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Clinical Potential of Emerging New Agents in Hepatitis B

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Abstract

Treatment of chronic hepatitis B is directed at interrupting the natural history and clinical outcomes of the disease. It needs to take into account the virology and replication cycle of the hepatitis B virus (HBV), and the host immune response to HBV. Long term follow-up of patients treated with interferon supports the paradigm that a sustained, major suppression of HBV replication, particularly that associated with hepatitis B e antigen (HBeAg) seroconversion, interrupts the natural history of hepatitis B. The availability of potent but well tolerated and orally available HBV antivirals, of which lamivudine is the prototype, has allowed clearer treatment objectives to be formulated. These are: temporary or permanent reduction of hepatitis (necroinflammatory) activity, arrest of fibrotic progression, prevention of cirrhosis and liver failure, and prevention of recurrent HBV infection after liver transplantation. Lamivudine has good medium term efficacy in achieving each of these objectives. The only significant problem for the longer term is emergence of antiviral resistance conferred by mutations in the YMDD (tyrosine-methionine-aspartic acid-aspartic acid) motif of the HBV reverse transcriptase. As a result, contentious issues remain about defining when antiviral therapy is indicated, whether to treat for a defined interval or indefinitely, and when to stop treatment if HBeAg seroconversion is not achieved. Some personal views are expressed in this review.

Among newer HBV antivirals in clinical studies, adefovir dipivoxil, entecavir and emtricitabine appear to be at least as potent as lamivudine in suppressing HBV replication. Famciclovir appears less potent. *In vitro* studies show that YMDD mutations confer cross-resistance between lamivudine, emtricitabine and β-L-Fd4C (L-2′,3′-didehydro-dideoxy-5-fluorocytidine). However, adefovir dipivoxil, lobucavir, entecavir, DAPD (β-D-2,6-diaminopurine dioxolane) and possibly clevudine (L-FMAU) suppress replication of YMDD mutant HBV, as well as wildtype. Preliminary studies indicate clinical efficacy of adefovir dipivoxil once resistance to lamivudine has developed. Immunomodulatory approaches to treatment of chronic hepatitis B are conceptually attractive, but newer agents used to date (thymalfasin, interleukin-12, therapeutic vaccines) have not demonstrated sufficient efficacy for widespread use. The next challenge for HBV treatment is to use antivirals in combination and/or in cyclical therapy to reduce the emergence of drug resistance and increase efficacy, particularly to achieve sustainable post-treatment suppression of hepatitis B.

The pathogenesis of chronic hepatitis B involves replication of the hepatitis B virus (HBV) and a T-cell mediated immune response to viral epitopes expressed on infected hepatocytes. The earlier stages of infection acquired in the first 3 years of life are associated with prolific HBV replication and complete immune tolerance to the virus. This immune tolerance later wanes and is followed by immunoelimination of free or episomal (non-integrated) HBV, resulting in disappearance of HBV DNA from blood [by less sensitive assays than polymerase chain reaction (PCR)], loss of hepatitis B e antigen (HBeAg) and appearance of anti-HBe. This constellation of events, which is termed HBeAg seroconversion, marks a major shift in the host-virus interaction. During the immunoelimination of HBV, there is a cytotoxic T cell-mediated attack on hepatocytes that express core epitopes of the virus, and it is this attack which results in hepatic inflammation and liver cell necrosis (hepatitis, or necroinflammatory activity) with its accompanying rise in serum alanine aminotransferase (ALT) levels.

Chronic hepatitis B occurs in the approximately 30% of people chronically infected with HBV who do not undergo spontaneous HBeAg seroconversion. There is intermittent or persistent elevation of ALT from the unresolved attempts at immunoelimination. The most important consequence of chronic hepatitis is progressive hepatic fibrosis leading to cirrhosis, portal hypertension, liver failure and hepatocellular carcinoma (HCC). In contrast to early childhood infection, development of chronic hepatitis B is distinctly uncommon (less than 5% of those infected) when HBV infection is acquired in older children or adults. However, HBV replication is facilitated by immunosuppression, and in clinical situations such as organ transplantation, the activity and rate of progression of chronic hepatitis B may be accentuated.

