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Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Update: Hepatitis B

Date of Review: August 2025

Date of Last Review: March 2017
Dates of Literature Search: 01/01/2017 – 03/19/2025

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
To identify and evaluate new comparative evidence for the safety and efficacy of medications used in the treatment of chronic hepatitis B infection published since the previous class review.

Plain Language Summary:

- Hepatitis B is an infection caused by the hepatitis B virus that affects the liver. This virus is very contagious and spreads through contact with blood or other body fluids from a person infected with the virus. The infection happens within 6 months of exposure to the virus.
- Most people with hepatitis B infection do not have symptoms and do not know they are infected. The viral infection can be short-term (acute) lasting a few weeks, or long-term (chronic), lasting for many years. If not treated, chronic hepatitis B infection can lead to liver damage, liver cancer, or death.
- The best way to prevent hepatitis B infection is to get vaccinated with a hepatitis B vaccine. Most babies born in the United States (U.S.) receive the first dose of the hepatitis B vaccination series 24 hours after birth. Two or three additional doses of the vaccine (depending on which vaccine is being used) must be given to provide full protection against the virus.
- Chronic hepatitis B infection is treated with oral antiviral medicines. These medicines prevent the virus from reproducing which decreases damage to the liver. All of the antiviral medicines (lamivudine, adefovir, entecavir, and tenofovir), are taken by mouth every day and are continued indefinitely to prevent reactivating the virus.
- Another medicine used to treat chronic hepatitis B infection, peginterferon, is injected under the skin once a week. Peginterferon boosts the infected person's immune system to help fight the virus. Unlike the oral medicines, peginterferon is only taken for 2 years. However, peginterferon has many side effects that may it make it difficult for people to continue taking it. Side effects reported with peginterferon include: flu-like symptoms, fatigue, mood disturbances, and weight loss in children. People that complete a course of peginterferon do not need to use the oral medicines to treat hepatitis B infection.
- Providers must explain to the Oregon Health Authority why someone needs oral medicine to treat chronic hepatitis B infection. This process is called prior authorization. Requests for peginterferon do not need prior authorization from the provider.

Author: Deanna Moretz, PharmD, BCPS

Date: August 2025

Research Questions:

1. Is there new evidence demonstrating differences in efficacy between oral antivirals for the management and prophylaxis of chronic hepatitis B virus (HBV) infection?
2. Is there new evidence demonstrating differences in the safety of oral antivirals for the management and prophylaxis of HBV infection?
3. Are there specific populations (e.g., pregnancy) in which one antiviral may be more effective or safer for the treatment or prophylaxis of HBV infection?

Conclusions:

Efficacy and Safety

- Since the last review, 1 systematic review[1] and 4 clinical practice guidelines[2-5] have been updated to guide management of HBV infection and prophylaxis.
- In 2022, Canada's Drug Agency published a health technology review on antiviral prophylaxis in patients with a history of HBV receiving immunosuppressive therapy.[1] One randomized controlled trial (RCT) and 2 retrospective cohort studies found no statistically significant differences between the 2 tenofovir formulations and entecavir administered over 24 weeks to 18 months for prophylaxis of hepatitis B virus reactivation (HBVr) in patients receiving chemotherapy or immunosuppressive therapy.[1] There were no statistically significant differences between tenofovir products and entecavir regarding renal function and other side effects.[1] Four guidelines included in this review strongly recommend the use of tenofovir or entecavir as antiviral prophylaxis in all patients with high risk of HBVr who are receiving chemotherapy or immunosuppressive therapy.[1]
- The American Association for the Study of Liver Diseases (AASLD) updated guidance for management of chronic HBV in 2018.[6] Updated recommendations for the treatment of patients with chronic HBV include:
    - The AASLD recommends antiviral therapy for adults with immune-active chronic hepatitis B (hepatitis B e-antigen [HBeAg] negative or HBeAg positive) to decrease the risk of liver-related complications (Strong Recommendation. Moderate-Quality Evidence).[6]
    - The AASLD recommends peginterferon (peg-IFN), entecavir, or tenofovir dipivoxil fumarate as preferred initial therapy for adults with immune-active chronic hepatitis B. (Strong Recommendation. Low-Quality Evidence).[6] Note: Tenofovir alafenamide is also preferred initial therapy for adults with immune-active chronic hepatitis B. Consider tenofovir alafenamide in patients at risk for renal dysfunction or bone disease. Tenofovir alafenamide is not recommended in patients with creatinine clearance (CrCl) less than 15 mL/min.[6]
- In 2024, the World Health Organization (WHO) published updated guidance for management of chronic hepatitis B infection.[3] The updated recommendations include guidance for first- and second-line antiviral treatment, inclusion of treatment criteria for adolescents, and use of antiviral prophylaxis in pregnancy.

    First-line antiviral therapies for chronic hepatitis B:

    - Antivirals with a low genetic barrier to resistance (i.e., lamivudine, adefovir) can lead to drug resistance and are not recommended (Strong Recommendation, Moderate-Certainty Evidence).[3]
    - For all adults, adolescents and children (2 years or older) for whom antiviral therapy is indicated, the antivirals that have a high genetic barrier to drug resistance, tenofovir disoproxil fumarate or entecavir, are recommended as preferred regimens. (Strong Recommendation, Moderate-Certainty Evidence).[3]
    - Entecavir or tenofovir alafenamide are recommended for people with established osteoporosis and/or impaired kidney function, and for children (entecavir for those aged two years or older) or adolescents (tenofovir alafenamide for those aged 12 years or older)* as an alternative regimen, for whom antiviral therapy is indicated. (Strong Recommendation, Moderate-Certainty Evidence).[3] *The Food and Drug Administration (FDA) expanded the use of tenofovir alafenamide to children 6 years of age and older in 2024.[7]

    Second-line antiviral therapies for chronic hepatitis B:

- Among people with evidence of treatment failure* due to confirmed or suspected antiviral resistance (based on history of previous exposure or primary non-response) to lamivudine, entecavir, or adefovir, switching to tenofovir disoproxil fumarate is recommended. Tenofovir alafenamide may be considered as an alternate regimen. (Strong Recommendation, Low-Certainty Evidence). *Treatment adherence should be reinforced for all people with confirmed or suspected antiviral resistance.[3]

Preventing mother-to-child transmission of HBV and use of antiviral prophylaxis:

- Prophylaxis with tenofovir disoproxil fumarate* is recommended for all HBV positive pregnant women with HBV DNA ≥ 200,000 IU/mL or positive HBeAg (preferably from the second trimester of pregnancy until at least delivery or completion of the infant HBV vaccination series), to prevent the mother-to-child transmission of HBV. (Strong Recommendation, Moderate-Certainty Evidence). *Tenofovir disoproxil fumarate may be considered for people (including pregnant women) with impaired kidney function or osteoporosis but is not FDA-approved for HBV treatment in pregnancy.[3]

