ABSTRACT

The availability of newer antiviral agents, as well as comprehensive treatment recommendations, has equipped clinicians with sufficient options to formulate hepatitis B virus (HBV) treatment regimens and individualize therapeutic strategies. These advances are particularly pertinent to Asian/Pacific Islander patients, who comprise the majority of chronic HBV infections in the United States and respond somewhat differently to certain drugs. This article reviews the most recent guideline recommendations on goals, treatment indications, therapeutic duration and endpoints, and monitoring of HBV treatment. In advocating an individualized approach to HBV treatment, currently available agents are further introduced separately. Treatment strategies for special populations (ie, pregnancy, HIV coinfection, cirrhosis, and post-liver transplantation) are also discussed. (Adv Stud Med. 2007;7[15]:482-490)

CURRENT TREATMENT RECOMMENDATIONS

GOALS OF HBV THERAPY

With sustained viral suppression considered critical to the reduction and/or prevention of complications from CHB, the primary goal of therapy is to reduce and maintain serum HBV DNA at the lowest possible levels (ie, durable HBV DNA suppression). Attaining this goal will, in turn, lead to other therapeutic milestones, including histologic improvement and alanine aminotransferase (ALT) normalization.

TREATMENT INDICATIONS

Two systemic recommendations for the management of HBV infection are available in the United States. As summarized in Tables 1 and 2, the American Association for the Study of Liver Disease (AASLD)
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guidelines were updated earlier this year and the Keeffe et al algorithm was updated in 2006.2,5 HBV viral load and ALT levels are the 2 major factors used in determining the need to treat. Treatment indications also vary, depending on hepatitis B e antigen (HBeAg) status. In treating Asian patients, clinicians must be aware that their ALT levels tend to be normal, serum HBV DNA may be high, and HBeAg conversion is lengthier.

According to the AASLD guidelines and Keeffe’s algorithm, a viral load of 20 000 IU/mL (ie, 100 000 copies/mL) or higher is used as a viral load threshold for treatment initiation in HBeAg (+) individuals.2,5 ALT levels help guide the decision further. Although both the AASLD guidelines and Keeffe’s algorithm recommend treating HBeAg (+) patients with elevated ALT levels, they differ somewhat on the degree of ALT elevation that warrants treatment (Tables 1 and 2). Both guidelines generally allow for a treatment delay of 3 to 6 months in individuals with compensated liver disease to determine if spontaneous HBeAg seroconversion occurs. Patients with normal ALT levels (especially those older than 40 years) may undergo a liver biopsy and only be treated if active disease is histologically confirmed.2,5

For HBeAg (-) patients, the AASLD guidelines differ from Keeffe’s algorithm on treatment indications. Because HBeAg (-) patients tend to have lower levels of serum HBV DNA than HBeAg (+) patients (yet still have disease), Keeffe et al recommends treating those with serum HBV DNA levels of 2000 IU/mL (ie, 10 000 copies/mL) or higher and any degree of ALT elevation.5 However, the AASLD guidelines denote a higher viral load threshold (20 000 IU/mL, or 100 000 copies/mL), with ALT levels of more than 2 times the upper limit of normal (ULN; Tables 1 and 2).

For patients with compensated cirrhosis, the AASLD guidelines recommend treatment if HBV DNA is higher than 2000 IU/mL, whereas Keeffe’s algorithm suggests treatment if HBV DNA is 2000 IU/mL or higher.2,5 For patients with decompensated cirrhosis, Keeffe et al recommends consideration of HBV treatment, regardless of HBV DNA levels.5 Management of these patients should be coordinated with transplant centers.2

| Table 1. HBV Treatment Criteria: HBeAg (+) or (-) Patients Without Cirrhosis |
|---------------------------------------------|-----------------|
| **HBeAg (+) Patients** | | |
| Viral load | >20 000 IU/mL (or >10^5 copies/mL) | ≥20 000 IU/mL (or ≥10^5 copies/mL) |
| ALT | >2 x ULN | Elevated |
| **HBeAg (-) Patients** | | |
| Viral load | >20 000 IU/mL (or >10^5 copies/mL) | ≥2 000 IU/mL (or ≥10^4 copies/mL) |
| ALT | >2 x ULN | Elevated |

