Choosing an Initial HBV Treatment Regimen

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Module 2: Treatment of HBV
Lesson 2: Choosing an Initial HBV Treatment Regimen

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Background

In the United States, the Food and Drug Administration (FDA) has approved a total of eight medications to treat chronic hepatitis B virus (HBV) infection (Figure 1). These medications are broadly classified as either immunomodulatory agents (interferon and peginterferon) or antiviral agents (nucleoside and nucleotide analogues).[1,2,3] A number of factors should be weighed when choosing an agent for initial treatment of an individual with chronic HBV infection: safety and efficacy of the treatment, risk of developing drug resistance, duration of treatment, cost of therapy, and additional factors, such as liver disease severity or pregnancy. Treatment decisions will also need to take individual preferences into account. This discussion will review considerations when deciding between using an oral antiviral versus peginterferon and when choosing among the variety of available oral antiviral options for initial HBV therapy.

Oral Antiviral Therapy Options for HBV

Currently, a total of six oral antiviral medications have been approved by the FDA for the treatment of chronic HBV, including three nucleoside analogues (entecavir, lamivudine, and telbivudine) and three nucleotide analogues (adefovir, tenofovir alafenamide, and tenofovir DF) (Table 1).[4] Telbivudine is no longer manufactured in the United States.[5] Lamivudine and adefovir are rarely used due to low potency and low genetic barrier to resistance. Emtricitabine—a nucleoside analogue used to treat HIV—is the seventh oral antiviral agent that has activity against HBV but is not currently FDA-approved for HBV treatment. The nucleoside and nucleotide analogues inhibit the RNA-dependent DNA polymerase reverse transcriptase; specifically, they inhibit reverse transcription of pregenomic HBV RNA to HBV DNA.[4] These agents, however, do not block formation of HBV covalently closed circular DNA (ccc DNA) and therefore are limited in their ability to eradicate HBV DNA and provide a functional cure.[6,7] Details on individual drug efficacy and safety are provided in the HBV Medication Section. The major factors that are considered in choosing among the oral antiviral agents are potency, barrier to drug resistance, long-term impact on liver disease, side effects, and food requirements.

- **Antiviral Potency**: Antiviral potency is considered low for adefovir, intermediate for lamivudine, and high for entecavir, tenofovir alafenamide, and tenofovir DF.[4,8] Available data have shown that 68 to 90% of persons with chronic hepatitis B who are treated with entecavir, tenofovir alafenamide, or tenofovir DF will achieve undetectable plasma HBV DNA levels after 48 weeks of therapy.[4,9,10,11,12] For persons with high HBV viral levels, neither adefovir nor lamivudine would be an ideal choice compared with the newer agents, primarily because of their lower potency.
- **Genetic Barrier to Resistance**: The necessity of long-term and potentially indefinite duration of therapy with oral antivirals makes the issue of drug resistance a key consideration when treating HBV with oral antiviral medications. The ease with which resistance emerges depends on the intrinsic molecular properties of the drug as well as the number of mutations needed to reduce susceptibility of the drug.[13] The rates of HBV resistance observed over time vary considerably with the different oral antiviral agents (Figure 2).[14] Lamivudine and adefovir are no longer recommended as initial therapy because of the significant risk of developing drug resistance, with 5-year cumulative resistance rates of 70% with lamivudine and 29% with adefovir.[14,15] In treatment-naïve adults, entecavir therapy has been associated with 5-year resistance rates of less than 1.2%, but these rates are markedly higher in persons who have preexisting resistance to lamivudine.[16,17] After 8 years of therapy with tenofovir DF in treatment-naïve adults with chronic hepatitis B, resistance has not been observed.[18,19] Although long-term resistance data are not available with tenofovir alafenamide, no substitutions associated with resistance were detected during a 96-week clinical trial.[20]
- **Impact on Liver Disease and Liver-Related Complications**: Overall, oral antivirals have been shown to reduce the risk of cirrhosis, decompensated liver disease, and hepatocellular carcinoma.[3,21,22,23] Entecavir and tenofovir DF are also favored as first-line therapy because the long-term use of these agents has been shown to reduce the risk of HCC and to improve liver dysfunction, necroinflammation, and fibrosis.[24] Sustained HBV suppression with tenofovir DF has been shown to slow liver disease progression, resulting in marked histologic improvement of necroinflammation and fibrosis with regression of baseline cirrhosis in up to 50% of individuals after 5 years.[23] Similarly, entecavir has been shown to lower the risk of hepatocellular carcinoma.[21] Eight-year survival rates in persons with chronic HBV treated with either entecavir or tenofovir DF are excellent and have been shown to approach those in the general population.[22,25]
- **Relative Efficacy of First-line Oral Antiviral Agents**: There are no formal prospective studies comparing the efficacy and safety of oral tenofovir DF, tenofovir alafenamide, and entecavir. There are, however, manufacturer-sponsored phase 3 trials that compared tenofovir alafenamide 25 mg once daily with tenofovir DF 300 mg once daily in both HBeAg-positive and HBeAg-negative participants.[26,27] Combined analysis of these two studies after 96 weeks of treatment showed that among HBeAg-positive participants receiving tenofovir alafenamide or tenofovir DF, there were no differences in rates of viral suppression (73% and 75%, respectively), HBeAg loss (22% versus 18%), or HBsAg loss (1% in each group); among HBsAg-negative participants, there were also no differences

in rates of viral suppression between tenofovir alafenamide and tenofovir DF (90% and 91%, respectively) or HBsAg loss (less than 1% in each group) (Figure 3).[10] With long-term use, there may be some advantages in terms of renal or bone safety that would favor tenofovir alafenamide over tenofovir DF.[10]