- The American Gastroenterology Association (AGA) updated guidance for prevention and treatment of HBVr in 2025.[4] Reactivation of the HBV is generally a result of chronic immunosuppression, induced either by drug therapy or by pathologic immunosuppression.[4]
  - For individuals at high risk of HBVr, the AGA recommends antiviral prophylaxis over monitoring alone. (Strong Recommendation, Moderate Certainty Evidence).[4]
  - For individuals at moderate risk of HBVr, the AGA suggests antiviral prophylaxis over monitoring alone. (Conditional Recommendation, Moderate Certainty Evidence).[4]
  - For individual at low risk of HBVr, the AGA suggests monitoring alone over using antiviral prophylaxis. (Conditional Recommendation, Moderate Certainty Evidence)**.[4]**
  - For individuals at risk of HBVr, the AGA recommends testing for HBV (Strong Recommendation, Moderate Certainty Evidence).[4]
- In 2025, the Office of AIDS Research Advisory Council (OARAC) guidelines were updated by a panel of representatives from the National Institutes of Health (NIH), HIV Medicine Association (HIVMA), and Infectious Diseases Society of America (IDSA) to provide recommendations for treatment of opportunistic infections in adults and adolescents with human immunodeficiency virus (HIV).[5] Specific guidance for co-infection with HBV includes a new section on use of oral antiviral regimens in people with past HBV, chronic HBV, and isolated hepatitis B core antibody positivity.[5] The use of peginterferon was changed from preferred therapy to an alternative treatment used only in rare cases.[5] HBV-active antiretroviral treatment (ART) (i.e., tenofovir with lamivudine or emtricitabine) decreases the risk for acute HBV infection, but it does not eliminate the risk, so taking ART alone is not a recommended strategy to prevent HBV infection.[5] The specific oral antiviral recommendations based on renal function are presented below in the clinical guideline section.

Guidance for Specific Populations

- There are specific populations (e.g., pregnancy, people with HIV coinfection, and people receiving chemotherapy) in which one antiviral may be more effective or safer for the treatment of HBV. WHO guidance provides specific recommendations for use of tenofovir disoproxil fumarate prophylaxis in patients that are positive for HBV infection during pregnancy to prevent maternal transmission to the fetus.[3] The AGA recommends antiviral prophylaxis with tenofovir or entecavir in patients at moderate to high risk for reactivation of the HBV who are receiving immunosuppressive therapy.[4] Preferred treatment recommendations issued by 2025 ORAC guidance for patients coinfected with HBV and HIV are tenofovir with lamivudine or emtricitabine adjusted for renal function as needed.[5]

Expanded Indications and Market Removals

- An expanded age range was approved by the FDA for VIREAD (tenofovir disoproxil fumarate) oral tablets in December 2018.[8] This approval extended the use of tenofovir disoproxil fumarate to pediatric patients aged 2 years of age and older weighing at least 10 kg for the treatment of chronic HBV infection.[8] Prior to this expanded indication, tenofovir disoproxil fumarate was approved for use in pediatric patients aged 12 years and older.

- In March 2024, an expanded age range was FDA-approved for VEMLIDY (tenofovir alafenamide) oral tablets.[7] This approval extended the use of tenofovir alafenamide to pediatric patients aged 6 years and older weighing at least 25 kg for the treatment of chronic HBV infection with compensated liver disease.[7] Prior to this expanded indication, the drug was approved for use in pediatric patients aged 12 years and older.
- TYZEKA (telbivudine) was removed from the United States (U.S.) market in 2016 by Novartis based on business factors, not safety or efficacy issues.

Recommendations:
- Based on recent guidelines, make entecavir tablets preferred on the preferred drug list (PDL). Due to viral resistance patterns with lamivudine, make this product nonpreferred on the PDL.
- Revise prior authorization (PA) criteria to include only nonpreferred hepatitis B antiviral agents.
- Review medication costs in executive session.

Summary of Prior Reviews and Current Policy:
- The Pharmacy and Therapeutics (P & T) Committee reviewed hepatitis B antiviral agents at the March 2017 meeting. No differences were reported in terms of efficacy or safety between entecavir and tenofovir disoproxil fumarate. Both antiviral agents are recommended as first-line treatments by clinical practice guidelines. One randomized trial showed tenofovir dipivoxil fumarate had favorable outcomes in treatment of HBV in known-lamivudine resistant patients. Switching to tenofovir disoproxil fumarate is recommended by guidelines in cases of known resistance to other antiviral agents. There is insufficient evidence of improved efficacy or effectiveness or safety of tenofovir alafenamide compared to other antivirals for the treatment of HBV. The recommendation to add tenofovir alafenamide to the PDL as a non-preferred antiviral was approved by the Committee.
- The PDL status of the hepatitis B antiviral agents is presented in **Appendix 1**. Preferred products are tenofovir disoproxil fumarate and lamivudine. Nonpreferred products include entecavir, adefovir, and tenofovir alafenamide. All antivirals require PA. PA criteria are included in **Appendix 4**. In the first quarter of 2025 (January 1, 2025-April 30, 2025), there were 4 claims for oral hepatitis B antivirals. Three claims were for entecavir, and one claim was for tenofovir disoproxil fumarate.

Background:
The HBV is a partially double-stranded deoxyribonucleic acid (DNA) virus that causes an infection in hepatic tissue, which is the primary site of HBV replication.[9] Once the hepatic cells get infected by the HBV, the viral DNA remains permanently inside the host cells and serves as a template for future viral replication.[10] Transmission of HBV occurs through perinatal, percutaneous or mucosal contact with blood, semen, or other bodily fluids.[6] The virus remains infectious on environmental surfaces for at least 7 days.[9] Symptoms of acute HBV infection can include abdominal pain, nausea, vomiting, dark urine, fatigue, fever, jaundice, and joint pain, although 70% of people with HBV are asymptomatic.[11] People at higher risk of HBV infection include infants born to people with hepatitis B; people born in countries where hepatitis B is more common; and people born in the United States (U.S.) who were not vaccinated as infants and whose parents were born in areas with high rates of hepatitis B (e.g., Africa, Asia, the Pacific Islands, the Caribbean, parts of South America, and Eastern Europe).[11] Other risk factors include people who have hepatitis C; those who have sexually transmitted infections such as HIV; people who are receiving dialysis; people receiving immunosuppressive therapy; and people with liver damage or inflammation.[11] In addition, people who have been incarcerated, those who inject drugs or share needles, sexual partners of people with hepatitis B, men who have sex with men, people who live with someone with hepatitis B, and health care workers exposed to blood and body fluids are at increased risk of contracting the virus.[11] The Advisory Committee on Immunization Practices (ACIP) recommends hepatitis B vaccination for all medically stable infants weighing 2,000 grams or more within 24 hours of birth, unvaccinated infants and children, and unvaccinated adults requesting protection from hepatitis B or who are at increased risk of infection.[9]

