Published in final edited form as:
Clin Infect Dis. 2010 November 15; 51(10): 1201–1208. doi:10.1086/656624.

Review of Hepatitis B Therapeutics

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Abstract

There are currently seven approved therapies for chronic hepatitis B infection, an increase from just three agents five years ago. This review will focus on the pharmacology, potency, and adverse events associated with immunomodulatory agents and nucleos(t)ide analogs, with an emphasis on targets of therapy within the hepatitis B lifecycle. We will also offer guidelines for the use of available anti-HBV agents and review the emerging challenges in hepatitis B management, including HBV drug resistance, its management, and the potential role of combination therapy.

Keywords

Hepatitis B; Therapy; Pharmacology; Side Effects; Drug Resistance

Hepatitis B virus (HBV) infection affects ~350 million people globally and is a leading cause of end stage liver disease, hepatocellular carcinoma, and mortality [1]. New therapeutic agents have increased the options for HBV treatment, but since current agents often require lifelong administration, optimizing initial therapy is essential. This review will focus on the pharmacology and adverse events of anti-HBV drugs and offer guidelines for their use.

Life Cycle of Hepatitis B

Knowledge of the HBV life cycle is important for understanding therapeutic approaches to HBV.[2] HBV is an enveloped, partially double- stranded DNA virus with four overlapping reading frames: the precore/core gene, the polymerase gene, the L-, M-, and S-gene which codes for the 3 envelope proteins; and the X gene. (Figure 1). HBV enters the hepatocyte through an unidentified receptor, is uncoated in the cytoplasm, and the DNA is transported to the nucleus. Here, the relaxed circular partially double-stranded DNA is converted to covalently closed circular DNA (cccDNA), a stable episomal form that becomes the template for viral mRNA transcription. In the cytoplasm, the pregenomic RNA (pgRNA) is translated into the core protein and the viral polymerase while the subgenomic RNA is translated to the three envelope proteins and the X protein. pgRNA is reverse transcribed to DNA by the HBV polymerase, the site of action of the oral anti-HBV therapeutics. The DNA can be either reimported into the nucleus to form additional cccDNA or can be enveloped for secretion. Since the available anti-HBV therapeutic agents do not work directly against the cccDNA, eradication of HBV is difficult.

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Potential Conflicts of Interest: All authors: no conflicts

Currently approved therapies

Standard interferon-α/Pegylated interferon-α—Interferon-α enhances the innate immune response by binding to the type 1 interferon receptor resulting in activation of the Jak-Stat pathway[3] and up-regulation of multiple interferon-stimulated genes, which limit viral dissemination. With the addition of polyethylene glycol, pegylated interferon-α has a longer half-life than interferon-α. Although there are two formulations of pegylated interferon-α, -2a and -2b, only the former is approved in the US for CHB treatment.

The dose of pegylated interferon α-2a is 180 mcg given subcutaneously once per week. The C_{max} occurs 72 -96 hours after administration with levels sustained up to 168 hours. It is cleared both by the kidney and liver but should be used with caution in patients with creatinine clearance (CrCl)< 50 mL/min, with dose adjustment required in hemodialysis (Table A). It should also be used with caution in patients on theophylline, whose level it increases. Adverse events in >25% of patients include pyrexia, myalgias, and headache, which can be ameliorated by pre-treatment with non-steroidal anti-inflammatory agents. Other adverse events include fatigue, arthralgias, alopecia, diarrhea, anorexia, insomnia, hypo-or hyperthyroidism, irritability and depression. Pegylated interferon-α is contraindicated in patients with untreated or severe depression or with decompensated cirrhosis [4].

In HBeAg-positive subjects, pegylated interferon-α was superior to standard interferon-α [5]. The recommended 48 weeks of pegylated interferon-α results in HBV DNA loss in 25% and 63% of patients with HBeAg-positive and -negative CHB, respectively (Table B)[6].

Nucleos(t)ide Analogues: These oral agents can be grouped by structure and function into three groups; the L-nucleosides, acyclic phosphonates, and other.

