Review Article

Current Scenario of Hepatitis B and Its Treatment in India

Gautam Ray*

Gastroenterology Unit, Department of Medicine, B.R.Singh Hospital, Kolkata, India

Abstract

Hepatitis B is a significant public health problem in India, yet disease awareness is very low among the general population. The disease is mostly acquired horizontally, but the role of vertical transmission should not be underestimated. In spite of the fact that the majority of cases are e negative disease, most patients present in the advanced stage and even with hepatocellular carcinoma, the leading cause of which is hepatitis B. High-risk groups (especially tribals) also harbour significant disease burden and have a high prevalence of occult infection, supporting the potential of unknowingly spreading the disease. Findings on the relation of genotypes with disease severity or drug action have been conflicting. Though recently, oral antivirals with high genetic barrier to resistance have shown good viral suppression in the long term, e and s seroconversion is poor and relapse is universal upon therapy discontinuation. As no cure is possible with the currently available therapy, the target is long-term viral suppression by prolonged administration of oral antivirals; unfortunately, this leads to poor treatment adherence, which along with the high cost of therapy results in disease progression and spread of infection. At present, therefore, emphasis should be put on health education of the general and high-risk populations, along with health care workers to increase knowledge on such preventive measures as avoiding unsafe injection practices, high-risk sex, performing unnecessary injection and blood transfusion and providing proper screening of blood products; these efforts should be combined with intensive screening and aggressive vaccination programs, especially in high-risk groups and areas of high endemicity. Vaccination strategies are still below par and logistics should be developed for wider coverage; in addition, further research should be carried out on the efficacy and mode of usage for different types of vaccine.

Keywords: Hepatitis B; Epidemiology; Clinical; Prevention; Treatment; India.

Abbreviations: AASLD, American Association for Study of Liver Diseases; ADV, adefovir; ALT, alanine aminotransferase; antiHBc, antibody to core antigen; antiHBe, HBe antibody; antiHBs, antibody to HBsAg; APASL, Asia Pacific Association for Study of Liver; APRI, aspartate aminotransferase to platelet ratio index; bcp, basal core promoter; CHB, chronic hepatitis B; CLD, chronic liver disease; CTP, Child-Turcotte-Pugh; e−ve, HBeAg negativity; e+ve, HBeAg positivity; EASL, European Association for Study of Liver; EOTR, end of treatment response; ETV, entecavir; HAART, highly active antiretroviral therapy; HBIg, hepatitis B immunoglobulin; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; LAM, lamivudine; LdT, telbivudine; LT, liver transplantation; MELD, model for end-stage liver disease; NA, nucleos(t)ide analogues; pc, precore; pegIFN, pegylated interferon; RCT, randomised controlled trials; SVR, sustained viral response; TDF, tenofovir; ULN, upper limit of normal.

Received: 18 March 2017; Revised: 18 May 2017; Accepted: 3 June 2017

***Correspondence to:** Gautam Ray, B.R.Singh Hospital, Sealdah, Kolkata 700014, West Bengal, India. Tel: +91-3323504075, Fax: +91-323507003, E-mail: gautam1910@yahoo.com

Citation of this article: Ray G. Current scenario of hepatitis B and its treatment in India. J Clin Transl Hepatol 2017;5(3): 277–296. doi: 10.14218/JCTH.2017.00024.

Introduction

Hepatitis B is a common disease all over the world, and countries have been divided into three groups (high, intermediate and low) according to its endemicity. It is estimated that about 200 cores of the world's population have been exposed to the hepatitis B virus (HBV), of whom 350 million harbour it chronically. India falls in the intermediate endemicity zone (prevalence of 2–7%, with an average of 4%), with a disease burden of about 50 million. Pockets of higher endemicity are found in tribal areas where the high burden is maintained through intracaste marriages, tribal customs, illiteracy and poor exposure to health care resources.

In India, chronic hepatitis B (CHB) is acquired predominantly by horizontal transmission in early childhood (mostly from family contacts) and to lesser extent by perinatal transmission. The exact mode of horizontal transmission remains undefined, but it may be due to contact of non-intact skin or mucous membranes with tears, saliva or blood containing HBV-infected secretions or through sharing of toothbrushes. The age of acquisition of HBV is an important determinant of outcome; the earlier the age, the higher the risk of chronicity (e.g., >90% in new-borns (vertical transmission), 30% in children aged 2–5 years and <5% in adults). The other mode is parenteral transmission at any age (i.e. transfusion of infected blood or blood products, intravenous drug use, unsafe therapeutic injections, occupational injuries or nosocomial transmission during healthcare-related procedures such as surgery, haemodialysis and organ transplantation).[1]

The disease passes through three phases in its natural history – (a) immunotolerant phase with e+ve and high DNA load with normal enzymes, (b) immune active phase with surge in enzymes, hepatitis B e antigen (HBeAg) negativity (a state known as e−ve) and clearance of DNA, and (c) inactive carrier phase with development of HBe antibody (antiHBe), normal enzyme levels and negativity for HBV DNA. A section of inactive carriers may revert back to DNA positivity with e−ve state and develop e−ve hepatitis. Some will remain as occult infection (hepatitis B surface antigen (HBsAg)-negative and HBeAg-negative but DNA-positive). A good number of cases (15–25%) will progress to CHB, decompensated cirrhosis and hepatocellular carcinoma (HCC). Risk factors for progression are HBeAg-positivity (the state known as e+v) and high DNA load, among others, and all treatment modalities target e seroconversion and DNA negativity as practically achievable end points.

Progression also occurs in e−ve hepatitis due to intermittent flares and in occult infection in immune-active disease but at a slower rate. A recent trend in decrease of HBV as the chief cause of chronic liver disease (CLD) is being observed in India, mostly due to rising incidence of alcohol-related disease; however, HBV infection still remains the leading cause of HCC. Till only a few years back, HBV-related CLD was regarded as a relative contraindication for liver transplantation (LT), but with recent availability of hepatitis B immunoglobulin (HBIg) and potent oral antiviral drugs such cases are being transplanted in India, where LT programmes have taken wing in the last few years.

Prevalence of HBV is also higher than average in high-risk groups like patients with chronic kidney disease, on dialysis, with thalassemia, haemophilia or leukaemias, or those receiving immunosuppressives or cancer chemotherapy. Fortunately, about two-thirds of the disease burden in India is represented by e−ve disease, with low or undetectable viral load which naturally mitigates the disease severity to some extent. However, this ameliorating effect, along with that of vaccination, may be offset by the rising burden of high-risk groups (especially patients on dialysis or with human immunodeficiency virus (HIV), people who are elderly, or those with cancer or on immunosuppressives), who are living longer with their disease. Pregnant women also need screening for HBV to stop perinatal/horizontal transmission.

HBV burden in CLD/HCC

Alcohol is presently the most common aetiology of CLD in India, and this representation has emerged over a span of the last few years (Fig. 1).[2–13] Interestingly, this is due to rising alcohol consumption rates and not due to a real decrease in prevalence of HBV infection (which has remained stable over the years[3]) nor the effect of vaccination (as the vaccine programme in India on mass basis started only in 2011). However, HBV infection still remains the most common aetiology of HCC all over India. A recent all-India survey revealed that 43% of HCC cases are HBV-associated;[14] prevalence among HCC cases is 42% in the south,[15] 39–69% in the north[16–20] and 82% in the west.[21]

In India, a large number of patients present in the advanced stage of the disease, even with HCC at the first clinical presentation, when curative treatment is not possible.[14,22] A recent series study on LT found that 80% of HCC in explants was associated with HBV and/or hepatitis C virus (HCV).[23] Primary liver cancer deaths and related years of life lost attributable to hepatitis B was found to be 67% (population-attributable fraction; real number being 17000) and 297000 in India.[24] This is despite the fact that the majority of patients are e−ve, which might cause silent and slow progression. E-negative disease has been reported in hospital-based studies to be 52–79% from the north,[25–29] 55–80% from the east,[3,22,30,31] 61% from the west[32] and 72–75% from the south,[12,33–35] with corresponding figures for e-negative hepatitis as 31–56%, 26–70%, 40% and 26–75% respectively. One community-based study from the east showed community prevalence of e-negative disease to be 90% and of e-negative hepatitis to be 32%.[36]

Mutants and disease

E-negative hepatitis results from mutation in the precore (pc) and basal core promoter (bcp) regions of HBV genome. Such infection results in hepatitis having lower DNA levels compared to e+ve disease and causes disease progression to occur silently to cirrhosis, with intermittent flares (often subclinical).[27,32] The other common mutation site is the surface gene (surface mutant) which renders the common screening marker HBsAg undetectable by normal assay method; in this manner, the disease is occult but active and with high DNA levels.