A common mutation in the pre-core region of the HBV genome results in a variant virus in which HBeAg is not expressed. Such 'pre-core mutant' HBV accounts for 30 to 90% of chronic hepatitis B, depending on geographic location and duration of HBV infection. In the case of wildtype (HBeAg positive) HBV infection, HBeAg seroconversion is a favoured end-point for treatment. It is associated with a substantial reduction in risk of liver failure, even if cirrhosis has developed.[1] It also confers a reduced risk of HCC,[2] although it does not abolish this risk.

Until 1999, the only approved treatment for chronic hepatitis B was interferon (IFN)-α. IFNα acts principally as an immunomodulatory agent. Treatment is rarely successful unless the patient exhibits substantial immunoreactivity to HBV, as reflected by high ALT levels. Further, HBeAg seroconversion is preceded by an abrupt, transient flare of hepatitis, as reflected by increased ALT; this can lead to liver failure in patients with cirrhosis. Thus, IFNα treatment is only useful for a small minority, perhaps 2 to 5% of patients with chronic hepatitis B in Asian-Pacific countries. It is contraindicated in patients with cirrhosis, it is not effective in pre-core mutant HBV or in the presence of immunosuppression, and it has many unpleasant adverse effects.

The purpose of the present review is to consider the potential of new and emerging therapies for hepatitis B from a clinician's perspective. The published and recently presented data are discussed as the basis for personal views on how to make balanced judgements about the use of HBV antivirals in individual patients.

1. Lamivudine

Lamivudine [(-)-β-L-2′3′-dideoxy-3′-thiacytidine] inhibits the RNA-dependent DNA polymerase (reverse transcriptase) of HBV ($K_i \approx 10$ nmol/L), and is a potent suppressor of HBV replication *in vivo*. A comprehensive review of the therapeutic potential of lamivudine has recently been published in *Drugs*,[3] and only a brief clinical perspective will be given here. Lamivudine is taken in single daily oral dosage and has minimal adverse effects. In more than 90% of treated patients, HBV DNA levels in blood are undetectable by sensitive hybridisation or branch chain DNA assays within 4 weeks, and there is a gradual reduction of ALT lev-

els; normal values are achieved in about two-thirds of patients after 12 months.[4-7]

The most important result of such suppression of HBV replication is almost complete control of hepatic necroinflammatory activity and arrest (or partial reversal) of fibrotic progression.[4,5,8-10] It is now clear that lamivudine interrupts transition of chronic hepatitis B to cirrhosis,[11] something that has not been documented with IFNα. In patients who already have more severe forms of the disease, response is associated with measurable improvements in liver function, such as an increase in serum albumin levels or resolution of liver failure.[12-14] None of these effects are dependent on pretreatment ALT or HBV DNA levels, and they can all be achieved with pre-core mutant HBV as well as wild-type infections.[15]

1.1 HBeAg Seroconversion with Lamivudine

HBeAg seroconversion can also be achieved with lamivudine. Further, and unlike IFNα, this is not associated with a major increase in ALT levels (ALT flares), although minor elevations have sometimes been noted.[5] After 12 months of lamivudine therapy, the rate of HBeAg seroconversion is 16 to 21%.[4-6] It increases to 27% after 24 months,[9] and to 40% after 36 months.[10] The seroconversion rate after 3 years among those with a baseline ALT >2 times normal was 65%.[16] The chance of HBeAg seroconversion during lamivudine therapy does not depend on such baseline characteristics as age, gender, ethnicity, previous IFNα treatment and fibrotic severity of liver disease. In fact, patients with cirrhosis respond at least as well as those without,[7,12] as do also those with the less common but often dangerous clinical pattern of frequent ALT flares. IFNα-resistant patients respond to lamivudine just as well as previously untreated patients.[17]

On the other hand, pretreatment ALT and HBV DNA appear to be just as important predictors of the likelihood of HBeAg seroconversion with lamivudine as they are with IFNα. For instance, in two recent studies,[6,7] seroconversion rates after 12 months treatment were 38 to 80% in those with an ALT more than 5 times the upper limit of the normal range, 15 to 23% if the ALT was 2 to 5 times normal and 5 to 11% if ALT <2 times normal; no patient with a normal ALT level had an HBeAg response to lamivudine. After 3 years of lamivudine, loss of HBeAg and gain of anti-HBe occurred in 65% of those with an ALT of 2 times normal;[16] most, but not all, of these patients had undetectable HBV DNA (note that the definition of HBeAg seroconversion has varied between studies).

