

Choosing an Initial HBV Treatment Regimen

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Module 1:

[Hepatitis B Online](#)

Lesson 6:

[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 antiviral agents (nucleoside and nucleotide analogues) or immunomodulatory agents (interferon and peginterferon).[\[1,2,3\]](#) Several 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, treatment duration, 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 emphasize considerations when choosing among 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] Among these, tenofovir alafenamide, tenofovir DF, and entecavir are considered first-line therapy. 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 the formation of HBV covalently closed circular DNA (ccc DNA) and therefore are limited in their ability to eradicate HBV DNA.^[6,7] Details on individual drug efficacy and safety are provided in the [HBV Medication Section](#).

Factors Considered in Choosing Initial Treatment Regimen

The factors considered in choosing among the oral antiviral agents include potency, barrier to drug resistance, long-term impact on liver disease, side effects, cost, 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 drug susceptibility.^[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] Resistance has not been observed after 8 years of therapy with tenofovir DF in treatment-naïve adults with chronic hepatitis B.^[18,19,20] Although long-term resistance data are not available for tenofovir alafenamide, no substitutions associated with resistance were detected during a 96-week clinical trial.^[21]
- **Impact on Liver Disease and Liver-Related Complications:** Overall, oral antivirals have been shown to reduce the risk of cirrhosis, decompensated liver disease, hepatocellular carcinoma (HCC), liver transplantation, and death.^[3,22,23,24,25] Entecavir, tenofovir DF, and tenofovir alafenamide are 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.^[26] 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.^[24] Similarly, entecavir has been shown to lower the risk of hepatocellular carcinoma.^[22] 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.^[23,27]
- **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.[28,29] 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] Outcomes out to 5 years for this cohort also did not demonstrate differences in viral suppression.[30,31] With long-term use, there may be some advantages related to renal or bone safety that would favor tenofovir alafenamide over tenofovir DF.[10,30] In patients with HIV and HBV coinfection, tenofovir alafenamide might offer superior HBV virologic efficacy compared to tenofovir DF based on results of the ALLIANCE trial, but these results have yet to be replicated.[32]

- **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.[33] Tenofovir alafenamide is associated with less decline in hip and spine bone mineral density than tenofovir DF, but the magnitude of these changes and the differences were small and of unclear clinical significance.[28,29,30,31,34] Entecavir has no known adverse impact on bone mineral density.
- **Nephrotoxicity:** Tenofovir DF has been associated with kidney injury in the form of proximal tubulopathy and, in severe cases, a Fanconi-like syndrome characterized by metabolic acidosis, hypophosphatemia, and glucosuria.[35] Nephrotoxicity is uncommon in those without existing renal disease, with clinically significant renal impairment occurring at a low rate (1–4% over several years) in the treatment of chronic HBV, with likely greater risk in those with risk factors, such as older age, diabetes, and hypertension.[36,37,38,39] 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.[40] 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 nephrotoxicity but must be renally dosed in patients with preexisting renal insufficiency.

Peginterferon-Based Therapy for HBV

The alpha interferons have both antiviral and immunomodulatory properties against HBV. The immune-enhancing activity of interferon-based therapies is thought to confer a possible “serologic” advantage over oral nucleoside and nucleotide analogues.[41] 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.[42] Sustained clearance of HBeAg with standard interferon has also been associated with reduced incidence of cirrhosis, decreased risk for hepatocellular carcinoma, and improved survival.[43,44,45,46] 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 favor peginterferon alfa-2a over interferon alfa-2b.[5,47] 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 in the treatment of HBV.[48,49]
- **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).[47] 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.[47]
- **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.[5,50,51] Among those who achieve HBeAg seroconversion, 81% maintain this response over a 3-year period.[52] 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%).[53] In a long-term follow-up study of these patients, 12% achieved HBsAg clearance 5 years post-treatment.[54]
- **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 reported rates as high as 12% (HBeAg-negative patients) and 30% (HBeAg-positive patients) among initial responders.[42,50,51,53,54,55]
- **Predictors of Response:** Treatment response with interferon-based therapy can vary significantly depending on patient-specific baseline characteristics. Elevated serum ALT, lower HBV DNA levels, female sex, and younger age have all been linked with a favorable treatment response.[50,56,57] 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.[58] 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.[59] At 12 weeks of treatment, a lack of significant decline in HBV DNA level (less than 2 log₁₀ IU/mL decrease) and quantitative HBsAg has been associated with a greater likelihood of poor treatment response and can be used as an indicator to discontinue therapy early in selected patients.[60]

- **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 score greater than 6) because of the risk of hepatic decompensation with immune-mediated hepatitis flares.[61,62,63] Autoimmune hepatitis (and other autoimmune conditions), severe psychiatric comorbidity (e.g., depression with suicidal ideation), poorly controlled seizure disorder, bone marrow suppression, and cardiopulmonary conditions are other important contraindications, since treatment may exacerbate these conditions. The use of interferon-based therapy is also not advised for use in pregnancy. Further, it should be noted that interferon products must be refrigerated, which can be a barrier for some persons.

Recommendations for Initial HBV Therapy

Choice Between Oral Therapy Versus Peginterferon

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.[64] The main drawbacks of promptly 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 the lack of drug resistance.[5,47] 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 it 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.