The prevalence of pc mutants has been found to be 12–29% (bcp 15–21%[30,36]) in the east, 15–71% in the north,[25–28] 26–40% in the west[5,32] and 7.1–30% in the south.[12,33,37] An all-India study[38] found bcp in 29.3% and pc in 21.3%, overall being 40%. Surface mutants were found in 10% in the east, 7.6–10.8% in the north[25,27] (including 29% in family contacts[39]), 3.2% in the south,[34] and 18% in the west.[32] Such infection is particularly prevalent among high-risk groups (e.g., voluntary blood donors (24%[40]), tribals (10–19.5%[30,41]) and other groups (20%[42]). This high rate is of sinister significance, as it not only results in silent disease progression but also spread of disease unknowingly via donated blood. High prevalence of occult infection has been demonstrated in HCC patients as well.[25,27,43,44]

Genotype and disease[31,44–65]

The most prevalent genotype in India is D followed by A, with the exception of east and north eastern India where genotype C is also high. In the northern half of India there is a gradual trend of increasing genotype C as one moves eastward, and this rise also represents a recent change[66] (Fig. 2). Studies have yielded conflicting results on the relation of genotype to severity of liver disease and drug response (Table 1). This may be partially related to the relation of genotype to different viral mutations, which can influence the type of liver disease manifested.[51,54,61,63] Also, the patients might be harbouring different genotypes (in blood and liver tissue) simultaneously, but one could be predominant and thereby be the detectable one, as has been exemplified in (a) liver tissue harbouring genotype C whereas peripheral blood harbours genotype D,[64] (b) presence of viral reverse transcriptase mutation in treatment-naïve patients (which is genotype related[67]) and (c) genotype switch while on therapy.[62] Genotype may also determine the mode of transmission (horizontal vs. vertical).

Hepatitis B in special populations

Children

Rates of HBsAg-positivity are 2.14–2.25% among children <5 years of age and 4.3–7.2% among the entire paediatric population (up to 12 years of age) attending general outpatient services with non-liver problems[68] (implying horizontal transmission), whereas it is 6.7% among those with liver disease.[69] In another study on CLD of non-viral aetiology, occult infection was found in 9% (markers in 39.3%).[70] Though horizontal transmission appears to be the predominant mode,[71] there is definite contribution of vertical transmission as well.[72,73]

Treatment with interferon (IFN) gives good results, with 52–60% sustained viral response (SVR) with HBeAg loss and seroconversion rates of 39–44% and 20–39%, higher in the horizontal group than in the vertical transmission group. Sequential combination with lamivudine (LAM) yielded better results, with HBsAg loss of 21.4%. Again, however, studies are few and with small patient number.[74,75]

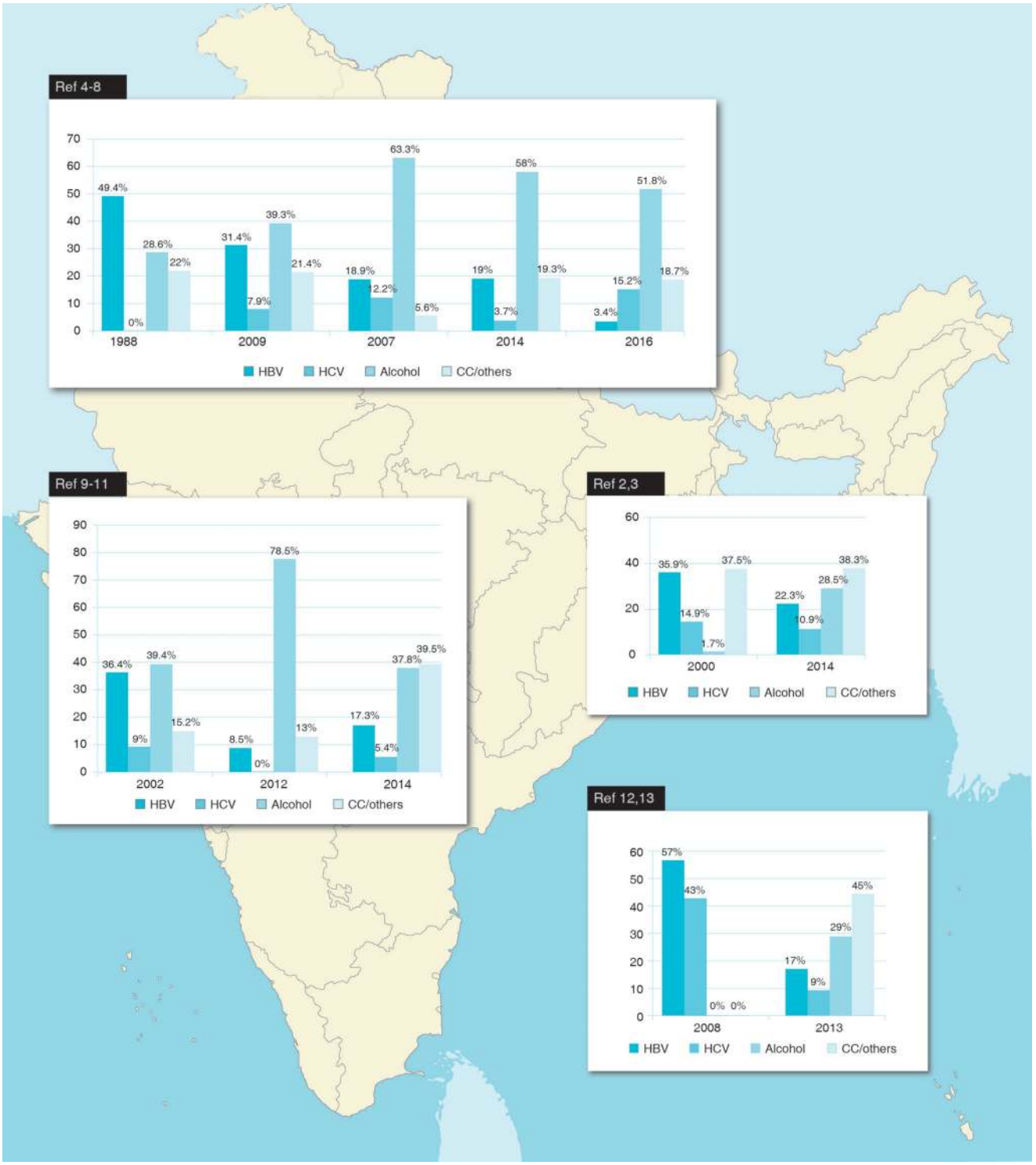

Fig. 1. Trends in aetiology of chronic liver disease in north, west, south and east India.

HIV

In India, the coinfection rate has been found to be 0.2–8% in peripheral HIV/sexually transmitted disease clinics and tuberculosis clinics.[76] In the major metropolis areas, the rates are 11.3% in Kolkata,[77] 16.7% in Mumbai,[78] 15% in Hyderabad,[79] 9% in Chennai,[80] and 5.3% in Delhi.[81] Cases are higher with sexually acquired HIV infection compared to parenterally acquired HIV infection. The genotype distribution is similar to that of the general HBV affected population, but