- **Impact on Bone Density**: Reduction in bone mineral density has been reported in persons receiving tenofovir DF for HBV therapy and in those receiving tenofovir-DF as a component of antiretroviral therapy for treatment of HIV.[28] At 48 weeks, tenofovir alafenamide was associated with less decline in hip and spine bone mineral density as compared with tenofovir DF, although the magnitude of these changes and the differences were small and of unclear clinical significance.[26,27,29] Entecavir does not have any known adverse impact on bone mineral density.
- **Nephrotoxicity**: Tenofovir DF has been associated with kidney injury in the form of a proximal tubulopathy and, in severe cases, a Fanconi-like syndrome characterized by metabolic acidosis, hypophosphatemia and glucosuria.[30] Nephrotoxicity in any form appears to occur at a very low rate in the treatment of chronic HBV.[31,32,33] In the main registration trials of tenofovir alafenamide versus tenofovir DF in HBeAg-positive and HBeAg-negative patients, after 96 weeks of treatment, tenofovir alafenamide was associated with less decline in estimated glomerular filtration rate (eGFR) than tenofovir DF.[8,10] More clinical data are emerging on improvements in eGFR in patients who switch from tenofovir DF to tenofovir alafenamide.[34] For persons receiving tenofovir DF, renal safety assessment before and periodically during treatment with tenofovir DF is recommended, with serum creatinine, serum phosphate, and urinalysis (including urine glucose and protein measurements). Entecavir does not have any known nephrotoxity.

Peginterferon-Based Therapy for HBV

The alpha interferons have both antiviral and immunomodulatory properties against HBV. It is the immune-enhancing activity of interferon-based therapies that is thought to confer a possible “serologic” advantage over oral nucleoside and nucleotide analogues.[35] When accompanied by HBV viral suppression, HBeAg loss and anti-HBeAg seroconversion represent immune-mediated control of HBV by the host. This immune-control or “inactive disease” phase is an important milestone in chronic HBV infection and is associated with a greater likelihood of eventual HBsAg clearance, a major goal of HBV therapy.[36] Sustained clearance of HBeAg with standard interferon has also been shown to be associated with reduced incidence of cirrhosis, decreased risk for hepatocellular carcinoma, and improved survival.[37,38,39,40] The ultimate advantage of interferon therapy is the potential for a functional cure, as defined by sustained loss of HBsAg and undetectable HBV DNA levels off of therapy, which is rarely achieved with oral antiviral therapy. The challenge, however, is identifying which patients would most likely respond to interferon, since responses can be quite heterogeneous and the toxicities of interferon can be significant.

- **FDA Approved Interferon-Based Treatments**: For the treatment of chronic HBV infection, the United States FDA has approved two interferon-based regimens: interferon alfa-2b and peginterferon alfa-2a. If an interferon preparation is used to treat chronic HBV, expert guidelines and clinicians clearly favor peginterferon alfa-2a over interferon alfa-2b.[5,14] Peginterferon is better tolerated than standard interferon, and the weekly injection of peginterferon is more convenient than the multiple injections per week required with standard interferon. In addition, several studies have shown that peginterferon is more effective than standard interferon with respect to serologic and virologic outcomes with treatment of HBV.[41,42]
- **Recommended Dosage**: The recommended adult dosage of peginterferon alfa-2a is 180 µg subcutaneously (in the thigh or abdomen) once weekly for 48 weeks.
- **Virologic Response**: A virologic response on interferon-based therapy is defined as a serum HBV DNA level less than 2,000 IU/mL, with this evaluation usually occurring at 6 months into treatment (week 24) and at the completion of treatment (week 48).[14] A sustained virologic response is usually defined as maintaining a serum HBV DNA level less than 2,000 IU/mL for at least 12 months after completing interferon-based therapy.[14]
- **Serologic Response for HBeAg**: The clearance of HBeAg with development of HBeAg seroconversion (loss of HBeAg and development of anti-HBe) occurs in approximately 20 to 30% of HBeAg-positive individuals 6 months after receiving 48 weeks of peginterferon-based treatment.[5,43,44] Among those who achieve HBeAg seroconversion, 81% maintain this response over a 3-year period.[45] Peginterferon may also have a role in treatment of HBeAg-negative individuals. One randomized controlled trial evaluated responses 6 months after completion of therapy and demonstrated that patients who received 48 weeks of peginterferon alfa-2a (with or without lamivudine) were more likely than lamivudine recipients to have normal alanine aminotransferase (ALT) values (59% versus 44%) and to have virologic responses as indicated by an HBV DNA level less than 20,000 copies/mL (43% versus 29%).[46] In a long-term follow-up study of these patients, 12% achieved HBsAg clearance 5 years post-treatment.[47]
- **Serologic Response for HBsAg**: The clearance of HBsAg, with or without anti-HBs seroconversion (loss of HBsAg combined with development of anti-HBs)is the ultimate serologic achievement in therapy and the closest to a clinical cure obtainable with current HBV therapies. The loss of HBsAg appears to occur earlier in persons treated with standard interferon or peginterferon than with oral antiviral agents, although there are inadequate comparative data. In studies involving peginterferon treatment, at 6 months after completion of therapy, HBsAg seroconversion occurred in 3 to 5% of HBeAg-positive patients and in 3% of HBeAg-negative patients treated with peginterferon six months after treatment with long-term follow-up studies reporting rates as high as 12% (HBeAg-negative) and 30% (HBeAg-positive) among initial responders.[36,43,44,46,47,48] In contrast, the HBsAg clearance rates with oral antivirals are typically very low (1 to 2%), but can increase marginally over time.[49]
- **Predictors of Response**: Treatment response with interferon therapy can vary significantly depending on patient-specific baseline characteristics. Elevated serum ALT, lower HBV DNA levels,