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.[47,65] Three oral antivirals are currently recommended as a preferred option for initial therapy: entecavir, tenofovir alafenamide, or tenofovir DF (Table 3).[47] 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 the 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 for the 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) 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, the 2025 AASLD/IDSA HBV Treatment Guideline, and the 2025 EASL Hepatitis B Guidelines.[5,14,66]

- **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.[5,47]
- **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.[5,47] 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 extrahepatic manifestations.[5,47] Therefore, when treating HBV in a person who has extrahepatic manifestations, entecavir, tenofovir alafenamide, or tenofovir DF should be used.[47] 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).[47]
- 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.[5,47] 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 4).[47,67] 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.[47] The recommended regimen in persons with HIV and HBV coinfection consists of: (1) a backbone of tenofovir alafenamide or tenofovir DF used in combination with lamivudine or emtricitabine and (2) a highly potent HIV anchor drug, typically an integrase strand transfer inhibitor.[5,67] 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.
- Prior Lamivudine Exposure:** The use of entecavir would not be advised in individuals with confirmed lamivudine resistance since entecavir 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.[68]. For patients with lamivudine experience without confirmed resistance, either formulation of tenofovir would be preferred, but if entecavir is to be used, a higher daily dose of 1 mg is recommended.[14,69]
- HIV 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 oral tenofovir DF-emtricitabine or tenofovir alafenamide-emtricitabine, then concomitant treatment of HBV would occur.[70] 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. It is important to note that long-acting injectable medications used for HIV PrEP, including intramuscular cabotegravir and subcutaneous lenacapavir, do not have any HBV activity.
- Pregnancy:** When HBV therapy is indicated during pregnancy, tenofovir DF has historically been the preferred medication, largely due to its known track record for safety in pregnancy (in women with HIV as well as HBV).[5,47,71] Although experience using tenofovir alafenamide during pregnancy is not as robust as that of tenofovir DF, there is ample evidence that tenofovir alafenamide is safe during pregnancy, and it is now listed as a preferred drug for the treatment of HIV during pregnancy.[66,72,73] 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 or tenofovir alafenamide is indicated starting at 28 weeks' gestation if the HBV DNA level is greater than 200,000 IU/mL at any time during the pregnancy.[66] Entecavir has not been adequately studied in

pregnancy and is not recommended. All interferon-based therapies for HBV should be avoided during pregnancy. If a woman is receiving entecavir or interferon-based therapy and becomes pregnant, the regimen should be discontinued and, if possible, tenofovir DF or tenofovir alafenamide should be started 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.[\[5,47\]](#) Renal disease here includes any of the following: reduced estimated renal glomerular filtration rate (eGFR less than 60 mL/min/1.73m²), albuminuria (greater than 30 mg per 24 hours or moderate on dipstick), low serum phosphate, or receipt of long-term chronic hemodialysis.[\[5,47\]](#) The dose of entecavir needs to be adjusted and reduced with a creatinine clearance of 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 creatinine clearance is greater than 15 mL/min or in persons with end-stage renal disease who are receiving hemodialysis. Tenofovir alafenamide should not be used in persons with a creatinine clearance of less than 15 mL/min who are not receiving hemodialysis. Note the GFR cutoff for tenofovir alafenamide is different from the cutoff for the combination pill tenofovir alafenamide–emtricitabine (used for HIV PrEP and HBV treatment), which should not be used in persons with a creatinine clearance of 15-29 mL/min or less than 15 mL/min and not receiving hemodialysis.

Summary Points

- Treatment options for chronic HBV include the use of oral antivirals (nucleoside and nucleotide analogues) or peginterferon-alfa 2a-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 the 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 a 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.

Citations

1. Yuen MF, Chen DS, Dusheiko GM, et al. Hepatitis B virus infection. Nat Rev Dis Primers. 2018;4:18035. [\[PubMed Abstract\]](#) -
2. Yuen MF, Ahn SH, Chen DS, et al. Chronic Hepatitis B Virus Infection: Disease Revisit and Management Recommendations. J Clin Gastroenterol. 2016;50:286-94. [\[PubMed Abstract\]](#) -
3. Lok AS, McMahon BJ, Brown RS Jr, et al. Antiviral therapy for chronic hepatitis B viral infection in adults: A systematic review and meta-analysis. Hepatology. 2016;63:284-306. [\[PubMed Abstract\]](#) -
4. Tang LSY, Covert E, Wilson E, Kottlilil S. Chronic Hepatitis B Infection: A Review. JAMA. 2018;319:1802-13. [\[PubMed Abstract\]](#) -
5. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67:1560-99. [\[PubMed Abstract\]](#) -
6. Likhitsup A, Lok AS. Understanding the Natural History of Hepatitis B Virus Infection and the New Definitions of Cure and the Endpoints of Clinical Trials. Clin Liver Dis. 2019;23:401-16. [\[PubMed Abstract\]](#) -
7. Nassal M. HBV cccDNA: viral persistence reservoir and key obstacle for a cure of chronic hepatitis B. Gut. 2015;64:1972-84. [\[PubMed Abstract\]](#) -
8. Seto WK, Lo YR, Pawlotsky JM, Yuen MF. Chronic hepatitis B virus infection. Lancet. 2018;392:2313-24. [\[PubMed Abstract\]](#) -
9. Ahn J, Lee HM, Lim JK, et al. Entecavir safety and effectiveness in a national cohort of treatment-naïve chronic hepatitis B patients in the US - the ENUMERATE study. Aliment Pharmacol Ther. 2016;43:134-44. [\[PubMed Abstract\]](#) -
10. 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. [\[PubMed Abstract\]](#) -
11. Chang TT, Gish RG, de Man R, et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. N Engl J Med. 2006;354:1001-10. [\[PubMed Abstract\]](#) -
12. Marcellin P, Heathcote EJ, Buti M, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. N Engl J Med. 2008;359:2442-55. [\[PubMed Abstract\]](#) -
13. Yuen MF, Fung J, Wong DK, Lai CL. Prevention and management of drug resistance for antihepatitis B treatment. Lancet Infect Dis. 2009;9:256-64. [\[PubMed Abstract\]](#) -

14. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol*. 2025;S0168-8278(25)00174-6.
[\[PubMed Abstract\]](#) -
15. Lai CL, Dienstag J, Schiff E, et al. Prevalence and clinical correlates of YMDD variants during lamivudine therapy for patients with chronic hepatitis B. *Clin Infect Dis*. 2003;36:687-96.
[\[PubMed Abstract\]](#) -
16. Tenney DJ, Rose RE, Baldick CJ, et al. Long-term monitoring shows hepatitis B virus resistance to entecavir in nucleoside-naïve patients is rare through 5 years of therapy. *Hepatology*. 2009;49:1503-14.
[\[PubMed Abstract\]](#) -
17. Tenney DJ, Rose RE, Baldick CJ, et al. Two-year assessment of entecavir resistance in Lamivudine-refractory hepatitis B virus patients reveals different clinical outcomes depending on the resistance substitutions present. *Antimicrob Agents Chemother*. 2006;51:902-11.
[\[PubMed Abstract\]](#) -
18. Liu Y, Corsa AC, Buti M, et al. No detectable resistance to tenofovir disoproxil fumarate in HBeAg+ and HBeAg- patients with chronic hepatitis B after 8 years of treatment. *J Viral Hepat*. 2017;24:68-74.
[\[PubMed Abstract\]](#) -
19. Buti M, Tsai N, Petersen J, et al. Seven-year efficacy and safety of treatment with tenofovir disoproxil fumarate for chronic hepatitis B virus infection. *Dig Dis Sci*. 2015;60:1457-64.
[\[PubMed Abstract\]](#) -
20. Lumley SF, Delphin M, Mokaya JF, et al. A systematic review and meta-analysis of the risk of hepatitis B virus (HBV) resistance in people treated with entecavir or tenofovir. *J Clin Virol*. 2024;174:105711.
[\[PubMed Abstract\]](#) -
21. Cathcart AL, Chan HL, Bhardwaj N, et al. No Resistance to Tenofovir Alafenamide Detected through 96 Weeks of Treatment in Patients with Chronic Hepatitis B Infection. *Antimicrob Agents Chemother*. 2018;62(10).pii: e01064-18
[\[PubMed Abstract\]](#) -
22. Ahn J, Lim JK, Lee HM, et al. Lower Observed Hepatocellular Carcinoma Incidence in Chronic Hepatitis B Patients Treated With Entecavir: Results of the ENUMERATE Study. *Am J Gastroenterol*. 2016;111:1297-304.
[\[PubMed Abstract\]](#) -
23. Chang TT, Liaw YF, Wu SS, et al. Long-term entecavir therapy results in the reversal of fibrosis/cirrhosis and continued histological improvement in patients with chronic hepatitis B. *Hepatology*. 2010;52:886-93.
[\[PubMed Abstract\]](#) -
24. Marcellin P, Gane E, Buti M, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. *Lancet*. 2013;381:468-75.
[\[PubMed Abstract\]](#) -
25. Lam L, Bourlière M, Pol S, Carrat F. Impact of Nucleos(t)ide Analogs on Major Clinical Outcomes in Patients With Chronic Hepatitis B: A 10-Year French Nationwide Cohort Study. *Aliment Pharmacol Ther*. 2025;61:865-75.
[\[PubMed Abstract\]](#) -

26. Papatheodoridis GV, Chan HL, Hansen BE, Janssen HL, Lampertico P. Risk of hepatocellular carcinoma in chronic hepatitis B: assessment and modification with current antiviral therapy. *J Hepatol.* 2015;62:956-67.
[\[PubMed Abstract\]](#) -
27. Papatheodoridis GV, Sypsa V, Dalekos G, et al. Eight-year survival in chronic hepatitis B patients under long-term entecavir or tenofovir therapy is similar to the general population. *J Hepatol.* 2018;68:1129-36.
[\[PubMed Abstract\]](#) -
28. Buti M, Gane E, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of patients with HBeAg-negative chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Gastroenterol Hepatol.* 2016;1:196-206.
[\[PubMed Abstract\]](#) -
29. Chan HL, Fung S, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Gastroenterol Hepatol.* 2016;1:185-95.
[\[PubMed Abstract\]](#) -
30. Chan HLY, Buti M, Lim YS, et al. Long-Term Treatment With Tenofovir Alafenamide for Chronic Hepatitis B Results in High Rates of Viral Suppression and Favorable Renal and Bone Safety. *Am J Gastroenterol.* 2024;119:486-96.
[\[PubMed Abstract\]](#) -
31. Buti M, Lim YS, Chan HLY, et al. Eight-year efficacy and safety of tenofovir alafenamide for treatment of chronic hepatitis B virus infection: Final results from two randomised phase 3 trials. *Aliment Pharmacol Ther.* 2024;60:1573-86.
[\[PubMed Abstract\]](#) -
32. Avihingsanon A, Lu H, Leong CL, et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 and hepatitis B coinfection (ALLIANCE): a double-blind, multicentre, randomised controlled, phase 3 non-inferiority trial. *Lancet HIV.* 2023;10:e640-e652.
[\[PubMed Abstract\]](#) -
33. Mateo L, Holgado S, Mariñoso ML, et al. Hypophosphatemic osteomalacia induced by tenofovir in HIV-infected patients. *Clin Rheumatol.* 2016;35:1271-9.
[\[PubMed Abstract\]](#) -
34. Gupta SK, Post FA, Arribas JR, et al. Renal safety of tenofovir alafenamide vs. tenofovir disoproxil fumarate: a pooled analysis of 26 clinical trials. *AIDS.* 2019;33:1455-65.
[\[PubMed Abstract\]](#) -
35. Cooper RD, Wiebe N, Smith N, Keiser P, Naicker S, Tonelli M. Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-infected patients. *Clin Infect Dis.* 2010;51:496-505.
[\[PubMed Abstract\]](#) -
36. Cho YY, Chang Y, Nam JY, et al. Long-term Nucleotide Analogue Treatment Has Higher Levels of Renal Toxicities than Does Entecavir in Patients with Chronic Hepatitis B. *Gut Liver.* 2020;14:225-31.
[\[PubMed Abstract\]](#) -
37. Marcellin P, Wong DK, Sievert W, et al. Ten-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B virus infection. *Liver Int.* 2019;39:1868-75.