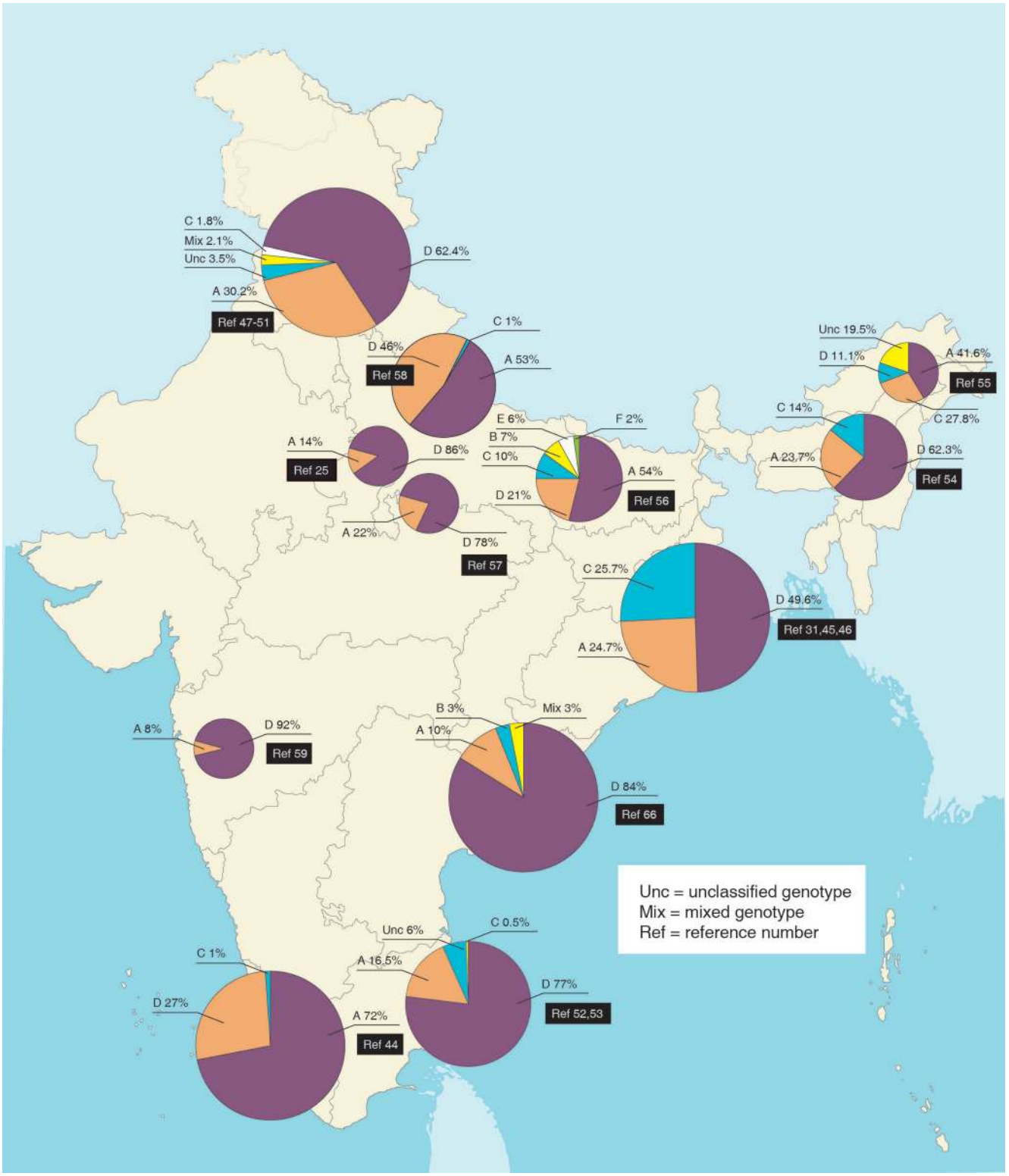

Fig. 2. Genotypic distribution of hepatitis B virus in different parts of India. Data are presented as percentage.

with more e+ve disease[77] and occult infections in up to 10.7%.[82] Long-term treatment with LAM-based highly active antiretroviral therapy (HAART) cause a greater number of mutations[83] than tenofovir (TDF)-based HAART therapy, which gave better results.[84] Drug-resistant mutations reportedly occur in 3.8%.[77]

Table 1. Relation of hepatitis B genotype to disease states or drug effects

Positive association	Negative association
Precore G1896A mutation was e−ve and genotype D-specific, but G1862T mutation was e+ve and genotype A-specific[63]	Disease states (acute hepatitis, chronic hepatitis, asymptomatic carriers, CLD or HCC), the hepatitis activity index and fibrosis stage and treatment response[50]
83% of G1862T mutations detected in genotype A cases vs, 17% in genotype D[31]	Disease severity[61]
Genotype D was associated with more severe liver disease in the incidentally-detected group, and was more prevalent in HCC patients of <40 years of age compared to the incidentally-detected group[47]	Acute, fulminant and incidentally-detected disease[59]
Genotype D:A = 2:1 in asymptomatic carriers, chronic hepatitis and CLD, but 1:1 in HCC. Precore G1896A in 46% of genotype D vs. 25% of genotype A[51]	CLD, chronic hepatitis or HCC cases[49]
Genotype D achieved higher SVR on LAM therapy than did genotype A[48]	Responders and non-responders to LAM therapy[48]
In the >25 year-old age subgroup, genotype A is more often associated with CLD than is genotype D[58]	Long-term response to TDF therapy[62]
More genotype A patients had Child class C disease[57]	LAM response and YMDD mutation[86]
Genotype C is associated with higher viral load, e+ve disease and increased risk of CLD[54]	ETV response[101]
bcp and pc mutations were more frequent in genotype D cases compared with genotype A cases[61]	
Genotype D cases showed significantly high acute hepatitis, whereas genotype C cases showed higher chronic hepatitis[60]	
All non-responders to ETV/TDF had genotype D[103]	
Genotype A or mixed genotype cases are more likely to undergo inter-genotype switch on long-term TDF therapy compared to genotype D cases[62]	
HCC patients infected with genotype A were significantly younger than those infected with genotype D. pc mutation G1862T and bcp mutation C1766T/T1768A were more frequent in genotype A cases and significantly associated with HCC[44]	

Abbreviations: LAM, lamivudine; ETV, entecavir; TDF, tenofovir; e+ve, HBeAg-positive; CLD, chronic liver disease; HCC, hepatocellular carcinoma; pc, precore; bcp, basal core promoter.

Blood-borne infections

Prevalence of HBsAg positivity in chronic kidney disease patients undergoing haemodialysis and renal transplant is 5.2–18.7%[85–88] but much higher when combined with detection of antibodies to HCV (37.1%),[89] depending on duration of therapy. In thalassemia patients, it was 35–69% in the 1990s, but is now as low as 2%;[1,90,91] but, the recent cases include a high rate of occult infection (50% in antibody to core antigen (antiHBc)+ and 16% in both antiHBc and antibody to HBsAg (antiHBs)+ cases[92]). Rate in haemophilia patients is 6–9%[91,93] and in acute leukaemia patients is 15.9%.[94] Voluntary blood donors have a rate of 0.2–4%,[1] with high prevalence of occult infection.[40]

Intravenous drug abuse

The rate of HBsAg positivity was reported earlier as 2.7–10.8% among intravenous drug users,[1] but in more recent studies it was reported as 7% in Chennai,[95] 9.7% in Delhi[96] and 5.1% in another region.[97] In an area reported with highest drug abuse, occult infection was found in 15.9%.[98]

Tribals

India has a large tribal population residing in different pockets spread all over the country and prevalence is very high among some (up to 65%), including occult infection rate of 10–9.5%.[30,41,99] The majority have genotype D infection.[100] As most infections are acquired early in life, chronicity is high and most cases are asymptomatic. The high burden is maintained through intracaste marriages, close living, tribal customs, illiteracy and poor exposure to health care resources.

In a study of occult HBV infections among different high-risk groups, overall prevalence was found to be 3.2% (10% in hepatitis C/cryptogenic cirrhosis cases, 7.7% in HIV cases, 2% in malignancy cases, 2% in alcoholic cirrhosis cases, 1.7% in alcohol dependence case, and none in blood donors and patients with chronic kidney disease).[42] Thus, in all such high-risk groups, a definite proportion have occult infection,

and remain undetectable on routine screening; such infections, however, might manifest in situations of jeopardised immunity or represent an unrecognised source of infection outbreak. There is also a high prevalence of occult infection among family contacts of HBsAg-positive patients.[39]

Pregnancy

Overall, the seroprevalence of HBsAg reported in three recent studies that involved screening of 3686, 20104 and 4000 pregnant females ranged from 0.9% to 1.1%;[101–103] this finding was not different from that in the normal population. HBV reportedly constitutes 25.6% of liver disease in pregnancy.[104] Vertical transmission has been found in 45.2% of cases,[103] attesting to the imprecise knowledge of HBV transmission dynamics; and, as stated above, the role of perinatal versus horizontal transmission among Indian children needs to be further refined.

Other modes of transmission

Sexual transmission

By itself this mode adds little to the chronicity burden (e.g., spouse 0%[3]) but it does represent the predominant mode of coinfection in sexually acquired HIV infection.