female gender, and younger age have all been linked with a favorable treatment response.[43,50,51] White adults also appear more likely to respond to interferon than Asian adults.[12] One of the strongest predictors of response with interferon remains HBV genotype. Patients with HBV genotype A or B are significantly more likely to clear HBeAg and HBsAg with peginterferon than genotypes C or D.[52] The cost-effectiveness and impact of peginterferon can also be maximized by applying early on-treatment stopping rules that have been shown to predict treatment nonresponse or low probability of HBeAg seroconversion and that permit early cessation of therapy.[53] At 12 weeks of treatment, a lack of significant decline in HBV DNA level (less than 2 log10 IU/mL decrease) and quantitative hepatitis B surface antigen have been associated with a greater likelihood of poor treatment response and can be used to discontinue therapy early in selected patients.[54]

- **Adverse Effects and Contraindications**: Interferon-based therapy is complicated by a number of potential adverse effects, including flu-like symptoms, myelosuppression, and psychiatric disturbances (Table 2).[4,5] Although interferon-based therapy has been used safely in patients with compensated cirrhosis, it is contraindicated in patients with decompensated cirrhosis (Child-Turcotte-Pugh class B or C) because of the risk of hepatic decompensation with immune-mediated hepatitis flares.[55,56,57] Autoimmune hepatitis (and other autoimmune conditions), severe psychiatric comorbidity (e.g., depression with suicidal ideation), poorly controlled seizure disorder, and severe cardiopulmonary conditions are other important contraindications to treatment with peginterferon or standard interferon. These medications are also not advised for use in pregnancy unless the benefits justify the potential risk to the fetus (pregnancy category C). In addition, it should be noted that interferon products must be refrigerated, which can be a barrier for persons living homeless.

Choosing Oral Antivirals versus Peginterferon

A primary decision point when choosing an initial therapy in a patient with chronic hepatitis B is whether to use an oral antiviral agent (nucleoside or nucleotide analogue) or an interferon-based agent (standard interferon or peginterferon).[5,14] When an interferon-based agent is used, peginterferon is clearly preferred over interferon, primarily due to more convenient dosing, improved efficacy, and better tolerance.[2,5,14] Thus, the following discussion will focus on comparing oral antivirals with peginterferon.

- **Comparative Features**: The main favorable features of oral antiviral therapy are excellent tolerability, dependable responses, and convenient once-daily oral administration. In addition, oral antivirals can be used safely in a wide range of patients, including those with decompensated liver disease, pre- and post-liver transplantation, and for the management of HBV-related extrahepatic manifestations.[58] The main drawbacks of oral antiviral therapy are the need for prolonged therapy (typically for many years and often continued indefinitely) and the potential for development of HBV drug resistance, although drug resistance rarely occurs with current recommended first-line oral HBV agents. Favorable features of peginterferon therapy are a finite duration of therapy (48 to 52 weeks), a potential for durable serologic and virologic responses after stopping treatment, and lack of drug resistance.[5,14] The main negative features of peginterferon are the potential side effects (e.g., fever, malaise, depression, hypothyroidism, and hematologic abnormalities) and the need to administer as a weekly subcutaneous injection.[1] In addition, peginterferon should not be used to treat HBV in persons with decompensated cirrhosis or women at any stage of pregnancy. The availability of safe, well-tolerated, highly potent oral antivirals that have a high genetic barrier to drug resistance, when taken together with the key disadvantages of peginterferon, have made oral antivirals the preferred treatment for most individuals with chronic HBV infection.
- **Comparative Data**: The oral antivirals have similar efficacy as peginterferon after 48 to 52 weeks of therapy (with respect to a variety of surrogate end points) for persons positive for hepatitis B e Ag (HBeAg) (Table 3) and those negative for HBeAg (Table 4).[14] Long-term follow-up studies have shown that sustained treatment with oral antiviral therapy in persons with chronic HBV markedly reduces the risk of developing cirrhosis, decompensated liver disease, and hepatocellular carcinoma (HCC).[1,3,21,22,23] There are studies that suggest interferon or peginterferon treatment for chronic HBV can reduce the risk of HCC and improve survival, but these data are less robust than for oral antivirals.[39,44,59]

Recommendations for Initial HBV Therapy

Preferred Initial HBV Therapy

When initiating treatment for chronic HBV, the recommended approach, in most circumstances, is to use a potent oral antiviral that has a high genetic barrier to resistance, typically with long-term administration of the medication.[14,60] Three oral antivirals are currently recommended as a preferred option for initial therapy: entecavir, tenofovir alafenamide, or tenofovir DF (Table 5).[14] For most individuals undergoing treatment for chronic HBV, any one of these three agents can be used. Some special situations, as outlined below, may favor one of these agents over another. Combination therapy, including use of two oral antivirals or one antiviral plus peginterferon, is not recommended for initial treatment, except for patients with HIV and HBV coinfection where dual oral antiviral therapy is indicated by virtue of concurrent treatment of HIV.