L-nucleosides: The L-nucleosides include lamivudine, emtricitabine, and telbivudine. Lamivudine and emtricitabine are cytidine analogues while telbivudine is a thymidine analogue. They are phosphorylated intracellularly to 5′-triphosphate active metabolites. They inhibit HBV DNA polymerase by competing with natural substrates for incorporation into viral DNA, with resulting chain termination[7-9]. As a class, adverse events include hepatic steatosis, lactic acidosis, and hepatic flares with discontinuation of drug. They do not affect the cytochrome P450 system and do not have significant drug-drug interactions. Their bioavailability is not affected by food and all are renally excreted, requiring dose adjustments for CrCl< 50 mL/min (Table A). Lamivudine and emtricitabine are active against HIV whereas the anti-HIV activity of telbivudine is controversial [10, 11].

Lamivudine is potent but is limited by the rapid development of resistance. The 100 mg dose of lamivudine results in a peak plasma concentration of 1.28 mcg/mL ± 0.56 mcg/mL that occurs between 0.5 and 2 hours after administration. The mean half-life is 5-7 hours[8].

In patients with CHB, lamivudine was associated with histologic improvement, HBeAg seroconversion, and ALT normalization in 56%, 16%, and 72% of patients, respectively. [12].

Emtricitabine, given 200 mg orally, is not FDA approved for HBV, but it has been extensively used with tenofovir in HIV/HBV coinfected patients. It reaches peak plasma concentrations of 1.8 ± 0.7 mcg/mL at 1–2 hours and has a plasma half-life of 10 hours[7]. It has slightly greater potency and efficacy than lamivudine but cannot be used as monotherapy due to high rates of resistance[13].

Telbivudine is effective at 600 mg daily and is renally excreted unchanged. Peak plasma concentrations of 3.69 ± 1.25 mcg/mL are reached 1-4 hours after administration and it has a

long intracellular half-life of 15 hours[9]. Unique adverse events that are uncommon include myopathy, myositis, creatine kinase elevations, and peripheral neuropathy. Although telbivudine demonstrated improved HBV DNA reductions compared to lamivudine, there was no difference in ALT normalization, HBeAg loss, or anti-HBe seroconversion[14] (Table B).

Acyclic diphosphonates: The two drugs in this group are adefovir dipivoxil (adefovir) and tenofovir disoproxil fumarate (TDF) with adefovir being the least potent anti-HBV agent and TDF being one of the most potent. This potency difference is due to the achievable drug levels of these two agents at their recommended doses. They are analogues of adenosine monophosphate that undergo intracellular phosphorylation to their active metabolite, which inhibits the HBV polymerase by competitive inhibition with deoxyadenosine 5′-triphosphate, resulting in chain termination[15, 16].

The major adverse effect of this class is nephrotoxicity. Adefovir was first associated with proximal renal tubular dysfunction and Fanconi's syndrome in HIV infection at doses of 60 and 120 mg daily.[17, 18] Although significant creatinine elevations were absent at the 10 mg dose at 48 weeks in HBV infection[19], renal impairment has been reported in long term follow-up[15, 20]. Thus, caution is advised in those with underlying renal dysfunction and patients taking concomitant nephrotoxic agents[15, 16]. Hepatic flares with discontinuation are noted in both. In addition to class adverse effects, decreased bone mineral density has been associated with TDF in HIV infection[16]. These agents do not affect the cytochrome P450 system.

The adefovir dose is 10 mg daily, which results in peak plasma concentrations of 0.018 ± . 006 mcg/mL between 0.6-4 hours. It is unaffected by food and is renally excreted requiring dose adjustments for CrCl <50 ml/min[15]. Clinical trials with adefovir and placebo showed modest benefits in HBeAg-positive and -negative subjects[19, 21]

The TDF dose is 300 mg daily with adjustment recommended for patients with a CrCl <50 mL/min. (Table A). TDF is renally excreted with maximum serum concentrations ~ 10× higher than adefovir (0.30 ± 0.09 mcg/mL) being achieved 1 hour after administration[16]. The serum elimination half-life is 17 hours whereas the intracellular half-life is 95 hours[22]. TDF oral bioavailability is increased after a high-fat meal.

