Approach to Chronic Hepatitis B Virus Infection

Tyagi P, Arora A.
Department of Gastroenterology and Hepatology, Sir Ganga Ram Hospital, New Delhi, India

ABSTRACT

Hepatitis B virus (HBV) infection constitutes one of the major global public health problems. Not only India and Nepal, East Asia is fighting with the same. About 30 percent of the world's population has serological evidence of current or past infection with HBV. By virtue of its different stage of presentation in different age groups of patients and the rapid mutation in the virus, the treatment of HBV requires thorough work-up and regular monitoring. Many new concepts have evolved in last decade in managing these patients, such as HBV Genotype, HBV DNA quantification and mutation analysis. The introduction of oral antivirals in the treatment of HBV infection has revolutionized the treatment.

INTRODUCTION

Chronic HBV infection is a serious clinical problem in the Asia-Pacific region where the prevalence of HBV is high. In this part of the world, the majority of HBV infection prevalence is acquired perinatally or in early childhood, and some patients may be superinfected with other viruses that may influence the clinical outcomes. Due to the poor basic health-service infrastructure, the lack of motivation of the government bodies and the lack of awareness on the part of the general population, and with a large pool of inactive carriers in India and nearby countries, chronic HBV infection poses a big threat and needs an urgent and active intervention.

EPIDEMIOLOGY

Hepatitis B surface antigen positivity (HBsAg) prevalence among the general population ranges from 0.1 % to 11.7 %, being 2 % to 8 % in most studies. The HBsAg prevalence rate among blood donors ranged from 1 % to 4.7 % with the exception of a higher HBsAg positivity in some Indian North Eastern states (~ 7 %).[1] A large study involving 8,575 pregnant women from Northern India documented the HBsAg carrier rate in antenatal mothers to be 3.7 %, HBeAg carrier rate as 7.8 % and the vertical transmission as observed in 18.6 %[2].A serological survey on 722 family members of 215 HBV infected index cases in eastern India revealed that the intrafamilial horizontal transmission is the more significant mode of transmission than the sexual mode of transmission in later life for maintaining the HBV carrier pool in this community[3].

Hepatitis B virus has been classified into at least eight genotypes on the basis of an intergroup divergence of 8 % or more in the complete genome nucleotide sequence. Subtypes are identified within some genotypes, but their clinical significance remains to be determined. Each genotype has its distinct geographical and ethnic distribution, worldwide and within the Asia-Pacific

Correspondence:
Dr. Anil Arora
Department of Gastroenterology and Hepatology,
Sir Ganga Ram Hospital, New Delhi, India
E-mail: dranilarora50@hotmail.com

region. HBV genotypes B and C are prevalent in East and South-East Asia, the Pacific Islands and Pakistan, whereas HBV genotypes D and A are prevalent in India. In general, genotype B is associated with a less progressive liver disease than genotype C, and genotype D has a less favorable prognosis than genotype A.

PATHOPHYSIOLOGY

The natural course of chronic HBV infection in this geographic region can be divided into
(i) immune-tolerant phase,
(ii) immune clearance phase, and
(iii) residual or inactive phase.
Hepatitis B virus reactivation and relapse of hepatitis may occur in some patients who are in the residual or inactive phase. Patients in the immune-tolerant phase are usually young, hepatitis B envelope antigen (HBeAg) seropositive with high viral loads (107 – 108 copies/mL) but normal serum alinine aminotransferase (ALT) levels and no or minimal clinicopathological changes. During the immune clearance phase, hepatitis activity and even acute flares with serum ALT levels over five times the upper limit of normal (ULN) may occur, and these may sometimes become complicated by hepatic decompensation. Higher ALT levels, therefore, usually reflect a more vigorous immune response against HBV and more extensive hepatocyte damage[4].This is eventually followed by HBeAg seroconversion to its antibody (anti-HBe) and/or undetectable HBV-DNA. The estimated annual incidence of spontaneous HBeAg seroconversion was 2 – 15 %, depending on factors such as age, ALT levels, and the HBV genotype[4,5]. HBeAg seroconversion is followed by clinical remission (inactive chronic HBV infection) in the majority of patients. However, active hepatitis may relapse due to HBeAg seroconversion or occurrence of HBeAg-negative hepatitis. The estimated annual incidence of hepatitis relapse was 2.2 – 3.3 %[6,7], being higher in males, genotypes C infected, and those who have HBeAg seroconversion after age 40[8].Spontaneous HBsAg seroclearance may occur after HBeAg seroconversion. A recent 11-year follow-up study in 1,965 asymptomatic anti-HBe positive subjects (age 16 – 76 years, median 34 years, showed an annual HBsAg seroclearance rate of 1.2 %. The cumulative HBsAg seroclearance rate was 8 % at 10 years, increased disproportionately to 25 % at 20 years, and was 45 % at 25 years of follow-up[9].HBsAg seroclearance usually confers excellent prognosis[10].