Initial HBV Therapy in Special Circumstances and Populations

There are specific clinical situations that should guide the choice of a specific oral agent (entecavir, tenofovir alafenamide, or tenofovir DF) over the other(s) for initial treatment of HBV. The following discussion briefly summarizes some unique situations and populations in which the standard treatment recommendation is modified. In addition, situations are highlighted where interferon-based therapy is preferred (coinfection with hepatitis D virus and HBV) or contraindicated (decompensated liver disease, extrahepatic manifestations, and pregnancy). The following does not include extensive information on each of these special populations and circumstances, but additional information about these topics can be found in the 2018 AASLD Hepatitis B Guidance) and the 2017 EASL Hepatitis B Guidelines.[5,14]

- **Bone Disease**: For individuals with osteoporosis, a history of fragility fracture, or taking any medication that worsens bone density, such as corticosteroids, the use of entecavir or tenofovir alafenamide is generally preferred over tenofovir DF.[5,14]

- **Decompensated Liver Disease**: If an individual has decompensated liver disease, they should be promptly referred to a hepatologist for management and for evaluation of liver transplantation.[5,14] For these patients, treatment with an oral antiviral should be promptly started, with entecavir, tenofovir alafenamide, or tenofovir DF all considered as reasonable treatment options, with the caveat that there are limited clinical data and experience with the use of tenofovir alafenamide in this population. Note that guidelines recommend using the higher dose of entecavir (1.0 mg once daily) in patients with decompensated liver disease.[5] In patients with decompensated liver disease, all interferon-based therapies should be avoided.

- **Extrahepatic Manifestations**: Persons with HBV infection can develop an array of extrahepatic manifestations, including vasculitis, polyarteritis nodosa, arthralgias, peripheral neuropathy, and glomerulonephritis. Since most HBV-related extrahepatic manifestations are immune mediated, the use of interferon-based therapy is not recommended since it may worsen the extrahepatic manifestation.[5,14] Therefore, when treating HBV in a person who has extrahepatic manifestations, entecavir, tenofovir alafenamide, or tenofovir DF should be used.[14] If the extrahepatic manifestations have resulted in renal disease, then additional considerations are warranted when choosing among these three preferred oral antivirals, as discussed below (Renal Disease).[14]

- **Hepatitis D Virus (HDV) Coinfection**: For individuals who have HDV and HBV coinfection, peginterferon alfa-2a for 48 to 52 weeks is recommended to treat HDV for those with elevated HDV RNA levels.[5,14] Peginterferon alfa-2a, however, should not be used in persons with decompensated liver disease. For those with HDV and HBV coinfection who also have elevated HBV DNA levels, then either entecavir, tenofovir alafenamide, or tenofovir DF should be added as concurrent therapy with peginterferon alfa-2a.[5]

- **HIV Coinfection**: Treatment of HBV in persons with HIV also needs to ensure concurrent full treatment of HIV (Table 6).[14,61] For persons with HIV and HBV coinfection, tenofovir alafenamide or tenofovir DF is preferred over entecavir as the main HBV antiviral, largely due to the full antiviral activity that both of these tenofovir preparations have against both HBV and HIV.[14] The recommended regimen in persons with HIV and HBV coinfection consists of (1) a backbone of tenofovir alafenamide or tenofovir DF used in conjunction with lamivudine or emtricitabine and (2) a highly-potent HIV anchor drug, typically an integrase strand transfer inhibitor.[5,61] Some individuals with HIV and HBV coinfection may have previously received lamivudine or emtricitabine, without tenofovir alafenamide or tenofovir DF, as part of HIV antiretroviral therapy, which would have resulted in monotherapy for HBV with possible development of HBV lamivudine resistance. The use of entecavir would not be advised in these individuals since it shares the same resistance mutation pathway as lamivudine; resistance to entecavir requires the prior selection of the M204V/I and L180M mutations, which are both signature lamivudine resistance-associated substitutions.[62]

- **Preexposure Prophylaxis**: For persons with chronic HBV who are at risk of acquiring HIV, preexposure prophylaxis (PrEP) to prevent HIV infection may be indicated. If HIV PrEP is initiated with either of the FDA-approved medications for PrEP (tenofovir DF-emtricitabine or tenofovir alafenamide-emtricitabine), then concomitant treatment of HBV would occur.[63] In this situation, if an individual were to stop or intermittently take the HIV PrEP medications, it could have a negative impact on HBV, including potential hepatic flares or the development of HBV drug resistance. Accordingly, it is important to test for chronic HBV in all persons initiating HIV PrEP. In addition, consultation with an expert may be indicated when persons with chronic HBV are initiating or receiving HIV PrEP.