AASLD = American Association for the Study of Liver Disease; ALT = alanine aminotransferase; HBeAg = hepatitis B e antigen; HBV = hepatitis B virus; ULN = upper limit of normal. Data from Lok and McMahon2 and Keeffe et al.5

| Table 2. HBV Treatment Criteria: HBeAg (+) or (-) Patients Without Cirrhosis and Normal (or ≤2 x ULN) ALT |
|---------------------------------------------|-----------------|
| **HBeAg (+)** | | |
| DNA | >20 000 IU/mL and ALT ≤ 2 x ULN | ≥20 000 IU/mL and normal ALT |
| Observe. Consider treatment when ALT becomes elevated. Consider liver biopsy if older than 40 years, or if ALT persistently higher than normal. | Consider liver biopsy. Treat if disease is present. |
| **HBeAg (-)** | | |
| HBV DNA | >20 000 IU/mL and ALT ≤ 2 x ULN | ≥2000 IU/mL and normal ALT |
| Observe. Consider liver biopsy. Treat if disease is present. | Consider liver biopsy. Treat if disease is present. |
| **HBeAg (+/-)** | | |
| HBV DNA | ≤20 000 IU/mL | HBV DNA <20 000/2000 IU/mL |
| Observe. Treat if HBV DNA or ALT becomes higher. | Monitor. Treat if evidence of significant histologic disease is present. |

AASLD = American Association for the Study of Liver Disease; ALT = alanine aminotransferase; HBeAg = hepatitis B e antigen; HBV = hepatitis B virus; ULN = upper limit of normal. Adapted from Lok and McMahon2 and Keeffe et al.5
**Duration of Therapy and Treatment Endpoints**

Currently available HBV drugs fall into the category of interferon (IFN) therapy or nucleoside or nucleotide analogs (NA; Table 3). IFNs are usually administered for predefined durations, whereas NAs are continued until specific endpoints are met.\(^2\) In HBeAg (+) patients, viral suppression with current treatment can be sustained in 50% to 90% of HBeAg (+) patients, if treatment ends 6 to 12 months after HBeAg seroconversion is attained.\(^2\) In patients who have HBeAg seroconversion but in whom HBV DNA levels are detectable and stable, treatment should be continued for 6 months, at which point, they should be reassessed for seroconversion and considered for treatment discontinuation if cirrhosis is not present.\(^5\) HBeAg (+) patients who do not lose HBeAg should receive long-term treatment because the possibility of HBeAg seroconversion increases with continuous therapy.

In HBeAg (-) patients, the treatment endpoint is also sustained HBV DNA suppression, but because relapse is frequent after treatment discontinuation, the endpoint for stopping treatment is currently unclear. Thus, before initiating treatment in these patients, it is important to fully balance the benefits and risks of indefinite HBV treatment.

Many of the treatment endpoints outlined in guidelines (eg, HBeAg seroconversion, a significant decrease in HBV DNA load, or normalization of ALT levels) are based on the assumption that CHB is likely to progress to HCC and cirrhosis only in patients with ALT elevation and a detectable viral load, and that treatment can be stopped once a patient achieves an inactive HBV carrier state. Although this logic applies to patients infected in adolescence or adulthood, it may not apply to Asian patients, most of whom are infected early in life. Recent studies have indicated that

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**Table 3. Comparison of Approved Treatments of Chronic Hepatitis B**

<table>
<thead>
<tr>
<th>Indications</th>
<th>IFNα</th>
<th>LAM</th>
<th>ADV</th>
<th>ETV</th>
<th>LdT</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg (+), normal ALT</td>
<td>Not indicated</td>
<td>Not indicated</td>
<td>Not indicated</td>
<td>Not indicated</td>
<td>Not indicated</td>
</tr>
<tr>
<td>HBeAg (+) chronic hepatitis</td>
<td>Indicated (in the absence of cirrhosis)</td>
<td>Not indicated*</td>
<td>Indicated*</td>
<td>Indicated</td>
<td>Indicated*</td>
</tr>
<tr>
<td>HBeAg (-) chronic hepatitis</td>
<td>Indicated (in the absence of cirrhosis)</td>
<td>Indicated*</td>
<td>Indicated</td>
<td>Indicated</td>
<td>Indicated</td>
</tr>
</tbody>
</table>

