Management of Chronic Hepatitis B Infection in India

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Abstract
Chronic hepatitis B (CHB) infection is a substantial global health problem with highest prevalence observed in the sub-Saharan Africa and East Asia. India lies in the intermediate endemicity zone with prevalence ranging from 0.1% to 11.7%. The predominant route of transmission is horizontal and the most commonly occurring genotypes are A and D. The high mortality and morbidity associated with CHB constitutes significant health and economic burden in developing countries like India. Antiviral agents decrease HBV DNA load and prevent disease progression. Several regional and country expert associations have developed treatment guidelines for appropriate management of CHB; however, various factors like prevalence, disease awareness, immunization status, cost implications, availability of resources, type of transmission and emerging significance of HBV genotypes have influenced the management of CHB in a country. This article focuses on expert’s recommendations on CHB management including initiation, monitoring and termination of treatment with emphasis on borderline cases. The article also throws light on the challenges to optimum management and provides preferred therapeutic approaches in Indian perspective.

Overview of Chronic Hepatitis B Infection

Chronic hepatitis B (CHB) infection is a significant health problem world wide with India categorized into intermediate zone of prevalence.¹ Considering an average carrier rate of 5% the total number of HBV carriers in the country was estimated to be about 50 million. Unlike in other parts of Asia, horizontal transmission, via intra-familial transmission is the main route of HBV transmission in India.²

Genotypes A and D are prevalent in the Indian subcontinent but a changing trend is being witnessed with emergence of genotypes B, E, F and G, which could be attributed to immigration, trafficking and use of banned drugs.²,³ Accumulating evidence clearly indicates significant influence of HBV genotypes on disease prognosis; genotype B is associated with less progressive liver disease than genotype C while genotype D has a less favourable prognosis than genotype A.⁴ Association of genotype A and D with disease severity and poor response was also observed in Indian patients.⁵,⁶

The natural course of the disease may be broadly divided into three phases as presented in Figure 1. The duration of these phases differ based on geographical locations, type of transmission and genotypes. The sustained clinical remission (inactive phase) and longer inactive state with low HBV DNA (<2000 units/mL) is found to be associated with favourable long term clinical outcomes.⁷ A sero-reversion to HBeAg positive status may occur in up to 4-20% cases. Among those who remain HBeAg-negative, 0-30% experience hepatitis flares or reactivation of the disease which is recognised as a variant form of immune clearance phase.⁸ The phenomenon of HBeAg-negative chronic hepatitis is on the rise worldwide; a retrospective analysis of CHB infection in India revealed a high percentage prevalence (61%) of HBeAg-negative chronic hepatitis patients.⁹ The HBsAg seroconversion is considered as a state closest to cure and usually confers the best surrogate marker of improved survival. However HCC may still occur, if cirrhosis had already developed before HBsAg seroclearance.⁴

Treatment strategies have evolved rapidly with the introduction of newer agents including parenteral antivirals [interferon-alpha (IFN-α), peg-interferon-alpha 2a (Peg-IFN-α2a)] and oral nucleoside/nucleotide analogues (NUC) [lamivudine (LAM), adefovir (ADV), entecavir (ETV), telbivudine (LdT), and...
tenofovir (TDF)]. Definitions of some common terminologies and diagnostic criteria have been elaborated in Table 1.

**Recommendations for Management in India**

Several professional societies like the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL) and Asian Pacific Association for the Study of the Liver (APASL) have developed guidelines to assist physicians in the management of CHB patients. These guidelines are flexible and the recommendations put forth by them may be applied by the physicians in view of its applicability in a given situation.

Practicing most of these recommendations may be challenging in resource-limited settings like India. Bristol-Myers Squibb (BMS) has deliberated an educational initiative, PATH (Professionals Acting Together on Hepatitis) to help physicians address the challenges faced in the diagnosis and management of CHB patients. An India specific consensus statement was developed based on the feedback given by experts in the field of hepatology to questionnaire on evaluation and management of CHB including special categories as well as ‘borderline cases’. An educational module developed based on all the guidelines and expert consensus was also presented in a continuing medical education forum.

