

# Combination Therapy for Chronic Hepatitis B: Current Indications

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**Abstract** Hepatitis B infection remains a major public health problem globally and in the United States, with significant use of healthcare resources. Several therapeutic agents active against viral and host targets are currently available for its treatment. The success of combination therapy in HIV infection, which has similarities to hepatitis B in both therapeutic targets and treatment options, stimulated studies on the efficacy and safety of various combinations of available drugs in the treatment of hepatitis B infection. In this review, we analyze the current role of combination therapy in chronic hepatitis B infection.

**Keywords** Hepatitis B · Combination therapy · Chronic hepatitis B

## Introduction

Hepatitis B virus (HBV) infection remains a major public health challenge, with an estimated 730,000 chronically

infected adults in the United States alone and an annual financial burden of \$1.3 billion [1, 2]. Currently available therapeutic options include both parenteral and oral agents, which act on various host and viral targets. These include medications such as standard interferon and pegylated interferon (peg-interferon), which target receptors on the host cell membranes, and nucleotide and nucleoside analogues, which inhibit HBV RNA-dependent DNA polymerase (lamivudine, telbivudine, entecavir, adefovir dipivoxil, and tenofovir disoproxil fumarate) [3].

The availability of agents acting on different targets makes the option of combination therapy to achieve better therapeutic results particularly attractive. The rationale for the trial of combination therapy in HBV includes the possibility that an additive effect of various medications may achieve more effective sustained viral suppression and a decreased incidence of drug resistance [4]. The success of combination therapy for HIV infection provides a model for this strategy, especially when considering that many agents available for the treatment of HBV are also part of combination regimens for HIV.

Several combinations have been tried in the treatment of HBV in various settings, with varying degrees of success. Table 1 summarizes the circumstances in which combination therapy using various regimens has been tried for HBV. This article reviews the use of combination therapy for chronic hepatitis B (CHB), and summarizes the recommendations of major professional societies regarding the role of combination therapy in current clinical management of CHB infection. For the purpose of this review, we defined combination therapy as the simultaneous use of more than one antiviral strategy with the aim of achieving clinical improvement in patients with CHB; sequential treatments with different agents were excluded.

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**Table 1** Indications and combinations tried for various HBV populations

Indication <sup>a</sup>	Combinations studied
HBeAg-positive chronic HBV	Interferon + lamivudine
	Interferon + telbivudine
	Interferon + ribavirin
	Interferon + thymosin
	Lamivudine + adefovir
	Lamivudine + telbivudine
	Lamivudine + thymosin
	Lamivudine + HBV vaccine
	Tenofovir + emtricitabine
	Adefovir + emtricitabine
	Clevudine + emtricitabine
	Adefovir + bicyclol
	Thymosin + bicyclol
HBeAg-negative chronic HBV	Interferon + lamivudine
	Interferon + adefovir
	Interferon + ribavirin
	Clevudine + emtricitabine
HBV and HIV coinfection	Lamivudine + HBV vaccine
	Interferon + adefovir
	Tenofovir + lamivudine
	Tenofovir + emtricitabine
HBV and hepatitis C coinfection	Lamivudine + entecavir
	Interferon + ribavirin
	Interferon + lamivudine
Interferon non-responders	Interferon + lamivudine
	Interferon + GM-CSF
	Interferon + HBV vaccine
Lamivudine-resistant HBV	Peginterferon + adefovir
	Adefovir + lamivudine
	Adefovir + entecavir (case reports)
	Adefovir + tenofovir (case reports)
	Tenofovir + lamivudine (case reports)
Adefovir non-responders	Adefovir + lamivudine
	Tenofovir + lamivudine
	Tenofovir + emtricitabine
Pediatric population	Lamivudine + interferon- $\alpha$
Acute HBV infection	Adefovir + lamivudine
Severe HBV reactivation	Nucleosides + steroids
Asymptomatic chronic carriers	Lamivudine + HBV vaccine
Prevent recurrence after liver transplantation in HBV-positive recipients	Lamivudine + HBIG
	Adefovir + HBIG
	Entecavir + HBIG
Prevent recurrence after liver transplantation with HBcAb-positive donor	Lamivudine + adefovir
	Lamivudine + HBIG