**Duration of treatment**

| HBeAg (+) chronic hepatitis  | 4–12 mo†                     | ≥1 y‡                        | ≥1 y‡                         | ≥1 y‡                         | ≥1 y‡                         |
| HBeAg (-) chronic hepatitis  | 1 y                          | >1 y                         | >1 y                          | >1 y                          | >1 y                          |

**Route**

| HBeAg (+) chronic hepatitis  | Subcutaneous                 | Oral                         | Oral                          | Oral                          | Oral                          |
| HBeAg (-) chronic hepatitis  |                             | Negligible                   | Potential nephrotoxicity      | Negligible                    | Negligible                    |

**Side effects**

| HBeAg (+) chronic hepatitis  | Many                         | ~20%, y 1                    | None, y 1                     | None, y 1                     | None, y 1                     |
| HBeAg (-) chronic hepatitis  | Subcutaneous                 |                               |                               |                               |                               |

**Drug resistance**

| HBeAg (+) chronic hepatitis  | --                            | ~70%, y 5                    | 29%, y 5                      | No 5-y data                   | No 5-y data                   |
| HBeAg (-) chronic hepatitis  |                               |                              |                               |                               |                               |

**Cost**

| HBeAg (+) chronic hepatitis  | High                          | Low                          | Intermediate                  | High                          | Intermediate                  |
| HBeAg (-) chronic hepatitis  | Subcutaneous                 |                               |                               |                               |                               |

*Not preferred drug due to high rate of resistance.
†PEG-IFN approved for 12 months.
‡Treatment for ≥12 months continuing for 6–12 months after anti-HBe seroconversion.
§Entecavir resistance reported within year 1 in patients with prior LAM resistance.
||Based on treatment duration of 1 year.
ADV = adefovir; ALT = alanine aminotransferase; anti-HBe = antibody to HBeAg; ETV = entecavir; HBeAg = hepatitis B e antigen; LAM = lamivudine; LdT = telbivudine; PEG-IFN = pegylated interferon.
Adapted with permission from Lok and McMahon. Hepatology 2007;45:507-539.
the majority of these patients may have disease progression despite HBeAg seroconversion, hepatitis B surface antigen (HBsAg) clearance, HBV DNA levels lower than 20,000 IU/mL (or even <2000 IU/mL), and ALT levels between 2 and 5 times the ULN. Therefore, HBeAg seroconversion may not be an adequate endpoint for these patients. Instead, the ideal treatment endpoints are permanent suppression of HBV DNA to levels undetectable by polymerase chain reaction (PCR) and reduction of ALT to less than 0.5 times the ULN.

_PATTERNS OF TREATMENT RESPONSE_

Because HBV treatment may result in different outcomes, it is important to understand the patterns of therapeutic responses. A virologic response is defined as a decrease in serum DNA to undetectable levels by PCR assays and loss of HBeAg in patients who were initially HBeAg (+). A biochemical response is characterized by normalization of once elevated ALT levels. An optimal treatment outcome involves a sustained off-therapy response, which can be determined 6 and 12 months after discontinuation of therapy. HBeAg seroconversion is defined as loss of HBeAg and appearance of antibody to HBeAg (anti-HBe).

_TREATMENT STRATEGY_

In choosing which agent to use as first-line therapy, consideration should be given to the safety and efficacy of the treatment, risks of drug resistance, and costs. A comparison of US Food and Drug Administration (FDA)-approved agents for HBV treatment is summarized in Table 3. When treatment is indicated for patients with HBeAg (+) CHB, adefovir, entecavir, or telbivudine are preferred for those with high HBV DNA levels and/or mildly elevated ALT levels because response to IFN therapy is low, and lamivudine is associated with a high rate of resistance. If telbivudine is used, the treatment response should be assessed at 24 weeks of therapy and alternative therapy considered if a virologic response has not been attained. This may apply to all nucleoside analogs, but controlled data to recommend a specific strategy are lacking. Asian patients tend to exhibit lower responses to IFN and lamivudine, because many of these individuals have normal ALT levels at presentation or may have had previous lamivudine exposure. Moreover, IFN rarely results in permanent clearance of HBV in Asian patients, as evidenced by a study showing that 91% of Chinese patients had detectable HBV DNA following IFN treatment, even after HBeAg seroconversion.

