# Hepatitis B Coinfection

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Module 4: Co-Occurring Conditions
Lesson 5: Hepatitis B Coinfection

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## Background

Hepatitis B virus (HBV) is a significant cause of liver disease among persons with HIV. For individuals with HIV who were born in the United States, acquisition of HBV occurs primarily through injection drug use and sexual contact, with most HBV infections occurring in adulthood.[1,2] Recommendations for hepatitis B immunization and vaccine schedules for HBV are addressed in detail in the Immunizations in Adults lesson in the Module Basic Primary Care.

### Epidemiology

In the United States, there are an estimated 660,000 people living with chronic HBV infection.[3] This corresponds to an estimated prevalence rate for chronic HBV of 0.2%, meaning roughly 1 in every 500 people in the United States are living with chronic HBV.[3] Globally, there are 10 HBV genotypic subtypes (types A-J). Genotype A is the predominant subtype in the United States among non-Asian people and genotype B or C among Asian people in the United States.[1,4,5] In the HIV Outpatient Study (HOPS) during the years 1996 through 2007, investigators reported 8.4% of persons with HIV tested positive for chronic HBV (either HBsAg positive or HBV DNA positive), (Figure 1) a markedly elevated prevalence compared to the prevalence in the general population.[6] In this same study, they reported the highest rate of chronic HBV and HIV coinfection occurred among men who have sex with men.[6]

### Impact of HIV and HBV Coinfection

When compared to individuals with HBV monoinfection, those with HBV and HIV coinfection have higher baseline HBV DNA levels, lower alanine aminotransferase (ALT) levels, accelerated progression of liver disease, increased risk of hepatocellular carcinoma, and increased liver-related mortality.[7,8,9] Among those with HIV and HBV coinfection, the highest liver-related mortality rates have occurred in individuals with low CD4 cell counts.[10] Multiple studies have found that HIV and HBV coinfection and HIV and HCV coinfection have both played a major role in liver-related deaths in persons with HIV.[11,12,13,14,15] Further, a large observational cohort study from the United Kingdom reported increased liver-related mortality in persons who had coinfection with either HBV or hepatitis C virus (HCV) when compared with HIV monoinfection, but the highest liver-related mortality was seen in those with triple HIV-HBV-HCV infection (Figure 2).[16] The impact of HBV on the natural history of HIV remains less clear, with some studies demonstrating no significant effect of HBV coinfection on HIV-related outcomes and others suggesting an adverse impact.[17,18,19]

# Screening for HBV in Persons with HIV

## Recommendations for Baseline Screening

All persons with HIV should undergo initial screening for HBV infection upon entry into medical care with a triple panel test that consists of hepatitis B surface antigen (HBsAg), antibody to hepatitis B surface antigen (anti-HBs), and total antibody to hepatitis B core antigen (total anti-HBc).[1] Chronic HBV infection is defined by the detection of HBsAg on two separate tests that have been obtained at least 6 months apart.[1] Individuals with confirmed chronic HBV should have further testing that includes HBV DNA, hepatitis B e antigen (HBeAg), and antibody to HBeAg (anti-HBe).[1] For persons with HIV who have negative HBsAg testing, HBV DNA testing should be considered if they have persistent elevation in ALT, or they have suspected acute HBV infection.[20]

## Interpretation of Hepatitis B Serologic Studies

Serologic testing for the diagnosis of HBV infection involves measurement of the full panel of distinct HBV-specific antigens and antibodies outlined above. Results of this serologic panel can help determine whether a patient is susceptible to infection, immune as a result of resolved infection, immune as a result of vaccination, acutely infected, or chronically infected (Table 1).[21,22]

## Laboratory Markers Following Acute HBV Infection

In persons with acute HBV infection, HBsAg can be detected in serum 4 to 10 weeks after HBV acquisition.[23] Although HBV DNA is usually detectable 10 to 20 days before the appearance of HBsAg, testing for HBV DNA is not part of routine HBV screening.[24] Concurrent with the onset of clinical symptoms, anti-HBc appears, primarily detectable as the IgM class (IgM anti-HBc). Although IgM anti-HBc antibodies typically decline to undetectable levels within 6 months, the IgG class (IgG anti-HBc) persists indefinitely (with active or resolved infection). If resolution of infection occurs, there is loss of HBsAg and the appearance of anti-HBs. It is important to note that for individuals who have cleared past infection, the epigenetic covalently closed circular (CCC) HBV DNA persists in hepatocyte nuclei and remains the main barrier to true viral eradication or cure. Indeed, individuals with prior HBV clearance remain at risk of HBV reactivation if they have severe immunosuppression, they are receiving immunosuppressive therapy (particularly B-lymphocyte-depleting treatments), or they are receiving direct-acting antiviral therapy for the treatment of HCV.[25]