- **Pregnancy**: If HBV therapy is indicated during pregnancy, tenofovir DF has been the preferred medication, largely due to its known track record for safety in pregnancy (in women with HIV as well as HBV).[5,14,64] For pregnant women not on therapy for HBV, with no other indication for starting other than prevention of perinatal transmission, initiation of HBV therapy with tenofovir DF is indicated in the third trimester if the HBV DNA level is greater than 200,000 IU/mL. Although lamivudine, telbivudine, and tenofovir DF have all been shown to significantly reduce perinatal HBV transmission, tenofovir DF is preferred given its comparatively greater potency, lower risk of treatment-emergent drug resistance, efficacy data, and extensive track record for safety in pregnancy.[5,65] Entecavir has not been adequately studied in pregnancy. Tenofovir alafenamide was found to be safe and effective in a prospective observational study in pregnancy, but data for use during pregnancy with tenofovir alafenamide are limited compared with tenofovir DF.[66] All interferon-based therapies for HBV should be avoided during pregnancy. If a woman is receiving interferon-based therapy and becomes pregnant, the regimen should be discontinued and, if possible, start tenofovir DF promptly to avoid a hepatitis flare.

- **Renal Disease**: The AASLD recommends renal safety assessment before and periodically during the administration of tenofovir DF, with serum creatinine, serum phosphate, and urinalysis (including urine glucose and protein measurements).[5] For persons with baseline renal disease, entecavir or tenofovir alafenamide is recommended over tenofovir DF.[5,14] Renal disease here includes any of the following: reduced renal glomerular filtration rate (creatinine clearance less than 60 mL/min/1.73m^2), albuminuria (greater than 30 mg per 24 hours or moderate on dipstick), low serum phosphate, or receipt of long-term chronic hemodialysis.[5,14] The dose of entecavir needs to be adjusted and reduced with eGFR less than 50 mL/min. The dose of tenofovir alafenamide in adults or adolescents (aged at least 12 years and of at least 35 kg body weight) does not need to be adjusted if the estimated creatinine clearance is greater than 15 mL/min or in persons with end-stage renal disease who are receiving hemodialysis. For persons with an estimated creatinine less than 15 mL/min who are not receiving hemodialysis, tenofovir alafenamide should not be used, given limited data on safety in this subgroup. Note that the creatinine clearance cutoff for tenofovir alafenamide is different than the cutoff for the combination pill tenofovir alafenamide–emtricitabine (used for HIV PrEP and HBV treatment), which should not be used in patients with a creatinine clearance less than 30mL/min.

Summary Points

- Treatment options for chronic HBV include the use of oral antivirals (nucleoside and nucleotide analogues) or interferon-based regimens.
- Oral antivirals (nucleoside and nucleotide analogues) have advantages over interferon-based therapy that include ease of administration, dependable antiviral responses, markedly fewer side effects, and ability to use in a wide range of patients, including those with decompensated liver disease.
- Peginterferon alfa-2a has several specific advantages over nucleoside and nucleotide analogues for hepatitis B treatment: fixed duration of therapy, potential for durable serologic and virologic responses off therapy, and no risk of drug resistance. Factors associated with greater likelihood of response to interferon-based therapy are elevated serum ALT, lower HBV DNA level and favorable HBV genotype.
- Subcutaneous injection, high variability in treatment response and potential for serious adverse effects are among the reasons peginterferon alfa-2a is less favored compared with oral antiviral therapy.
- Tenofovir DF, tenofovir alafenamide, and entecavir are the preferred oral antiviral medications for initial oral therapy for chronic HBV. These are the preferred oral antiviral agents due to their greater potency and higher genetic barrier for resistance compared with other oral antiviral agents.
- Specific patient characteristics and circumstances may dictate the use of one of the first-line oral antiviral medications over the others, including bone disease, decompensated liver disease, extrahepatic manifestations, hepatitis D virus (HDV) coinfection, HIV coinfection, receipt of HIV PrEP, pregnancy, and renal disease.
- It is important to avoid using any interferon-based treatment to treat HBV in persons with decompensated liver disease, pregnant women, and those with HBV-related extrahepatic manifestations.

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Figures

Figure 1 Agents Approved by the U.S. FDA for the Treatment of Hepatitis B Virus (HBV) Infection

This graphic shows the timeline of FDA approval in the United States for agents used to treat chronic HBV infection.