In patients with HBeAg (-) CHB, adefovir, entecavir, or tenofovir (not currently approved by the US FDA) are preferred in view of the need for long-term treatment. Patients without cirrhosis may be treated with pegylated interferon (PEG-IFN) in selected cases, and those who fail to achieve sustained HBV DNA clearance may be retreated with NAs. Likewise, patients who fail to achieve a primary response (as evidenced by a <2-log decrease in serum HBV DNA) after at least 6 months of NA therapy should be assessed for alternative treatment or combination therapy. Research evaluating more effective, combined regimens is ongoing but will not be discussed in this article in the interest of focusing more on the general principles of HBV therapy.

_TREATMENT MONITORING_

Regular monitoring during HBV treatment is essential and involves evaluating patient tolerance/adverse effects, drug resistance, and the treatment response. Open discussion and continuous support are important in ensuring patient adherence with HBV treatment. Monitoring for adverse effects is particularly important in those receiving IFN, which may cause flu-like symptoms, depression, blood dyscrasias (ie, neutropenia or thrombocytopenia), and hepatitis flares leading to decompensation in patients with cirrhosis. Because adefovir and, to a lesser extent, tenofovir are rarely associated with renal toxicity, patients receiving these agents should have appropriate renal function tests, especially if they have impaired renal functions before initiating treatment.

In regard to laboratory markers, ALT, HBeAg/anti-HBe, and HBV DNA should be monitored at least every 3 months. After cessation of therapy, ALT and HBV DNA should be monitored monthly for the first 3 months (in patients with cirrhosis and those who remain HBeAg/HBV DNA positive) to 6 months (in responders). In nonresponders, further monitoring is required to recognize a delayed response and plan for retreatment.

_ANTIVIRAL RESISTANCE_

A major concern with long-term NA treatment is the selection of antiviral-resistant HBV mutations, which may be associated with loss of initial virologic response (ie, HBV DNA rebound) followed by
increasing ALT levels. In some cases, antiviral resistance can be associated with severe exacerbations of liver disease. The terms and definitions related to antiviral resistance are well summarized in the literature (Table 4).\textsuperscript{2,5,9} Generally, genotypic resistance is defined as in vitro detection of a mutation that confers NA resistance, whereas phenotypic resistance is in vitro confirmation that the detected mutation decreases susceptibility to a particular NA. The reported rates of antiviral-resistant HBV mutations vary with individual NAs and are summarized in Table 3.\textsuperscript{2,5,9} Judicious use of NAs (eg, regular monitoring and choosing potent agents with low rates of genotypic resistance) is the most effective prophylaxis against development of antiviral-resistant HBV.\textsuperscript{2} Several regimens of “switching” or “adding on” therapy have been reported, and ongoing studies are evaluating more effective strategies.\textsuperscript{2,5,9} Because management of individuals who develop antiviral resistance could be complicated, it is this author’s opinion that these patients be referred to experienced gastroenterologists/hepatologists.

**INDIVIDUAL AGENTS FOR HBV TREATMENT**

This section provides a more detailed discussion of the individual agents that comprise an evidence-based, individualized treatment approach for HBV.

### Table 4. Terms Relating to HBV Antiviral Resistance

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary treatment failure</td>
<td>Inability of NA or nucleoside analogue to reduce serum HBV DNA by ≥1 log(_{10}) after first 6 mo of treatment</td>
</tr>
<tr>
<td>Virologic breakthrough</td>
<td>Increase in serum HBV DNA by &gt;1 log(_{10}) (10-fold) above nadir after achieving virologic response, during continued treatment</td>
</tr>
<tr>
<td>Viral rebound</td>
<td>Increase in serum HBV DNA to &gt;20 000 IU/mL or above pretreatment level after achieving virologic response, during continued treatment</td>
</tr>
<tr>
<td>Biochemical breakthrough</td>
<td>Increase in ALT above ULN after achieving normalization, during continued treatment</td>
</tr>
<tr>
<td>Genotypic resistance</td>
<td>Detection of mutations that have been shown in in vitro studies to confer resistance to the NA that is being administered</td>
</tr>
<tr>
<td>Phenotypic resistance</td>
<td>In vitro confirmation that the mutation detected decreases susceptibility (as demonstrated by increase in inhibitory concentrations) to the NA administered</td>
</tr>
<tr>
<td>Cross-resistance</td>
<td>Decreased susceptibility to &gt;1 antiviral drug conferred by the same amino acid substitution or combination of amino acid substitutions</td>
</tr>
</tbody>
</table>

ALT = alanine aminotransferase; HBV = hepatitis B virus; NA = nucleotide analogue; ULN = upper limit of normal.