## Management of Isolated Hepatitis B Core Antibody

Among persons with HIV who undergo serologic testing for HBV, an estimated 17 to 41% have isolated anti-HBc.[26,27] There are four possible interpretations of this finding: (1) resolved HBV infection with waning anti-HBs titers (most common), (2) a false-positive anti-HBc test, (3) occult "low-level" chronic HBV infection, or (4) resolving acute HBV infection.[22,28] For persons with HIV and isolated anti-HBc, the Adult and Adolescent OI Guidelines recommend the following approach (Figure 3).[1]

- Administer a one-time standard dose of any hepatitis B vaccine and check anti-HBs 1 to 2 months later.
    - If the anti-HBs titer is greater than 100 IU/mL, then no further vaccination is required. Note that the cut-off value of 100 IU/mL used in this setting is higher than the usual cutoff of 10 IU/mL to document immunity following routine immunization with hepatitis B vaccine.[29]
    - If the anti-HBs titer is less than 100 IU/mL, then complete the HBV vaccine series, followed by anti-HBs testing 1 to 2 months after completing the series. The full vaccine series options include the 2-dose series using standard-dose *Heplisav-B* or the 3-dose series with double-dose vaccine using *Engerix-B* or *Recombivax HB*.

## Screening Before Initiating NRTI-Sparing Antiretroviral Regimens

The importance of HBV screening is essential when starting or switching to a nucleoside reverse transcriptase inhibitor (NRTI)-limited or NRTI-sparing antiretroviral regimen, including the 2-drug regimens dolutegravir-lamivudine, dolutegravir-rilpivirine, and injectable cabotegravir plus rilpivirine, since these regimens do not provide adequate treatment for HBV.[30] In addition, the 3-drug antiretroviral regimen dolutegravir-abacavir-lamivudine does not provide adequate treatment of HBV. Screening for HBV is this setting can identify (1) persons with chronic HBV who may not be a good candidate to receive a regimen that does not have adequate HBV treatment or who would need additional HBV treatment if they switch to that regimen, (2) persons without protective HBV immunity who can benefit from HBV vaccination, and (3) persons with prior HBV infection who will need monitoring if they start on an NRTI-sparing or NRTI-limited regimen. The following factors should be considered:

- Persons with chronic HIV and HBV coinfection should avoid treatment with an antiretroviral regimen, such as dolutegravir-lamivudine, dolutegravir-rilpivirine, injectable cabotegravir plus rilpivirine, or dolutegravir-abacavir-lamivudine, that does not contain two agents with strong HBV activity.
- If the NRTI-limited or NRTI-sparing regimen is used in the setting of needing to avoid use of tenofovir DF and tenofovir alafenamide, then entecavir should be added, unless the regimen already includes lamivudine. If there has been prior exposure to lamivudine (without a second anti-HBV agent), then entecavir resistance may have occurred, and expert consultation should be obtained.
- People with HIV who had prior resolved HBV infection (indicated by negative HBsAg, positive anti-HBc, and either positive or negative anti-HBs) have less than 1% risk of HBV reactivation, and an even lower risk of reactivation hepatitis. Among this group, people with positive anti-HBs have the lowest risk of reactivation of HBV.[30,31]
- For individuals with HIV who had prior HBV exposure but do not have active HBV infection, the antiretroviral guidelines suggest ALT monitoring every 1 to 3 months for 6 months after switching to an NRTI-sparing or NRTI-limited regimen. If there is an increase in ALT levels, HBV DNA testing is warranted to check for HBV reactivation hepatitis.[30]

# Initial Evaluation with HBV and HIV Coinfection

Individuals with HIV who are also diagnosed with chronic HBV (positive HBsAg on two occasions at least 6 months apart) should undergo further HBV-related evaluation and receive counseling. The following information summarizes key recommendations for the initial evaluation of persons diagnosed with HBV in the setting of HIV coinfection.[1]