This article reviews recommendations of the three professional society guidelines (AASLD, EASL and APASL and provides recommendations of Indian experts.

### A. Management of CHB

**Counseling and Prevention of Transmission**

Educating patients and spreading awareness about HBV infection is crucial for successful antiviral therapy and can curb the spread of this infection. Published guidelines recommend proper counseling of patients on prevention of transmission of HBV, advice on lifestyle (activity, diet, alcohol use, etc.) and other predisposing factors as well as vaccination of high risk patients (sexual and household members in close contact with patients/carriers, HBeAg positive mothers, healthcare workers, dialysis patients, incarcerated patients, etc.). Additionally, use of hepatitis B immune globulin (HBIG) is advocated for infants born to infected mothers along with hepatitis B vaccine (at delivery followed by complete vaccination series). Experts in India suggest at least two sessions of counseling, one at initial visit and the other after investigations with focus on alleviating undue anxiety of the patient. The main discussion points include stage of the disease and its prognosis, prevention of disease transmission, available treatment options, their side effects and the importance of compliance to therapy.

**Initial Evaluation of Newly Diagnosed Patients**

Initial evaluation, advised by all guidelines, allows staging of the disease and further assesses the need for treatment and surveillance. It should include medical history, physical examination, laboratory investigations (liver profile, liver imaging and viral markers (HBeAg, HBeAb, IgM anti-HBc, HBV DNA load)) to assess liver disease and HBV replication status. In addition to this, Indian experts also suggest obtaining information on family history of HCC/cirrhosis which is a risk factor for advanced disease.

**Decision to Treat**

Serum HBV DNA, serum ALT levels and liver disease stage (based on liver biopsy and/or non-invasive markers of fibrosis and/or imaging) are the criteria for treatment initiation, however, the cut-off values and the need for liver biopsy prior to treatment initiation differs among the guidelines (Table 2). In line with the global guidelines,
Table 1: Definitions and Diagnostic Criteria

<table>
<thead>
<tr>
<th>Definitions</th>
<th>Diagnostic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemical response</td>
<td>Biochemical response is defined as normalization of ALT levels</td>
</tr>
<tr>
<td>Serological response for HBeAg</td>
<td>Serological response for HBeAg applies only to patients with HBeAg-positive CHB and is defined as HBeAg loss with seroconversion to anti-HBe.</td>
</tr>
<tr>
<td>Serological response for HBsAg</td>
<td>Serological response for HBsAg applies to all CHB patients and is defined as HBsAg loss with development of anti-HBs</td>
</tr>
<tr>
<td>Histological response</td>
<td>Histological response is defined as decrease in necroinflammatory activity without worsening in fibrosis compared to pre-treatment histological findings.</td>
</tr>
<tr>
<td>Complete response</td>
<td>Complete response is defined as sustained off-treatment virological response together with loss of HBsAg</td>
</tr>
<tr>
<td>Virological response</td>
<td>Virological response is defined as undetectable levels of HBV DNA and loss of HBeAg in patients initially HBeAg positive</td>
</tr>
<tr>
<td>Primary non-response</td>
<td>Primary non-response is defined as decrease in serum HBV DNA by &lt;2 log10 IU/mL after at least 24 weeks of therapy in compliant patient</td>
</tr>
<tr>
<td>Virologic relapse</td>
<td>Virologic relapse is defined as increase in serum HBV DNA of 1 log10 IU/mL after discontinuation of treatment in at least 2 determinations more than 4 weeks apart</td>
</tr>
<tr>
<td>Virologic breakthrough</td>
<td>Increase in HBV DNA by &gt;1 log10 above nadir after achieving virologic response, during continued treatment</td>
</tr>
<tr>
<td>Viral rebound</td>
<td>Increase in serum HBV DNA to &gt;20,000 IU/mL or above pre-treatment level after achieving virologic response, during continued treatment</td>
</tr>
<tr>
<td>HBeAg reversion</td>
<td>Reappearance of HBeAg in a person who was previously HBeAg-negative, anti-HBe-positive.</td>
</tr>
<tr>
<td>Biochemical breakthrough</td>
<td>Increase in ALT above upper limit of normal after achieving normalization, during continued treatment</td>
</tr>
<tr>
<td>Genotypic resistance</td>
<td>Detection of mutations that have been shown in in vitro studies to confer resistance to the NA that is being administered</td>
</tr>
<tr>
<td>Phenotypic resistance</td>
<td>In vitro confirmation that the mutation detected decreases susceptibility (as demonstrated by increase in inhibitory concentrations) to the NA administered</td>
</tr>
<tr>
<td>Hepatic decompensation</td>
<td>Significant liver function abnormality as indicated by raised serum bilirubin and prolonged prothrombin time or occurrence of complications such as ascites.</td>
</tr>
<tr>
<td>Hepatitis flare</td>
<td>Abrupt increase of serum ALT</td>
</tr>
<tr>
<td>Undetectable serum HBV DNA</td>
<td>Serum HBV DNA below detection limit of a PCR-based assay</td>
</tr>
</tbody>
</table>

