evidence of HBV infection should be vaccinated. Higher doses or reinforced vaccine may be required to achieve anti-HBs response in immunocompromised patients.[3]

HBsAg-Positive Patients

All HBsAg-positive patients receiving chemotherapy or immunosuppressive therapy should start potent NA as a treatment or as prophylaxis with ETV, TDF or TAF. In a study preventive antiviral therapy reduced the rate of HBV reactivation significantly compared to a non-preventive group (13.3% vs. 60%).[145] Prophylaxis should continue for at least 12 months (18 months for rituximab-based regimens) after cessation of the immunosuppressive treatment. Liver function tests and HBV DNA should be tested every 3–6 months during prophylaxis and for at least 12 months after NA withdrawal as a large proportion of HBV reactivations develops after NA discontinuation.[3,146–150]

HBsAg-Negative, Anti-HBc Positive Subjects

If IgG anti-HBc is positive without HBsAg or HBV DNA, irrespective of anti-HBs, serum HBV DNA and HBsAg should be tested regularly and preventive antiviral therapy should be considered if either reappears during immunosuppressive treatment/chemotherapy. Preventive antiviral therapy in patients with isolated anti-HBc can be initiated in high-risk groups such as patients with lymphoma under a rituximab-containing regimen or those with leukemia who undergo hematopoietic stem cell transplantation. Serum HBV DNA should be monitored periodically during and after preventive antiviral therapy. Preventive antiviral therapy should be maintained for at least 12 months (18 months for rituximab-based regimens) after the termination of immunosuppressive treatment/chemotherapy.

Consensus Statements

- ***Prior to initiation of immunosuppressive treatment or chemotherapy screening for HBsAg and IgG anti-HBc is recommended. If either is positive, serum HBV DNA should be tested. (A1)***
- ***Patients without evidence of HBV infection should be vaccinated. (B1)***
- ***Consider preventive antiviral therapy with ETV, TDF, or TAF simultaneously with the initiation of immunosuppressive treatment/chemotherapy if HBsAg or HBV DNA is positive. (A1)***
- ***If IgG anti-HBc is positive without HBsAg or HBV DNA, irrespective of anti-HBs titers, serum HBV DNA and HBsAg should be tested regularly and pre-emptive antiviral therapy should be considered if either reappears during immunosuppressive treatment/chemotherapy. (A1) Pre-emptive antiviral therapy in patients with isolated anti-HBc can be initiated in high-risk groups such as patients with lymphoma under a rituximab-containing regimen or those with leukemia who undergo hematopoietic stem cell transplantation. (B2)***
- ***Serum HBV DNA should be monitored periodically during and after preventive antiviral therapy. (A1)***
- ***Preventive antiviral therapy should be maintained for at least 12 months (18 months for rituximab-based regimens) after the termination of immunosuppressive treatment/chemotherapy. (C1)***

DIALYSIS AND RENAL TRANSPLANT PATIENTS

All dialysis and renal transplant patients should be screened for HBV markers. HBV sero-negative patients should be vaccinated, preferentially with a reinforced vaccine.[3,151]

Dialysis Patients

Patients under dialysis are relatively prone to being exposed to HBV infection, which might exert a negative influence on their long-term prognosis. Patients with chronic HBV infection but not chronic hepatitis B should be monitored, as there is no strong evidence to suggest they have increased mordibity and mortality.[3] In contrast, all patients with HBeAg-positive or -negative chronic hepatitis B should receive a NA, as the preferred treatment strategy, independently of the transplantation program.[3,146,151,152] ETV, TDF or TAF can be used, however; doses of NAs should be adjusted according to eGFR values in patients with eGFR <50 ml/min, except for TAF, which does not require dose adjustment if eGFR is >15 ml/min. PegIFN-α could be also used in selected patients. Given that dialysis may reduce ALT levels, caution must be taken to use this marker to assess treatment indications.

Renal Transplant Recipients

Exacerbation of hepatitis B is of particular importance for immunosuppression after renal transplantation.[7] All HBsAg-positive patients should receive anti-HBV prophylaxis or treatment with a NA.[146,151,152] ETV or TAF are the preferred options, while, TDF should be avoided because of renal safety issues. Long-term NA therapy has been

shown to reduce liver complications and improve survival.[3] PegIFN-α is contraindicated because of the risk of rejection. Renal function should be carefully monitored during treatment with NAs. HBsAg-negative, anti-HBc positive subjects should be monitored for HBV infection after renal transplantation.

Consensus Statements

- ***All dialysis and renal transplant recipients should be screened for HBV markers (B1).***
- ***Vaccination is recommended for patients under dialysis negative for HBsAg and anti-HBs. (A1)***
- ***Oral NAs such as entecavir and tenofovir are preferable to interferon therapy in patients under dialysis. (B1)***
- ***NAs should be dose-adjusted according to residual renal function. (A1)***
- ***All HBsAg-positive renal transplant recipients should receive ETV or TAF as prophylaxis or treatment. (B1)***
- ***HBsAg-negative, anti-HBc positive subjects should be monitored for HBV infection after renal transplantation. (C1)***

EXTRAHEPATIC MANIFESTATIONS

HBV related extra-hepatic manifestations include polyarteritis nodosa, vasculitis, skin manifestations (purpura), peripheral neuropathy, arthralgias, and glomerulonephritis. Mixed cryoglobulinemias, positive rheumatoid factor or inflammatory markers (complement factors C3/C4, C-reactive protein, blood sedimentation rate) may be found in these patients. HBsAg-positive patients with extrahepatic manifestations and active HBV replication may respond to antiviral therapy. PegIFN-α can worsen some immune mediated extrahepatic manifestations and should not be administered in HBV infected patients with immune-related extrahepatic manifestations. Patients with replicative HBV infection and extrahepatic manifestations should receive antiviral treatment with NA. Plasmapheresis, corticosteroids and potentially other immune-suppressive drugs during the initial phase can be useful in addition to NA therapy in special cases.[3]

Consensus Statements

- ***Patients with replicative HBV infection and extrahepatic manifestations should receive antiviral treatment with NA. (B1)***
- ***PegIFN-α should not be administered in patients with immune-related extrahepatic manifestations. (C1)***

CONCLUSIONS

There is a large burden of HBV infection in India. The currently available therapeutic armamentarium for treatment of chronic HBV infection is far from ideal. Apart from poor HBsAg clearance, the biggest hindrance with currently available therapies is persistence of cccDNA, which has significant clinical consequences. Understanding the cellular and molecular mechanisms involving HBV replication and cccDNA dynamics is pivotal in devising more effective strategies. Exciting targets have been identified which definitely hint at better treatment outcomes including achieving the elusive "complete cure" in HBV infection. The above consensus statements on prevention, diagnosis and management of HBV infection summarize the INASL position for management of HBV in India with currently approved, available drugs in India. These are the first guidelines on HBV being published from India. We hope that these guidelines will become basis of further research in India so that better quality evidence emerges from India in coming years, and subsequent versions of these guidelines will become more 'Indianized'. Considerations for the treatment of HBV in India should include the cost of therapy, and socio-economic status, and poor healthcare infrastructure in India. These guidelines will bring some uniformity in the way Indian patients of HBV are being diagnosed, monitored and treated. This uniformity is essential to generate more data on India-specific issues on management of HBV. The current guidance will be updated once more Indian data and newer diagnostic and therapeutic armamentarium become available in India.

CONFLICTS OF INTEREST

The authors have none to declare.

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