Health care workers and unsafe injection practices[1]

The risk of contracting HBV is four-times greater for health care workers compared to that of the general adult population. While prevalence in the 1990s was (2.21–10%), recent studies show lower prevalence (0.4–1.4%), possibly due to better preventive measures and awareness. The highest rates are seen among dentists, physicians, laboratory workers, dialysis workers, cleaning service employees, and nurses.

Annual injection rates in India are considered to be between 4–5 billion and two-thirds are considered unsafe due to inadequate sterilization, use of faulty techniques or unsatisfactory injection waste disposal. The estimated median population-attributable fraction for chronic hepatitis B linked to injections in India is reportedly 46%.

The other high-risk groups in whom HBV may flare up from past infection, carrier state and occult infection are those with diseases being treated with biologics or immunosuppressive medicines (e.g., inflammatory bowel disease, autoimmune disorders, psoriasis, post-organ transplant, cancer chemotherapy, etc.). Presently, there are very limited data on HBV disease in these groups, but their number is rising; moreover, as these individuals live longer with their disease, they are likely to add to the disease burden. Strict vigilance is needed to monitor the status of HBV in such people, as well as the effects of early institution of pre-emptive therapy to prevent flare up.

Initiation and end point of treatment

The ultimate goal of therapy is global eradication of HBV infection by different strategies of vaccination, treatment and prevention of transmission. Treatment is aimed at prevention of disease progression to end stage and transmission to others, along with improving survival and quality of life for the patients. The best way to achieve this goal is complete cure of HBV by eradicating the covalently closed circular DNA from liver, resulting in complete loss of HBsAg (the ideal end point of therapy also). As this is not possible with the currently available drugs, the next best realistic goal is sustained suppression of HBV replication in both e+ve and e−ve patients, with/without e seroconversion in e+ve patients by long-term therapy. Reducing histological activity lessens the risk of cirrhosis and HCC, particularly in non-cirrhotic patients. Sustained virologic remission when off therapy can also be a satisfactory end point.

The indications for treatment are generally based on the e antigen status, serum alanine aminotransferase (ALT) and DNA levels, and severity of liver disease (assessed clinically or by liver biopsy/non-invasive methods). Guidelines published by various societies (European Association for Study of Liver (EASL), American Association for Study of Liver Diseases (AASLD) and Asia Pacific Association for Study of Liver (APASL))[105–107] regarding initiation and termination of therapy are shown in Tables 2 and 3. For optimal therapy, other factors that need consideration are treatment duration, rapidity of drug action and its adverse effect profile, prevention of drug resistance along with management of viral breakthrough. All guidelines recommend initial treatment with drugs that have high potency and high genetic barrier to resistance (entecavir (ETV), TDF or pegylated (peg) IFN) to minimise the DNA level as quickly as possible, thereby reducing the risk of resistance development.

However, in India, though all first-line approved agents are available, the major hurdle in treatment initiation and maintenance is unaffordability due to high cost of therapy. The cost of oral therapy with nucleos(t)ide analogues (NAs) ranges from 76 to 1707 USD($) for CHB/compensated cirrhosis to 15000 USD for HCC patients, and may be as high as 20000 USD in patients with decompensated cirrhosis.[108] As patients have to bear the cost of medicines from their own pocket, their preference also needs consideration in deciding therapy. Due to cost constraints, patients either skip/split the dose or discontinue therapy, avoid new prescriptions, delay refills and use generics. This results in inadequate control and increases the risk of resistance/virologic breakthrough.

The other problems are poor follow-up, lack of awareness about the importance of treatment adherence and social obstacles like lack of screening programs, social stigma, and limited resource allocation (i.e. laboratories, staff, health care practitioners and reimbursement of drugs/tests). Thus, although a guideline for HBV therapy in India formulated by Indian experts was published,[109] the adherence to it by patients and physicians is uncertain. This leads to dismal efficacy results on intention-to-treat analysis and uncertain per-protocol analysis results in drug trials.[110]

Drug therapy

Different drugs for treatment of CHB and the years of their availability is summarized (1990 – Interferon alpha; 1998 – Lamivudine; 2002 – Adefovir; 2005 – Pegylated interferon & Entecavir; 2006 – Telbivudine; 2008 – Tenofovir). These drugs can be used either singly or in combination, according to indications. The most popular therapy presently is ETV or TDF administered as monotherapy. Combination therapy is still controversial, and if it is to be used then it should be administered as either two NAs simultaneously/add-on or as an IFN and a NA simultaneously/sequentially. The logic of using NA combination is that two agents acting through

Table 2. Recommendations for treatment initiation

Parameter			Recommendation of guidelines		
HBeAg	HBV-DNA (IU/mL)	ALT	AASLD (2015) (ULN: ALT = 30 (men) and 19 (women) IU/mL)[&]	APASL (2015) (ULN: ALT = 40 IU/mL)	EASL (2012) (ULN: ALT = 40 IU/mL, DNA = 2000 IU/mL)
Positive	<2000	< or >ULN	Treat if cirrhotic	Assess[*]	NA
Positive	>2000	<ULN	No treatment with 6-month interval monitoring of ALT if in the immune-tolerant phase. Treat if age >40 years, DNA >10^6 and significant necroinflammation or fibrosis on liver biopsy.	If DNA >20000 and ALT persistently normal (age < 30) (immune-tolerant phase) → Assess[*]	Monitor at 3- to 6-month intervals. Liver biopsy and therapy if age >30 years or family history of HCC. Treat if moderate or greater inflammation.
Positive	>2000	1–2 ULN	Exclude other causes of elevated ALT[#]	Assess[*]	Monitor at 3- to 6-month intervals. Liver biopsy recommended. Treat if moderate to severe necroinflammation and/or at least moderate fibrosis
Positive	>20000	>2 ULN	Treat. Exclude other causes of elevated ALT.	If no threat of decompensation, wait for 3 months to check spontaneous e antigen loss or else treat. Assess histology non-invasively.	Start treatment without biopsy
Negative	<2000	<ULN	No treatment if in the inactive phase (persistently normal ALT). Monitor ALT, HBeAg and DNA at 3- to 6-month intervals for e seroreversion, reactivation of hepatitis. Treat[#]	Monitor ALT every 3–6 months and/or DNA every 6–12 months. Assess[*]	No treatment. Monitor.
Negative	2000–20000	<ULN	Treat[#]	Assess[*]	No treatment. Monitor ALT at 3-month interval and DNA at 6- to 12-month intervals for 3 years. Fibroscan might be useful.
Negative		1–2 ULN	Exclude other causes of elevated ALT[#]	Assess[*]	Treat if liver disease is evident on Fibroscan or biopsy
Negative		>2 ULN	Exclude other causes of elevated ALT[#]	DNA > 2000 →If no threat of decompensation, observe for 3 months or else treat. Assess histology non-invasively.	Treat if liver disease is evident on Fibroscan or biopsy
Negative	>20000	>2 ULN	Treat. Exclude other causes of elevated ALT		Start treatment without biopsy. Fibroscan may be done.
Compensated cirrhosis (any e antigen status)	>2000 <2000	<ULN >ULN	Treat for any ALT and DNA level	Treat Treat (assess histology by biopsy or non-invasive method)	Treat for any ALT and DNA level

(*continued*)

Table 2. (*continued*)

Parameter			Recommendation of guidelines		
Decompensated cirrhosis	Any	Any	Treat	Treat ± LT. No biopsy.	Treat
1st line drugs (any e antigen status)			PegIFN alpha 2a 180 mcg for 48 weeks (except cirrhosis and contraindications), TDF 300 mg, ETV 0.5 or 1 mg. Monotherapy recommended.[$]	PegIFN alpha 2a 180 mcg or pegIFN alpha 2b 1.5 mcg/kg for 48 weeks (except cirrhosis and contraindications), TDF 300 mg, ETV 0.5 or 1 mg. Monotherapy recommended.	PegIFN alpha 2a 180 mcg (except cirrhosis and contraindications), TDF 300 mg, ETV 0.5 or 1 mg. Monotherapy recommended.
Drug response			PegIFN: DNA <2000–40000 (e+ve), <20000 (e−ve) and NA: <60 for both response and relapse	PegIFN: DNA <2000 for both e+ve and e−ve). NA: undetectable DNA (response), >2000 (relapse).	