**Diagnostic criteria**

**Chronic hepatitis B**
1. HBsAg+ve for >6 months
2. Serum HBV DNA:
   - HBeAg+ve: >20,000 IU/mL
   - HBeAg-ve: 2,000-20,000 IU/mL
3. Persistent or intermittent elevation in ALT levels
4. Liver biopsy: Mild/Moderate/severe necroinflammation

**Inactive carrier state**
1. HBsAg+ve for >6 months
2. HBeAg-ve and anti-HB +ve
3. Serum HBV DNA <2,000 IU/mL
4. Persistently normal ALT levels
5. Liver biopsy: Absence of significant inflammation

**Resolved hepatitis B**
1. Previous known history of acute or chronic Hep B or the presence of anti-HBc ± anti-HBs
2. HBsAg-ve
3. Undetectable serum HBV DNA
4. Normal ALT levels (40 IU/ml for Indians)

**Marginal ALT elevation**
ALT between 1-1.5 ULN

Physicians in the subcontinent also suggest initiating treatment immediately in all patients having evidence of active CHB with decompensated cirrhosis, acute on chronic liver failure, patients with high risk for disease progression and development of HCC as well as patients undergoing immunosuppressive therapy. On the other hand, treatment is not recommended in patients who have low HBV DNA (<2000 IU/ml), persistently normal alanine transaminase (ALT), and histological evidence of mild liver disease as well as children in immune-tolerant phase.

The upper limit of normal (ULN) of ALT has shown variability due to heterogeneity within target populations and differences in the commercial assays. The appropriate normal cut-off to determine the risk of disease progression in Indian patients has been set to 40 IU/ml. In HBeAg-negative patients a stringent HBV DNA criterion of >2000 IU/ml is considered for starting therapy. Guidelines slightly differ in the recommendations of liver biopsy in patients above 40 years of age and borderline ALT with AASLD and APASL advocating biopsy if HBV DNA level is >20,000 IU/ml. EASL recommends cut-off of HBV DNA >2000 IU/ml in patients over 30 years of age and/or with a family history of HCC or cirrhosis.

Horizontal transmission being prevalent in the country, advanced disease sets in around the age of 40 years with higher chances of HBeAg-negative disease. Therefore, experts advocate liver biopsy whenever there is uncertainty about initiating a treatment based on laboratory investigations especially in patients above 40 years.