**CONVENTIONAL IFNα**

IFNα-2b has been used for over 2 decades in both HBeAg (+) and HBeAg (-) CHB, but its efficacy is limited to highly selected patients. Studies of Asian patients with HBeAg (+) CHB found that response in individuals with normal ALT levels was poor, but response in those with elevated ALT levels was similar to that in Caucasians. Indeed, the strongest predictor of response to IFN is higher pretreatment ALT levels.\textsuperscript{2} Other predictors include lower HBV DNA levels, greater disease activity on biopsy, and specific HBV genotype.\textsuperscript{2} Patients infected with HBV genotypes A and B (prevalent in Asia) respond better to IFN than those with genotypes C (prevalent in Asia) and D.\textsuperscript{10} Infection at birth or in early childhood is a negative predictor of response to IFN.\textsuperscript{3}

**PEG-IFNα-2A**

PEG-IFNα-2a has replaced use of conventional IFN, because it is more convenient to administer (weekly vs daily or thrice-weekly dosing) and has a higher response rate.\textsuperscript{2,11,12} In one Asian study, a 24-week course of weekly PEG-IFN yielded a higher HBeAg seroconversion rate than did conventional IFN, even in patients with a low likelihood of response to IFN.\textsuperscript{11} In 2 trials, a 1-year course of PEG-IFN yielded higher 6-month post-treatment sustained rates of loss of HBsAg, HBeAg, and HBV DNA and higher rates of
improvements in ALT levels and histology than a 1-year course of lamivudine. \(^{13,14}\) Although longer duration of lamivudine treatment is associated with higher treatment response rates, development of lamivudine-resistant strains (YMDD mutation) is a major concern. A higher response rate to PEG-IFN has been reported in patients with HBV genotype A infection. \(^{15}\) Although PEG-IFN treatment requires subcutaneous injection and is associated with a variety of adverse effects, it is not associated with antiviral resistance and is given for a fixed treatment course, which may be beneficial for those who will not, or cannot, undergo a prolonged course of HBV treatment with NAs.

**LAMIVUDINE**

The first NA to become available for CHB, lamivudine has been primarily used as a continuous, long-term therapy and has historically been effective in achieving HBV DNA suppression, ALT normalization, and improvement in liver histology in both HBeAg (+) and HBeAg (-) patients. \(^{4,12}\) HBeAg seroconversion after 1 year of lamivudine therapy is reported to be approximately 17%, a rate that is similar to that of a 16-week course of standard IFN but lower than that of a 1-year course of PEG-IFN. \(^{24}\) In HBeAg (+) patients, higher pretreatment ALT levels are associated with better responses to lamivudine. In general, lamivudine is well tolerated, with adverse events including a mild (2- to 3-fold) increase in ALT levels. \(^{2}\) Asian patients respond similarly to lamivudine as Caucasian patients, but studies from Asia reported lower rates of durability (50%-60%) compared to those seen in non-Asian countries (77%). \(^{2}\) The durability of response appears to be low in patients with genotype C HBV infection, in older patients, and if treatment is continued for less than 4 to 8 months after HBeAg seroconversion. \(^{4}\)

Unfortunately, lamivudine is associated with a high rate of antiviral resistance, affecting 70% of patients after 4 to 5 years of treatment. \(^{16,17}\) Studies suggest that patients with HBV genotype A experience a higher rate of resistance to lamivudine than those with genotype D. \(^{10}\) No difference in the risk of lamivudine resistance is found between patients with HBV genotypes B and C. \(^{10}\) Because newer therapies with lower risks of resistance are currently available, lamivudine is no longer a preferred first-line drug for HBV treatment. \(^{25}\)

A switch to alternative treatment or combination treatment should be considered in patients who have received lamivudine for more than 2 years and who need ongoing treatment. \(^{2}\)