In humans, there are 8 major HBV genotypes (A-H).[10] In North America and Africa, the HBV infections are primarily genotype A. Genotype C is almost as common in the U.S. as genotype A. HBV infections in East Asia are most commonly genotypes B and C and infections in Southern Europe and India are genotype D.[10] The HBV genotype A responds most favorably to interferon-based therapy relative to other genotypes, and the genotype C is associated with more advanced liver fibrosis and an increased risk of hepatocellular carcinoma.[10] Commercial testing for HBV genotype is not required for clinical care except when interferon-based therapy is considered, or when knowledge of the HBV genotype may aid risk stratification of disease progression.[10]

The risk of developing chronic hepatitis B depends on the age at which the individual becomes infected, with the majority of chronic infection developing in people initially exposed in infancy and childhood.[11] Approximately 90% of infants infected with the HBV in the perinatal period will develop chronic hepatitis B, whereas only 5% of adults acutely infected will develop chronic hepatitis B.[11] Recognition of the virus as a foreign antigen activates the host immunity to target and destroy infected liver cells, resulting in inflammation and necrosis of liver tissue.[10] The HBV does not directly kill hepatic cells.[10] People with chronic HBV infection are at increased risk for liver cancer and cirrhosis and are 70%–85% more likely to die prematurely than the general population, if not treated.[11] An estimated 580,000 to 2.4 million persons are living with chronic HBV in the U.S., two thirds of whom may be unaware of their infection.[11] Chronic HBV infection disproportionately affects persons born outside the United States; non-U.S.–born persons account for 14% of the general population, but account for 69% of the U.S. population living with chronic HBV infection.[11] The Centers for Disease Control and Prevention (CDC) estimates that about 640,000 adults in the U.S. have chronic HBV.[11] In 2022, the rate of newly reported chronic HBV cases was 11 times higher among non-Hispanic, Asian/Pacific Islander persons than among non-Hispanic, White people.[11]

Individuals with chronic HBV infection are typically asymptomatic and are diagnosed during routine health maintenance or screening (e.g., blood donation or an evaluation for an elevated level of liver enzymes).[10] Evaluation of individuals with chronic HBV includes a complete history, examination, and serologic testing.[2] There should be an emphasis on signs and symptoms of cirrhosis, evaluation of alcohol intake and metabolic risk factors, family history of hepatocellular carcinoma (HCC), and hepatitis A and B vaccination status.[2] The presence of Hepatitis B surface antigen (HBsAG) in the blood provides a definitive diagnosis of hepatitis B infection.[11] Chronic hepatitis B infection is defined by the presence of HBsAG on two occasions at least 6 months apart.[6] Screening for HBV includes testing for HBsAg and, if positive, testing for antibodies to HBsAg (anti-HBs) and hepatitis B core antigen (anti-HBc) to distinguish between infection and immunity.[2] Interpretation of viral markers to diagnosis acute or chronic HBV is presented in **Table 1**.

Routine assessment of additional serologic markers, such as HBV DNA, hepatitis B e-antigen (HBeAg), and alanine aminotransferase (ALT) levels, should be performed in order to guide the management of HBV infection.[2] The assessment of HBV DNA is a measure of viral load and reflects viral replication.[9] Hepatitis B e-antigen can be detected in persons with acute or chronic HBV infection; the presence of HBeAg correlates with viral replication and high infectivity; antibody to HBeAg (anti-HBe) correlates with the loss of replicating virus, although reversion to HBeAg positivity can occur.[9] Additional testing to determine the advancement of liver fibrosis through non-invasive tests such as aspartate aminotransferase (AST)-to-platelet ratio index (APRI), transient elastography (FibroScan) or FibroTest is also recommended.[2]

Table 1. Diagnosis of Acute and Chronic HBV Infection[10]

Interpretation	HBsAg	Anti-HBs	Anti-HBc	HBV DNA Detected	Interpretation Details
HBV Infection	Positive	Negative	Positive	Positive	• Presence of HBsAg for > 6 months defines chronic infection • In acute infection, Anti-HBc is in the form of IgM

Resolved Infection	Negative	Positive	Positive	Negative	• Adults infected with HBV will resolve the acute infection within 6 months • HBsAg is no longer detected (termed HBsAg loss) • 80% of adults will develop anti-HBs (termed anti-HBs seroconversion) • Anti-HBc is present in the form of IgG
Immunity	Negative	Positive	Negative	Negative	• Immunity gained through vaccination
Isolated Core	Negative	Negative	Positive	Negative or Positive	• Undetectable HBV DNA: previous infection without anti-HBs or level of anti-HBs is below the level of detection by serological test. May indicate individuals at risk of disease reactivation and should be identified prior to immunosuppressive therapy. • Detectable HBV DNA: occult HBV infection. May indicate individuals at risk of disease reactivation and should be identified prior to immunosuppressive therapy. • Period during acute infection either immediately after infection and before the appearance of HBsAg or during the resolution of infection after HBsAg loss and before appearance of anti-HBs. • False-positive test result
Abbreviations: Anti-HBc = antibodies to hepatitis B core antigen; Anti-HBs = antibodies to hepatitis B surface antigen; DNA = deoxyribonucleic acid; HBsAg = hepatitis B surface antigen; HBV = Hepatitis B Virus; IgG = Immunoglobulin G; IgM = Immunoglobulin M					

The CDC recommends all adults aged 18 years and older should be screened for the presence of the HBsAg at least once in their lifetime.[11] All pregnant patients should be tested for the HBsAg during an early prenatal visit for each pregnancy and all infants born to antigen-positive people should be tested.[11] The following populations, activities, exposures, or conditions associated with increased risk for HBV infection should also be tested for the HBsAg: persons incarcerated or formerly incarcerated in a jail, prison, or other detention setting; persons with a history of sexually transmitted infections or multiple sex partners; and persons with a history of hepatitis C virus infection.[11] In addition, to provide increased access to testing, anyone who requests HBV testing should receive it, regardless of disclosure of risk, because many persons may be reluctant to disclose stigmatizing risks.[11]