[*] APASL recommends monitoring every 3 months and exclusion of other causes in cases of elevated ALT. Assess fibrosis noninvasively. Biopsy if ALT becomes elevated (in cases of normal ALT) or remains persistently elevated (in cases of increased ALT), non-invasive tests suggest significant fibrosis, age >35 years, family history of HCC or cirrhosis. Treat if there is moderate to severe inflammation or significant fibrosis. Moderate to severe inflammation on liver biopsy means either hepatic activity index by Ishak activity score of >3/18 or METAVIR activity score of A2 or A3.

Significant fibrosis on liver biopsy means F ≥2 by METAVIR fibrosis score or Ishak fibrosis stage of ≥3.

Liver stiffness of ≥8 kPa (by Fibroscan) or aspartate aminotransferase to platelet ratio index (APRI) of ≥1.5 indicates significant fibrosis; Liver stiffness ≥11 kPa (by Fibroscan) or APRI ≥2.0 indicates cirrhosis.

[#] AASLD recommends treatment if significant liver disease or cirrhosis on biopsy or non-invasive testing in such cases.

[&] Therapy decisions should also be based on the following (especially in cases of DNA below threshold or ALT <2 ULN): Age >40 years (significant histological disease), family history of HCC, previous treatment history with pegIFN (delayed HBeAg and HBsAg loss) or NA (risk for drug resistance), presence of extrahepatic manifestations (indication for treatment independent of liver disease severity).

Level of HBV DNA should be compatible with immune-active disease and the cut-offs recommended should be viewed as a sufficient, but not absolute, requirement for treatment.

[$] There is no superiority of one drug over other, recommendation based on lack of resistance on long-term use. Choice of drugs based on: desire for finite therapy (pegIFN), tolerability of treatment side effects, comorbidities (peg-IFN is contraindicated in persons with autoimmune disease, uncontrolled psychiatric disease, cytopenias, severe cardiac disease, uncontrolled seizures, anddecompensated cirrhosis), previous history of LAM resistance (ETV not preferred here), family planning (finite therapy with pegIFN pre-pregnancy or use of NA that is safe in pregnancy is best), HBV genotype (A and B genotypes are more likely to achieve HBeAg and HBsAg loss with pegIFN than non-A/B genotypes), medication costs.

Abbreviations: ALT, alanine aminotransferase; DNA, HBV DNA in IU/mL; LT, liver transplantation; PegIFN, pegylated interferon; ULN, upper limit of normal.

Table 3. Recommendation for termination of treatment

Society	Non-cirrhotic patient		Compensated cirrhosis		Decompensated cirrhosis
	HBeAg+ve	HBeAg−ve	HBeAg+ve	HBeAg−ve	Either
AASLD (2015)	HBsAg negative OR e seroconversion with normal ALT and negative DNA and completed 12 months additional therapy. Monitor at 3-month interval for 1 year.	HBsAg negative OR indefinite therapy unless competing rationale for stoppage.* Monitor at 3-month interval for 1 year.	HBsAg loss OR indefinite therapy with NA even in those who seroconvert unless competing rationale for stoppage. *Monitor at 3-month interval for 1 year for recurrent viremia, ALT flares, seroreversion and clinical decompensation.	HBsAg loss OR indefinite therapy with NA unless competing rationale for stoppage. *Monitor at 3-month interval for 1 year for recurrent viremia, ALT flares, seroreversion and clinical decompensation.	Lifelong therapy ± OLT
APASL (2015)	HBsAg loss OR e seroconversion and completed 1 year (preferably 3 years) additional therapy with persistently normal ALT and undetectable DNA by PCR. Monitor monthly for 3 months, then at 3- to 6-month intervals.	[1] HBsAg loss following antiHBs seroconversion and completed at least 1 year additional therapy post-HBsAg loss [2] Therapy for at least 2 years with undetectable DNA documented on 3 separate occasions 6 months apart. Monitor monthly for 3 months, then at 3- to 6-month intervals.	Indefinite therapy but treatment can be stopped with careful off-therapy monitoring plan	Indefinite therapy but treatment can be stopped with careful off-therapy monitoring plan	Lifelong therapy ± LT
EASL (2012)	HBsAg loss ± antiHBs. OR e seroconversion and completed 1 year additional therapy with persistently normal ALT and DNA <2000	HBsAg loss OR negative DNA and persistently normal ALT after long-term therapy	HBsAg loss with antiHBs seroconversion OR e seroconversion followed by 12 months of consolidation therapy	HBsAg loss with antiHBs seroconversion followed by 12 months of consolidation therapy	Life-long therapy

*Competing rationale: Decisions regarding treatment duration and length of consolidation before treatment discontinuation require careful consideration of risks and benefits for health outcomes, including: (i) risk for virological relapse, hepatic decompensation, liver cancer, and death; (ii) burden of continued antiviral therapy, financial concerns associated with medication costs and long-term monitoring, adherence, and potential for drug resistance with treatment interruptions; and (iii) patient and provider preferences.

Abbreviations: ALT, alanine aminotransferase, LT, liver transplantation.

different mechanisms related to distinctive stages of the viral life cycle (especially those with high and low genetic barrier to resistance and complementary cross-resistance profile) can suppress the virus and decrease synthesis of covalently closed circular DNA in newly-infected cells as well as its pool in chronically-infected cells more effectively than monotherapy; this will possibly restore the immune response to achieve most robust seroconversion, HBsAg clearance and durable off-treatment response, as well as reduce risk of resistance. This may also lead to a more effective eradication, shorter duration of therapy and dose reductions, thereby resulting in fewer drug side-effects. Unfortunately, higher cost, increased toxicity and drug interactions are potential disadvantages.

Interferons are effective immune response inducers in susceptible patients, but have only mild virus-suppressive activity; whereas, NAs have shown a marked virus-suppressive activity in the majority of patients, but have poor immunomodulatory effects. Therefore, the combination of the two could possibly provide both viral suppression and immunomodulation to increase the response rate.[111]

Most of the early series on HBV treatment in India have involved recombinant alpha IFN and LAM, the two earliest drugs to be available either singly or in combination. Daily dosing of IFN escalated the cost and side effects of therapy, and as such efficacy of lower dose was also examined. PegIFN treatment was investigated after 2005 because of its once weekly dosing schedule, but its use was also found to be limited due to very high cost and serious side effects. The availability of potent NAs (ETV, TDF, and telbivudine (LdT)) in recent years has raised hope for better results; but, although these agents can cause sustained viral suppression, complete eradication has not been possible, even with long-term use. The results of various drug trials in India are listed in Table 4.

IFN and its combinations

IFN[112–118] in dosages of 3–6 mIU thrice weekly for 16–24 weeks resulted in SVR rates of 21–100% (6–15% incremental over end of treatment response (EOTR) rates)), HBeAg loss in 50–100% and HBsAg loss in 7–15%. Relapse was universal among cases of e−ve disease[113] but one study found high e seroconversion (50%) that was sustained.[114] Though short-term results appear good, most of the studies have short follow-up, making sustained drug efficacy difficult to assess. Study of sequential LAM + IFN versus LAM alone for 52 weeks[117] showed comparable HBeAg loss and EOTR; however, the overall HBeAg loss and SVR was significantly higher in the combination group at week 76, which was better in preventing relapse.

Studies on pegIFN[118–121] have yielded even more conflicting results. When single agent treatment was administered, long-term SVR in naïve patients was 7.1–14.8% in response to 24 weeks of treatment (HBeAg loss of 14.8–17%) and 50% in response to 1 year of treatment, with e seroconversion of 25%. SVR rates for the combination treatment of LAM and pegIFN given for 6 months were 50–60% for treatment-naïve patients and 33.3% for treatment-experienced patients, and the corresponding figures for 1 year of therapy were 50% and 0–60%, all less than EOTR rates. Sequential therapy achieved better SVR and e seroconversion rates.

A review of world literature on such combination therapies[111] also shows mixed results, which could be due to variability in the three potential phases of the combination therapies. For e+ve disease, simultaneous and sequential combination therapy with IFN + LAM showed a greater on-treatment viral suppression ability and higher SVR than LAM alone, but no difference was observed for the SVR when compared to IFN alone. The simultaneous combination of LAM and pegIFN showed higher SVR than LAM alone, but no difference was observed when compared to pegIFN alone. For e−ve disease, simultaneous IFN plus LAM yielded negative results and high relapse rates, but delayed YMDD selection and for sequential therapy; response rates were similar to monotherapy with IFN or LAM.