The durability of HBeAg seroconversion after stopping lamivudine appears to be good,[18,19] although a high relapse rate has been noted from Korea.[20] In US studies, HBeAg seroconversion was maintained (at least for more than 6 months; median 15 months in one study) in 80 to 90% of patients;[18,19] loss of HBsAg occurs rarely.[19] HBeAg seroconversion (or simply loss of HBeAg) is usually associated with sustained suppression of HBV DNA and improvement or normalisation of ALT levels.[19]

1.2 Clinical Importance of Drug Resistance

A critical unresolved issue about lamivudine monotherapy is whether the great advantage of suppressing (or reversing) fibrotic progression of liver disease, and therefore hopefully abrogating development of life-threatening complications, could eventually be overshadowed in significance by the emergence of drug-resistant variants of HBV. Mutations in the YMDD (tyrosine-methionine-aspartic acid-aspartic acid) motif of the DNA polymerase confer what is effectively complete resistance to lamivudine;[3,21] doses 3 to 4 logs higher would be required to suppress replication of these forms. Emergence of YMDD resistance is rarely noted during the first 6 months of treatment, but thereafter the rate appears to accrue steadily to be 14% at 1 year, 42% at 2 years and 53% at 3 years.[4,5,9,10,22] In clinical practice, it is important to monitor HBV DNA levels during lamivudine therapy (every 3 or 6 months), and if detectable values are found to first check whether the patient has been fully compliant. Testing for YMDD resistance may soon be commercially available using a line-probe type of hybridisation assay.[23]

YMDD mutant forms of HBV are less replication competent than wildtype, and may therefore be less pathogenic. Thus, following the emergence of YMDD resistance, serum levels of HBV DNA and ALT do not usually return to pretreatment values, and after a relatively abrupt rise in ALT, values frequently fall back to within the normal range. Further, histological suppression of necroinflammatory disease activity appears to be maintained for at least 1 to 2 years after the emergence of YMDD resistance.[10] It should also be noted that development of YMDD variants does not abrogate the possibility of later HBeAg seroconversion.[22] On the other hand, in a subset of patients, drug-resistance is followed by significant reactivation of liver disease.[22] It remains unclear whether a substantial proportion of patients with YMDD variants will eventually progress to cirrhosis or develop hepatic decompensation. In the transplant context, emergence of lamivudine resistant variants has been associated with development of liver failure.[24,25]

When lamivudine is stopped after emergence of YMDD variants, wildtype HBV re-emerges and becomes the dominant form.[26] In light of the above considerations about the relative pathogenicity of YMDD and wildtype HBV, it is currently recommended that lamivudine should usually be continued if drug resistance is evident.

2. Case Selection for Lamivudine Monotherapy: Indications, End-Points and Treatment Duration

2.1 Hepatitis B Virus (HBV) Replication and ALT

Only patients with active HBV replication (HBeAg positive and/or HBV DNA positive by hybridisation or branched chain DNA assays) are suitable for antiviral therapy of chronic hepatitis B. In addition, it is also critical to consider the other host and disease-related variables that predicate the natural history and clinical outcomes of chronic HBV infection. Thus, younger patients with normal ALT levels should not be treated. They have a negligible HBeAg seroconversion rate with either lamivudine or IFNα, and in any event have a high chance of eventually undergoing a spontaneous seroconversion.

The severity of liver disease should be assessed, irrespective of age, in any patient with persistently elevated ALT (any level >2 times normal). This usually requires a liver biopsy to establish the stage of fibrosis. Patients who have repeated ALT flares (these are associated with ALT values that exceed 500 U/L, often with jaundice) should also be considered for lamivudine therapy – such flares may ultimately be fatal in individuals with cirrhosis.[27] A liver biopsy may not be essential in such cases if there is clinical evidence of cirrhosis (splenomegaly, ascites, encephalopathy) or if hepatic imaging by modalities such as magnetic resonance imaging or spiral computed tomographic scanning shows unequivocal evidence of cirrhosis. Patients with liver failure (Child-Pugh stage B/C cirrhosis) should be treated with lamivudine only after considering the option and possible timing of liver transplantation. Lamivudine is associated with improvement in liver function in many patients,[14,28] although the long term benefits are not yet clear.