[\[PubMed Abstract\]](#) -

38. Wong GL, Chan HL, Tse YK, et al. Chronic kidney disease progression in patients with chronic hepatitis B on tenofovir, entecavir, or no treatment. *Aliment Pharmacol Ther.* 2018;48:984-92.
[\[PubMed Abstract\]](#) -
39. Tsai HJ, Chuang YW, Yang SS, Chang YZ, Chang HR, Lee TY. Evaluating the renal safety of tenofovir disoproxil fumarate in hepatitis B patients without chronic kidney disease. *J Viral Hepat.* 2021;28:1579-86.
[\[PubMed Abstract\]](#) -
40. Toyoda H, Leong J, Landis C, et al. Treatment and Renal Outcomes Up to 96 Weeks After Tenofovir Alafenamide Switch From Tenofovir Disoproxil Fumarate in Routine Practice. *Hepatology.* 2021;74:656-66.
[\[PubMed Abstract\]](#) -
41. Kao JH. HBeAg-positive chronic hepatitis B: why do I treat my patients with pegylated interferon? *Liver Int.* 2014;34 Suppl 1:112-9.
[\[PubMed Abstract\]](#) -
42. Buster EH, Flink HJ, Simsek H, et al. Early HBeAg loss during peginterferon alpha-2b therapy predicts HBsAg loss: results of a long-term follow-up study in chronic hepatitis B patients. *Am J Gastroenterol.* 2009;104:2449-57.
[\[PubMed Abstract\]](#) -
43. Lau DT, Everhart J, Kleiner DE, et al. Long-term follow-up of patients with chronic hepatitis B treated with interferon alfa. *Gastroenterology.* 1997;113:1660-7.
[\[PubMed Abstract\]](#) -
44. Lin SM, Sheen IS, Chien RN, Chu CM, Liaw YF. Long-term beneficial effect of interferon therapy in patients with chronic hepatitis B virus infection. *Hepatology.* 1999;29:971-5.
[\[PubMed Abstract\]](#) -
45. Niederau C, Heintges T, Lange S, et al. Long-term follow-up of HBeAg-positive patients treated with interferon alfa for chronic hepatitis B. *N Engl J Med.* 1996;334:1422-7.
[\[PubMed Abstract\]](#) -
46. van Zonneveld M, Honkoop P, Hansen BE, et al. Long-term follow-up of alpha-interferon treatment of patients with chronic hepatitis B. *Hepatology.* 2004;39:804-10.
[\[PubMed Abstract\]](#) -
47. 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.
[\[PubMed Abstract\]](#) -
48. Cooksley WG, Piratvisuth T, Lee SD, et al. Peginterferon alpha-2a (40 kDa): an advance in the treatment of hepatitis B e antigen-positive chronic hepatitis B. *J Viral Hepat.* 2003;10:298-305.
[\[PubMed Abstract\]](#) -
49. Zhao H, Si CW, Wei L, et al. A multicenter, randomized, open-label study of the safety and effectiveness of pegylated interferon alpha 2b and interferon alpha 2b in treating HBeAg positive chronic hepatitis B patients. 2006;14:323-6.
[\[PubMed Abstract\]](#) -