**Monitoring and Decision to Stop Treatment**

All patients on CHB therapy should be closely monitored for response, tolerability and adherence to treatment. Experts
Table 2: Recommendations for Treatment Initiation

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Recommendations of Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg</td>
<td>EASL (2012)&lt;sup&gt;13&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>[UL: DNA= 2000 IU/ml; ALT= 40 IU/ml]</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>APASL (2012)&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>[UL: DNA= 20,000 IU/ml; ALT= 40 IU/ml]</td>
</tr>
<tr>
<td>ALT</td>
<td>AASLD (2009)&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>[UL: DNA= 20,000 IU/ml; ALT= 30 (men) and 19 (women) IU/ml]</td>
</tr>
<tr>
<td></td>
<td>Indian experts</td>
</tr>
<tr>
<td></td>
<td>[UL: DNA= 2000 IU/ml; ALT= 40 IU/ml]</td>
</tr>
</tbody>
</table>

**Positive > 2000 < ULN**
- Monitor 3-6 months.
- Liver biopsy and therapy if age > 30 years or family h/o HCC.
- Treat if moderate or greater inflammation

**Positive > 2000 > ULN**
- Monitor 3-6 months.
- Liver biopsy recommended.
- Treat if moderate or greater inflammation

**Positive > 20,000 > 2 X ULN**
- Start treatment without biopsy

**Negative < 2000 < ULN**
- No treatment.
- Monitor

**Negative 2000-20,000 < ULN**
- No treatment.
- Monitor ALT every 3 months and HBV DNA every 6-12 months for 3 years.
- Fibroscan might be useful

**Negative 2000-20,000 1-2 X ULN**
- Not applicable

**Negative 2000-20,000 > 2 X ULN**
- Not applicable

**Negative > 20,000 > 2 X ULN**
- Start treatment without biopsy

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ALT: Alanine transaminase; HBV DNA: Hepatitis B virus deoxyribonucleic acid; UL: Upper limit; ULN: Upper limit of normal.

World over consider normalization of serum ALT levels, decrease in serum HBV DNA level, loss of HBeAg, HBeAg seroconversion and HBsAg loss to be important response indicators. For patients on IFN therapy, HBV DNA levels should be monitored every 3 to 6 months; in HBeAg-positive patients, the HBeAg /anti-HBeAg status is to be monitored every 6 months as per the American and European guidelines<sup>12,13</sup> while the APASL advocates a more frequent 3 monthly monitoring.<sup>4</sup> If treated with a NUC, liver panel should be performed every 3 months whereas HBV DNA levels and HBeAg/anti-HBeAg status need monitoring every 3 to 6 months.

For their known side effects, patients on IFN therapy require frequent monitoring of blood...
counts and liver panel; AASLD and EASL guidelines recommend monthly monitoring\textsuperscript{12,13} while APASL recommends monitoring every 3 months.\textsuperscript{4} Also, the thyroid stimulating hormone should be monitored every quarter. Those on TDF/ADV therapy need monitoring of renal function as it causes nephrotoxicity, proximal tubular damage, Fanconi syndrome, osteomalacia while muscle weakness and creatine kinase should be monitored for patients on LD1T and lactic acidosis in patients on TDF/ADV therapy need monitoring every quarter. Those on TDF/ADV therapy need monitoring of renal function as it causes nephrotoxicity, proximal tubular damage, Fanconi syndrome, osteomalacia while muscle weakness and creatine kinase should be monitored for patients on TDF/ADV therapy need monitoring every quarter.

**Termination of treatment**

Termination of treatment depends on HBsAg status, HBV DNA levels, age and/or disease progression and the recommendations are tabulated in Table 3. Experts in India have given importance to patient's age at seroconversion while deciding treatment goal; patients achieving seroconversion after 40 years of age have additional criteria of HBsAg clearance. A life-long treatment is advocated in patients with compensated or decompensated cirrhosis.

**Hepatocellular Carcinoma Surveillance**

The AASLD guidelines recommend screening for HCC in HBV carriers, who are at high risk of HCC, every 6-12 months\textsuperscript{12} while European group recommends HCC surveillance in CHB patients in whom cirrhosis has developed before HBsAg loss.\textsuperscript{13} The risk factors for HCC in Indian patients are gender, age, family history of HCC, heavy use of alcohol, history of sero-reversion, cirrhosis, HBV genotype C, core promoter mutation and co-infection with HCV. Screening tools include alpha-fetoprotein (AFP) and ultrasound (US); the sensitivity, specificity and diagnostic accuracy of US is higher and hence is the preferred tool. Almost a third of patients with HCC in India have normal values of AFP.\textsuperscript{14} Indian experts believe a well-organized HCC surveillance can be effective at reducing disease-specific mortality with acceptable cost-effectiveness among selected patient groups.\textsuperscript{15} HCC screening is advocated in cirrhotic patients and high-risk non-cirrhotic patients including inactive carriers >50 years. Experts prefer US however do not deny AFP as a surveillance tool.