2.2 Treatment End-Point for Wildtype (HBeAg Positive) Hepatitis B

The gradual emergence of drug resistance after the first 6 months of treatment has dampened enthusiasm for prolonged lamivudine treatment if this is not justified by the severity of liver disease and the resultant prognosis. Therefore, it is important to identify a point at which treatment can be stopped without loss of antiviral and anti-hepatitis efficacy. At present, this would seem to be when HBeAg seroconversion occurs for wildtype infections. It can be reasoned that those with fibrosis stages 2, 3 (bridging fibrosis) or compensated cirrhosis (stage 4) should be treated until HBeAg seroconversion is obtained, or indefinitely if HBeAg seroconversion does not occur.

Patients with less severe liver disease (stages 0 or 1) can be considered for a course of lamivudine. Again, treatment should be stopped when HBeAg seroconversion is obtained. If HBeAg seroconver-

sion is not obtained, the author's preference would be to stop lamivudine after 12 to 18 months in patients with less severe chronic hepatitis because of the risk of emergence of drug-resistant HBV variants. However, the validity of this approach in mild chronic hepatitis B (compared with no treatment or treatment continued indefinitely) has not yet been documented. If a choice is made to discontinue antiviral therapy without obtaining HBeAg seroconversion, further histological monitoring of disease progression is indicated, with a repeat liver biopsy between 1 and 3 years later.

2.3 Interferon-α or Lamivudine?

When ALT levels are high (at least 3 times normal), an alternative approach favoured by some hepatologists is to use IFNα first and to reserve lamivudine for those who do not respond. In this category of patients, the results for HBeAg seroconversion seem similar with IFNα (30 to 40%) as for lamivudine, and the treatment course is shorter with IFNα. However, patients must be given the information on which to make their own informed decision about treatment; many will choose lamivudine therapy because oral therapy is more convenient and lamivudine is better tolerated than IFNα. For patients with lower ALT levels (<2 times normal) in whom treatment is indicated because of severe liver disease, including those with cirrhosis or recurrent ALT flares, IFNα is relatively ineffective or dangerous, and lamivudine is clearly the treatment of choice.

2.4 Treatment Course for Pre-Core Mutant (HBeAg Negative, HBV DNA Positive) Hepatitis B

The problem with pre-core mutant HBV is that there is no serological or biochemical end-point that can be used to identify when permanent suppression of virus replication has been achieved. The rate is about 20% at one year,[15] but there are few data on more prolonged therapy. The available options appear to be continued use of lamivudine for at least 3 years, or a trial course (12 to 18 months) of lamivudine, followed by discontinuation. Despite earlier concerns based on a few anecdotal reports, reactivation of hepatitis after stopping lamivudine does not usually amount to a major flare,[4-6,26] and treatment can be reintroduced if this seems warranted by the stage of the underlying chronic hepatitis. At present, patients with stage 2 fibrosis or more severe liver disease should probably be treated indefinitely, while awaiting the results of larger long term studies. The author's preference is not to treat those with no or minor (stage 1) fibrosis, unless they have significant symptoms or until there is clear evidence of fibrotic progression.

2.5 Special Situations

Lamivudine has not generally been licensed for use in children with chronic hepatitis B. Children appear to respond to lamivudine, but definitive studies are in progress to establish long term efficacy and indications for treatment.

Patients with immunosuppression will not generally respond to IFNα treatment for chronic hepatitis B. Lamivudine does suppress HBV replication and resultant hepatitis in immunosuppressed patients, but emergence of drug-resistant variants can be associated with severe liver disease.[24,25] The optimal approach in future is likely to involve multiple agents, some of which, such as adefovir dipivoxil,[24] have already shown promise.

Antiviral therapy plays an important role in liver transplantation for chronic hepatitis B. The most promising approach to preventing re-infection of the grafted liver, with its attendant risks of severe chronic hepatitis, is to administer lamivudine before transplantation and hyperimmune hepatitis B immunoglobulin (HBIG) both at the time of transplantation and at regular intervals thereafter. The success of this approach, and recommended treatment paradigms have been reviewed recently.[29]

3. Interferon-α and Lamivudine in Combination

An adequate cytotoxic T cell response is required to eliminate HBV. Although suppression of HBV replication by lamivudine has been shown to improve cell-mediated immunity by *in vitro* tests,[30]

this does not appear adequate for HBeAg seroconversion in those with minimal elevations of ALT. For this reason, there is a conceptual basis for combining lamivudine with IFNα or another immune-enhancing agent (see section 4).