GM-CSF granulocyte-macrophage colony-stimulating factor, HBcAb hepatitis B core antibody, HBeAg hepatitis B early antigen, HBIG hepatitis B immune globulin, HBV hepatitis B virus

<sup>a</sup>The current review focuses only on populations with chronic HBV infection

## HBeAg-Positive Chronic HBV

Various combinations of interferon with oral agents, and one or more oral agents, have been tried for treatment-naïve patients with hepatitis B early antigen (HBeAg)-positive CHB. A recent meta-analysis combined data from randomized controlled trials evaluating various treatment strategies in HBeAg-positive HBV patients [5••]. The three combinations addressed in this study included peg-interferon with lamivudine ( $n=461$ ), lamivudine with telbivudine ( $n=41$ ), and lamivudine with adefovir ( $n=53$ ). Among all treatment options considered (including monotherapy with various agents), peg-interferon with lamivudine had the highest rate of HBeAg loss, although tenofovir monotherapy dominated all other therapies for other endpoints, including HBV DNA suppression, normalization of alanine aminotransferase (ALT), and histological improvement. Combinations of lamivudine with adefovir or telbivudine did not fare better than lamivudine monotherapy in final analysis. Data from this analysis suggest that, based on current data, monotherapy with tenofovir or entecavir delivers better outcomes for HBeAg-positive chronic HBV than the combinations analyzed.

Hui et al. [6] studied the combination of adefovir and emtricitabine against adefovir alone in 30 patients for 96 weeks. Although HBV DNA suppression and ALT normalization were significantly higher in the combination group, HBeAg seroconversion rate was similar in both groups. A recent trial of 112 patients evaluated the combination of tenofovir and emtricitabine against either tenofovir or entecavir monotherapy, and found that the combination arm had comparable rates of HBeAg seroconversion/loss and similar side effect profile compared to tenofovir monotherapy [7]. Clevudine/emtricitabine combination for 24 weeks in a mixed population of HBeAg-positive and HBeAg-negative patients demonstrated no significant benefits at the end of treatment (24 weeks) compared to emtricitabine alone, although combination therapy had more durable posttreatment HBV DNA suppression at 48 weeks with no difference in HBeAg seroconversion between groups [8]. The authors did not provide a breakdown of HBeAg-positive and HBeAg-negative groups for the 48-week data. A study of interferon/telbivudine combination was terminated early because of reports of increased incidence of peripheral neuropathy in the combination arm [9].

The success of combined interferon and ribavirin therapy in HBV/hepatitis C virus (HCV)-coinfecting patients (discussed later in this article) led to trials on the use of this combination in monoinfected HBeAg-positive CHB patients. Liu et al. [10] studied interferon- $\alpha$ -2b with ribavirin against interferon alone in 119 patients for 28 weeks. At follow-up after 52 weeks, there was no

significant difference in the composite endpoint of HBeAg seroconversion and undetectable HBV DNA between the two arms.

Therapeutic vaccination in concert with an antiviral agent has also been studied for the treatment of CHB. Senturk et al. [11] studied the effect of adding a pre-S2-containing vaccine to lamivudine in patients with CHB. Of 19 HBeAg-positive patients treated for 6 months with lamivudine, 100 mg twice daily, and six doses of pre-S2-containing vaccine, five (26%) lost HBeAg at the end of 6 months, 18 of 19 had undetectable levels of HBV DNA, with normalization of ALT in the five who had seroconversion. At follow-up after 364 weeks, all five who had seroconverted remained in sustained remission. Because these authors did not have an untreated comparator arm, or lamivudine monotherapy, it is difficult to confirm that the combination was superior to monotherapy alone. In fact, Vandepapeliere et al. [12] randomly assigned 195 HBeAg-positive patients to receive lamivudine alone or lamivudine with hepatitis B surface antigen (HBsAg)/AS02B adjuvant candidate vaccine for 52 weeks, and found that addition of this vaccine did not enhance the HBeAg conversion rate. Hoa et al. [13] randomly assigned 180 patients to a pre-S1/pre-S2/S vaccine or lamivudine or combination for 6 to 8 months, and found no difference in HBeAg seroconversion among the three groups at 18-months' follow-up, although the combination arm had significantly more viral suppression. Thus, although therapeutic vaccination remains attractive as part of a combination, studies have not shown a clear benefit compared to lamivudine monotherapy. However, it should be noted that the vaccines used were slightly different in each of these studies, and thus direct comparison of results is not possible.