Terminology and natural history of Chronic HBV infection

The consensus definition and diagnostic criteria for clinical terms relating to HBV infection adopted at the National Institutes of Health (NIH) conferences on Management of Hepatitis B in 2000 and 2009 are summarized in Table 1[11,12].

Table -1

Chronic hepatitis B — Chronic necroinflammatory disease of the liver caused by persistent infection with hepatitis B virus. Chronic hepatitis B can be subdivided into HBeAg-positive and HBeAg-negative chronic hepatitis B.

Inactive HBsAg carrier state — Persistent HBV infection of the liver without significant, ongoing necroinflammatory disease.

Resolved hepatitis B — Previous HBV infection without further virologic, biochemical or histological evidence of active virus infection or disease.

Acute exacerbation or flare of hepatitis B — Intermittent elevations of aminotransferase activity to more than 10 times the upper limit of normal and more than twice the baseline value.

Reactivation of hepatitis B — Reappearance of active necroinflammatory disease of the liver in a person known to have the inactive HBsAg carrier state or resolved hepatitis B.

Evaluation and management of patients with chronic HBV infection: initial evaluation-

A detailed history and a physical examination form part of every management protocol. In case of HBV, special emphasis is paid on risk factors for co-infection, alcohol use, and family history of HBV infection and liver cancer. The laboratory tests should include assessment of liver disease, markers of HBV replication, and tests for co-infection with hepatitis C virus, hepatitis D virus or HIV in those at risk (Table 2).

Table 2 – Evaluation of patients with infection

1. Evaluation & physical examination
2. Family hisrory liver disease
3. Laboratory test to asscss liver disease:
   - complete blood counts with platelets, Liver function & prothrombin time
4. Tests for HBV replication:
   - HBcAg/anti-HBV DNA quantification
5. Ultrasound of liver/Rule out-HCV, HDV, Alcohol
6. Tests to screen for HCC (AFP)
7. Consider liver biopsy to grade and stage liver disease for patients who meet critria for chronic

Once the patient is found to be HBsAg positive, then the next step is to find the replicative status and the status of the liver injury by the virus.

Step 1: The replicative status is diagnosed with the help of getting the serological marker that is HBeAg and HBeAb. The HBeAg is marker for the replication. With the increasing prevalence of the HBeAg negative chronic hepatitis B (CHB), the virus multiply in the liver but do not produce the HBeAg antigen due to mutation. The role of HBeAg as the marker of replicative stage has taken a backseat. Nowadays, most clinicians get the HBV DNA quantitative serum levels to know the replicative state of the virus. The levels of the HBV DNA do not depend on the HBeAg status and also help in following the patients on therapy.

Step 2: After knowing the replicative status, the next important step is to know about the extent of the injury in the liver. There are two components of the damage: fibrosis and inflammation. Fibrosis in the liver occurs due to the long-term inflammation leading to the activation of the hepatic stellate cells. This can only be estimated with the help of the liver biopsy though the role of the fibroscan for the same is coming up in the literature but still has not been placed in the guidelines. The next important step is to know about the extent of the inflammation in the liver which can be judged either by the liver biopsy or indirectly by the AST/ALT levels. The importance of the ALT levels also lies in the fact that indication for starting the treatment depends on the ALT levels which usually must be > 1.5 - 2 times the upper limit of the normal depending upon various guidelines.

Step 3: The third step is to know about the status of the liver disease, that is whether it is in the state of hepatitis or the state of chronic liver disease. The features that suggest chronic liver disease are: shrunken liver, ascites, dilated portal vein, splenomegaly, esophageal varices. The presence of these features changes the choice of the treatment protocol.

LIVER BIOPSY

The purpose of a liver biopsy is to assess the degree of liver damage and to rule out other causes of liver disease. As per the latest guidelines from various groups, the liver biopsy is not usually required in the treatment decision except in the condition where there are no clear-cut guidelines for the treatment, for example in patients with HBsAg positive with the ALT levels in the range of 1 - 2 times the upper limit of the normal in a person above 40 years[12].