**Partial Response / Non-Response / Breakthrough**

Frequently viruses undergo mutations which can decrease the response to NUCs. Non-compliance to these agents is the main reason for mutations which may further result in partial response, no response or viral breakthrough. Physicians suggest assessing compliance of patients with primary non-respons to any NUC. Genotyping of HBV strains in compliant patients with a primary non-response to ADV may help in formulating a rescue strategy. In patients with primary non-response to ADV,
a rapid switch to TDF or ETV is recommended. Patients with partial response to LAM/LdT (at week 24)/ADV (at week 48) or with viral breakthrough may be switched to ETV/TDF. It is advisable to get 3 monthly DNA for the first year as it is the indicator of response as well as compliance. Treatment with same antiviral agents may be continued in patients with declining HBV DNA levels if there is an increase in viral response and a low risk of resistance with long term therapy (drugs with higher genetic barrier to resistance, such as entecavir or tenofovir will have lower risk of resistance with long term therapy).

B. Management of Special Population

Pediatric Population

HBV infection in children is mostly asymptomatic and therefore the disease burden is likely to be underappreciated; there is limited information on CHB in Indian children. According to a clinic study conducted in 460 children of different age groups in north India, 4.35% tested HBsAg-positive with highest (6.09%) prevalence in 1-4 years of age and the least in 10-14 years age group.16 Few other studies, assessing HBsAg positivity, revealed that prevalence varies in different regions in India and the overall positivity ranges from 1.3-12.7%.17 Most children with HBV infection are considered to be in the immunotolerant phase when treatment is not indicated. All guidelines view children with overt hepatic decompensation as candidates for treatment. Children with elevated ALT levels should be observed for spontaneous HBeAg seroconversion before initiating treatment with IFN and LAM. In general a conservative approach is warranted in children because of apparent lack of long term benefits and the risk associated with drug therapy.

Pregnancy

HBV infection can affect the outcome of pregnancy leading to spontaneous abortion, stillbirth or prematurity in addition to risk of vertical transmission. Studies from different parts of the country have revealed a prevalence of 0.9 to 9% of HBsAg positivity in pregnant women.18,19 IFN-based therapy may be preferred for women who wish to conceive in future and wish to try a finite duration therapy in order to become HBV negative before becoming pregnant, although the chances of achieving this result are very low. Pregnant women with a low HBV viral load do not require immediate treatment; passive immunization and active HBV vaccination of the newborn reduces chance of acquiring infection in such cases. Antiviral therapy in pregnancy could be limited to patients with high HBV viral load; therapy is advised during third trimester of pregnancy and should be continued for atleast 12 weeks after delivery in order to reduce the risk of mother to child transmission.20 IFN is contraindicated during pregnancy and Category B drugs such as LdT or TDF are recommended. Women who have significant liver disease may continue anti-viral treatment throughout their pregnancy and for long duration even after delivery (such patients themselves have an indication for anti-viral therapy. However, safety of these drugs has not been established in breast-fed infants.