In HIV co-infected subjects, there are significant drug interactions between TDF and atazanavir and didanosine [16]. When administered with TDF, the C_{min} of atazanavir is reduced by 40%; thus ritonavir should be given with atazanavir to increase atazanavir levels. When TDF and didanosine are coadminstered, the area under the curve (AUC) of didanosine increases from 14% -60% therefore, patients should not receive didanosine and TDF.

In randomized trials compared to adefovir, subjects receiving TDF had higher percentages of HBV DNA<400 copies/ml [23]. In HBeAg+ subjects, the biochemical response was higher with TDF, but HBeAg seroconversion, histologic response, and durability of HBeAg seroconversion were similar between adefovir and TDF[23].

Other: Currently, the only agent in this group is entecavir, a guanosine analog that is one of the most potent anti-HBV agents. Its mechanism of action is unique because it inhibits the three functions of the HBV DNA polymerase: priming of the HBV DNA polymerase, reverse transcription of the negative strand, and synthesis of the positive strand HBV DNA[24].

The recommended dose is 0.5 mg for nucleoside naïve patients and 1.0 mg for patients with prior lamivudine use with dose adjustment for patients with a CrCl <50 mL/min. (Table A)

Entecavir is predominantly cleared by the kidney with peak plasma concentrations of .0082 mcg/mL for the 1.0 mg dose, occurring between 0.5-1.5 hours after ingestion[24]. Despite low plasma concentrations entecavir is potent because of a long intracellular half-life resulting in the significant accumulation of intracellular entecavir tri-phosphate[25]. It should be taken on an empty stomach.

In general, side effects are mild and include headaches, diarrhea, arthralgias, and insomnia. However, a recent report documented lactic acidosis in 5 of 16 cirrhotic patients treated with entecavir. All five patients had MELD scores ≥ 20.[26]

In randomized trials compared to lamivudine, HBeAg+ and HBeAg-negative subjects receiving entecavir had improved histologic responses, higher percentages of HBV DNA suppression, and higher percentages of patients with either ALT normalization or improvement [27-28]. In HBeAg+ subjects, there was no difference in HBeAg seroconversion rates [28].

Entecavir is active against HIV and, when given as monotherapy, can result in the HIV lamivudine resistance mutation, M184V; thus limiting HIV therapeutic options[29]. As with tenofovir, lamivudine, and emtricitabine, patients receiving entecavir should be tested for HIV infection. Entecavir should not be used in HIV/HBV coinfected patients with uncontrolled HIV viremia.

Potency and Resistance

Potency and the genetic barrier to resistance are the two most important considerations in deciding which agent(s) to use. The ideal drug is one that is potent and has a high barrier to resistance. Although potency is difficult to quantify, some have used a semiquantitative scale based on rapidity of viral load suppression (Figure 2).

The genetic barrier to resistance determines how quickly resistance develops and is qualitatively determined by the number of mutations required for resistance and the ease with which those mutations occur. Lamivudine has the lowest barrier to resistance, which develops with one mutation (rtM204V)[30]. Entecavir has a high barrier to resistance since at least three mutations are required[31]. Figure 2 illustrates the relative potency versus the relative barrier to resistance of each of the nucleos(t)ide analogues, which shows TDF and entecavir with the most favorable characteristics.

It is easiest to understand drug-resistant HBV based on the nucleos(t)ide groups above. The L-nucleosides share the primary resistance mutation, rtM204V/I. Thus, if drug-resistant HBV to one of these drugs emerges, then the virus is resistant to all others in the group. Since the rtM204V/I occurs easily, resistance rates are highest with these drugs. After four years of lamivudine monotherapy, 70%[32] and 90%[33] of patients with HBV monoinfection and HIV/HBV coinfection, respectively, develop the rtM204V/I. For emtricitabine, the rates of resistance in HBV monoinfection are 18% at 96 weeks, [34] and for telbivudine, they are 25% after 96 weeks in HBeAg+ patients [35].