HBV DNA ASSAYS

As has been discussed above, HBV DNA quantification in serum is a crucial component in the evaluation of patients with chronic HBV infection and in the assessment of the efficacy of antiviral treatment. As HBV DNA persists even in persons who have had serological recovery from acute hepatitis B infection, low levels of HBV DNA may not be associated with progressive liver disease. An arbitrary value of 20,000 IU/mL was chosen as a diagnostic criterion for CHB at the 2000 NIH Conference[11].It has been observed that serial monitoring of HBV DNA levels is more important than any single arbitrary cut-off value in prognostication and in determining the need for treatment. It is now recognized that lower HBV DNA levels (3 - 5 log10 IU/mL) may be associated with progressive liver disease and may warrant treatment, particularly in those who are HBeAg negative or have already developed cirrhosis.

HEPATITIS B SURFACE ANTIGEN (HBSAG)

HBsAg synthesis during the HBV viral life cycle is complex, and usually occurs in the endoplasmic reticulum (ER). The HBsAg particles are produced in excess and the subviral HBsAg particles exceed virions by 10^2 – 10^5 and can accumulate in concentrations of up to several hundred micrograms per millilitre of serum. The incidence of spontaneous HBsAg seroclearance varies considerably in different series with an annual incidence of 0.5 - 1%. An older age, HBeAg seronegativity, clinical remission and cirrhosis are factors for HBsAg seroclearance. Treatment of CHB with interferon has been found to enhance HBsAg seroclearance by approximately three-fold in Western studies and six-fold in Asian studies.

HBsAg seroclearance is almost always associated with the loss of all serum markers of HBV replication. The long-term outcome after HBsAg seroclearance is excellent. This is supported by natural history studies showing increased survival, lower rates of hepatic decompensation and reduction in the frequency of HCC in patients who have cleared their HBsAg .

HBSAG QUANTITATION

HBsAg particles give us a lot more information, which can be used to follow the course of infection. Serum HBsAg appears to correlate with transcriptionally active cccDNA and is considered a surrogate marker of the number of infected cells. HBsAg quantitation provides different but complimentary information that may aid us in the characterization of an individual's infection status. The Architect HBsAg quantitative assay (Abbott Diagnostics) requires a 1:100 to 1:1000 dilution of the patient's sera in most instances. An excellent correlation between the Architect assay and the Elecsys HBsAg II assay (Roche Diagnostics) has been demonstrated. The quantitiative HBsAg is proving to be a prognostic marker in HBV infection. Brunetto et al showed in their study that an HBsAg level of < 10 IU/mL at week 48 and an on-treatment decline of

> 1 log (10) IU/mL were significantly associated with sustained HBsAg clearance three years after treatment (both P < 0.0001)[13].In a recent study, a single-point quantification combining HBsAg (< 1000 IU/ml) and HBV DNA (< 2000 IU/ml) provided the most accurate identification on inactive carriers (94.3% diagnostic accuracy, 91.1 % sensitivity, 95.4 % specificity, 87.9 % positive predictive value, 96.7% negative predictive value), which was similar to that of long-term regular monitoring[14].

TREATMENT OF CHRONIC HEPATITIS B

Every patient with chronic HBV infection is potentially infectious and at risk for liver complications and is ideally a candidate for therapy, if the virus can be eradicated [15].However, current medications rarely achieve viral eradication in patients with chronic HBV infection and therefore only patients who are at risk for progression to advanced liver disease should be considered for treatment.

Chronic hepatitis B is a chronic disease which is slowly progressive, with dreaded results in the form of chronic liver disease and hepatocellular carcinoma (HCC). Thus, the aims of treatment are to achieve sustained suppression of HBV replication and remission of liver disease in order to prevent liver cirrhosis, hepatic failure and HCC. The indications of treatment in patients with CHB are: ALT > 1.5 times the upper limit of normal, no evidence of the chronic liver disease as outlined above, DNA more than 20,000 IU/mL and 2000 IU/mL in HBeAg positive and HBeAg negative patients, respectively[16,17].Treatment algorithms for chronic HBV infection are outlined in Figures 1 and 2.

Currently, there are seven drugs licensed for treatment of chronic Hepatitis B: standard IFN-α, pegylated IFNα-2a (Peg - IFNalpha-2a) (Peg - IFNα-2b is also licensed in some countries), lamivudine, adefovir dipivoxil, entecavir, telbivudine and tenofovir disoproxil fumarate. Thus, two different classes of drugs are available for treatment - interferon therapy and oral nucleoside/tide therapy.