Other compounds that were tried in combination with more commonly used HBV medications include bicyclol and thymosin- $\alpha$ . Bicyclol is the active component of a Chinese herb used for treatment of hepatitis B. Studies have been reported mainly in the Chinese literature. Combination of bicyclol with adefovir in one randomized trial achieved better HBV DNA suppression as compared to adefovir alone [14]. Thymosin- $\alpha$ , a synthetic hormone initially isolated from the thymus, has been used in combination with bicyclol and was reported to have significantly higher HBeAg conversion rates compared to bicyclol alone [15]. A recent meta-analysis comparing lamivudine/thymosin combination against lamivudine alone identified significantly better outcomes for combination therapy, including HBeAg seroconversion rates (45% vs 15%) [16]. Thymosin has also been tried in combination with interferon- $\alpha$ , with Lim et al. [17] reporting a trend toward increased HBeAg loss in those who received the combination. These medications are not widely used in the United States for management of hepatitis B.

In conclusion, trials to date have not confirmed superiority for commonly available combinations when compared to monotherapy for HBeAg-positive chronic HBV. A recent study from France showed that despite this lack of superiority, 15% of treatment-naïve HBV patients were receiving adefovir/lamivudine combination as initial therapy [18]. The American Association for the Study of Liver Diseases (AASLD) guidelines recommend monotherapy with any of the available agents as first-line therapy for HBeAg-positive chronic HBV, although peg-interferon, tenofovir, and entecavir are preferred [19••].

### HBeAg-Negative Chronic HBV

Peg-interferon- $\alpha$  is the current standard of therapy for treatment of HBeAg-negative hepatitis B, although tenofovir and entecavir have been added to the list of preferred first-line agents in the latest revision of the AASLD guidelines [19••]. A meta-analysis by Woo et al. [5••] of 296 HBeAg-negative patients suggested that peg-interferon/lamivudine was more effective than monotherapy in achieving undetectable HBV DNA levels, although it was less effective in normalization of ALT levels. Another meta-analysis, which included nine trials with 942 patients, also found no benefit for interferon/lamivudine combination in HBeAg-negative patients, although the combination arm had a lower YMDD mutation rate [20]. A recent randomized trial compared peg-interferon and adefovir dipivoxil to peg-interferon monotherapy for 48 weeks and demonstrated higher rates of HBV DNA suppression and ALT normalization, although sustained viral response at 72 weeks was equivalent in the two arms [21].

Based on reports of possible benefit of peg-interferon/ribavirin combination among HBV/HCV-coinfected patients, this combination also was tried for patients with HBeAg-negative disease. However, a randomized trial in 138 patients with HBeAg-negative disease failed to find any significant benefit for the combination over peg-interferon alone [22].

The study by Senturk et al. [11] mentioned above, which studied a lamivudine/pre-S2 vaccine combination, also analyzed 29 patients who were HBeAg-negative, and reported normalization of ALT and loss of HBV DNA in 18 of 29. However, this study did not have a comparator monotherapy arm.

Thus, various combination therapies for HBeAg-negative hepatitis B have not established a benefit over monotherapy, although there has been decreased development of resistance with the combination of interferon and lamivudine. However, availability of more effective medications (eg, tenofovir and entecavir), which also have low reported resistance levels, eliminates this advantage.

### HIV/HBV Coinfection

HIV and HBV share common routes of entry, and about 10% of all HIV-infected patients are coinfecting with HBV [23]. The success of combination therapy for HIV was a strong driving force for trials of combination therapy for HBV. The higher chance of developing resistance to HIV with oral monotherapy for HBV, when using medications with some activity against HIV, also prompted the evaluation of combination therapy for coinfecting patients.