There are limited studies of lamivudine and IFNα in combination. Such studies are difficult to design because the recommended duration of treatment differs for each agent, and IFNα-mediated HBeAg seroconversion temporarily increases liver inflammation.[27] In one study of 20 patients who did not respond to IFNα treated for 12 to 16 weeks with combination therapy,[31] 4 (20%) showed HBeAg seroconversion, but this was sustained in only a single patient. In another study of patients who did not respond to IFNα,[17] lamivudine monotherapy for 52 weeks produced more HBeAg seroconversions (33%) than combination therapy for 6 months (21%).

In a head-to-head comparison among previously untreated patients, IFNα (for 16 weeks) and lamivudine (for 52 weeks) produced essentially identical HBeAg seroconversion rates at 52 weeks (19 and 18%, respectively).[6] However, combination therapy produced seroconversion in 36% (by the per-protocol analysis), which appeared to be better than for either monotherapy. Therefore, it remains possible that a subgroup of previously untreated patients with intermediate immune responsiveness to HBV, as indicated by ALT levels between 2 and 5 times normal, may benefit from the combination of IFNα or other immunomodulatory treatment with lamivudine.[6] This requires further study.

4. Other Immune Modulators and Therapeutic Vaccines

Thymalfasin (thymosin α1) and interleukin (IL)-12 have both shown some promise against chronic hepatitis B, but definitive studies are lacking.[32-34] In one controlled trial, similar HBeAg seroconversion rates were obtained with thymalfasin as with IFNα,[33] albeit often after completion of the treatment course. The treatment was well tolerated. Thymalfasin has been used with famciclovir, but there was no evidence of synergistic efficacy. More definitive phase III studies of thymalfasin alone or in combination with other HBV antivirals would be of interest.

Corticosteroid 'priming' (a short course followed by abrupt discontinuation) improves the response to IFNα among those with lower ALT levels, and similar synergism for HBeAg seroconversion has been observed in preliminary studies with lamivudine.[35,36] Further investigation is warranted. Steroid priming can be dangerous when larger doses are used in patients with cirrhosis, but doses of 30mg daily appear relatively well tolerated.[27] This approach is not recommended outside the context of a clinical trial.

Therapeutic vaccines are an attempt to overcome the immune tolerance to HBV that allows continuing infection and chronic hepatitis. One approach is a vaccine that incorporates a T cell epitope as well as core peptides. Preliminary studies of such a prototype vaccine used on its own produced disappointing results.[37] Development of more potent T cell stimulants, and their use in association with HBV antivirals may be trialed in the future. Other approaches using foreign DNA, such as antisense oligodeoxynucleotides to block viral gene expression and ribozymes to cleave virus-specific transcripts have shown efficacy in cellular systems,[38] but have not yet reached the stage of clinical trial.

5. Newer HBV Antivirals

There are now at least 7 other potent HBV antivirals that have been tested *in vitro* or in animal studies against the analogous woodchuck hepadnavirus (WHV);[39] some of these agents are in clinical trial or trials are about to start. Not included among these is lobucavir; it was shown to have similar potential as adefovir dipivoxil (see section 5.2) in phase II studies,[40] but was withdrawn in early 1999 because foregut and liver tumours occurred during long term carcinogenesis studies in rodents. Famciclovir will also not be discussed because it appears to have suboptimal potency compared with lamivudine,[41,42] and a higher rate of emergence of drug resistance.[43] Ganciclovir has

been used in a few patients after liver transplantation, but is not practical in most clinical settings because it must be administered in large doses intravenously.

Each of the agents discussed below exhibits considerable specificity as an inhibitor of HBV DNA synthesis.[39] Thus, doses required to cause cytotoxicity *in vitro* are generally at least 1000-fold greater than those inhibitory against HBV replication, and such concentrations do not inhibit synthesis of mitochondrial DNA.