- **Baseline HBV DNA Level:** A quantitative HBV DNA level, in conjunction with serum ALT, provides key information that can help determine whether the patient has active infection. In persons with HBV monoinfection, the baseline HBV DNA level has also been shown to predict subsequent risk for cirrhosis and liver cancer.[32,33] If the person with HIV is already receiving HIV antiretroviral therapy with agents that have activity against HBV (e.g., tenofovir alafenamide, tenofovir DF, emtricitabine, and lamivudine), the HBV DNA level may be undetectable.
- **HBeAg and anti-HBe**: Although HBeAg and anti-HBe are not recommended as part of routine screening for HBV, these tests are recommended as baseline testing in all persons diagnosed with active HBV. A positive HBeAg status typically indicates higher levels of HBV DNA, greater risk of HBV transmission, and higher risk of developing hepatocellular carcinoma.[34,35] In addition, the loss of HBeAg associated with anti-HBe seroconversion during HBV treatment is an important benchmark of successful therapy.
- **HBV Genotype and Baseline Resistance Assay**: Routine baseline HBV genotyping and resistance testing are not recommended.
- **Serologic Studies for Hepatitis A Virus (HAV):** Assess for immunity to HAV with HAV antibody (IgG or total). Persons without immunity to HAV should receive the HAV vaccine series.
- **Serologic Studies for Hepatitis C Virus (HCV):** Assess for HCV coinfection with HCV antibody (with reflex to HCV RNA for reactive antibody tests). Persons with HIV who have coinfection with both HBV and HCV have markedly accelerated progression of liver fibrosis and, therefore, should receive HBV and HCV treatment as soon as possible.
- **Studies for Hepatitis D virus (HDV)**: In the United States, approximately 4% of individuals with HIV and HBV coinfection also have a positive HDV serologic test.[36] Hepatitis D virus (HDV) can only persist in people who have HBV infection. Screen with the HDV antibody test (anti-HDV). Individuals with a reactive anti-HDV serologic test should have testing for HDV RNA.[30]
- **Basic Evaluation and Monitoring of Liver Activity and Function:** Evaluate the individual's liver disease severity with platelet count, albumin, bilirubin, alkaline phosphatase, and prothrombin time, and hepatitis activity with ALT, aspartate aminotransferase (AST) at baseline and every 6 months.
- **Staging of Liver Fibrosis:** Consider noninvasive methods of staging, such as aspartate aminotransferase-to-Platelet Ratio Index (APRI), Fibrosis-4 (Fib-4) Index, FibroTest (FibroSURE), and transient elastography (FibroScan) to assess for liver fibrosis.[37] Note that FibroTest and transient elastography have not been validated for use in clinical decision-making for patients with chronic HBV, with or without HIV.
- **Counseling**: Initial counseling should include recommendations to (1) abstain from alcohol and (2) use effective methods to prevent secondary HBV transmission. These include the use of consistent barrier protection with sex partners, as well as testing and vaccination of susceptible partners and household members.

# Treatment of HBV in People with HIV Coinfection

## Goals for HBV Treatment in Persons with HIV Coinfection

The short-term goals for treating HBV in persons with HIV coinfection are the same as in persons with HBV monoinfection: normalize ALT levels, obtain HBeAg seroconversion (if HBe-antigen positive at baseline), and maintain suppression of HBV replication.[38] The long-term goals of HBV treatment are to halt or reverse fibrosis progression, reduce the risk of hepatic decompensation, prevent the development of hepatocellular carcinoma, and decrease HBV-associated mortality.[38,39,40] Data from persons with HBV monoinfection suggest HBV therapy can achieve these goals, but similar long-term studies in persons with HIV and HBV coinfection have not been published.[39,41] Nevertheless, cohort studies with at least a few years of follow-up time suggest that antiviral therapy can readily achieve the shorter-term goals of virologic suppression and HBeAg seroconversion in persons with HIV coinfection.[42,43,44]

## General Approach

Initiation of HIV antiretroviral therapy is recommended in all persons with HIV, including those with HBV coinfection.[45] For persons with HIV and active HBV coinfection, the antiretroviral regimen should provide maximal suppression of both HIV and HBV.[1,30] Specifically, for persons with chronic HBV, the antiretroviral regimen should include two agents that also have full activity against HBV.[1,30] Some experts recommend the same approach in persons with isolated anti-HBc.[1] There are four HIV antiretroviral NRTI medications that also have antiviral activity against HBV: tenofovir alafenamide, tenofovir DF, emtricitabine, and lamivudine. Tenofovir alafenamide and tenofovir DF are both highly active against HBV and have a high genetic barrier for development of HBV drug resistance.[30,46] Although emtricitabine and lamivudine can be used interchangeably, they should not be used together and neither provide adequate HBV treatment when used alone. Use of peginterferon or adefovir to treat HBV is not recommended in persons with HIV.[1,30] Entecavir is highly effective against HBV and a preferred agent for treating HBV monoinfection. In contrast, entecavir alone is not recommended to treat HBV in persons with HIV, since it has some activity against HIV, and, can cause an M184V mutation to develop if used without a fully suppressive antiretroviral regimen.[30,47]