A randomized trial from Thailand studied tenofovir/lamivudine combination against monotherapy with either agent alone in antiretroviral-naïve HIV/HBV-coinfecting patients, and found that the combination did not do better than tenofovir alone for HBV [24]. Another study comparing tenofovir/lamivudine combination against tenofovir monotherapy for lamivudine failures followed 75 patients over 116 weeks of treatment, and found no significant benefit for combination over tenofovir monotherapy [25]. However, a cross-sectional analysis of 122 US and Australian HIV/HBV-coinfecting patients on antiretroviral therapy demonstrated significantly lower HBV DNA levels in patients using tenofovir in combination with lamivudine or emtricitabine, than in those using tenofovir or lamivudine alone as part of the HIV regimen [26]. Tenofovir/emtricitabine-based antiretroviral therapy resulted in undetectable HBV DNA levels in 15 of 16 patients in one trial, although HBV levels rebounded in those who underwent a structured treatment interruption [27]. Pessôa et al. [28] added entecavir to HIV/HBV-coinfecting patients who were already on a lamivudine-based antiretroviral regimen, and demonstrated significant reductions in HBV DNA levels with no demonstrable increase in side effects or HIV viremia.

In a small trial, coinfecting patients with lamivudine-resistant HBV were given peg-interferon/adafovir combination; no maintenance of on-treatment benefits was observed after discontinuation of therapy, although the combination was well-tolerated [29].

Thus, although current data do not indicate a large benefit for combination therapy, the use of dual-acting medications in combination is nevertheless the standard of care in HIV/HBV-coinfecting patients because of concerns about development of HIV resistance. Structured treatment interruptions for HIV may adversely affect the HBV infection in such coinfecting patients.

### HBV/HCV Coinfection

HBV and HCV also share a common route of entry, and an estimated 18% of patients with chronic HBV are coinfecting with HCV [30]. Active hepatitis in such patients is more

likely from HCV than HBV [30], and hence treatment is often directed against HCV, with some studies also showing a concomitant improvement in HBV markers.

A large trial, which included 161 patients with HBV/HCV coinfection treated with peg-interferon/ribavirin combination, had 11.2% HBsAg clearance rate at the end of treatment for HCV [31]. However, during the course of therapy, 77 patients who previously had negative HBV DNA levels started expressing HBV DNA, although this was not associated with clinically significant hepatic disease. A smaller study by Hung et al. [32] reported similar findings with interferon/ribavirin combination. Another recent report suggested that any HBV viral response achieved following such combination therapy may not be sustained long-term [33].

Marrone et al. [34] studied interferon/lamivudine combination in eight patients with coinfection and reported HBeAg seroconversion in three. However, no further studies have been performed using this combination. No studies are available for a combination of interferon and ribavirin with any of the other anti-HBV therapies in coinfecting patients. Thus, current data indicate that treatment of HBV/HCV coinfection is essentially aimed at the predominant virus, which in many cases happens to be HCV.

### HBV Unresponsive to Interferon

Interferon monotherapy for HBV has only 25% to 40% therapeutic efficacy, setting the stage for trials in patients who are unresponsive to such monotherapy [35]. One such study randomly assigned patients who failed interferon monotherapy to receive interferon/lamivudine or interferon/granulocyte-macrophage colony-stimulating factor (GM-CSF), and noted sustained loss of HBeAg and HBV DNA suppression in 28% on the interferon/lamivudine arm, as opposed to 40% in the interferon/GM-CSF arm [35]. However, Schiff et al. [36] studied 238 interferon non-responders, and found that lamivudine monotherapy outperformed interferon/lamivudine combination in all respects, including HBeAg loss. Akyuz et al. [37] studied 45 HBeAg-negative non-responders to interferon, and found that interferon/lamivudine combination was not better than lamivudine monotherapy. Heintges et al. [38] used interferon/hepatitis B vaccination in interferon non-responders, and reported HBeAg loss in 7 of 18 and undetectable HBV DNA in 9 of 18 while on therapy, although posttreatment sustained response rates were not reported in this trial. Thus, combination therapy does not appear any more effective than monotherapy for interferon non-responders. Current AASLD guidelines recommend monotherapy with tenofovir or entecavir in interferon non-responders [19••].