Although most patients with chronic HBV infection will not develop liver-related complications, the 5-year incidence of cirrhosis is approximately 8-20%, with relatively few of these cases developing HCC (2-5%).[5] Additional risk factors for developing cirrhosis and HCC in patients with chronic HBV infection include high serum HBV DNA (>2,000 IU/mL), elevated ALT levels, prolonged time to HBeAg seroconversion and development of HBeAg-negative chronic HBV.[5] In 2022, a total of 2,126 cases of acute HBV infection were reported in the U.S. but experts estimate the actual number is much higher, and likely around 13,800.[11] In 2022, HBV-related death rates among non-Hispanic, Asian/Pacific Islander people and non-Hispanic, Black people were 8.5 times and 2.6 times as high as the rate among non-Hispanic, White people, respectively.[11]

Although antiviral treatment is not considered curative, antiviral treatment, monitoring, and liver cancer surveillance can reduce morbidity and mortality associated with chronic HBV infection.[11] Current antiviral therapy for chronic HBV does not eradicate the virus and is not considered curative, but can produce an

immunological cure, defined as loss of HBsAg from the serum and sustained HBV DNA suppression.[2] There is no evidence that antiviral treatment is effective for managing acute HBV infection.[2] The goal of chronic HBV antiviral therapy is to reduce the incidence of liver-related complications including cirrhosis and HCC.[6] Treatment is indicated during the immunoactive phase of chronic HBV infection when liver injury and fibrosis occur.[10] The immunoactive phase is when a patient has an ALT level greater than the upper limit of normal in combination with a high HBV DNA level (>2,000 IU/mL if negative for HBeAg or >20,000 IU/mL if positive for HBeAg), or if a patient has evidence of at least moderate liver inflammation or fibrosis.[10]

The available treatment options for chronic HBV infection include pegylated interferon (peginterferon) and oral nucleoside/nucleotide analogs (NAs).[5] Peginterferon activates the host immune system to combat the infection but it does not kill the virus.[10] The primary drawback of peginterferon is tolerability because it is associated with frequent adverse effects (i.e., flu-like symptoms, fatigue, mood disturbances, cytopenias, autoimmune disorders in adults, and anorexia and weight loss in children).[2] The preferred formulation is peginterferon alfa-2a, which should be administered as 180 mcg once weekly via subcutaneous injection for 48 weeks for HBeAg-positive or HBeAg-negative chronic HBV infection.[2] The finite duration of therapy may be advantageous for women positive for the HBeAg with high HBV DNA levels planning on getting pregnant in the future.[10] However, peginterferon is contraindicated during pregnancy.[10] No viral resistance has been reported with peginterferon.[10]

The oral NAs target the HBV by inhibiting viral polymerase.[2] They have excellent tolerability profiles; however, the duration of their use is often indefinite because of frequent relapses or reactivation of HBV after cessation of treatment.[2] The cure rates (defined as hepatitis B surface antigen loss with undetectable viral DNA) after treatment remain low (3%-7% with peginterferon and 1%-12% with NA therapy).[10] The 5 FDA-approved NAs are described in **Table 2.** The 2024 WHO guidance recommends tenofovir disoproxil fumarate or entecavir, the 2 NAs with a high genetic barrier to resistance, as preferred first-line regimens.[3] Lamivudine, adefovir, entecavir, and tenofovir disoproxil fumarate require dose adjustment for CrCl less than 50 mL/min.[10] Tenofovir alafenamide is not recommended in patients with CrCl less than 15 mL/min.[7] All NAs carry a black box warning for the risk of lactic acidosis and severe hepatomegaly.[10] Efficacy of antiviral therapy should be assessed by serologic testing every 6 months.[10]

Table 2. Nucleoside/Nucleotide Analogs (NAs) FDA-Approved for Treatment of Chronic Hepatitis B[6,10]

Drug (BRAND NAME)	Adult Dose (all oral)	Pediatric Dose (all oral)	Development of Resistance	Pregnancy Category*
Adefovir dipivoxil (HEPSERA)	10 mg once daily	Age ≥ 12 years: 10 mg once daily	Resistance among 20% to 29% after 5 years	C
Entecavir (BARACLUDE)	Age ≥ 16 years: 0.5 mg once daily. 1 mg once daily in known lamivudine-resistance or decompensated cirrhosis.	Age ≥ 2 years and weight ≥10 kg: weight-based dosing up to 30 kg. Weight > 30 kg: 0.5 mg once daily	Resistance among 1.2% after 5 years in NA-naïve patients. Resistance increased to > 50% among patients with resistance to lamivudine.	C
Lamivudine (EPIVIR-HBV)	100 mg once daily	Age ≥ 2 years: 3 mg/kg once daily up to maximum dose of 100 mg per day	Resistance among 24% to 30% after 1 year and 70% after 5 years	C
Tenofovir alafenamide (VEMLIDY)	25 mg once daily	Age ≥ 6 years and weight ≥ 25 kg: 25 mg once daily with food	No resistance reported through 8 years of treatment.	Insufficient data for use in pregnancy

Tenofovir dipivoxil fumarate (VIREAD)	300 mg once daily	Age ≥ 2 years and weight ≥ 10 kg: 8 mg/kg once daily, maximum dose of 300 mg once daily	No resistance reported for up to 7 years.	B
*Pregnancy Category B: Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. *Pregnancy Category C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.				
Abbreviations: FDA = Food and Drug Administration; kg = kilograms; mg = milligrams				

Methods:

A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Oregon Mental Health Clinical Advisory Group (MHCAG), the Scottish Intercollegiate Guidelines Network (SIGN), and Canada's Drug Agency (CDA-AMA) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

Canada's Drug Agency: Antiviral Prophylaxis with Tenofovir for Patients with History of HBV Receiving Oncology Treatment

In 2022, Canada's Drug Agency published a health technology review for antiviral prophylaxis in patients with a history of HBV receiving immunosuppressive therapy for hematologic and solid tumor malginancies.[1] Literature was searched through July 2022.[1] Two RCTs, 2 observational studies, and 8 evidence-based guidelines met inclusion criteria.[1] One RCT and 2 retrospective cohort studies found no statistically significant differences between either tenofovir formulation and entecavir administered from 24 weeks to 18 months for prophylaxis of HBV reactivation in patients who were hepatitis B surface antigen positive and/or hepatitis B core antibody positive receiving chemotherapy or immunosuppressive therapy.[1] There were no statistically significant differences between these 3 antivirals renal function and other side effects.[1] Guidelines focused on antiviral prophylaxis in patients receiving immunosuppressive therapy were published in Australia, Germany, Brazil, India, Italy, the U.S., and Canada from 2017 through 2022.[1] All 8 included guidelines strongly recommend the use of tenofovir or entecavir as antiviral prophylaxis in all patients with high risk of HBV reactivation (hepatitis B surface antigen positive and/or hepatitis B core antibody positive) during chemotherapy or immunosuppressive therapy.[1]