50. Janssen HL, van Zonneveld M, Senturk H, et al. Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomised trial. *Lancet*. 2005;365:123-9. [[PubMed Abstract](#)] -
51. Lau GK, Piratvisuth T, Luo KX, et al. Peginterferon Alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. *N Engl J Med*. 2005;352:2682-95. [[PubMed Abstract](#)] -
52. Buster EH, Flink HJ, Cakaloglu Y, et al. Sustained HBeAg and HBsAg loss after long-term follow-up of HBeAg-positive patients treated with peginterferon alpha-2b. *Gastroenterology*. 2008;135:459-67. [[PubMed Abstract](#)] -
53. Marcellin P, Lau GK, Bonino F, et al. Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. *N Engl J Med*. 2004;351:1206-17. [[PubMed Abstract](#)] -
54. Marcellin P, Bonino F, Yurdaydin C, et al. Hepatitis B surface antigen levels: association with 5-year response to peginterferon alfa-2a in hepatitis B e-antigen-negative patients. *Hepatology*. 2013;7:88-97. [[PubMed Abstract](#)] -
55. Marcellin P, Piratvisuth T, Brunetto M, et al. Increasing rates of HBsAg clearance and seroconversion in patients with HBeAg-Negative disease treated with peginterferon ALFA-2A ± Lamivudine: Results of 5-year post-treatment follow up. *J Hepatol* 2009;50:S336. [[Google Scholar](#)] -
56. Bonino F, Marcellin P, Lau GK, et al. Predicting response to peginterferon alpha-2a, lamivudine and the two combined for HBeAg-negative chronic hepatitis B. *Gut*. 2007;56:699-705. [[PubMed Abstract](#)] -
57. Craxì A, Di Bona D, Cammà C. Interferon-alpha for HBeAg-positive chronic hepatitis B. *J Hepatol*. 2003;39 Suppl 1:S99-105. [[PubMed Abstract](#)] -
58. Flink HJ, van Zonneveld M, Hansen BE, de Man RA, Schalm SW, Janssen HL. Treatment with Peginterferon alpha-2b for HBeAg-positive chronic hepatitis B: HBsAg loss is associated with HBV genotype. *Am J Gastroenterol*. 2006;101:297-303. [[PubMed Abstract](#)] -
59. Pavlovic V, Yang L, Chan HL, et al. Peginterferon alfa-2a (40 kD) stopping rules in chronic hepatitis B: a systematic review and meta-analysis of individual participant data. *Antivir Ther*. 2019;24:133-40. [[PubMed Abstract](#)] -
60. Cornberg M, Wong VW, Locarnini S, Brunetto M, Janssen HLA, Chan HL. The role of quantitative hepatitis B surface antigen revisited. *J Hepatol*. 2017;66:398-411. [[PubMed Abstract](#)] -
61. Buster EH, Hansen BE, Buti M, et al. Peginterferon alpha-2b is safe and effective in HBeAg-positive chronic hepatitis B patients with advanced fibrosis. *Hepatology*. 2007;46:388-94. [[PubMed Abstract](#)] -
62. Flink HJ, Sprengers D, Hansen BE, et al. Flares in chronic hepatitis B patients induced by the host or the virus? Relation to treatment response during Peg-interferon {alpha}-2b therapy. *Gut*. 2005;54:1604-9.

[[PubMed Abstract](#)] -

63. Janssen HL, Brouwer JT, Nevens F, Sanchez-Tapias JM, Craxi A, Hadziyannis S. Fatal hepatic decompensation associated with interferon alfa. European concerted action on viral hepatitis (Eurohep). *BMJ*. 1993;306:107-8.
[[PubMed Abstract](#)] -
64. Buti M, Riveiro-Barciela M, Esteban R. Long-term safety and efficacy of nucleo(t)side analogue therapy in hepatitis B. *Liver Int*. 2018;38 Suppl 1:84-9.
[[PubMed Abstract](#)] -
65. Tang AS, Thornton K, and HBV Primary Care Workgroup. Hepatitis B Management: Guidance for the Primary Care Provider. February 25, 2020.
[[HBV Primary Care Workgroup](#)] -
66. Ghany MG, Pan CQ, Lok AS, et al. AASLD/IDSA Practice Guideline on treatment of chronic hepatitis B. *Hepatology*. 2025 Nov 4. Online ahead of print.
[[PubMed Abstract](#)] -
67. Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Hepatitis B virus infection. Last Updated: December 16, 2024.
[[HIV.gov](#)] -
68. Baldick CJ, Tenney DJ, Mazzucco CE, et al. Comprehensive evaluation of hepatitis B virus reverse transcriptase substitutions associated with entecavir resistance. *Hepatology*. 2008;47:1473-82.
[[PubMed Abstract](#)] -
69. Terrault NA. Benefits and risks of combination therapy for hepatitis B. *Hepatology*. 2009;49:S122-8.
[[PubMed Abstract](#)] -
70. Centers for Disease Control and Prevention: US Public Health Service: Preexposure prophylaxis for the prevention of HIV infection in the United States—2021 Update: a clinical practice guideline. December 2021:1-108.
[[CDC](#)] -
71. Funk AL, Lu Y, Yoshida K, et al. Efficacy and safety of antiviral prophylaxis during pregnancy to prevent mother-to-child transmission of hepatitis B virus: a systematic review and meta-analysis. *Lancet Infect Dis*. 2021;21:70-84.
[[PubMed Abstract](#)] -
72. Zeng QL, Yu ZJ, Ji F, et al. Tenofovir Alafenamide to Prevent Perinatal Hepatitis B Transmission: A Multicenter, Prospective, Observational Study. *Clin Infect Dis*. 2021;73:e3324-e3332.
[[PubMed Abstract](#)] -
73. Pan CQ, Zhu L, Yu AS, Zhao Y, Zhu B, Dai E. Tenofovir Alafenamide Versus Tenofovir Disoproxil Fumarate for Preventing Vertical Transmission in Chronic Hepatitis B Mothers: A Systematic Review and Meta-Analysis. *Clin Infect Dis*. 2024;79:953-64.
[[PubMed Abstract](#)] -