Once the rtM204V/I emerges, compensatory mutations can develop including rtV173L and/or rtL180M, which can enhance replication fitness[36]. Due to overlapping reading frames, HBV Pol mutations also lead to changes in HBsAg, which may potentially lead to serious consequences. For example, the rtM204V+ rtV173L + rtL180M triple polymerase mutant leads to envelope changes that behave as a vaccine escape mutant in vitro[37].

In the acyclic phosphonates, the primary adefovir resistance mutation is rtN236T while rtA181V/T has also been described. In one study, either mutation occurred in 20% of

HBeAg + patients after a median of five years [38]. Although viruses with rtN236T are not resistant to TDF, they have a slower response to TDF than do wild type viruses [22]. Primary TDF resistance mutations have not been well defined. One study reported rtA194T as a TDF resistance mutation;[39] however, this pattern was not confirmed in another study[22] and was not associated with non-response to TDF in another study[40]. Thus, longer-term studies of patients on TDF are needed to define TDF-resistant HBV.

Resistance to entecavir requires a baseline rtM204V/I and rtL180M mutation plus either rtT184S/A/I/L, rtS202G/C, or rtM250L[31]. In nucleoside-naïve patients, entecavir resistance is ≤1% at 5 yrs [41, 42] while in patients with a pre-existing rtM204V/I, entecavir resistance is 51% after 5 yrs [41].

Treatment of chronic hepatitis B

The therapeutic goal is to decrease the risk of cirrhosis and hepatocellular carcinoma. Suppression of HBV replication and HBeAg seroconversion are surrogate markers of this goal. Criteria for initiation of therapy from various guidelines use HBV DNA along with an assessment of liver disease (Table C).

Recommendations for therapy—In treatment-naïve patients, TDF or entecavir are the preferred choices since they are potent with high genetic barriers to resistance. In patients with or at risk for renal insufficiency, entecavir is preferred. Pegylated interferon-α may be considered in patients who are noncirrhotic, have low HBV DNA, and elevated ALT. Although telbivudine is a potent agent, its resistance rate precludes its use as first-line therapy. It could be considered as a second-line agent with careful monitoring of HBV DNA levels to minimize the risk of developing resistance. Lamivudine and emtricitabine should not be used as monotherapy given the high rates of resistance. Because of its low potency adefovir is not recommended as single agent therapy.

Special Populations

HIV/HBV coinfection: Several guidelines recommend the use of combination therapy with TDF/FTC or TDF/3TC since those drugs are also included as first-line anti-HIV agents[43]. Entecavir should not be used unless HIV viremia is suppressed (see above). Pegylated interferon-α has not been tested in HIV-HBV co-infection but studies of standard interferon-α prior to HAART therapy demonstrated poor efficacy [44]; thus pegylated interferon-α is a 2nd line option.

HBV/HCV coinfection: The recommended treatment is pegylated interferon and ribavirin as per HCV guidelines. If, after pegylated interferon discontinuation, HBV DNA is still detectable or rebounds, these patients should be subsequently treated with HBV nucleos(t)ide analogues[45].

Chemotherapy/Immunosuppression: All patients receiving immunosuppression or chemotherapy, including anti-TNF-alpha agents, should be screened for HBsAg and anti-HBc. Those who are HBsAg+ should have HBV DNA determined. If criteria are met for HBV treatment, then treatment should be initiated. Those with HBV <2000 IU/ml should receive therapy during and for six months after chemotherapy completion. Those with DNA>2000 IU/ml should receive therapy until standard treatment endpoints are met. If treatment criteria are not met and HBV DNA is undetectable, then prophylaxis to prevent reactivation with lamivudine or telbivudine for short course immunosuppressive therapy (<12 months) or with tenofovir or entecavir for longer immunosuppressive therapy is recommended. Patients with anti-HBc alone or anti-HBc and anti-HBs should be monitored closely for HBV DNA elevation and treated if HBV viremia occurs[6, 45, 46].