Simultaneous pegIFN + LAM was no better than pegIFN alone, and similar sequential therapy was no better than LAM alone. Two meta-analysis (not restricted to treatment-naïve subjects) concluded that, in comparable e+ve populations, pegIFN monotherapy is likely to be equally or more efficacious than conventional IFN and LAM combination therapy; thus, the pegIFN monotherapy was recommended as the treatment of choice, with no added benefit from LAM addition. However, when conventional IFN is used, its combination with LAM should be considered. Most such trials have used the LAM dose of 150 mg/day and IFN doses of 5–10 million units, as well as pegIFN administration of 1 year.

The results of Indian studies with IFNs and their combination by and large seem similar, notwithstanding the lacunae represented by the fact that they are few in number, most are uncontrolled and with small patient number, patient selection criteria is often biased in favour of drug affordability and drug dosing and duration of therapy are variable. However, IFN therapy has been shown not to be cost effective for the number of life-years gained.[122]

NA combinations

LAM and adefovir (ADV):[22,48,123–128] A good number of studies are available on these two drugs, as they are of affordable cost; but, in most studies, the long-term follow-up is not available, precluding determination of relapse rates. However, the usual high resistance rates with LAM upon long-term use and low efficacy of ADV is evident in Indian patients. LAM given for 6–46 months results in SVR rates of 13–35%, with e seroconversion of 6–40% (depending on length of therapy), but relapse is about 35%. Drug-resistant mutations reportedly develop in 11–50% (with 50% breakthrough reported in one study)[123,125,128,129] and is higher in those with high baseline DNA and those with longer duration of therapy.

A number of studies have uncovered occurrence of multiple reverse transcriptase mutations with or without association to LAM resistance, even in treatment-naïve subjects. Examples of this include: (a) in 47.9% patients at pretherapy, but with primary drug resistance mutations in 8.8%;[130] (b) in genotype D cases, both among treatment-naïve (65%) and treated patients (56.2%), and cases with reduced drug effectiveness were common among the non-responders to therapy as well as among the treatment-naïve patients, but classical drug resistance mutations were not detected;[67] (c) core promoter mutations in 68% of cases with viral breakthrough (vs. 25% in those without breakthrough) among patients on long-term LAM therapy and being independent of YMDD mutation;[131] (d) spontaneous drug-resistant mutations in 25% of treatment-naïve patients;[51] and (e) naturally occurring HBV surface mutants in 3.5% of patients at pretherapy and 24.5% that had developed multiple new S-gene mutations during

Table 4. Summary results of drug trials

Ref	Study protocol	EOTR/SVR	e-loss/antiHBe seroconversion	Remarks
113	RCT of IFN 3 mIU s/c alternate day for 4 months in *n* = 20 vs. no therapy in 21. All e+ve	50% vs. 4.8% (EOTR)/ 65% SVR in treatment group	50%/35% (vs/4.8%/4.8% at 6 months). 65% e loss at 1 year.	No reactivation. 15% lost HBsAg at 1 year.
114	IFN 3 mIU s/c alternate day for 4 months in antiHBe-positive cases, *n* = 18 (open label)	72.2% EOTR. 54% relapse.		All 18 HBV DNA-positive at end of FU
115	*n* = 24 (all e+ve) non-randomised trial, 14 treated with IFN, 3 mIU 3/week for 4 months vs. 10 controls (no treatment affordability). FU at 2-month interval for at least 1 year after therapy. Patients who cleared HBeAg had FU for mean of 2.2 (1–4) years for HBsAg clearance.		e-loss was 64% in IFN group (vs. 10% in control group) after mean of 17.3 (8–32) weeks. Anti-HBe in 50% during FU of mean 2.4 years.	HBeAg-negative in all 64% after mean FU of 2.2 (1–4) years. 1/9 (11%) lost HBsAg.
116	IFN 6 mIU, 3/week for 6 months in dual infection with hepatitis B and C, *n* = 14, 7 CLD (group I), remaining 7 (group II) had NHL (*n* = 2), acute leukaemia (*n* = 2), thalassaemia (*n* = 2), CKD (*n* = 1). 3 e+ve (open label).	EOTR 86%/SVR 100% in group I. In group II 43% SVR.	All 3 (100%)	No resp. in NHL group
117	IFN 5 mIU/day for 4 months, then FU for 6 months (open label).	EOTR 15%/SVR 21%		
118	RCT involving 75 treatment-naïve e +ve given LAM at 100 mg per day for 52 weeks (group B, *n* = 37) or same treatment plus recombinant IFN at 5 mIU per day added for 16 weeks after the first 8 weeks (group A, *n* = 38).	26.3% (A) vs. 13.5% (B) ($p = 0.2$) had EOTR. SVR seen in 39.5% (A) vs. 16.2% (B) ($p = 0.039$).	39.5%/26.3% (A) vs. 37.8%/ 13.5% (B) at week 52. 44.7%/ 36.8% (A) vs. 18.9%/10.8% (B) ($p = 0.025$) at week 76.	Relapse in 20% with sequential therapy vs. 80% in LAM monotherapy.
119 and 3	[1] IFN 3 mIU s/c 3/week × 24 weeks *n* = 4 (all 4 e+). [2] PegIFN alpha 2b 1.5 mcg/kg/ week s/c × 24 weeks *n* = 14 (12 e+). [3] PegIFN alpha 2b 1.5 mcg/kg/ week s/c + LAM 100 mg/d × 48 weeks, *n* = 4 (all e+). All FU for mean 4 (3–5) years. (All are open label studies in treatment naïve patients).	[1] 75%/25%. [2] 93%/14.3% but 1 relapse after 1 year. [3] 100%/100% but 2 relapses after 1 year. Overall long-term SVR. 18.2% up to 5 years FU	[1] 0/4 [2] 2/12 (17%) [3] 3/4 (75%) Overall 5/20 (25%) seroconverted up to 5 years FU.	1 year therapy better than 6 months, but long-term SVR and e seroconversion rates are very low.

(*continued*)

Table 4. (*continued*)

Ref	Study protocol	EOTR/SVR	e-loss/antiHBe seroconversion	Remarks
120	*n* = 25 with LAM at 100 mg daily and pegIFN at 1.5 mcg/kg/week s/c in 1) e−ve treatment-naïve × 12 months, 2) e−ve treatment failure to at least two regimens × 12 months, 3) e+ve treatment-naïve × 6 months 4) e+ve treatment failure to at least two regimens × 6 months (open label)	[1] 66.6%/50%. [2] 80%/60%. [3] 80%/60%. [4] 55.5%/33.3%. Overall, 65%/45%.		5% HBsAg loss
121	Combination of pegIFN and LAM × 52 weeks in patients who had failed previous treatment (IFN-α 5 mIU sc daily for 6 months or LAM 100 mg PO daily for at least 24 months or a combination of IFN and LAM for at least 12 months). *n* = 20, 16 e+ve (open label).	EOTR 5/20 (25%) all in e+ve. At 76 weeks, all 5 relapsed. No SVR.		
122	RCT with 63 treatment-naïve e+ve patients who received placebo for 4 weeks followed by pegIFN 1.0 mcg/kg/week for the next 24 weeks (group A, *n* = 27) or LAM 100 mg/day for 4 week followed by pegIFN 1.0 mcg/kg/week for the next 24 weeks (group B, *n* = 36). FU for next 24 weeks.	EOTR 29.6% vs. 44.4%. SVR 14.8% vs. 50% ($p = 0.028$).	e-loss was 29.6% vs. 41.7% ($p = 0.43$) at 24 weeks. 14.8% vs. 38.9% ($p = 0.05$) at 48 weeks.	Improved SVR with sequential therapy
	SINGLE NA TRIALS			
63	LAM 100 mg/day for 12 months. *n* = 76, 45 e+ve (open label)	34%/14%		Genotype D achieved higher SVR
124	LAM 100 mg/day for 13 months (8–24 months). *n* = 147, 93 e+ve (open label).	EOTR 35%	AntiHBe in 7%	YMDD mutation in 27%
125	LAM 100 mg/day (*n* = 60, all e+ve). Treatment given for maximum of 3 years if not seroconverted. In those who seroconverted (*n* = 20), the drug was discontinued after 6 months and FU carried out every 3 months to check for relapse (open label).	DNA negativity in 19/21 (90%) at 3 months. Relapse in 35% (7/20) after median of 6 months of LAM stoppage.	Annual loss of HBeAg/antiHBe +ve was 41.6%/28.6% at 1 year, 55%/36.6% at 2 years and 58.3%/40% at 3 years	Breakthrough in 24% with no e loss, more in those with high DNA and long treatment