References

- Baqai S, Proudfoot J, Xu R, Kane S, Clark M, Gish R. Comparable efficacy with entecavir monotherapy and tenofovir-entecavir combination in chronic hepatitis B patients. *BMJ Open Gastroenterol.* 2015;2:e000030.
[\[PubMed Abstract\]](#) -
- Buti M, Riveiro-Barciela M, Esteban R. Treatment of Chronic Hepatitis B Virus with Oral Anti-Viral Therapy. *Clin Liver Dis.* 2021;25:725-40.
[\[PubMed Abstract\]](#) -
- Chang TT, Lai CL, Kew Yoon S, et al. Entecavir treatment for up to 5 years in patients with hepatitis B e antigen-positive chronic hepatitis B. *Hepatology.* 2010;51:422-30.
[\[PubMed Abstract\]](#) -
- Gish RG, Chang TT, Lai CL, et al. Loss of HBsAg antigen during treatment with entecavir or lamivudine in nucleoside-naïve HBeAg-positive patients with chronic hepatitis B. *J Viral Hepat.* 2009;17:16-22.
[\[PubMed Abstract\]](#) -
- Gish RG, Chang TT, Lai CL, et al. Quantitative hepatitis B surface antigen analysis in hepatitis B e antigen-positive nucleoside-naïve patients treated with entecavir. *Antivir Ther.* 2013;18:691-8.
[\[PubMed Abstract\]](#) -
- Gish RG, Lok AS, Chang TT, et al. Entecavir therapy for up to 96 weeks in patients with HBeAg-positive chronic hepatitis B. *Gastroenterology.* 2007;133:1437-44.
[\[PubMed Abstract\]](#) -
- Heathcote EJ, Marcellin P, Buti M, et al. Three-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B. *Gastroenterology.* 2011;140:132-43.
[\[PubMed Abstract\]](#) -
- Hong H, Cho M, Lim C, et al. Longitudinal changes in renal function in patients with chronic hepatitis B on antiviral treatment. *Aliment Pharmacol Ther.* 2024;59:515-25.
[\[PubMed Abstract\]](#) -
- Huang ZH, Lu GY, Qiu LX, et al. Risk of hepatocellular carcinoma in antiviral treatment-naïve chronic hepatitis B patients treated with entecavir or tenofovir disoproxil fumarate: a network meta-analysis. *BMC Cancer.* 2022;22:287.
[\[PubMed Abstract\]](#) -
- Lee HY, Oh H, Park CH, Yeo YH, Nguyen MH, Jun DW. Comparison of renal safety of tenofovir and entecavir in patients with chronic hepatitis B: Systematic review with meta-analysis. *World J Gastroenterol.* 2019;25:2961-2972.
[\[PubMed Abstract\]](#) -
- Liang KH, Hsu CW, Chang ML, Chen YC, Lai MW, Yeh CT. Peginterferon Is Superior to Nucleos(t)ide Analogues for Prevention of Hepatocellular Carcinoma in Chronic Hepatitis B. *J Infect Dis.* 2016;213:966-74.
[\[PubMed Abstract\]](#) -
- Liang LY, Yip TC, Lai JC, et al. Tenofovir alafenamide is associated with improved alanine aminotransferase and renal safety compared to tenofovir disoproxil fumarate. *J Med Virol.* 2022;94:4440-8.
[\[PubMed Abstract\]](#) -
- Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission.

Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Interventions to Reduce Perinatal HIV Transmission in the United States. Antepartum Care. Recommendations for Use of Antiretroviral Drugs During Pregnancy. Table 6. What to Start: Initial Antiretroviral Regimens During Pregnancy When Antiretroviral Therapy Has Never Been Received. June 12, 2025.
[\[HIV.gov\]](#) -

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.