**ADEFOVIR DIPIVOXIL**

Adefovir is associated with a relatively modest decrease in HBV DNA levels compared to entecavir, telbivudine, or tenofovir. Seroconversion rates for adefovir after 12 months of treatment are marginally lower than other nucleoside analogs. HBeAg (+) patients with high pretreatment ALT levels are more likely to undergo HBeAg seroconversion. \(^{2}\) Higher pretreatment HBV DNA levels, adefovir resistance, and the agent’s modest antiviral activity may be predispositions to nonresponse. \(^{12}\) Higher doses have greater potency but are associated with a high rate of renal toxicity, which has been reported in compensated patients receiving long-term therapy (4–5 years), transplant recipients, and in those with decompensated cirrhosis. \(^{2}\)

The main advantage of adefovir is related to its lower rate of antiviral resistance (compared to lamivudine and telbivudine), rendering it a viable option for lamivudine-resistant HBV. \(^{12}\) The agent has been shown to result in significant improvements in at least 50% of patients with lamivudine resistance. Conversely, adefovir-resistant strains are susceptible to lamivudine, which may be used as rescue therapy in adefovir-resistant patients. \(^{17}\) Adefovir is associated with a high rate of durability, as shown in one study in which 92% of patients maintained seroconversion after 80 weeks of treatment. \(^{2}\) Adefovir has similar efficacy in Asian versus Caucasian patients and across all HBV genotypes. \(^{4,10}\) Tenofovir, which is currently under investigation, with a higher potency and similar resistance pattern, may replace adefovir in the future if preliminary observations are confirmed in larger trials, especially in those with lamivudine-resistant strains.

**ENTECAVIR**

This agent has been shown to be more potent than lamivudine, telbivudine, and adefovir and to have high rates of HBV DNA suppression. \(^{2,12}\) Rates of HBeAg clearance at 1 year were somewhat similar to those of lamivudine, telbivudine, and adefovir. Preliminary reports in patients receiving entecavir for 2 years indicate maintained suppression of HBV DNA to undetectable levels in more than 85% of patients with both HBeAg (+) and HBeAg (-) disease. \(^{12}\) Antiviral resistance to entecavir occurred in less than 1% of NA-
 naïve patients after 1- and 2-year courses of therapy. However, resistance is significantly higher in those who had previous lamivudine exposure. Cumulative resistance rates of 14% and 32% at 2 years and 3 years have been reported in lamivudine-resistant strains. Although entecavir resistance and only modest response rates were reported among patients with pre-existing lamivudine resistance, a recent study of patients with lamivudine-refractory CHB found that switching to entecavir provided superior histologic improvement, viral load reduction, and ALT normalization compared with continuing lamivudine.

Nevertheless, entecavir is not the treatment of choice for patients with lamivudine resistance. Patients with lamivudine resistance should be considered for treatment with adefovir or tenofovir as monotherapy, or preferably in combination with lamivudine. Entecavir-resistant strains of HBV appear to be sensitive to adefovir or tenofovir. Entecavir appears to have similar efficacy in Asian and Caucasian patients, across HBV genotypes, and in a wide range of pretreatment HBV DNA levels. HBeAg seroconversion rates tend to be higher in patients with increased pretreatment ALT levels. Entecavir's adverse effect profile is similar to that of lamivudine and commonly includes headache, fatigue, dizziness, and nausea.

**TELBIVUDINE**

A potent NA, telbivudine has been shown to be more effective in suppressing HBV replication than lamivudine. In one large trial of HBeAg (+) patients, telbivudine produced a 60% rate of HBV DNA loss, compared with a 40% rate associated with lamivudine. In HBeAg (-) patients, HBV DNA loss was seen in 88% of patients treated with telbivudine compared to 71% of those given lamivudine. Telbivudine may have lower rates of resistance compared with lamivudine (17.8% vs 30.1% at 2 years in HBeAg [+] patients, and 7.3% vs 16.6% in HBeAg [-] patients), but the agent is still associated with higher rates of resistance compared to other therapies and exhibits cross-resistance with lamivudine.

Because undetectable HBV DNA at 24 weeks of treatment is associated with a significantly lower rate of telbivudine resistance, it is important to monitor treatment response in patients given telbivudine, or any other NAs for that matter. Those who show suboptimal response rates at week 24 may be considered for alternate treatments or combination treatment. However, the optimal use of combination treatment has not been established in controlled trials.