Combination therapy: Combination therapy has not consistently been associated with increased virologic suppression but decreased resistance has been demonstrated. In HBV monoinfection, adefovir with either lamivudine or emtricitabine was associated with greater HBV suppression [47, 48], but other combinations have not demonstrated this [49-50]. In HIV-HBV coinfected patients naïve to therapy, TDF-lamivudine combination was superior to lamivudine monotherapy, but it was not superior to TDF monotherapy[51]. Similarly, while combination therapy reduces the incidence of resistance to drugs with low barriers of resistance [52], it is unknown whether this will occur with TDF or entecavir combinations as resistance rates are already low with these agents. Currently, combination therapy is recommended in HIV coinfection[6, 43, 45, 46, 53, 54], in patients with drug resistance[6, 45, 46], and in patients with decompensated cirrhosis [46].

Suppression with lamivudine monotherapy: Despite high resistance rates, some patients remain virologically suppressed on lamivudine monotherapy. Data to guide optimal management of these patients do not exist. Some recommend changing to a more potent agent[6], such as tenofovir, which is preferred over entecavir in this situation since entecavir and lamivudine share resistance mutations. Others recommend basing the decision on the duration of lamivudine where those with two or more years of lamivudine who suppressed within 6-12 months are continued with careful evaluation for transaminitis and HBV DNA reactivation[55]. All others, change to tenofovir.

Management of HBV Drug Resistance

Lamivudine Resistance: The options include changing to TDF, adding TDF, or changing to TDF/emtricitabine. Some advocate the latter two from extension of adefovir studies that show 0-2% adefovir resistance [56, 57] when added to a failing lamivudine regimen compared to 21% (3/14) adefovir resistance when lamivudine is replaced by adefovir [57]. Entecavir is not recommended since rates of entecavir resistance are high with pre-existing lamivudine resistance[41]; however, if TDF cannot be used, then it is a second-line option with careful HBV DNA monitoring.

Adefovir resistance: A change to combination TDF/lamivudine or TDF/emtricitabine should be considered. Although TDF monotherapy has been used [58, 59], in vitro evidence suggests a 3-4 fold decreased activity of TDF in this setting [22].

Entecavir resistance: Both adefovir and TDF retain activity against entecavir-resistant virus with TDF being preferred due to its higher potency. There are as yet no clinical trial data to further guide management [6].

Duration of Therapy and Follow-up—In HBeAg-positive patients, many consider cessation of therapy 6-12[6, 45, 46] months after eAg seroconversion. In cirrhotics, for whom rebound hepatitis can be severe, many experts continue therapy indefinitely. In HBeAg-negative patients, duration of therapy with the currently available agents should be lifelong given the high incidence of rebound viremia and transaminitis with therapy cessation[60].

With the nucleos(t)ide analogs, HBV DNA should be measured at 12 and 24 weeks. If virologic suppression is achieved then HBV DNA can be monitored every 24 weeks thereafter [46]. In patients with HBeAg+ CHB, HBeAg and anti-HBe should be monitored every 6 months. In addition, monitoring for hepatocellular carcinoma should occur every 6 months in high risk patients [6].

Summary

Over the last several years, several new agents have been added to the armamentarium of drugs against hepatitis B infection. Currently the optimal agents for first line therapy are entecavir, TDF, and potentially pegylated interferon in some situations. Several challenges in this field remain including the inability to eradicate a latent reservoir of HBV, emerging drug resistance, and the need to define the role of optimal combination antiviral therapy.

Acknowledgments

Financial Support: National Institutes of Health (AI071820 and AI060449 to C.L.T. and KAI066983A to DB), UCLA Center for AIDS Research, and Johns Hopkins University Center for AIDS Research.