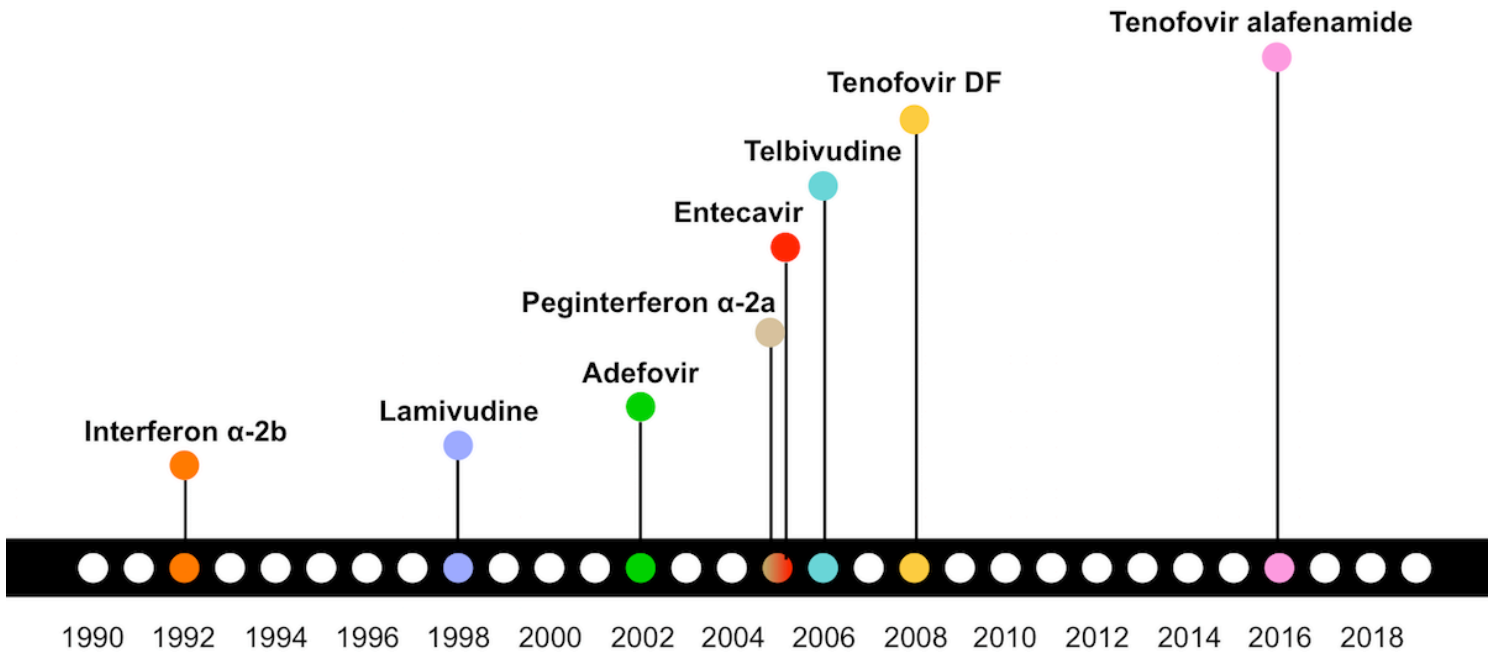


Figure 2 Cumulative Incidence of HBV Resistance with Oral Antiviral Agents

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>]

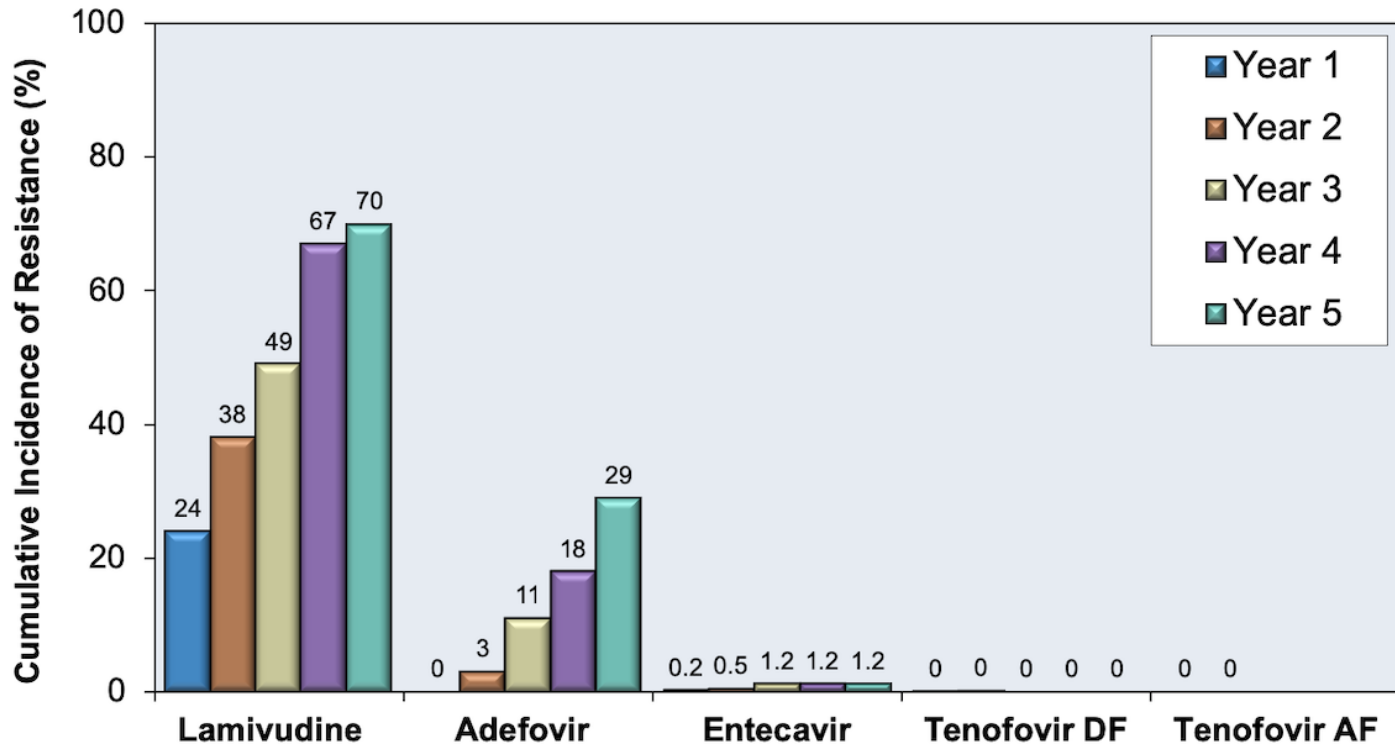


Figure 3 Tenofovir alafenamide versus Tenofovir DF for HBeAg-Positive and Negative Persons: Viral Suppression at Week 96

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.