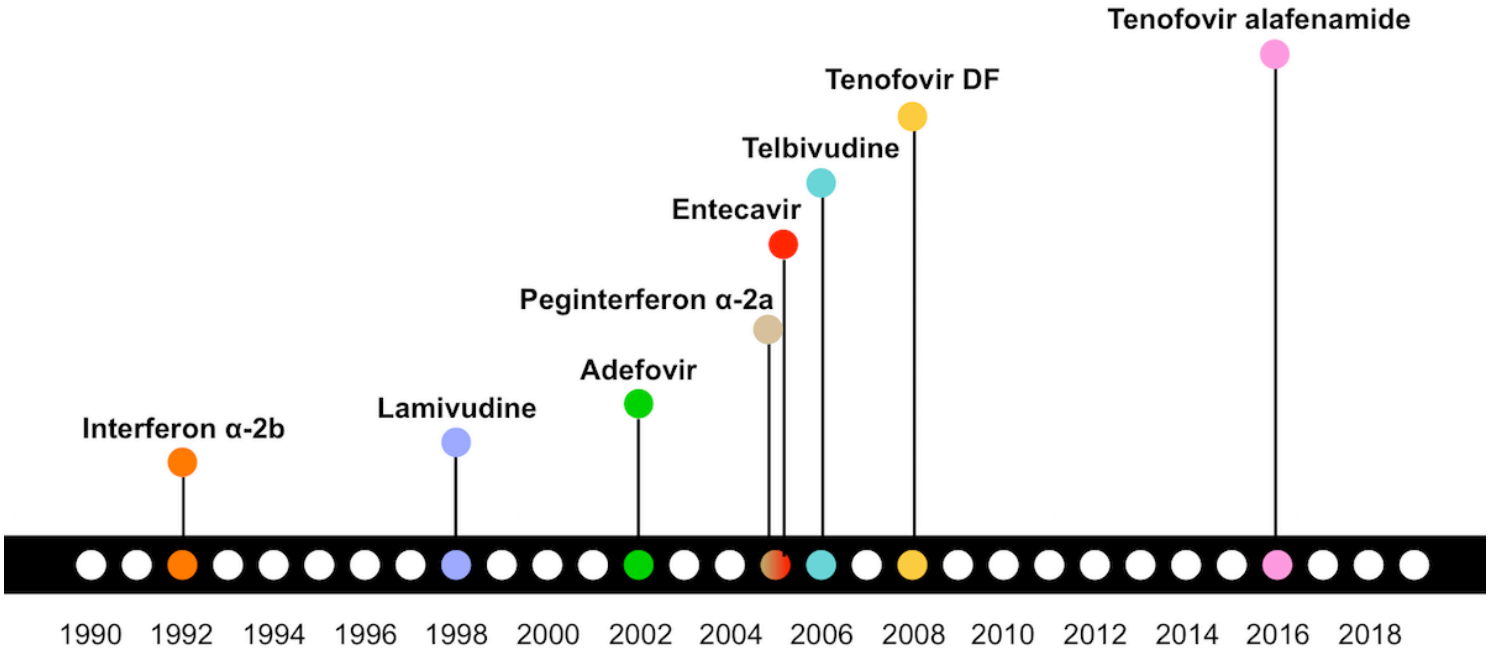

Figure 2 Cumulative Incidence of HBV Resistance with Oral Antiviral Agents

Abbreviations: tenofovir DF = tenofovir disoproxil fumarate; tenofovir AF = tenofovir alafenamide

Source: European Association For The Study Of The Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67:370-98. Reproduced with permission from Journal of Hepatology [https://www.journal-of-hepatology.eu]