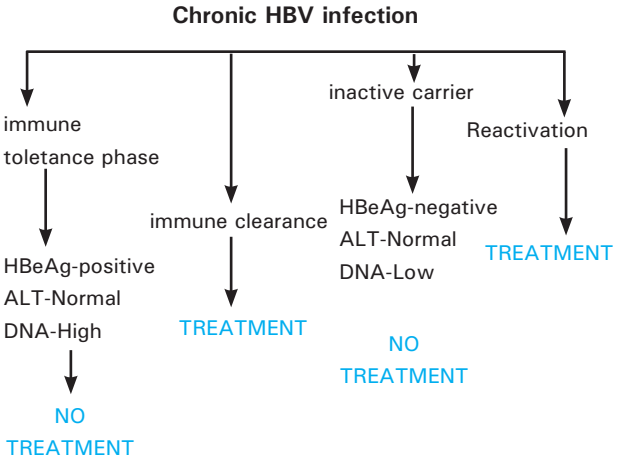

Figure 1- Treatment protocol according to the different phase of HBV infection

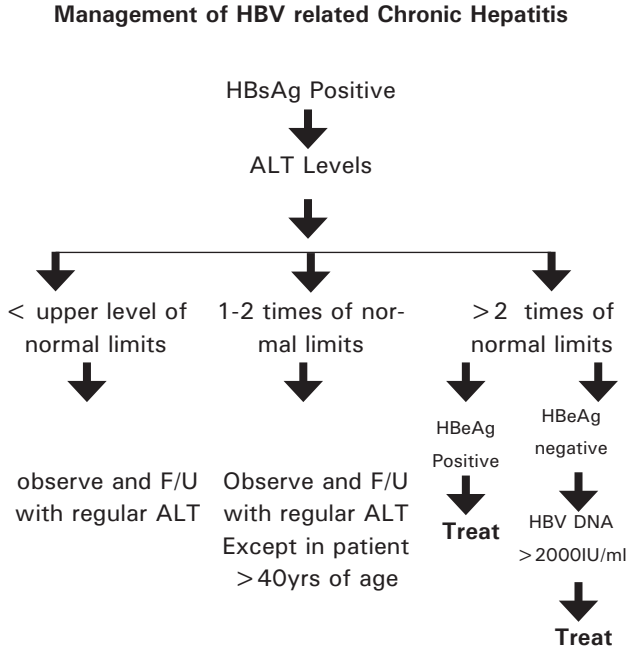

Figure 2 – Management of HBV related CHB in HBeAg positive individual

The merits and drawbacks of these two are outlined in Table 3. A summary of treatment according to the different factors and drug dosages are tabulated, respectively in Tables 4 and 5.

Table 3- Different assays and their range used for HBV quantiative estimation

Assay	Method used	Method used
Hbv hybrid capture ii	Signal amplification	1.4×10^5 - 1.7×10^9 copies/ml
Amplicor hbv monitor	Target amplification	10^3- 4×10^6 copies/ml
Cobas hbv monitor	Target amplification	2×10^2 – 2×10^5 copies/ml
Versant hbv bdna	Signal amplification	3.6×10^2 - 1.8×10^7 U/ml
Realart hbv pcr kit	Target amplification	2×10^1 - 10^8 U/ml
Cobas taqman	Target amplification	3×10^1 - 1.10^8 U/ml

Table 4 - Drug dosage and duration for chronic hepatitis B therapy

Drug	Dose	Duration in HBeAg positive	Duration in HBeAg negative
IFN alpha	5 MU /day 10 MU thrice weekly	16 – 24 wks	48 wks
Peg IFN	1.5ug/kg/day 180ug/kg/day	48 wks	> 48 wks
Entecavir	0.5mg OD 1 mg OD	> 1 yr	> 2 yrs
Tenofovir	300 mg OD	> 1 yr	> 2 yrs
Lamivudine	100 mg OD	> 1 yr	> 2 yrs

Table 5 - Merits and demerits of IFN therapy and oral drugs in HBV infection

	Merits	Demerits
Interferon	Finite treatment No resistence Loss of HBsAg	Injectable Side effects Cost
Oral drugs	Oral drugs Negligible side effects Low price	Drug resistance Long term therapy

INTERFERON-ALFA

Interferons (IFNs) have antiviral, antiproliferative, and immunomodulatory effects. IFN has been shown to be effective in suppressing HBV replication and in inducing remission of liver disease. IFN are of two types: conventional and pegylated IFN. IFN is administered as subcutaneous injections.