Hepatic Decompensation

All guidelines advocate prompt initiation of treatment using NUCs in patients with liver decompensation regardless of HBV DNA levels; this will lead to clinical stabilization and will minimize the need of transplant. IFN is contraindicated in this setting because of the risk of serious bacterial infection and possible exacerbation of liver disease. Potent NUCs with good resistance profile such as ETV or TDF are preferred. EASL recommends dose adjustment of all NUCs in patients with low creatinine clearance (<50 ml/min).4,12,13

Co-infection with HCV, HDV or HIV

Hepatitis B virus, hepatitis C virus (HCV), hepatitis delta virus (HDV) and human immunodeficiency virus (HIV) share similar transmission routes. Concurrent infection with these viruses in general complicates the natural course of CHB resulting in more severe and progressive liver disease.4 Indian epidemiological studies on co-infections have been performed only in HIV positive patients with reported prevalence of 5.3% to 9%.21-23 Insufficient data exists to reach firm conclusions on the management of patients co-infected with HCV and/or HDV. However, it is generally agreed that the dominant virus should be identified before deciding therapeutic strategy. If HCV is dominant, finite Peg-IFN therapy in combination with ribavirin can achieve a sustained virological response. However, since there exists a potential risk of HBV reactivation during treatment or after clearance of HCV, HBV DNA monitoring is recommended and HCV therapy may be followed by NUCs for HBV. In patients co-infected with HDV, high doses of IFN/peg-IFN have demonstrated long term beneficial effects. For HIV co-infected patients it is globally recommended that peg-IFN or ADV should be initiated in patients who do not require highly active antiretroviral therapy whereas patients requiring treatment against both HBV and HIV should receive therapies effective against both viruses e.g. LAM+TDF or emtricitabine +TDF.4,12 Patients with HIV/HBV co-infection generally have lower ALT levels, hence a liver biopsy is considered to stage the disease. Treatment experiences in patients co-infected with HIV in Indian settings remains poorly documented. However, one study in a cohort of HIV/HBV co-infected patients demonstrated positive
screening and vaccination of HBV seronegative patients is highly recommended. Pre-emptive oral antiviral therapy is advocated for HBsAg-positive patients and HBsAg-negative patients with detectable HBV DNA levels; treatment should be continued for at least 12 months after cessation of immunosuppressive treatment. HBsAg-negative patients with antibodies against HBV core protein (anti-HBc) but undetectable serum HBV DNA should be followed carefully by means of ALT and HBV DNA testing regardless of anti-HBs status and should be treated with NUC therapy upon HBV reactivation even before ALT elevation is evident. Treatment guidelines recommend protection of at-risk patients with NUC of high antiviral potency and low risk of resistance.

Co-morbidities

Nucleotide/nucleoside analogues are cleared by the kidneys with nucleotide analogues having more nephrotoxic potential. Serum creatinine levels and estimated creatinine clearance should be determined before starting NUC in all patients. High renal risks include decompensated cirrhosis, creatinine clearance <60 ml/min, poorly controlled hypertension, proteinuria, uncontrolled diabetes, active glomerulonephritis, concomitant nephrotic drugs, solid organ transplantation. Therefore elderly patients or patients with one or more of the above conditions must be closely monitored for renal parameters and dose adjustments may be considered. Indian physicians also recommend close monitoring of patients receiving NUCs and advice monitoring of creatinine clearance rather than only creatinine value.

C. Management of Borderline Cases

The natural course of disease may present a dilemma while managing certain sub-groups of immune-tolerant patients and inactive carriers. Guidelines do not recommend therapy in immune-tolerant patients; however the importance of age, duration of infection, ALT levels, family history of cirrhosis/HCC, the severity of histology and other comorbidities cannot be neglected. A similar challenge is to monitor relapse in ‘inactive carriers’ and distinguish between ‘inactive carriers’ and HBeAg-negative chronic hepatitis.