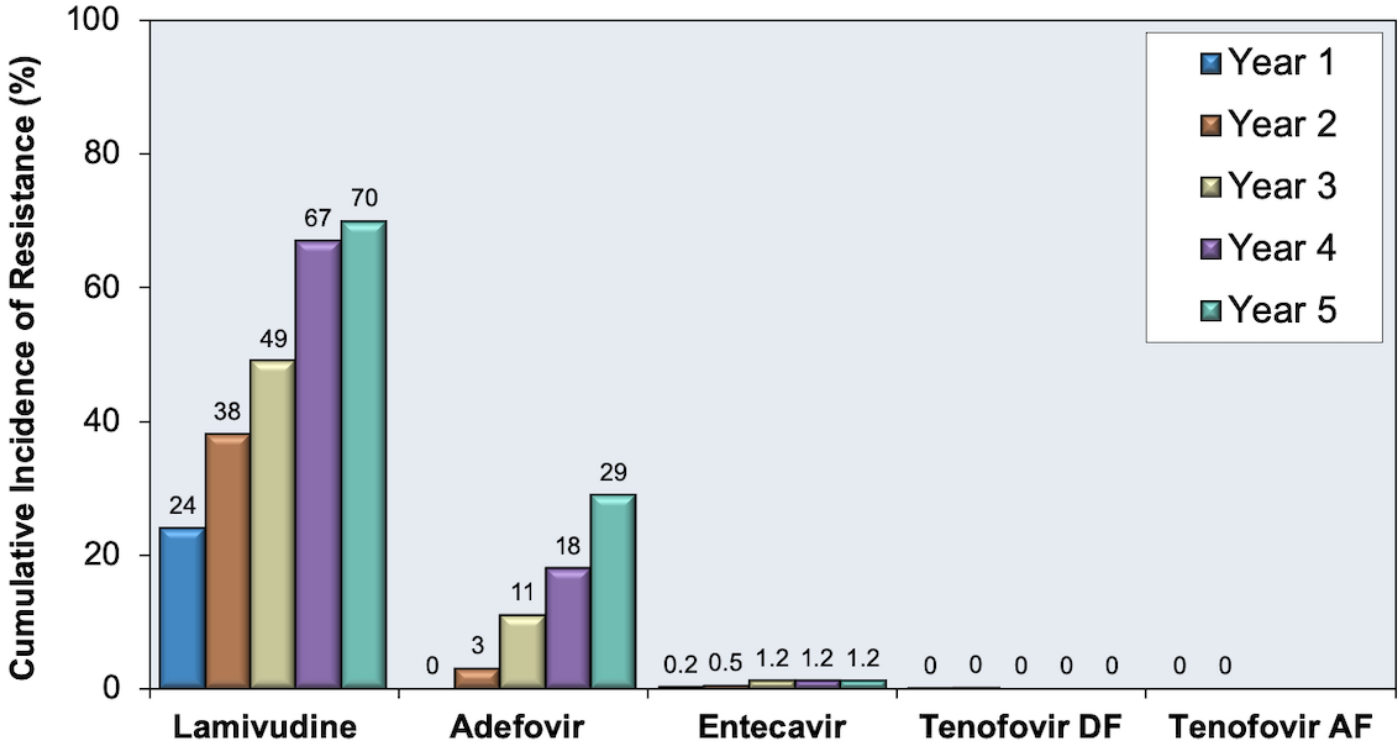

Figure 3 Tenofovir alafenamide versus Tenofovir DF for HBeAg-Positive and Negative Persons: Viral Suppression at Week 96

Source: Agarwal K, Brunetto M, Seto WK, et al. 96 weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. J Hepatol. 2018;68:672-81.

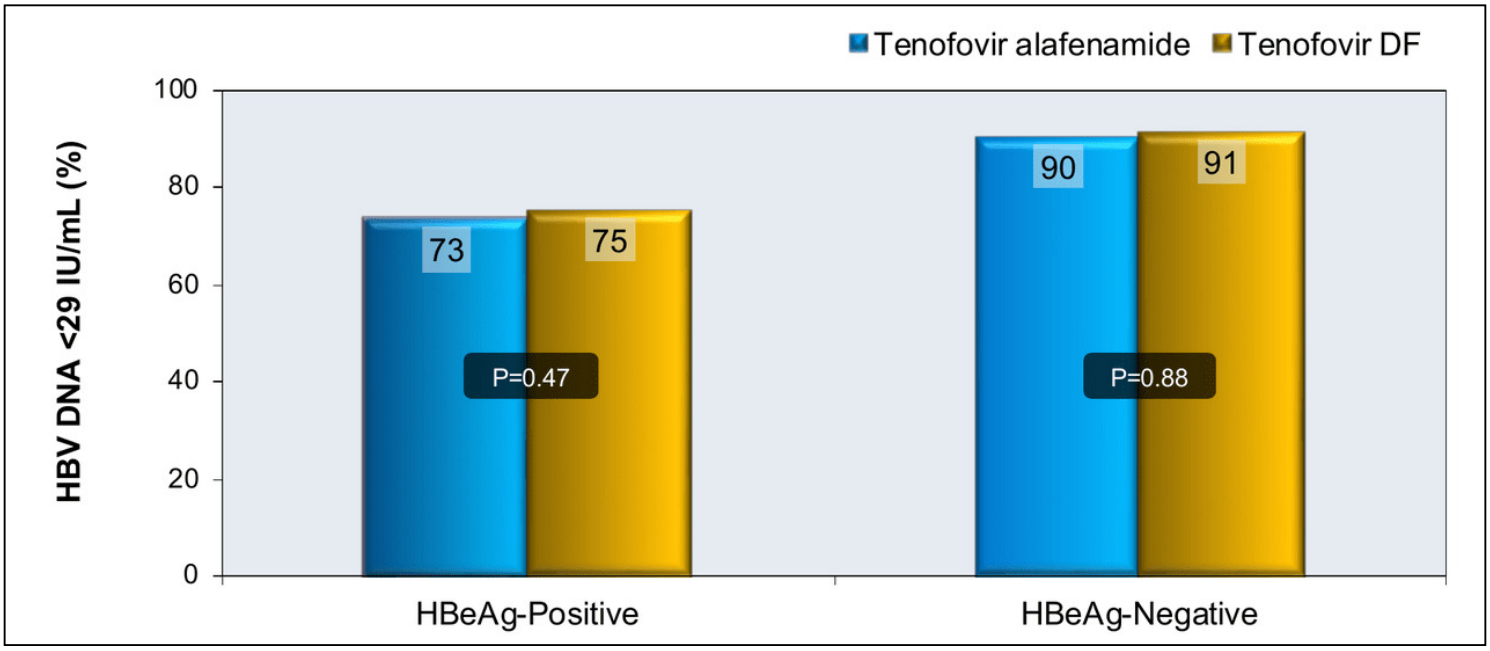

Table 1.

Key Characteristics of Oral Antiviral Agents Used to Treat HBV*

Medications	Trade Name	Category	Oral Dosing (Adults)	Potency	Barrier to Resistance
Adefovir	*Hepsera*	Nucleotide analogue	10 mg once daily	Low	Moderate
Entecavir	*Baraclude*	Nucleoside analogue	0.5 mg once daily^	High	High
Lamivudine	*Epivir-HB*	Nucleoside analogue	100 mg once daily	Moderate	Low
Tenofovir alafenamide	*Vemlidy*	Nucleotide analogue	25 mg once daily	High	High
Tenofovir DF	*Viread*	Nucleotide analogue	300 mg once daily	High	High

*Telbivudine is not included as it is no longer manufactured in the United States
^Increase entecavir to 1.0 mg once daily in persons with: a history of 1) hepatitis B viremia while receiving lamivudine, 2) known lamivudine or telbivudine resistance substitutions rtM204I/V (with or without rtL180M, rtL80I/V, or rtV173L, or 3)decompensated cirrhosis.

Table 2.