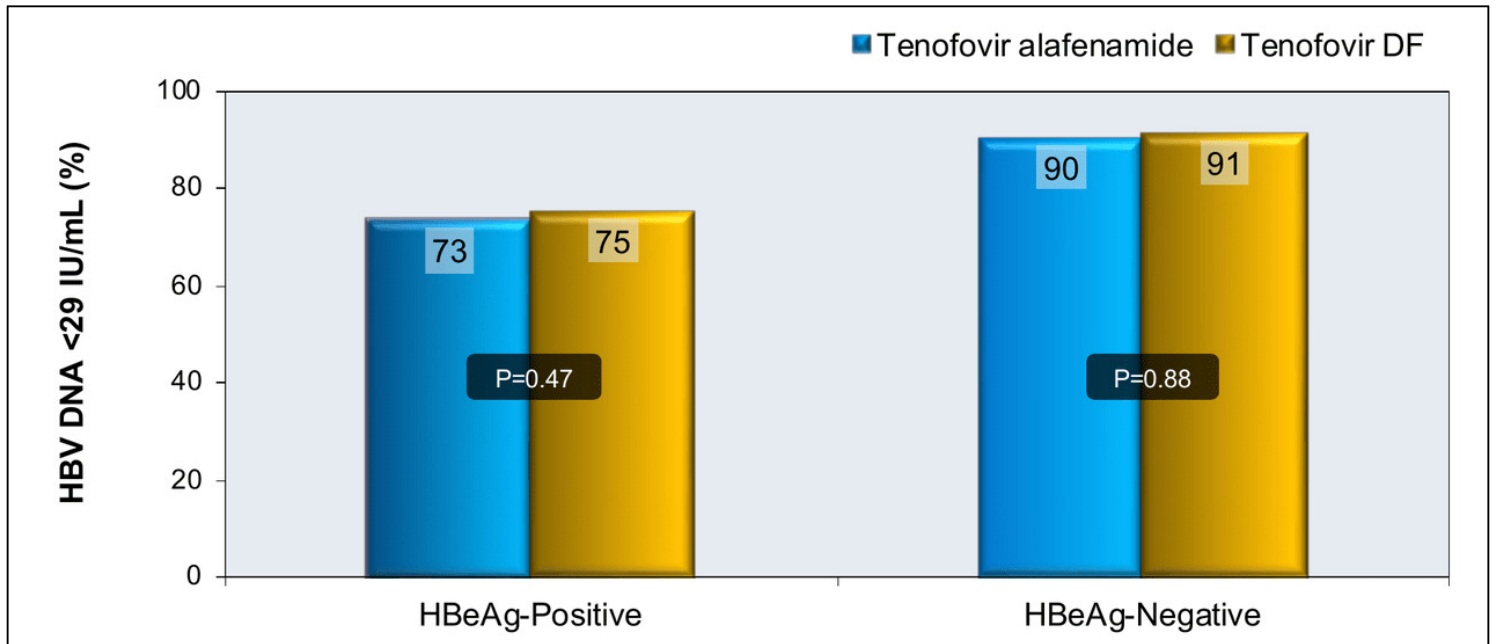


Table 1. Characteristics of Oral Antiviral Agents Used to Treat HBV*

Medications	Trade Name	Category	Oral Dosing (Adults)	Potency	Barrier to Resistance
Adefovir	<i>Hepsera</i>	Nucleotide analogue	10 mg once daily	Low	Moderate
Entecavir	<i>Baraclude</i>	Nucleoside analogue	0.5 mg once daily [†]	High	High
Lamivudine	<i>Epivir-HB</i>	Nucleoside analogue	100 mg once daily	Moderate	Low
Tenofovir alafenamide	<i>Vemlidy</i>	Nucleotide analogue	25 mg once daily	High	High
Tenofovir DF	<i>Viread</i>	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 resistance substitutions rtM204I/V (with or without rtL180M, rtL80I/V, or rtV173L, or (3) decompensated cirrhosis.

Table 2. Potential Peginterferon-Related Adverse Effects

Category	Adverse Effect	
Systemic	<ul style="list-style-type: none"> • Fever • Myalgias/Arthralgias • Fatigue 	
Mood	<ul style="list-style-type: none"> • Depression • Irritability • Insomnia 	
Hematologic	<ul style="list-style-type: none"> • Neutropenia • Anemia • Thrombocytopenia 	
Endocrine	<ul style="list-style-type: none"> • Hypothyroidism • Hyperthyroidism 	
Dermatologic	<ul style="list-style-type: none"> • Rash • Dry skin • Pruritus • Thinning of hair 	
Gastrointestinal	<ul style="list-style-type: none"> • Anorexia • Nausea • Weight loss 	

Table 3. Key Characteristics of Preferred Oral Antiviral Agents to Treat Chronic Hepatitis B Infection

Medications	Entecavir	Tenofovir alafenamide	Tenofovir DF
Trade Name	<i>Baraclude</i>	<i>Vemlidy</i>	<i>Viread</i>
Adult Dose (oral)	0.5 mg once daily [^]	25 mg once daily	300 mg once daily
Food Requirement	Empty stomach	With food	With or without food
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	No change in dosing is required in patients with hepatic impairment
Renal Impairment	<u>Dose adjust when CrCl <50 mL/min:</u> <ul style="list-style-type: none"> • 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 	<u>No dose adjustment for CrCl ≥15 mL/min</u> <ul style="list-style-type: none"> • <15 mL/min and NOT on HD: not recommended for use • HD: 25 mg after completion of each dialysis 	<u>Adjust Dose when CrCl <50 mL/min:</u> <ul style="list-style-type: none"> • 30-49 mL/min: 300 mg every 48 hours • 10-29 mL/min: 300 mg every 72 hours • <10 mL/min: 300 mg every 7 days, NOT on HD. Data are limited. Make individualized recommendations. • HD: 300 mg every 7 days, total of 300 mg per week, approx 72 hours

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 lamivudine or telbivudine; 2) known lamivudine or telbivudine resistance substitutions rtM204I/V (with or without rtL180M, rtL80I/V, or rtV173L, or 3) decompensated cirrhosis.

Table 4. Features of Oral Antiviral Agents Used to Treat HBV and/or HIV

Key Characteristics of Oral Antiviral Agents Used to Treat HBV and/or HIV*		
Medication		Potency A
Adefovir		L
Entecavir		H
Lamivudine		Mod
Tenofovir alafenamide		H
Tenofovir DF		H
*Telbivudine is not included as it is no lon		