A definite indication for the treatment in patients with HBV DNA within defined threshold is the ALT level of >2 times ULN. Studies have however shown that a substantial proportion of CHB patients with marginally elevated or persistently normal ALT who remain ineligible for therapy have significant histological damage. Management of such patients should be individualized based on liver histological status. Treatment can be deferred in patients who show minimal necroinflammation and mild (stage 1) fibrosis. Liver biopsy provides more sensitive and specific information on liver disease progression. However, liver biopsy is invasive and carries a risk of complication, albeit low. The limitations of liver biopsy can be overcome by use of a rapid, non-invasive transient elastography (Fibroscan); a study by Goyal et al., revealed that fibroscan could avoid liver biopsy in 70% patients with an accuracy >90% in CHB patients. However, owing to resource constraints, facilities of biopsy or fibroscan may be unavailable and in such situations a “risk impact” assessment score along with the HBV DNA level may be useful to guide treatment decisions. A similar risk impact score is deduced based on age, gender, ALT levels, BCP mutations, HCC in first-degree relatives and those with low albumin/platelet values for cirrhosis. In this system, a numerical score has been assigned for each risk factor and if the score is ≥3 and the HBV DNA is >2,000 IU/mL, treatment is advised. Experts have recommended AST/ALT ratio reversal (even if ALT is marginally raised), low albumin, low platelet count and mild splenomegaly on USG as useful indicators of fibrosis in India; presence of such indicators should reduce the threshold for doing a liver biopsy.

Patients with marginally elevated or persistently normal ALT may be categorized based on the HBeAg status and HBV DNA levels to strategize management (Figure 2).

HBeAg Positive Patients

Those with marginally elevated ALT and/or HBV DNA <20,000 IU/mL require biopsy if HBV DNA increases or remains stable over 6 months. Treatment can be delayed, if the HBV DNA levels decrease as patients may undergo spontaneous seroconversion except in pregnant females and healthcare professional where treatment initiation is advocated. Patients with PNALT, persistently high HBV DNA levels and prolongation of HBeAg positive status are at increased risk of HCC and disease progression. Biopsy is suggested in patients between 30 to 40 years of age. Treatment is advocated in patients >40 years of age. However, age of treatment initiation should be reduced in those with positive family history for HCC.

HBeAg Negative Patients

Those with marginally elevated ALT and/or HBV DNA between 2,000 and 20,000 IU/mL need close monitoring with a liver biopsy before initiating therapy. Patients with PNALT and/or HBV DNA >2000 IU/mL need frequent monitoring of ALT.
Barriers to Effective Management in India

Important factors that need to be taken into account for optimization of anti-viral therapy include the severity of liver disease, duration of recommended therapy, rapidity of action and the adverse effect profile of the drugs. Emergence of drug resistance with oral antiviral agents is also a major challenge confronting clinicians. Thus, prevention of antiviral drug resistance and appropriate management of viral breakthrough is an added treatment goal. Guidelines recommend selection of drugs with high potency and low risk of resistance; therefore most guidelines advocate initial treatment with ETV, TDF or peg-IFN.4,12,13

There is insufficient safety and efficacy data on antiviral agents in India.29-31 Few studies have reported positive outcomes with antivirals. ETV has been associated with significantly higher rates of serological, viral and biochemical improvement with no resistance observed up to 40 weeks of treatment.32,33 ADV was found to be less potent though the frequency of resistance mutations was low.31 TDF and LdT were reported to reverse decompensation and improve hepatic functional status with significant reduction in HBV DNA levels.34-36 LAM-resistant mutations observed in 27% patients, were strongly associated with longer treatment duration.37

Though all approved agents are available in India, treatment with guideline recommended first-line agents is a challenge, the major hurdle being unaffordability due to high cost of therapy. The cost of oral anti-viral therapy ranging from 76 to 1707 US$ for CHB/compensated cirrhosis, to 15,000 US$ for HCC patients and may be as high as 20,000 US$ in patients with decompensated cirrhosis.38 Due to cost constraints, patients either discontinue therapy or skip/split the dose, delay refills, avoid new prescriptions or use generics. This results in inadequate management and increases the risk of resistance/virologic breakthrough.39,40 Thus, in countries like India with low per capita income, patient’s preference also becomes an important factor in deciding drug therapy. The advocated first line agents may therefore have to be substituted with cost-effective older agents or combinations thereof.29-31 Jayakumar, et al in their study have demonstrated comparable efficacy of LAM/ADV combination with ETV and TDF as monotherapy.41 Therefore for patients with compensated cirrhosis, ETV, LdT, TDF or their combinations, whereas for others a LAM/ADV combination can be a good alternative to more expensive first line treatments. Similarly in chronic hepatitis with or without grade II fibrosis-monotherapy with either TDF or ETV or LdT or IFN can be recommended in patients who can afford whereas monotherapy with LAM may be advised in others with close monitoring of viral breakthrough or non-response.