## HBV Unresponsive to Lamivudine

Lamivudine was the first oral therapy available for HBV infection, and remains an attractive option in many parts of the world because of its relatively safe side effect profile and low cost. However, rapid development of resistance is the major limitation of therapy.

Adefovir added to lamivudine has been studied extensively in patients with lamivudine failure. A recent meta-analysis included six trials with 442 patients, and concluded that the combination performed better than adefovir monotherapy with respect to HBV DNA suppression and development of adefovir resistance, although there was no significant difference in HBeAg seroconversion or ALT normalization [39]. A 56-month follow-up trial published after this meta-analysis confirmed the findings of improved virological suppression with the combination, although there was no difference in the development of resistance to adefovir [40].

A trial of 235 patients comparing peginterferon/lamivudine combination against adefovir/lamivudine showed that addition of peginterferon had a better HBeAg seroconversion rate and greater reduction of quantitative HBsAg assay, suggesting that this could be a better option for lamivudine-resistant HBV [41]. Although case reports have suggested that adefovir/entecavir, adefovir/tenofovir, and tenofovir/lamivudine combinations may be effective in lamivudine-resistant patients, no studies are available for these at present.

Current AASLD guidelines recommend the addition of adefovir or tenofovir to lamivudine in patients with lamivudine resistance [19••].

## HBV Unresponsive to Adefovir

With increasing use of adefovir, resistance to this agent has also become a problem. The cumulative resistance at 4 years is about 15%, and another 30% of patients have primary non-response [19••]. There are few studies on management of adefovir non-responsive patients, and the available trials have looked at combination of medications.

Choe et al. [42] treated six patients who were adefovir non-responders with tenofovir/lamivudine combination, resulting in undetectable viral levels in all by 12 months, with ALT improvement in four of six. A retrospective study looked at adefovir/lamivudine combination in patients who had failed sequential lamivudine and adefovir monotherapy, and had 0% virological breakthrough at 18 months against 55% in patients who were switched to entecavir monotherapy [43]. The AASLD guidelines currently recommend add-on therapy with lamivudine as the first-line option for managing adefovir non-responders [19••].

## Pediatric Population

Children infected with hepatitis B are generally in an immune-tolerant phase, usually do not achieve HBeAg seroconversion or sustained HBV DNA reductions, and hence may not benefit from therapy. There are also concerns about using nucleoside agents for treatment, because of the likely need for lifelong therapy and development of resistance [44•]. Combination therapy studies in this population have usually focused on interferon-based treatments.

Kansu et al. [45] studied 177 children with CHB and compared simultaneous therapy versus staggered therapy with interferon and lamivudine; they noted that simultaneous therapy produced earlier HBeAg seroconversion and viral clearance and higher rates of complete response (55% vs 28%). However, another trial comparing the combination to interferon alone found that although HBeAg seroconversion and HBV DNA loss occurred earlier with combination therapy, the final outcome at 12 months did not differ between the groups [46]. The current standard of care for children with HBV who are considered for treatment is interferon or lamivudine monotherapy [19••].

## Side Effects of Combination Therapy

Side effects of combination therapy would be expected to be more frequent than monotherapy. A recent review from our group outlines the side effects of the various oral agents currently available for HBV [47•]. However, combination therapy may sometimes give rise to otherwise unanticipated side effects. A trial on interferon/telbivudine was terminated early because of high incidence of peripheral neuropathy [9]. Interferon/ribavirin combination therapy in HBV/HCV-coinfected patients may lead to new detection of HBV DNA in patients in whom it was previously suppressed, although this has not been associated with worsening of liver function [31, 32]. Hepatic flare has been noted in HIV/HBV-coinfected patients after initiation of HBV-specific therapy, and is probably an immune reconstitution syndrome, although it is not currently clear if combination therapy has any worse risk of causing this as compared to HBV monotherapy [48].