(*continued*)

Table 4. (*continued*)

Ref	Study protocol	EOTR/SVR	e-loss/antiHBe seroconversion	Remarks
126	*n* = 26. LAM at 100 mg/day × 4 weeks, then stopped for 2 weeks, then continued till 3 months after seroconversion or up to 2 years (open label).	SVR in 31%	e-loss in 31%	YMDD mutations in 11.5%
127	ADF at 10 mg/day for 12 months (6–18 months). *n* = 30. 50% e+ (open label).	EOTR 7% at 12 months	27% e loss	Mutation in 7%
128	LAM and ADV, *n* = 15 in each group treated for 6 months. 87% e+ve (open label).	ADV group 26.7%, LAM group, 13.3% SVR	ADV group 13.3%, LAM group 6.7% antiHBe	Reduction in hepatitis activity index and fibrosis score in both
22	*n* = 253 patients,151 in treatment group of LAM (*n* = 133, 88%) or ADV (*n* = 18, 12%), with 122 (81%) receiving therapy for mean of 46 months (1–72 months). 114 e+ve. 102 untreated (could not afford treatment), making it a non-randomised study.		Sustained antiHBe in 14% and seroreversion in 25%. Survival independent of e status.	Mortality 14% after mean FU of 48 months (9–304 months). 5-year survival of 21%, mean survival after decompensation of 28 months (3–244 months). All better than the non-treated group.
129	*n* = 158 (96 e+ve), LAM (*n* = 28), ADV (*n* = 24), TDF (*n* = 26), ETV (*n* = 25), LAM + ADV (*n* = 28) and LAM + TDF (*n* = 27) prospectively studied for 24 months (open label)	EOTR 0 in LAM, 16.7% in ADV, 73% in TDF, 68% in ETV, 53.5% in LAM + ADV and 85% in LAM + TDF group patients (no difference between compensated vs. decompensated and e+ve vs. e−ve, except ADV → more in e+ve compensated and ETV → more in e+ve).	AntiHBe in 33% of patients with all the regimens, except LAM (28%) and LAM+TDF (20%)	Mutations: 53% LAM and 16.4% ADV. None with TDF, ETV, or LAM + ADV/TDF. All regimes (except LAM and ADV) improved CTP/MELD scores. Virologic breakthrough 50% in LAM and 33.3% in ADV and 7% LAM + ADV.
135	ETV (0.5 or 1 mg/day) in treatment-naïve patients × 1–5 years, *n* = 106. e+ve 31%. Mean FU of 2.5 years (1–5 years) (open label).	89% to 98% at 1 to 5 years. Relapse universal after stoppage of therapy.	18.2% at 5 years	
136	ETV in treatment-naïve patients. *n* = 38 all e+ve. 0.5 mg × 40 weeks (open label).	64.3%	10 (35.71%)	
137	ETV in treatment-naïve patients, *n* = 45, e+ve 26. Median treatment duration of 6 months (6–11 months) (open label).	EOTR 38 (84%)		No ETV resistance mutations found

(*continued*)

Table 4. (*continued*)

Ref	Study protocol	EOTR/SVR	e-loss/antiHBe seroconversion	Remarks
138	ETV *n* = 180, e+ve 38.8%, decompensated 50%, previous treatment failures 23.9%. TDF *n* = 220. e+ve 38.6%, decompensated 54.5%, 21.4% previous treatment failures with LAM/ADV (open label). Mean FU of 36 months (11–60 months).	Overall EOTR 67.7% at 6 months, 88.8% at 1 year and 97.7% at last FU (TDF 97.8% and ETV 97.2%). In treatment failure group 85 (94%) after median of 13 months (3–18 months) of therapy.	32% at last FU (TDF 36.3% and ETV 32%)	Stable or improved CTP score in 90%
139	*n* = 69. ETV or TDF for 1 year (open label).	EOTR 94.2%	56%	
140	96 decompensated CLD. TDF for 2 years. 63 e+ (open label).	EOTR 71.4% in e+ve and 27.3% in e–ve group		Improved CTP, MELD score
141	5-year TDF, *n* = 121 e+ve 67. 98 (81%) treatment-naïve, 23 previously exposed to LAM and/or ADV (open label).	EOTR in 80.6% of e+ve and 83.3% of e–ve during median FU of 144 (24–260) and 132 (24–260) weeks, respectively.	AntiHBe in 29.9% at median of 48 weeks	13.4% e+ve [6 naïve, 3 exposed to ADV) and 7.4% e–ve (all naïve) had virological breakthrough. 1 (0.8%) lost HBsAg.
	COMBINATION NAs			
134	*n* = 60, e+ve 58.3%, 21, 20 and 19 patients treated with LAM (100 mg/day) plus ADV (10 mg/day), ETV (0.5 mg/day) and TDF (300 mg/day), respectively for 6 months (open label).	EOTR 19%, 55%, 42% at 24 weeks. Response better with monotherapies.	e-loss in 70%, 46.6% and 50%	HBsAg loss in 1/19 (5.3%) in the TDF group, none in others
142	*n* = 67 non-cirrhotic primary treatment failure and resistance to therapy cases. (31 to LAM, 29 to LAM + ADV, and 7 to pegIFN + LAM). Given LdT (600 mg) + TDF (300 mg) OD (group A), LAM (100 mg) + TDF (300 mg) OD (group B) or ETV (0.5 mg) + TDF (300 mg) OD (group C). Prospective study for 2 years (open label).	DNA negativity in group C is best at 2 years (100% vs. 84.2% and 63.2%), but group A showed most increased eGFR.		
111	*n* = 21, 30% e+ve given a combination of LdT (600 mg) + TDF (300 mg). Response at week 24 and 52 was evaluated (open label).	EOTR 24% at 24 weeks and 91% at 52 weeks		HBA DNA decline at week 24, and at week 52 was not higher than with monotherapy

(*continued*)

Table 4. *(continued)*

Ref	Study protocol	EOTR/SVR	e-loss/antiHBe seroconversion	Remarks
72	*n* = 25 (12 vertical transmission, 13 horizontal transmission) HBeAg+ children up to 12 years-old. Dose to 75,000 IU/kg subcutaneously, every alternate day for 4–6 months = the mean dose between 4.5 to 9 MIU/week. FU for 6 months (open label).	44% EOTR and overall SVR 52%. 10% relapse at FU.	44% e-loss and overall antiHBe in 20%, higher in horizontal but not significantly different from the vertical transmission group (53.8% vs. 33%) and (57% vs. 25%).	
71	*n* = 28. LAM × 8 weeks, then combined with recombinant interferon × 44 weeks (open label).	60.7% EOTR and SVR	AntiHBe seroconversion in 39.3%	21.4% HBsAg loss

Abbreviations: ADV, adefovir; CKD, chronic kidney disease; CLD, chronic liver disease; e-ve, HBeAg-negative; e+ve, HBeAg-positive; EOTR, end of treatment response; ETV, entecavir; FU, follow-up; IFN, interferon; LAM, lamivudine; LdT, telbivudine; NHL, non-Hodgkin's lymphoma; pegIFN, pegylated interferon; RCT, randomised controlled trial; SVR, sustained viral response; TDF, tenofovir.

therapy.[132] All such findings highlight issues therapeutic concern for LAM.

ADV[126–128] administered for 6–46 months results in viral suppression rates of 7–26.7% and e seroconversion in 13.3–33% of cases. Drug-resistant mutations reportedly develop in 7–16.4% (with 33% breakthrough). Combination of ADV + LAM[128,133] administered for 6–24 months was shown to result in rates of viral suppression of 42–53.3% and e seroconversion of 33–50%. Drug-resistant mutations occurred in only 7%, without any viral breakthrough. However, data on long-term sustained off-therapy response are lacking.

ETV:[128,133–138] When administered for mean 6–36 months (maximum 5 years), ETV has resulted in viral suppression rates of 55–98%, and even higher rates were achieved with longer therapy duration (with e seroconversion in 18–56%). One study showed less response in genotype D, and another showed better response in e+ve cases; no drug resistance mutations were detected. In the longest study (lasting 5 years), DNA negativity was seen in 98%.