**TENOFOVIR DISOPROXIL FUMARATE AND EMTRICITABINE**

Tenofovir, an NA, is more potent than adefovir and is effective against lamivudine-resistant HBV strains. Tenofovir is currently not approved by the US FDA for treatment of HBV. In one study with a 48-week follow-up, all 35 patients treated with 300 mg of tenofovir daily were HBV DNA negative, compared with 44% of those treated with 10 mg of adefovir daily. Data on tenofovir's resistance profile are limited; additional clinical trials are ongoing. Tenofovir may be used as an off-label rescue therapy in patients with lamivudine resistance who have had an inadequate response to adefovir. Emtricitabine is structurally similar to lamivudine and therefore, is similar to lamivudine in efficacy and pattern of resistance. A combination product containing tenofovir and emtricitabine is approved for HIV infection and is being tested for HBV treatment.

**SPECIAL POPULATIONS**

**PREGNANCY**

Interferon is contraindicated during pregnancy, and entecavir and adefovir are classified as pregnancy category C. Although lamivudine, telbivudine, emtricitabine, and tenofovir are classified as pregnancy category B, there are no clinical trials evaluating safety and efficacy of these NAs in pregnant patients with CHB in the United States. However, in China studies have reported on the safety and potential benefits of lamivudine in the prevention of mother-child transmission of HBV in late pregnancy. In the United States, lamivudine is routinely recommended for HIV-infected women during pregnancy, and therefore, may be used as an off-label agent in HBV-infected pregnant women if the potential benefit of treatment during pregnancy outweighs potential risks to the mother or fetus.

**HIV/HBV COINFECTION**

Many of the agents (lamivudine, tenofovir, and emtricitabine) used to treat HIV have activity against HBV. Patients with lamivudine resistance, which is frequent in patients with HIV/HBV coinfection who have been treated for prolonged periods, may be switched to tenofovir. A combination of tenofovir and
Entecitabine is approved for HIV and is being considered as optimal therapy for patients with HIV/HBV coinfection. In recent reports, entecitabine was shown to promote selection of antiviral-resistant mutations of HIV and therefore, should not be used in patients coinfected with HIV who are not receiving highly active antiretroviral therapy. Clinicians should also be aware that treatment of HIV may lead to more severe hepatitis with immune restitution.

If patients with HIV/HBV coinfection are considered for HBV treatment alone (for those who do not need HIV treatment), it is important to select a drug with no activity against HIV to reduce antiviral-resistant mutation of HIV. Adefovir (10 mg) or telbivudine are potential agents in these situations.

**Decompensated Patients**

Interferon is contraindicated in patients with decompensated liver disease due to potentially life-threatening adverse events, but NAs may be safely and effectively used in patients with advanced HBV-related cirrhosis. In one study from Asia, long-term lamivudine therapy was associated with improved survival and lower rates of HCC in patients with HBV and cirrhosis or advanced liver disease. The demonstrated benefits, which were most pronounced among patients who maintained a virologic response and did not develop lamivudine resistance, suggest that patients with advanced fibrosis and cirrhosis and high levels of HBV DNA should receive NA treatment. Because the majority of these patients require lifelong treatment, drugs with the lowest resistance rates are preferred. Despite the absence of any controlled trials, many experts prefer combination treatment (drugs with different resistance profiles) for patients with decompensated cirrhosis. It is preferable to refer these patients for treatment to hepatologists with experience in treating complex patients with HBV.

**Liver Transplantation for CHB Infection**

Recurrent HBV infection can be prevented in most patients after liver transplantation with use of high doses of hepatitis B immune globulin in combination with NAs. Although uncommon, breakthrough HBV infections may occur and are usually related to development of resistance to the antiviral agents used to prevent re-infection. Combination NA therapy is considered potentially beneficial in certain posttransplant patients, but the combination should be chosen based on previous exposure and patterns of resistance. Additional studies are needed to optimize HBV treatment regimens in this special population.

**Conclusions**

In the past decade, significant advances have been made in the management of CHB infection. The availability of PEG-IFN and several NAs has equipped clinicians with sufficient options to individualize HBV treatment strategies and optimize treatment response based on considerations of factors relating to the host, virus, and drug therapy.

**References**