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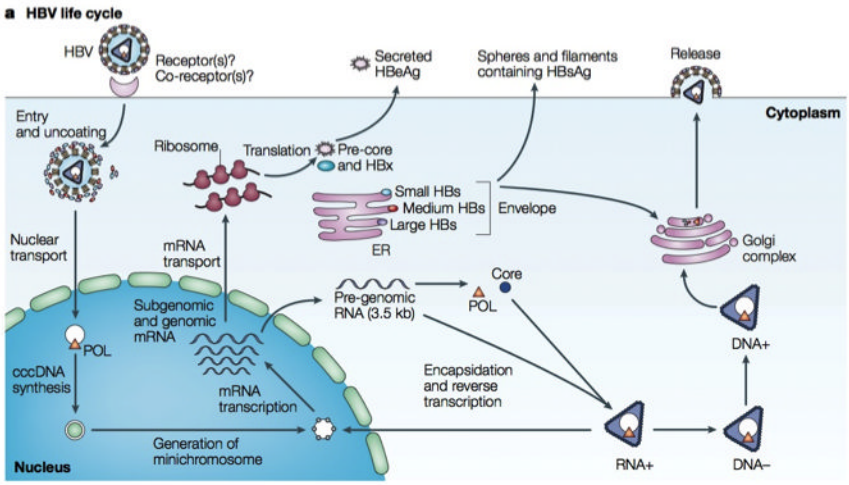
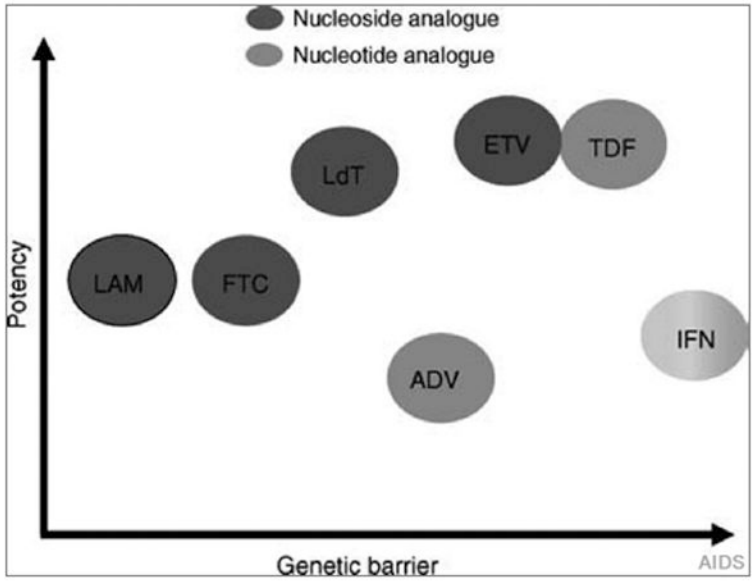


Figure 1.

Life cycle of hepatitis B virus (HBV). Reprinted from Rehermann and Nascimbeni [3], with permission from the Nature Publishing Group. cccDNA, covalently closed circular DNA; ER, endoplasmic reticulum; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBx, HBVX protein; mRNA, messenger RNA; POL, polymerase.



Potency and genetic barrier for resistance of antihepatitis B virus drugs. ADV, adefovir; ETV, entecavir; FTC, emtricitabine; IFN, interferon; LAM, lamivudine; LdT, telbivudine; TDF, tenofovir.

Figure 2.

Potency and emergence of resistance. Reprinted from Soriano et al [55], with permission from Wolters Kluwer Health. ADV. adefovir; ETV, entecavir; FTC, emtricitabine; IFN, interferon; LAM, lamivudine; LdT, telbivudine; TDF, tenofovir.