TDF:[128,133,137–140] When administered for 6–60 months, TDF resulted in viral suppression rates of 19–98%, which were higher with longer duration of therapy (with e seroconversion in 30–70%). One study showed less response in genotype D; no drug-resistant mutations were detected. In the longest study (lasting 5 years), DNA negativity was seen in 81.8%.

Combination treatment: Increased dosages of NAs in combination treatment of patients with previous treatment failure yielded good results (e.g. sustained viral suppression rates were achieved with TDF + LAM for 2 years (85%),[128,141] TDF + LdT for 1–2 years (84–90%)[110,141] and ETV + TDF for 2 years (100%)[141]), but these results were not better than those achieved with monotherapies.

Thus, although DNA suppression is much higher and resistance is much lower with ETV and TDF, the e seroconversion rates are lower and not much different from that achieved with LAM + ADV; moreover, relapse following discontinuation is almost universal, without significant HBsAg loss even when the treatment is administered on a long-term schedule. Review of worldwide literature[111] shows agreement. Although higher viral suppression is attained with NAs, the therapeutic effect is not sustained over the long-term or after post-therapy cessation, and higher suppression rates do not translate into higher rates of e seroconversion.

Again, the limitations of most studies include their uncontrolled nature with non-uniform patient selection criteria that are often biased in treatment group in favour of drug affordability, their non-uniform reporting of outcome measures, their inadequate follow-up data on long-term treatment and their uncertainty regarding proper adherence to therapy. Notwithstanding these shortfalls, treatment with pegIFN and NAs give definite survival advantage,[3,22] with LAM, ETV and TDF showing improvement in Child-Turcotte-Pugh (CTP)/model for end-stage liver disease (MELD) scores and histology.[22,127,128,137,140,142] A recent meta-analysis of RCT also showed significant benefit of NA therapy on all primary efficacy measures, including virological response, biochemical response, histological response, e seroconversion and HBeAg loss, without adverse effects.[143]

The other major benefit of the NA treatment has been realized in cases of LT with hepatitis B. HBV-related CLD was considered a relative contraindication for LT until the introduction of high-cost HBIg. Recently, the availability of potent NAs (ETV, TDF) has allowed for the possibility of HBIg to be

avoided or used at low dose, thus reducing the cost substantially.[144] In a study of 75 cases of live-donor LT for HBV-related CLD, among patients who were not given HBIg and were instead treated with NAs (19 with LAM + ADV, 42 with ETV, 12 with TDF, and 2 with ETV + TDF), all patients were found to be DNA-negative at median follow-up of 21 months; moreover, 80% cleared the HBsAg and 32% developed anti-HBs. The 8% cases of recurrence were all salvaged by changing the NAs used, and there was no mortality.[145] Another study of LT cases compared the cost of 6 months post-transplant HBIg with that of hyperimmune plasma (containing high antiHBs titre), along with ETV therapy in both groups; the latter was found to be 14-times less costly and to yield low and transient HBsAg reactivity.[146] The benefit of TDF has also been shown in cases of acute-on-chronic liver failure due to HBV in reducing mortality for up to 3 months.[147]

Counselling and prevention of transmission

Awareness about HBV infection is dismally low in India, and this problem is compounded by the absence of symptoms (until late stage of disease) in a large majority of cases. Drug adherence is poor, which decreases the cure rate and increases the spread of infection. Education about HBV infection is crucial for curbing its spread. Published guidelines recommend proper counselling of patients on prevention of transmission, advice on lifestyle (i.e. avoiding high-risk sex, diet, alcohol use and other predisposing factors like unsafe injection practices and tattooing) and importance of continuous adherence to long-term treatment regimens. It is recommended that regular screening and vaccination be performed for high-risk patients (i.e. sexual and household members in close contact with patients/carriers, health care workers, dialysis patients, intravenous drug users, persons who receive multiple blood transfusions, participate in acupuncture, are incarcerated, or on immunosuppressives, biologics or cancer chemotherapy, etc.).

Early treatment of HBsAg-positive mothers and with HBIg for infants born to infected mothers, along with hepatitis B vaccination (at delivery and followed by complete vaccination series) is advocated. Avoidance of sharing of needles and syringes by intravenous drug users and use of separate equipment for HBsAg-positive patients undergoing haemodialysis should be emphasized. Health education not only of the population in general and high-risk population in particular but also of the health care workers is needed regarding avoidance of unnecessary injections, and adopting safe injection practices (like use of aseptic technique and disposable syringes or fluid infusion sets for multiple patients, and taking proper precautions when multiple-dose vials are used). Following universal precautions in health care settings, such as care to prevent needle-stick injuries and implementing post-exposure prophylaxis, can reduce transmission of HBV infection. The unnecessary use of blood transfusions without clear indication should be curbed as well. It appears that most high-risk groups have significant prevalence of occult infection, which needs more vigilant screening.

Provision of safe blood and blood products

A survey of blood transfusion practices in India showed that screening for transfusion-transmitted infections is unsatisfactory and poorly regulated with poor enforcement of the existing guidelines. A strict audit of blood banking practices is required to prevent transmission of the disease. Use of nucleic acid testing has been proposed for preventing transmission of HBV in Indian blood donors, but this would increase the cost of screening and is not routinely recommended.[1]

There is also a need to map out areas of high endemicity levels within each state in greater detail, especially for tribal areas, which are known to have very high prevalence and are areas that should be the focus of intensive screening and protective measures.

Vaccination

The most essential step in treatment is prevention of HBV infection by vaccination. A universal immunisation programme (containing vaccination against hepatitis B) was introduced in India in 1985 and became part of the Child Survival and Safe Motherhood programme in 1992. A cost efficacy study[148] showed that the inclusion of hepatitis B vaccine in India's national immunization program would lead to a reduction in HBV carrier rate from 4.0% to 1.15%. Vaccination against hepatitis B was piloted in 2002–03 and subsequently integrated into National Rural Health Mission in 2005. Initially, it was introduced in certain districts and cities in 2003, and its subsequent success was followed by its being taken up by 10 states in 2008; full-country coverage started in 2011.[149]

A study of 5–11 year-old rural children in five districts in Andhra Pradesh state, where childhood HBV immunization began in 2003, compared markers of HBV infection in HBV-vaccinated children (born in 2003/2004; n = 2674) and HBV-unvaccinated children (born in 2001/2002; n = 2350). Though antiHBs protective level (10 mIU/mL) was found in 59% of those vaccinated by 6 years-old, only 13% had protective levels at 11 years-old; moreover, although antiHBc was higher in the unvaccinated group (1.79%) it was still present in the vaccinated group (1.05%) and the HBsAg carrier rate was similar (0.17% and 0.15%).[150] Some impact within the paediatric population was evident, however, according to the major decrease in HBV as aetiology of HCC observed in recent years,[151] like in Taiwan. That proper vaccination can be efficacious in reducing the disease burden is demonstrated by its recent success in tribals of Andaman and Nicobar Islands.[152]

Since it takes at least 15–20 years from the time of vaccination for any meaningful impact on overall adult disease prevalence to be made, time is still not ripe to observe this impact. Also, the type of vaccine, the number, amount and interval of dosage (including booster), and effectiveness in high-risk and immune-jeopardised groups needs further study. Research into development of more efficacious newer vaccines should be encouraged.[153]

Conclusions

Hepatitis B is a significant public health problem in India, yet disease awareness among its people—the key to decreasing disease burden—is dismally low. The majority of disease cases progress silently and patients present in advanced stages, when decompensated CLD or HCC has already developed. With the currently available drugs, complete cure is not possible and the aim is long-term suppression of the virus by prolonged therapy, which itself can lead to poor treatment adherence along with prohibitive cost of therapy.

Ultimately, this underlies poor disease control, with progression and spread of infection.

Although a programme aiming to provide countrywide vaccination coverage was launched recently, the logistics are not yet adequate for proper disease control. As the arrival of novel drugs that target viral life cycle or modulate host immune response (which might lead to disease "cure") is eagerly awaited, the present emphasis should be on (1) health education of general and high-risk populations regarding lifestyle, preventive measures, early disease detection and proper adherence to drugs and of health care workers on adoption of proper precautions while carrying out their duties, and (2) aggressive vaccination strategies in the population, especially for tribals and high-risk groups.

Conflict of interest

The author has no conflict of interest related to this publication.

Author contributions

Collected, analysed and interpreted all data and wrote the manuscript (GR).

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