After review, 4 systematic reviews were excluded due to poor quality (e.g., indirect network-meta-analyses or failure to meet AMSTAR criteria),[12,13] wrong study design of included trials (e.g., observational),[14-16] comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:

High Quality Guidelines:

American Association For The Study Of Liver Diseases: Update On Prevention, Diagnosis, and Treatment Of Chronic HBV Infection

The AASLD updated guidance for management of chronic HBV infection in 2018.[6] Tenofovir alafenamide received FDA-approval for treatment of chronic HBV infection in adults, after the publication of the 2016 AASLD HBV treatment guideline, so the guideline was updated to include the new tenofovir formulation.[6] Head-to-head comparisons of antiviral therapies failed to show superiority of one therapy over another in achieving risk reduction in liver-related complications.[6] However, in recommending pegylated interferon (peg-IFN), tenofovir, and entecavir as preferred therapies, the most important factor considered by the AALD panel was the lack of viral resistance with long-term use.[6] Patient-specific factors that should be considered in choosing therapeutic options include:

- the anticipated tolerability of treatment side effects,
- comorbidities (interferon is contraindicated in people with autoimmune disease, uncontrolled psychiatric disease, cytopenia, severe cardiac disease, uncontrolled seizures, and decompensated cirrhosis),
- previous history of lamivudine resistance (entecavir is preferred in this setting),
- family planning: finite therapy with peg-IFN pre-pregnancy or use of an oral antiviral that is safe in pregnancy (preferably tenofovir dipivoxil fumarate),
- HBV genotype: A and B genotypes are likely to achieve HBeAg and HBsAg loss with peg-IFN than non-A or non-B genotypes, and
- medication costs.[6]

Additional guidance:

- Peg-IFN is preferred over nonpegylated forms for simplicity.[6]
- For patients treated with peg-IFN, 48 weeks duration is used in most studies and is preferred. This treatment duration yields HBeAg seroconversion rates of 20% to 31% and sustained off-treatment HBV DNA suppression of less than 2,000 IU/mL in 65% of persons who achieve HBeAg to anti-HBe seroconversion. The combination of peg-IFN and NAs has not yielded higher rates of off-treatment serological or virological responses and is not recommended.[6]
- Duration of therapy for NA-based therapy is variable and influenced by HBeAg status, duration of HBV DNA suppression, and presence of cirrhosis and/or decompensation. All NAs except tenofovir alafenamide require dose adjustment in persons with CrCl less than 50 mL/min.[6]
- Evaluation for cirrhosis using noninvasive methods or a liver biopsy is useful to guide treatment decisions, including duration of therapy.[6]
- Treatment with antivirals does not eliminate the risk of HCC, and surveillance for HCC should continue in persons who are at risk.[6]

Updated recommendations on the treatment of patients with chronic HBV infection:

- The AASLD recommends antiviral therapy for adults with immune-active chronic HBV infection (HBeAg negative or HBeAg positive) to decrease the risk of liver-related complications (Quality and Certainty of Evidence: Moderate*;* Strength of Recommendation: Strong*).*[6]
- The AASLD recommends peg-IFN, entecavir, or tenofovir dipivoxil fumarate as preferred initial therapy for adults with immune-active chronic hepatitis B. (Quality and Certainty of Evidence: Low; Strength of Recommendation: Strong).[6] Note: Tenofovir alafenamide is also preferred initial therapy for adults with immune-active chronic HBV infection. Consider tenofovir alafenamide in patients at risk for renal dysfunction or bone disease. Tenofovir alafenamide is not recommended in patients with creatinine clearance less than 15 mL/min.[6]

World Health Organization: Guidelines For the Prevention, Diagnosis, Care and Treatment for People with Chronic HBV Infection

In 2024, WHO published updated guidance for management of chronic HBV infection.[3] Updated recommendations include guidance for who should be treated, inclusion of treatment criteria for adolescents, first- and second-line antiviral treatment use of antiviral prophylaxis in pregnancy, and monitoring for people receiving treatment.

Treatment is recommended for all adults and adolescents (aged ≥ 12 years with chronic HBV infection (including pregnant women and girls and women of reproductive age) with:

- Evidence of significant fibrosis (≥ F2) based on an APRI score of > 0.5 or transient elastography value of > 7 kPa or evidence of cirrhosis (F4) based on clinical criteria (or an APRI score of >1 or transient elastography value of > 12.5 kPa), regardless of HBV DNA or ALT levels. (Adults: Strong Recommendation, Moderate-Certainty Evidence; Adolescents: Strong Recommendation, Low-Certainty Evidence).
  OR
- HBV DNA >2000 IU/mL and an ALT level above the upper limit of normal (ULN) (30 U/L for men and boys and 19 U/L for women and girls). For adolescents, this should be based on ALT>ULN on at least 2 occasions in a 6- to 12-month period. (Adults: Strong Recommendation, High-Certainty Evidence [HBV DNA >20 000 IU/mL] and low-certainty evidence [HBV DNA 2000–20 000 IU/mL]; Adolescents: Conditional Recommendation, Low-Certainty Evidence).
  OR
- Presence of coinfections (such as HIV, hepatitis D or hepatitis C); family history of liver cancer or cirrhosis; immune suppression (such as long-term steroid use, solid organ or stem cell transplant); comorbidities (such as diabetes or metabolic dysfunction-associated steatotic liver disease); or extrahepatic manifestations (such as glomerulonephritis or vasculitis), regardless of the APRI score or HBV DNA or ALT levels. (Adults: Strong Recommendation, Moderate-Certainty Evidence; Adolescents: Conditional Recommendation, Low-Certainty Evidence).
  OR
- In the absence of access to an HBV DNA assay: Persistently abnormal ALT levels alone (defined as two ALT values above the ULN at unspecified intervals during a 6- to 12-month period), regardless of APRI score. (Adults And Adolescents: Conditional Recommendation, Very-Low Certainty Evidence).[3]

First-line antiviral therapies for chronic hepatitis B:

- NAs with a low genetic barrier to resistance (lamivudine, adefovir) can lead to drug resistance and are not recommended (Strong Recommendation, Moderate-Certainty Evidence).[3]
- For all adults, adolescents and children (2 years or older) for whom antiviral therapy is indicated, the NAs that have a high genetic barrier to drug resistance, monotherapy with tenofovir disoproxil fumarate or entecavir are recommended as preferred regimens. Tenofovir disoproxil fumarate plus lamivudine or tenofovir disoproxil fumarate plus emtricitabine are recommended as alternative regimens (where tenofovir disoproxil fumarate monotherapy is not available) (Strong Recommendation, Moderate-Certainty Evidence).[3]
- Entecavir or tenofovir alafenamide (if available) are recommended for people with established osteoporosis and/or impaired kidney function, and for children (entecavir for those aged two years or older) or adolescents (for those aged 12 years or older) as alternative regimen, for whom antiviral therapy is indicated (Strong Recommendation, Moderate-Certainty Evidence).[3]