In India, ETV, LdT and TDF can be recommended in compliant patients who can afford good treatment while LAM/ADV combination may be advised for non-affording patients with well compensated cirrhosis while LAM alone may be advised in those with grade II fibrosis. De-novo combination is advised in fibrotic patients with high viral load (Table 4).

The cost constraint, together with lack of awareness of disease, lack of screening programs, social stigma, limited resource allocation (laboratories / staff and HCPs), and sub-optimal management and limited reimbursement of drugs/tests are other obstacles to effective management of CHB in India.

Conclusions

This article serves as guidance to clinicians while formulating strategies for management of CHB patients in India. Experts have adapted recommendations of the three international guidelines.
Table 4: Recommendations of Treatment for Indians

<table>
<thead>
<tr>
<th>Liver status</th>
<th>HBeAg status</th>
<th>HBV DNA levels (copies/ml)</th>
<th>Therapy</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compensated liver disease</td>
<td>Positive</td>
<td>&gt;5 logs</td>
<td>ETV/LdT/IFN</td>
<td>3 monthly for HBV DNA</td>
</tr>
<tr>
<td>Compensated liver disease</td>
<td>Negative</td>
<td>&gt;3 logs and &lt;6 log</td>
<td>Monotherapy: ETV/LdT</td>
<td>3 monthly for HBV DNA</td>
</tr>
<tr>
<td></td>
<td>Positive/ Positive</td>
<td>&gt;9 logs</td>
<td>Combination therapy: LAM + TDF OR</td>
<td>6 monthly for HBV DNA</td>
</tr>
<tr>
<td>Fibrosis (grade II)</td>
<td>Negative</td>
<td>&lt;9 logs</td>
<td>LAM + TDF</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Positive/ Negative</td>
<td>&gt;9 logs</td>
<td>LdT / ETV / TDF</td>
<td></td>
</tr>
<tr>
<td>Compensated cirrhosis</td>
<td>Positive</td>
<td>&gt;3 logs and &lt;6 log</td>
<td>LAM + ADV/TDF OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>&lt;3 logs and &gt;6 log</td>
<td>LAM + TDF</td>
<td></td>
</tr>
<tr>
<td>Fibrosis (grade II)</td>
<td>Positive</td>
<td>&lt;9 logs</td>
<td>LdT/ETV/IFN/TDF</td>
<td>3 monthly for HBV DNA</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>&gt;9 logs</td>
<td>ETV/IFN/TDF</td>
<td>3 monthly for HBV DNA</td>
</tr>
<tr>
<td>Acute failure</td>
<td>Positive</td>
<td>-</td>
<td>ETV/LdT/TDF</td>
<td>If PCR positive in 6 months, start combination therapy</td>
</tr>
<tr>
<td></td>
<td>Negative/ Positive</td>
<td>-</td>
<td>LdT/ETV/TDF</td>
<td>If resistance, add second drug</td>
</tr>
<tr>
<td>Acute failure</td>
<td>Negative</td>
<td>Negative</td>
<td>If transplant candidate, start antiviral</td>
<td></td>
</tr>
</tbody>
</table>

Notes:
HBeAg positive:- Low viral load for LAM is <6 log and for Others is <7 log
HBeAg negative:- Low viral load for LAM: <5 log and for Others: <6 log
For fibrotic patients with high viral load, consider de-novo combination
Use IFN with caution

ADV: Adefovir; ETV: Entecavir; HBV DNA: Hepatitis B deoxyribonucleic acid; IFN: ; LAM: Lamivudine; LdT: Telbivudine; PCR: Polymerase chain reaction; TDF: Tenofovir

However, commendations like substituting biopsy with cirrhosis score and potent expensive drugs with cost effective combination therapy will be appropriate in management of CHB in resource limited Indian setting.

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