## Current Recommendations for Combination Therapy in Hepatitis B

From our review, it appears that currently there are only limited circumstances in which combination therapy has an advantage over monotherapy with one of the newer agents.

In the current AASLD guidelines [19•], combination therapy is recommended for the following:

1. Lamivudine or telbivudine resistance: addition of adefovir or tenofovir to existing treatment, or switch to tenofovir/emtricitabine combination.
2. Adefovir resistance:
  - a. Addition of lamivudine, telbivudine, or entecavir to adefovir
  - b. Replacing adefovir with tenofovir in combination with lamivudine or emtricitabine.
  - c. If previous lamivudine resistance with current adefovir resistance, replacing adefovir with tenofovir and lamivudine, emtricitabine, or entecavir.
3. Entecavir resistance: switching to tenofovir/emtricitabine is one of the options listed.
4. HIV/HBV coinfection where treatment of both pathogens is indicated:
  - a. Tenofovir/lamivudine or tenofovir/emtricitabine.
  - b. If lamivudine resistance, add tenofovir to lamivudine.

The European Association for the Study of the Liver (EASL) guidelines are generally similar to AASLD guidelines in their recommendations about combination therapy, with the following differences [49•]:

1. Tenofovir is considered the preferred add-on therapy for lamivudine or telbivudine resistance.
2. In adefovir resistance, it is recommended that adefovir be discontinued and tenofovir added with a second agent:
  - a. If N236T substitution, the second agent should be lamivudine, entecavir, telbivudine, or emtricitabine.
  - b. If A181T/V substitution, the second agent should be entecavir or emtricitabine.
3. In entecavir resistance, the recommendation is to add tenofovir to entecavir.
4. In case of tenofovir resistance, the recommendation is to add entecavir, lamivudine, telbivudine, or emtricitabine. This issue was not addressed in the AASLD guidelines.
5. HIV/HBV coinfection:
  - a. For those needing comanagement of both infections, tenofovir/emtricitabine combination is recommended.
  - b. Where HBV is treated first, adefovir/telbivudine combination is first-line therapy.

The Asian-Pacific Association for the Study of the Liver (APASL) recommendations for HBV therapy include the following indications for combination therapy [50•]:

1. Lamivudine resistance: add-on adefovir is first-line therapy.

2. Adefovir resistance: add or switch to lamivudine or telbivudine or entecavir.
3. Telbivudine resistance: add-on adefovir is recommended.
4. For HIV/HBV coinfection, tenofovir/lamivudine combination is recommended if concurrent treatment of both infections is required.

### Barriers to Combination Therapy

Initial enthusiasm about the potential of combination therapy for HBV more recently was tempered by equivocal results of studies. Several barriers currently exist to combination therapy for HBV. For one, although combination therapy for HBV has often been modeled after therapy for HIV, the treatment of HIV involves using at least three different drugs acting on two different viral targets. The only viral target for the current crop of HBV medications is the RNA-dependent DNA-polymerase. Treatment for HIV is also commonly life-long, despite undetectable viral loads, based on the understanding that discontinuation of therapy will lead to recurrence of the infection. The combination therapy trials for HBV so far have been time-limited, and it is difficult to predict if longer therapeutic duration might provide better results without increasing resistance. Long-term follow-up of patients with HIV/HBV coinfection who are on medications active against both viruses (eg, tenofovir/emtricitabine or tenofovir/lamivudine combinations) is more likely to yield an answer to these questions. Finally, the cost of the medications continues to be an issue for a large proportion of HBV-infected individuals who live in third-world countries. The combination of expensive drugs will be more expensive than monotherapy.

### Conclusions

Despite its initial promise, combination therapy for chronic HBV infection has not been shown to be more effective than monotherapy in most treatment-naïve patients. Although combination therapy lowers the incidence of drug resistance, the availability of oral monotherapeutic agents with very low resistance levels eliminates this advantage. Current indications for combination therapy are limited to special populations, such as drug-resistant HBV infection and HIV/HBV coinfection. More trials are currently under way for combination therapy for various HBV populations.

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