Second-line antiviral therapies for chronic hepatitis B:

- Among people with evidence of treatment failure* due to confirmed or suspected antiviral resistance (based on history of previous exposure or primary non-response) to lamivudine, entecavir, or adefovir, switching to tenofovir disoproxil fumarate is recommended. Tenofovir alafenamide may be considered as an alternate regimen, if available (Strong Recommendation, Low-Certainty Evidence).
  *Treatment adherence should be reinforced for all people with confirmed or suspected antiviral resistance.[3]

Preventing mother-to-child transmission of hepatitis B and use of antiviral prophylaxis:

- In settings where HBV DNA or HBeAg testing is available, prophylaxis with tenofovir disoproxil fumarate* is recommended for all HBV positive (HBsAg-positive) pregnant women with HBV DNA ≥200 000 IU/mL or positive HBeAg (preferably from the second trimester of pregnancy until at least delivery or completion of the infant HBV vaccination series), to prevent the mother-to-child transmission of HBV. (Strong Recommendation, Moderate-Certainty Evidence).
  *Tenofovir disoproxil fumarate may be considered for people (including pregnant women) with impaired kidney function and/or osteoporosis but is not approved for HBV treatment in pregnancy.[3]

For people receiving treatment, the following are recommended to be monitored at least annually:

- Non-invasive tests (APRI score or transient elastography) to assess stage of disease and progression of fibrosis or cirrhosis; and
  ALT levels (and AST for APRI), HBV DNA levels (when HBV DNA testing is available), HBsAg and HBeAg/anti-Hb (Strong Recommendation, Moderate-Certainty Evidence).[3]
- Treatment adherence should be monitored regularly and at each visit (Strong Recommendation, Moderate-Certainty Evidence).[3]

Office of AIDS Research Advisory Council: Clinical Guideline for Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV

In 2025 OARAC guidelines were updated by a panel of representatives from the NIH, HIVMA, and IDSA to provide recommendations for treatment of opportunistic infections in adults and adolescents with HIV.[5] Globally and in North America, approximately 8% of people with HIV have evidence of chronic HBV infection, but this varies by region of the world.[5] Compared with people with HBV mono-infection, those with HIV/HBV coinfection have higher levels of HBV viremia and lower likelihood of resolved infection following acute HBV infection.[17] People with HIV/HBV are also more likely to have detectable HBeAg,[18] lower rates of seroconversion to anti-HBe, and increased risk of HCC and liver-related mortality and morbidity.[19] In HIV/HBV coinfection, monitoring and treatment are focused on the simultaneous and immediate treatment of both viruses regardless of HBV phase.[5]

Waning immunity is typically seen in people with low CD4 cell counts (<350 cells/mm^3) and may be a consequence of the height of the initial antibody response after immunization.[3] In a study of people with HIV who had antibody titers assessed 4 weeks after completing the three-dose hepatitis B vaccine series, those who had a titer less than 100 mIU/mL were significantly more likely to have waning immunity over the next 5 years compared with individuals who had higher titers after vaccination.[20] HBV-active ART (i.e., tenofovir with lamivudine or emtricitabine) decreases the risk for acute HBV infection, but it does not eliminate the risk, so taking ART alone is not a recommended strategy to prevent HBV infection.[5] Therefore, hepatitis B vaccination is recommended even if receiving an HBV-active ART regimen.[5]

Specific guidance for co-infection with HBV includes a new section on use of NA regimens in people with past HBV, chronic HBV, and isolated hepatitis B core antibody positivity.[5] The use of peginterferon was changed from preferred to an alternative treatment used only in rare cases.[5] The rating system for OARRAC recommendations is presented in **Table 3**.

Table 3. Rating System for Office of AIDs Research Advisory Council Recommendations[3]

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement **B:** Moderate recommendation for the statement **C:** Weak recommendation for the statement	**I**: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints. **II**: One or more well-designed, non-randomized trials or observational cohort studies with long clinical outcomes. **III**: Expert Opinion

Strength of Recommendations and Quality of Evidence are **bolded** at the end of each statement based on definitions in **Table 3**.

Indication for Therapy

- All people with HIV/HBV coinfection (HBsAg positive), including pregnant people, regardless of CD4 count and HBV DNA level**,** should be treated with an ART regimen that includes drugs active against both HIV and HBV infections **(AII).**
- Tenofovir, entecavir, lamivudine, and emtricitabine should not be used alone in the absence of a fully HIV-suppressive ART regimen because of the potential for development of HIV drug**-**resistance mutations **(AI).[5]**

Preferred Therapy (CrCl ≥60 mL/min)

- The ART regimen should include two oral drugs active against HBV, preferably with:
  - tenofovir alafenamide (10 or 25 mg)* plus emtricitabine 200 mg OR tenofovir alafenamide 25 mg plus lamivudine 300 mg once daily (**AII**), or
  - tenofovir disoproxil fumarate 300 mg plus (emtricitabine 200 mg or lamivudine 300 mg) once daily (**AII**).[5]

  *Tenofovir alafenamide 10 mg dose is in the fixed-dose combination tablets of elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine and darunavir/cobicistat/tenofovir alafenamide/emtricitabine when tenofovir alafenamide is used with other antiretrovirals, the dose is 25 mg.[5]

Preferred Therapy (CrCl 30–59 mL/min)

- The ART regimen should include two oral drugs active against HBV, preferably with tenofovir alafenamide (10 or 25 mg) plus emtricitabine 200 mg once daily (**AII**).[5]

Preferred Therapy (CrCl <30 mL/min, Not Receiving Hemodialysis)

- Renally dosed entecavir (in place of tenofovir disoproxil fumarate/emtricitabine or tenofovir disoproxil fumarate/lamivudine or tenofovir alafenamide/lamivudine, with a fully suppressive antiretroviral regimen), (**AIII**) or
- ART with renally dose-adjusted tenofovir disoproxil fumarate and (emtricitabine or lamivudine) when recovery of renal function is unlikely (**AIII**).[5]
- If CrCl ≥ 15 to 29 mL/min, then ART with tenofovir alafenamide (10 or 25 mg) once daily plus renally dose-adjusted emtricitabine or lamivudine is an option (**AIII**).
- Some clinicians may choose to continue full-dose emtricitabine or lamivudine to allow for people with CrCl 15–29 mL/min to remain on fixed-dose tenofovir alafenamide/emtricitabine products.[5]

Preferred Therapy (Receiving Hemodialysis)

- ART with renally dose-adjusted tenofovir disoproxil fumarate plus (emtricitabine 200 mg or lamivudine 300 mg once daily) (**AII**) or
- ART with tenofovir alafenamide (10 or 25 mg)* plus emtricitabine 200 mg PO once daily (given after HD on dialysis days) (**AII**).[5]
  *Tenofovir alafenamide and emtricitabine do not require renal dose adjustment in people receiving HD; therefore, fixed dose tenofovir alafenamide and emtricitabine products may be continued.[5]

Duration of Therapy/Monitoring During Therapy

- People on treatment for HBV and HIV should receive therapy indefinitely (**AIII**).
- HBV DNA should be monitored at 6-month intervals (**AII**).
- HBsAg should be monitored yearly (**AIII**).