The recommended dose for conventional IFN in adults is 5 MU daily or 10 MU thrice weekly and for children 6 MU/m thrice weekly with a maximum of 10 MU. The recommended duration of treatment for patients with HBeAg-positive CHB is 16 to 24 weeks. The current data suggest that patients with HBeAg-negative CHB should be treated for at least 12 months. Pegylated interferon has been found to be more effective than conventional interferon in the treatment of HBV infection. Doses of 1.0 μg/kg body weight of pegylated interferon alfa-2b and 180 μg of pegylated interferon alfa-2a are given once weekly. IFN induced HBeAg clearance has been reported to be durable in 80 % to 90 % of patients after a follow-up period of 4 to 8 years. In a study comparing the outcome of treated patients and controls from Taiwan, an 8-year follow-up of 101 male patients who participated in a controlled trial of IFN therapy found that treated patients had a lower incidence of HCC (1.5 % vs 12 %, p = 0.04) and a higher survival rate (98 % vs 57 %, p = 0.02)[18]. But these good results are not seen in the HBeAg-negative patients, in whom the relapse after cessation of IFN treatment is frequent, with sustained response rates of only 15 % to 30 %.

NUCLEOSIDE ANALOGUES

Nucleoside analogues replace natural nucleosides during the synthesis of the first or second strand (or both) of HBV DNA. They thus serve as competitive inhibitors of the viral reverse transcriptase and DNA polymerase. Nucleoside analogues have excellent oral bioavailability, a good safety record and antiviral efficacy comparable to that observed with interferon alfa-2b. They also are considerably less expensive than interferon when given for 48 weeks. One of the important drawbacks of the oral nucleoside analogues is the development of resistance (Table 6).

Table 6- Resistance pattern in different oral drugs in HBV treatment

	1st yr	2nd	3rd	4th	5th	6th
Lamivudine	23	46	55	71	80	
Adefovir	0	3	6	18	29	
Tenofovir	0	0	-	-	-	
Entecavir	0.2	0.5	1.2	1.2	1.2	1.2

LAMIVUDINE

Lamivudine has been shown to be a relatively potent inhibitor of viral replication, convenient to administer and free of severe adverse effects. Clinical trials

demonstrated that a one-year course of lamivudine resulted in suppression of viral replication and improvement in histologic findings in the liver[17].In one study, HBeAg seroconversion and HBeAg loss occurred in 17 % and 32 % of patients, respectively [19].Prolongation of treatment beyond one year, however, has been associated with incremental changes in viral resistance (38 % at 2 years), and the longer treatment is continued, the more frequently resistance is seen (65 % at Year 5)[20].In an Indian study, the annual incremental loss of HBeAg in patients receiving lamivudine was 41.6 % at the end of one year, 55 % at 2 years and 58.3 % at third year[21].

ADEFOVIR DIPIVOXIL

Adefovir dipivoxil is the acyclic phosphonate nucleotide analogue of adenosine mono-phosphate. The rates of HBeAg seroconversion and HBeAg loss were slightly lower than those achieved with lamivudine for 52 weeks (12 % and 24 %, respectively). Point mutations (A181V, N236T) of the HBV polymerase gene affect HBV susceptibility to adefovir but occur in 18 % of patients at four years and 29 % at five years. In comparison, lamivudine resistance is approximately 15 to 20 times as common at the same time intervals. Adefovir is clinically and virologically effective in patients with lamivudine-resistant HBV, whether they have clinically stable disease, decompensated cirrhosis, or recurrent hepatitis B after liver transplantation. Adefovir has the disadvantage of being potentially nephrotoxic, and dose reductions may be necessary in patients likely to experience compromised renal function.