Table A

Dose Adjustments for Renal Insufficiency

Drug and Creatinine Clearance (mL/min)	Recommended Dose
Pegylated interferon α-2a	
≥50	180 mcg sc q week
ESRD (hemodialysis patients)	135 mcg sc q week
Lamivudine*	
≥50	100 mg po qd
30-49	100 mg first dose, then 50 mg qd
15-29	35 mg first dose, then 25 mg qd
5-14	35 mg first dose, then 15 mg qd
<5	35 mg first dose, then 10 mg qd
Emtricitabine*	
≥50	200 mg q24
30-49	200 mg q48
15-29	200 mg q72
<15 or on HD	200 mg q96 (after dialysis
Telbivudine*	
≥50	600 mg qd
30-49	600 mg q 48 hrs
<30 (without dialysis)	600 mg q 72 hrs
ESRD (dialysis patients)	600 mg q 96 hrs after HD
Adefovir	
≥50	10 mg qd
20-49	10 mg q other day
10-19	10 mg q third day
Hemodialysis patients	10 mg q week after dialysis
Tenofovir	
≥50	300 mg q24 hrs
30-49	300 mg q48 hrs
10-29	300 mg q72-96 hrs
<10 with dialysis	300 mg q week or post 12 hrs of dialysis
<10 without dialysis	No recommendation available
Entecavir*	
≥50	1 mg qd
30-49	0.5 mg qd or 1 mg q48
10-29	1 mg q72
<10 or HD or CAPD	1 mg q7 days (after dialysis)

*Lamivudine, emtricitabine, telbivudine, and entecavir are all available in oral solution. Oral solution dosing can be found in the package inserts.

Adapted from Lok 2009

Table B

Comparisons of Antiviral Agent Efficacy

	Placebo/Control Groups from Studies	Pegylated IFN 48 wk	Adefovir 48 wk	Lamivudine 48-52 wk	Telbivudine 52 wk	Entecavir 48 wk	Tenofovir 48 wk
Loss of serum HBV DNA*							
HBeAg +	0%–17%	25%	21%	40%–44%	60%	67%	76%
HBeAg -	0%–20%	63%	51%	63-73%	88%	90%	93%
Loss of HBeAg	6%–12%	30%/34%	24%	17%–32%	26%	22%	--
HBeAg seroconversion	4%–6%	27%/32%†	12%	16%–21%	22%	21%	21%
Loss of HBsAg							
HBeAg +	0%–1%	3%	0	1%	0%	2%	3.2%
Normalization of ALT							
HBeAg +	7%–24%	39%	48%	41%–75%	77%	68%	68%
HBeAg -	10%–29%	38%	72%	60-79%	74%	78%	76%
Histologic Improvement							
HBeAg +	n/a	38%‡	53%	49%–56%	65%	72%	72%
HBeAg -	33%	48%	72%	60%–66%	67%	70%	72%
Durability of Response							
HBeAg +		Na	90%	50%–80%	80%	69%	--
HBeAg -		20%	~5%	<10%	na	3%	--

*Some lamivudine studies used hybridization or branched chain DNA assays (lower limit of detection 20,000-200,000 IU/mL).

All other studies used PCR assays (lower limit of detection approximately 50 IU/mL).

†Responses at week 48 / week 72 (24 weeks after stopping treatment).

‡Biopsy performed at week 72 (24 weeks after stopping treatment).

Modified from Lok 2009

Table C

Comparisons of Indications for HBV Therapy

Patients for Whom Treatment Indicated	AASLD Guidelines[a] 2009	US guidelines[b] 2008	EASL[c] 2009
HBeAg –Positive Disease	HBV DNA > 20,000 IU/ML and ALT > 2 ULN	HBV DNA >20,000 IU/Ml and elevated ALT (ULN for men 30, women 19)	HBV DNA >2000 IU/mL and/or elevated ALT and suggestive liver biopsy*
HBeAg- Negative Disease	HBV DNA >2000 IU/mL and ALT >2 ULN	HBV DNA >2000 IU/Ml and elevated ALT (ULN for men 30, women 19)	HBV DNA >2000 IU/mL and/or elevated ALT and suggestive liver biopsy*

[a] American Association for the Study of Liver Diseases (AASLD)

[b] US Guidelines: American Gastroenterological Association (AGA)

* A suggestive liver biopsy would demonstrate moderate to severe active necroinflammation and/or fibrosis.

Non-invasive markers, when validated in HBV infection, may also be utilized.