The American Gastroenterology Association: Prevention and Treatment of HBV Reactivation in At-Risk Individuals

The AGA updated guidance for prevention and treatment of HBVr in 2025.[4] HBV reactivation is characterized by a loss of immunologic suppression of HBV activity in patients who are either positive for HBsAg or HB core antibody.[4] Reactivation of the HBV is generally a consequence of chronic immunosuppression, induced either by drug therapy or by pathologic immunosuppression.[4] Rituximab, and other B cell–depleting agents, are traditionally associated with a notably high risk of HBVr.[4] The current update provides guidance on the prevention and management of HBVr in individuals taking immune checkpoint inhibitors, anti-interleukin therapies, chimeric antigen receptor T cell (CAR-T) therapies, cytokine/integrin inhibitor therapies, tyrosine kinase inhibitors, anti T-cell therapies, and Janus kinase inhibitors, and updated the guidance provided for anti–tumor necrosis factor (TNF) therapies in light of new evidence.[4] The updated guideline also provides guidance on the prevention and management of HBVr among individuals undergoing transcatheter arterial chemoembolization (TACE) for HCC, and individuals who are co-infected with hepatitis C virus (HCV) and undergoing direct-acting antiviral (DAA) treatment.[4]

In keeping with the definitions established in the 2014 guideline, the AGA panel defined HBVr as either the de novo appearance of HBV-DNA in a patient with previously undetectable HBV-DNA or at least a 10-fold increase in HBV-DNA value compared with their baseline.[4] Permissible surrogates were new detection of HBsAg or HBeAg.[4] Hepatitis flare due to HBVr is defined as an elevation in serum ALT level at least 3-times the baseline level that, at a minimum, is beyond the reference range. Additional outcomes of interest were interruption of treatment (e.g., chemotherapy) and adverse events from antiviral prophylaxis against HBVr.[4]

To date, 3 RCTs have compared the duration of antiviral prophylaxis after withdrawal of the exposure of interest. When comparing a longer with a shorter duration of prophylaxis (3 months after withdrawal of exposure in 1 study; 6 months in 2 studies), a relative risk (RR) of 0.99 (95% CI, 0.76–1.28) for HBVr and a RR 1.24 (95% CI, 0.46–3.39) for hepatitis flare from HBVr were found on pooled analysis of these trials.[4] The certainty in these effect estimates was downgraded to low due to concerns regarding very serious imprecision.[4] On subgroup analysis, 2 RCTs comparing 12 months of antiviral continuation after cessation of exposure with 6 months found a RR of 1.07 (95% CI, 0.68–1.68) for HBVr and a RR of 1.35 (95% CI, 0.45–3.99) for hepatitis flare from HBVr.[4] These findings suggest that the current body of evidence suffers from imprecision.[4] The panel concluded that antiviral prophylaxis should be continued for at least 6 months after cessation of exposure of interest.[4] However, in cases when the risk of HBVr is considered high, extension of antiviral therapy to 12 months is reasonable.[4] In cases of exposure to B cell–depleting agents, antiviral prophylaxis should be extended to at least 12 months after end of exposure to B cell–depleting agents, given several case reports of delayed HBVr beyond 12 months.[4]

The undesirable consequences of antiviral therapy were considered small when prescribing antiviral prophylaxis.[4] With use of tenofovir disoproxil fumarate, there can be concern regarding its impact on renal function and bone mineral density, although the overall effect remains small.[4] Tenofovir alafenamide does not adversely impact renal function or bone mineral density compared with tenofovir disoproxil fumarate.[4]

- For individuals at high risk of HBVr, the AGA recommends antiviral prophylaxis over monitoring alone (strong recommendation, moderate certainty evidence).[4] This recommendation assumes the use of antivirals with a high barrier to resistance. Antiviral prophylaxis should be started before medications that impose risk of HBVr and should be continued for at least 6 months after discontinuation of risk-imposing therapy (at least 12 months for B cell–depleting agents).[4]

- For individuals at moderate risk of HBVr, the AGA suggests antiviral prophylaxis over monitoring alone (conditional recommendation, moderate certainty evidence).[4] This recommendation assumes the use of antivirals with a high barrier to resistance. Patients who place a higher value on avoiding long-term use of antiviral therapy and the cost associated with its use, and a lower value on avoiding the small risk of reactivation (particularly in those who are HBsAg-negative) may reasonably select active monitoring over antiviral prophylaxis, with careful consideration of feasibility and likelihood of adherence to long-term monitoring. Monitoring should be performed at 1- to 3-month intervals, and must include assessment of hepatitis B viral load in addition to assessment of ALT.[4]

- For individual at low risk of HBVr, the AGA suggests monitoring alone over using antiviral prophylaxis (conditional recommendation, moderate certainty evidence)**.**[4] This recommendation assumes regular and sufficient follow-up that ensures continued monitoring. Patients who place a higher value on avoiding the small risk of reactivation (particularly those who may be on more than 1 low-risk immunosuppressive medication) and a lower value on the burden and cost of antiviral therapy may reasonably select antiviral therapy.[4]

- For individuals at risk of HBVr, the AGA recommends testing for hepatitis B (strong recommendation, moderate certainty evidence).[4] Given universal CDC screening guidance for hepatitis B for all adults by testing for HBsAg, anti-HBs, and total anti-HBc, stratifying screening practices by magnitude of HBVr risk is no longer needed. It is reasonable to test initially for serologic markers alone (at minimum for HBsAg, anti-HBc) followed by viral load testing (HBV-DNA) if HBsAg and/or anti-HBc is positive.[4]

New Indications or Market Removals:

- December 2018: An expanded age range was approved for VIREAD (tenofovir disoproxil fumarate) oral tablets.[8] This approval extended the use of tenofovir disoproxil fumarate to pediatric patients aged 2 years of age and older weighing at least 10 kg for the treatment of chronic HBV infection or in combination with other antiretroviral agents for the treatment of HIV infection.[8] The recommended pediatric dose for both indications is 8 mg/kg up to a maximum of 300 mg taken once daily.[8] Prior to this expanded indication, tenofovir disoproxil fumarate was approved for use in pediatric patients aged 12 years and older. The safety and efficacy of tenofovir in children aged 2 to 12 years with chronic hepatitis B was evaluated in a placebo-controlled, double blind RCT (NCT01651403).[8] Eighty-nine children were enrolled and 60 were assigned to weight-based tenofovir 8 mg/kg once daily, while 29 were assigned to receive placebo once daily over 48 weeks.[8] At week 48, 77% (46/60) of tenofovir-treated patients had achieved serum hepatitis B DNA < 400 copies/mL (60 IU/mL) compared with 7% (2/29) of placebo-treated patients who achieved this primary endpoint.[8] The adverse reactions observed in pediatric subjects who received treatment with tenofovir were consistent with those observed with tenofovir in clinical trials in adults.[8]

- March 2024: An expanded age range was approved for VEMLIDY (tenofovir alafenamide) oral tablets.[7] This approval extended the use of tenofovir alafenamide to pediatric patients aged 6 years and older weighing at least 25 kg for the treatment of chronic HBV infection with compensated liver disease.[7] Prior to this expanded indication, the drug was approved for use in pediatric patients aged 12 years and older. The pediatric dose is the same as adults, 25 mg taken orally once daily with food.[7] The safety and efficacy of tenofovir alafenamide in pediatric patients was evaluated in an ongoing phase 2 trial (NCT02932150), which enrolled 88 patients with chronic hepatitis B infection aged 6 years to 18 years. Fifty-nine patients received tenofovir alafenamide and 29 patients received placebo once daily over 24 weeks in the double-blind RCT.[7] The study met its primary endpoint of percentage of patients with HBV DNA levels below 20 IU/mL at 24 weeks of therapy.[7] In total, 19% (11/59)of patients who received the treatment achieved the reduction in HBV DNA levels, compared to 0% (0/29) in the placebo group.[7] The safety profile of tenofovir alafenamide in pediatric patients was similar to that observed in adults.[7]

- Telbivudine (TYZEKA) was removed from the United States (U.S.) market in 2016 by the manufacturer based on business factors, not safety or efficacy issues.

Randomized Controlled Trials:
A total of 116 citations were manually reviewed from the initial literature search. After further review, 116 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
tenofovir disoproxil fumarate	VIREAD	ORAL	POWDER	N
entecavir	BARACLUDE	ORAL	SOLUTION	N
adefovir dipivoxil	ADEFOVIR DIPIVOXIL	ORAL	TABLET	N
entecavir	BARACLUDE	ORAL	TABLET	N
entecavir	ENTECAVIR	ORAL	TABLET	N
lamivudine	LAMIVUDINE HBV	ORAL	TABLET	Y
tenofovir disoproxil fumarate	TENOFOVIR DISOPROXIL FUMARATE	ORAL	TABLET	Y
tenofovir alafenamide	VEMLIDY	ORAL	TABLET	N
tenofovir disoproxil fumarate	VIREAD	ORAL	TABLET	Y

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) ALL <1946 to March 19, 2025>

1	Tenofovir/	5785
2	Antiviral Agents/ or entecavir.mp.	107790
3	Antiviral Agents/ or adefovir.mp. or HBV/	134262
4	Lamivudine/	7058
5	Hepatitis B/th [Therapy]	1983
6	1 or 2 or 3 or 4	41896
7	5 and 6	809
8	limit 7 to (english language and humans and yr="2017 -Current")	116

Appendix 3: Key Inclusion Criteria

Population	People with chronic HBV infection
Intervention	Peginterferon or oral antiviral agents (tenofovir disoproxil fumarate, tenofovir alafenamide, lamivudine, adefovir, entecavir)
Comparator	Other antiviral agents or peginterferon
Outcomes	Progression to cirrhosis or hepatocellular carcinoma
Timing	5 to 10 years
Setting	Outpatient

Hepatitis B Antivirals

Goal(s):

- Approve treatment supported by medical evidence and consensus guidelines
- Cover preferred products when feasible for covered diagnosis

Length of Authorization:

- Up to 12 months; quantity limited to a 30-day supply per dispensing.

Requires PA:

- All nonpreferred Hepatitis B antivirals

Covered Alternatives:

- Preferred alternatives listed at http://www.orpdl.org/drugs/

Pediatric Age Restrictions:

- lamivudine (Epivir HBV) – ≥ 2 years ~~2-17 years~~
- ~~teblivdine (Tyzkea) – 16 years~~
- adefovir dipivoxil (Hepsera) – ≥ 12 years
- entecavir (Baraclude) – ≥ 2 years
- tenofovir disoproxil fumarate (Viread) – ≥ 2 years and weight ≥ 10 kg ~~safety and effectiveness not established in pediatrics~~
- tenofovir alafenamide (Vemlidy) – ≥ 6 years and ≥ 25 kg

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is the request for an antiviral for the treatment of HIV/AIDS?	**Yes:** Approve for up to 12 months	**No:** Go to #3
3. Is the request for treatment of chronic Hepatitis B Virus infection?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
4. Is the request for a pediatric patient?	**Yes**: Go to #5	**No:** Go to #6
5. Does the pediatric patient meet the age and weight requirements for the requested drug (see Pediatric Age Restrictions above).	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is this a continuation of current therapy previously approved by the FFS program (i.e. filled prescription within prior 90 days)? Verify via pharmacy claims. ~~***If request is for Pegasys, refer to PA criteria "Pegylated Interferon and Ribavirin".***~~	**Yes:** Go to Renewal Criteria	**No:** Go to #7
7. Has the client tried and is intolerant to, resistant to, or has a contraindication to the preferred products?	**Yes:** Document intolerance, resistance, or contraindication. Approve requested treatment for 6 months with monthly quantity limit of 30-day supply.	**No:** Go to #8
8. Will the prescriber consider a change to a preferred product?	**Yes:** Inform prescriber of covered alternatives in class	**No:** Approve requested treatment for 6 months with monthly quantity limit of 30-day supply

Renewal Criteria		
1. Is the patient adherent with the requested treatment (see refill history)?	**Yes:** Go to #2	No: Deny; Pass to RPh for provider consult

Renewal Criteria		
2. Is HBV DNA undetectable (below 10 IU/mL by real time PCR) or the patient has evidence of cirrhosis? Note: Antiviral treatment is indicated irrespective of HBV DNA level in patients with cirrhosis to prevent reactivation.	**Yes:** Approve for up to 1 year with monthly quantity limit of 30-day supply	No: Deny; pass to RPh for provider consult

P&T Review: *8/25 (DM); 3/17(MH); 3/12*
Implementation: *TBD; 4/1/17; 5/29/14; 1/13*