5.1 Emtricitabine

Emtricitabine (2′3′-dideoxy-5′-fluoro-3′-thiacytidine, FTC) is a 5-fluoro oxathiolane derivative, closely related to lamivudine. Not surprisingly, it exhibits similar potency as an inhibitor of HBV replication *in vitro* and in woodchucks.[44,45] Phase I/II dose-ranging studies indicate similar potency as lamivudine in patients with chronic hepatitis B. Also as would be expected, this analogue does not exhibit activity against YMDD mutant forms of HBV.[46] Phase III studies are awaited, but inference from preliminary data and the structural resemblance to lamivudine are that the results with emtricitabine monotherapy are likely to be similar to those with lamivudine, both in beneficial effects and in the emergence of YMDD resistance; the latter is already documented for HIV.[47]

5.2 Adefovir Dipivoxil

Adefovir dipivoxil is the oral prodrug of an acyclic nucleotide monophosphate adenine analogue [9-(2-phosphonylmethyl)-adenine, PMEA].[48] It is a selective inhibitor of viral polymerases and reverse transcriptases with broad spectrum activity, including HIV and hepadnaviruses. *In vitro* studies have shown that it is also a potent inhibitor of YMDD resistant HBV, indicating clinical potential against chronic hepatitis B with resistance to lamivudine.[46,48-50]

In two phase II studies of previously untreated patients with chronic hepatitis B, a single daily dose of adefovir dipivoxil 30mg or 60mg given for 12 weeks reduced HBV DNA levels by a median of 4.1 logs.[51,52] As for lamivudine, this was associated with a gradual reduction in ALT levels. In this small number of patients, HBeAg seroconversion rates at 36 month follow-up were 20 to 27%, compared with none in controls. Development of adefovir dipivoxil for HIV has been terminated in the US because of nephrotoxicity at doses of 60 mg/day or higher.[47,48] Further development of adefovir dipivoxil for hepatitis B is continuing with doses of 10 to 30 mg/day, which appear to be effective and well tolerated.[52,53]

There are now reports of efficacy in patients with YMDD resistance during lamivudine therapy for recurrent hepatitis B after liver transplantation.[24,53] Further development of adefovir dipivoxil as monotherapy, or as add-in therapy after the development of YMDD resistance with lamivudine, and in combination therapy for first treatment of previously untreated patients is currently underway.

5.3 Entecavir

Entecavir, until recently known as BMS-200475, is a cyclopentyl guanosine analogue. It is a highly potent inhibitor (K_i 3.7 nmol/L) of HBV replication in hepatoma cell lines,[54,55] and is the most potent antiviral agent against WHV.[56] It has recently entered phase I/II human studies.

5.4 DAPD

DAPD (β-D-2,6-diaminopurine dioxolane) is a purine nucleoside analogue that is active against wildtype and YMDD mutant HBV *in vitro*.[57]

5.5 Clevudine

Clevudine (L-FMAU; 2′-fluoro-5-methyl-β-L-arabinofuranosyl uracil) is a pyrimidine nucleoside analogue that also exhibits potent HBV antiviral properties *in vitro*,[57] although there are conflicting reports of efficacy against YMDD mutant HBV.[46,47] Like DAPD, clevudine suppresses WHV DNA levels in blood and WHV core antigen expression in the liver of woodchucks. Human studies are awaited with these interesting agents.

5.6 β-L-FddC and β-L-Fd4C

β-L-FddC (β-L-2′,3′-dideoxy-5-fluorocytidine) is another nucleoside analogue that is a potent inhibitor of HBV DNA in hepatoma cell lines.[58] The closely related β-L-Fd4C (L-2′,3′-didehydro-dideoxy-5-fluorocytidine) has a more potent antiviral effect than lamivudine both in culture[59] and in woodchucks.[39,60] Unfortunately, there appears to be cross-resistance between lamivudine and β-L-Fd4C.[46] They do not alter mitochondrial DNA synthesis.[59]

6. The Future: Combination Therapy

The extensive experience with highly active anti-retroviral therapy (HAART) for HIV/AIDS, as well as the emerging experience of lamivudine in chronic hepatitis B, indicate that monotherapy is not the optimal treatment of a chronic viral infection. The emergence of drug resistance is likely to be associated eventually with progression of liver disease, at least in some individuals. In order to prevent the emergence of such resistance, combination therapy with antivirals that act at different sites in the HBV replication cycle is desirable; synergism of antiviral activity can be readily demonstrated *in vitro* with some HBV antivirals.[38,39] Translating the promise of less resistance and possibly greater efficacy to the clinical context of controlling chronic hepatitis B is the next exciting chapter to be written in the development of HBV antiviral therapy.

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