Peginterferon-Related Adverse Effects

Category	Adverse Effect
Systemic	• Fever • Myalgias/Arthralgias • Fatigue
Mood	• Depression • Irritability • Insomnia
Hematologic	• Neutropenia • Anemia • Thrombocytopenia
Endocrine	• Hypothyroidism • Hyperthyroidism
Dermatologic	• Rash • Dry skin • Pruritus • Thinning of hair
Gastrointestinal	• Anorexia • Nausea • Weight loss

Table 3. **EASL 2017 Clinical Practice Guidelines on the Management of HBV Infection**

Treatment Responses Among Treatment-Naïve Persons with HBeAg-Positive Chronic HBV*

	Peginterferon[#]	Nucleoside Analogues[^]		
Therapeutic Endpoints	Peginterferon alfa-2a	Lamivudine	Entecavir	Adefovir
Dose	180 µg SQ once weekly	100 mg PO daily	0.5 mg PO daily	10 mg PO d
Anti-HBe-Seroconversion	32%	16-18%	21%	12-18%
HBV DNA <60-80 IU/mL	14%	36-44%	67%	13-21%
ALT Normalization	41%	41-72%	68%	48-54%
HBsAg Loss	3%	0-1%	2%	0%

Abbreviations: EASL = European Association for the Study of the Liver; Tenofovir DF = tenofovir disoproxil fumarate subcutaneous; PO = per os (oral) ALT = alanine aminotransferase
*Treatment responses shown at 6 months following 48 or 52 weeks of peginterferon therapy and at 48 or 52 weeks therapy.
[#]Peginterferon alfa-2b is not shown in this modified version of the original table since it is not FDA-approved for the
[^]The nucleoside analogue telbivudine is not shown in this modified version of the original table
[$]In the original table, a formulation of tenofovir (tenofovir disoproxil Mylan) is listed and the dose of this medication
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Source:

- European Association For The Study Of The Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67:370-98. [PubMed Abstract]

Table 4. **EASL 2017 Clinical Practice Guidelines on the Management of HBV Infection**

Treatment Responses Among Treatment-Naïve Persons with HBeAg-Negative Chronic HBV*

	Peginterferon[#]	Nucleoside Analogues[^]		
Therapeutic Endpoints	Peginterferon alfa-2a	Lamivudine	Entecavir	Adefovir
Dose	180 µg SQ once weekly	100 mg PO daily	0.5 mg PO daily	10 mg PO da
HBV DNA <60-80 IU/mL	19%	72-73%	90%	51-63%
ALT Normalization	59%	71-79%	78%	72-77%
HBsAg Loss	4%	0%	0%	0%

Abbreviations: EASL = European Association for the Study of the Liver; Tenofovir DF = tenofovir disoproxil fumarate alanine aminotransferase
*Treatment responses shown at 6 months following 48 weeks of peginterferon therapy and at 48 or 52 weeks of nuc therapy.
[#]Peginterferon alfa-2b is not shown in this modified version of the original table since it is not FDA-approved for the
[^]The nucleoside analogue telbivudine is not shown in this modified version of the original table
[$]In the original table, a formulation of tenofovir (tenofovir disoproxil Mylan) is listed and the dose of this medication

Source:

- European Association For The Study Of The Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67:370-98. [PubMed Abstract]

Table 5.

Key Characteristics of Preferred Oral Antiviral Agents to Treat Chronic Hepatitis B Infection*

Medications	Entecavir	Tenofovir alafenamide	Te
Trade Name	*Baraclude*	*Vemlidy*	*Vi*
Adult Dose (oral)	0.5 mg once daily^	25 mg once daily	30
Food Requirement	Empty stomach	With food	W
Hepatic Impairment	The recommended dose with decompensated liver disease is 1 mg once daily	Not recommended in patients with decompensated (Child-Pugh B or C) hepatic impairment	N do pa im
Renal Impairment	Dose adjust when CrCl <50 mL/min: • 30-49 mL/min: 0.5 mg every 48 hours, *OR* 0.25 mg once daily • 10-29 mL/min: 0.5 mg every 72 hours, *OR* 0.15 mg once daily • < 10 mL/min: 0.5 mg every 7 days, *OR* 0.05 mg once daily • HD or CAPD: 0.5 mg every 7 days, *OR* 0.05 mg once daily	No dose adjustment for CrCl ≥15 mL/min • <15 mL/min and NOT on HD: not recommended for use • HD: 25 mg after completion of each dialysis	A ≤

Abbreviations: CrCl = creatinine clearance; HD = hemodialysis; CAPD = chronic ambulatory peritoneal dialysis

^Increase entecavir to 1.0 mg once daily in persons with: a history of 1) hepatitis B viremia while receiving lamivudi or telbivudine resistance substitutions rtM204I/V (with or without rtL180M, rtL80I/V, or rtV173L, or 3) decompensate

Table 6.

Key Characteristics of Oral Antiviral Agents Used to Treat HBV and/or HIV*

	Hepatitis B Virus		
Medication	Potency Against HBV	Barrier to HBV Resistance	Po
Adefovir	Low	Moderate	
Entecavir	High	High	
Lamivudine	Moderate	Low	
Tenofovir alafenamide	High	High	
Tenofovir DF	High	High	
*Telbivudine is not included as it is no longer manufactured in the United States			