TENOFOVIR DISOPROXIL FUMARATE

Tenofovir, an acyclic nucleotide inhibitor of HBV polymerase and HIV reverse transcriptase, is similar chemically to adefovir dipivoxil. Tenofovir has been licensed for the treatment of HIV infection, and its antiviral activity against HBV has been reported to be greater than that of the 10-mg dose of adefovir in lamivudine-resistant patients. More than 90 % of HBeAg-negative patients and nearly 80 % of HBeAg-positive patients treated with tenofovir have persistent virologic responses and HBV DNA levels less than 400 copies/mL by 72 weeks, with minimal side effects. Although the nucleotide analogues have been associated with renal toxicity, the risk of renal toxicity associated with tenofovir is 1 % or less per year; it can be reduced even further by calculating renal function through the use of the Cockroft-Gault equation or the Modification of Diet in Renal Disease equation prior to therapy and adjusting the dosage accordingly. With profound HBV DNA suppression, HBsAg loss occurs in about 5 % of tenofovir-treated patients at 64 weeks. Treatment with tenofovir in treatment-experienced patients leads to potent suppression of HBV DNA independent of HBV genotype, HBV mutations (YMDD mutations) that signal lamivudine resistance, or HBeAg status at the baseline. Patients with genotypic resistance to adefovir at the baseline had a lower probability of achieving HBV DNA suppression during treatment with tenofovir[22].

ENTECAVIR

Entecavir induces profound suppression of HBV DNA (to undetectable levels by 24 to 36 weeks) in patients who are HBeAg-positive or-negative, regardless of the baseline HBV DNA levels; resistance rates are very low in treatment-naive patients, and entecavir is therefore considered the first-line therapy[23].More than 90 % of HBeAg-positive or –negative patients who have adhered are adherent to entecavir are HBV DNA-negative at five years. Loss of HBsAg is 5 % in entecavir -treated patients at follow-up of approximately 80 weeks, which is roughly double the rate of HBsAg loss with lamivudine[24].Entecavir is effective against both the wild type and the lamivudine-resistant HBV. It is more potent than either lamivudine or adefovir.

ANTIVIRAL THERAPY IN SPECIAL POPULATIONS PREGNANT WOMEN

Antiviral therapy can be considered during pregnancy to protect the health of the mother, and to prevent breakthrough HBV infection in HBV vaccinated newborns. However, none of the current antiviral agents is licensed for use in pregnancy. Extensive experience with tenofovir exists in HIV-HBV co-infected mothers. Lamivudine is a category B drug in HIV-infected pregnant women but a category C drug in HBV-infected women. Tenofovir is also considered as a category B drug in HBV-infected mothers. Because lamivudine has a long record of safety and has had the most extensive use during pregnancy in HIV-infected women, many hepatologists prefer to prescribe this agent whenever they feel compelled to treat hepatitis B in a pregnant woman. Defects in bone mineral density, including osteomalacia, have been described with tenofovir in HIV-infected patients. Interferon is contraindicated during pregnancy largely because of its antiproliferative effects. In the event of pregnancy, interferon should be discontinued. Breast feeding is not recommended during the first year of the infant's life for mothers who are undergoing antiviral therapy.

PERSONS WITH ACUTE HEPATITIS

Because of the high rate (> 95 %) of complete immunologic recovery from acute hepatitis B, definitive recommendations about the treatment of acute hepatitis B cannot be made. The serious nature of acute liver failure and the safety of nucleoside analogue

therapy support its use in patients at the first sign of severe injury or impending liver failure (prolongation of prothrombin time or hepatic encephalopathy)[25].

PERSONS WITH CIRRHOSIS

Nucleoside analogue therapy has been shown to be safe in patients with cirrhosis. Interferon is contraindicated in patients with even mildly decompensated cirrhosis because immune mediated flares of serum ALT levels may occur. Practice guidelines of the AASLD suggest that nucleoside analogue therapy is preferred in all cases of HBV-related cirrhosis.

PERSONS WITH HUMAN IMMUNODEFICIENCY VIRUS AND HEPATITIS B VIRUS CO-INFECTION

Antiviral therapy for hepatitis B should be considered for all HIV-HBV co-infected patients with evidence of liver disease, irrespective of the CD4 count. The choice of treatment varies with the stage of HIV infection. Adefovir and pegylated interferon may be employed for patients not on anti-retroviral therapy while those on anti-retroviral therapy can be started on tenofovir along with either of emtricitabine or lamivudine.

CONCLUSION

The decision to treat any patient with chronic HBV infection should be based on reasonable clinical judgement. Therapeutic strategies for CHB can be summarized as therapies of finite duration aiming to offer sustained off-therapy response and long-term therapies aiming to maintain remission under oral antiviral agents. Due to the high rate of resistance against the oral antiviral drugs, judicious use of oral anti-HBV agents is recommended, particularly in patients with mild liver disease. Regardless of the anti-HBV agent used, compliance should always be ascertained and most current guidelines recommend HBV DNA testing at least every 6 months for the prompt diagnosis of lack of response or virological breakthroughs and timely treatment modification.

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