## Recommend Regimens for Treatment of HBV and HIV Coinfection

The antiretroviral treatment regimen for people with HBV and HIV coinfection should consist of a fully suppressive HIV regimen that includes an NRTI backbone of either tenofovir alafenamide-emtricitabine, tenofovir DF-emtricitabine, or tenofovir DF-lamivudine.[1,30] Since tenofovir alafenamide-emtricitabine and tenofovir DF-emtricitabine are commonly used as the backbone NRTIs in most preferred HIV antiretroviral regimens for initial therapy, concomitant treatment of HIV and HBV can be achieved in nearly all circumstances without having to make special adjustments (Table 2).[1,30,48]

## Switching or Starting Nucleos(t)ide-Sparing Regimens

Several antiretroviral regimens are effective for HIV treatment but not for HBV. The regimens with inadequate HBV activity are referred to as nucleoside/nucleotide-sparing reverse transcriptase inhibitor regimens.[1] This situation most often involves the 2-drug regimens dolutegravir-lamivudine, dolutegravir-rilpivirine, or injectable cabotegravir and rilpivirine. In addition, the recommended 3-drug antiretroviral regimen dolutegravir-abacavir-lamivudine does not effectively treat HBV. Note the regimens dolutegravir-lamivudine and dolutegravir-abacavir-lamivudine are not technically nucleoside-sparing (since lamivudine and abacavir are nucleoside reverse transcriptase inhibitors), but without one of the nucleotide reverse transcriptase inhibitors (tenofovir alafenamide or tenofovir DF) these regimens are not adequate to treat HBV. The following table summarizes considerations when starting or switching a nucleoside/nucleotide-sparing reverse transcriptase inhibitor regimen in a person with chronic HBV (Table 3).[1]

## Additional Considerations and Treatment During Pregnancy

The management of HBV in persons with HIV can be complex and some aspects of care may require consultation with a specialist. The following table addresses multiple additional considerations in persons with HIV and HBV coinfection, including treatment of HCV coinfection, hepatic flare with medication discontinuation, HBV reactivation in the setting of receiving immunosuppressive therapies, and management during and immediately after pregnancy (Table 4).[1]

# Monitoring of HBV Treatment Response

## Monitoring Response to HBV Treatment

Monitoring the virologic response to HBV therapy should consist of checking HBV DNA levels every 3 to 6 months.[1] The HBV DNA levels accurately predict response to therapy, and regular monitoring during therapy is recommended to prevent or minimize the development of drug-resistant variants. In addition, for those individuals who are HBeAg positive at baseline, testing for HBeAg every 6 months is recommended after the person achieves HBV viral suppression. The decline to an undetectable HBV DNA level typically takes longer than the time to an undetectable HIV RNA in response to antiretroviral therapy. An incompletely suppressed HBV DNA level after 24 weeks often occurs with HBV therapy, particularly if the baseline level exceeds 100,000 IU/mL. Once the HBV levels become undetectable, the frequency of monitoring HBV DNA levels can change to every 6 months.

## Definitions of Treatment Response

The Adult and Adolescent OI Guidelines provide the following definitions for the different virologic responses, based on those generated by the European Association for the Study of the Liver (EASL) (Figure 10).[1]

- **Primary Virologic Nonresponse**: less than 1 $\log_{10}$ IU/mL decline in HBV DNA levels 12 weeks after starting therapy
- **Partial Virologic Response**: greater than or equal to 1 $\log_{10}$ IU/mL decline in HBV DNA levels at 24 weeks, but HBV DNA remains detectable
- **Complete Virologic Response**: undetectable HBV DNA levels at 24 to 48 weeks using a real-time HBV DNA assay
- **Maintained Virologic Response**: complete virologic response that continues while the individual is on therapy for HBV
- **Sustained Virologic Response**: a virologic response that is still present 6 months after discontinuing therapy

## Monitoring for Medication-Related Toxicity

The Adult and Adolescent OI Guidelines also highlight the additional risks associated with the use of specific anti-HBV medications and recommend the following additional monitoring strategies.[1]

- **Tenofovir DF**: Similar to patients with HIV monoinfection who take tenofovir DF, persons with HIV and HBV coinfection should have electrolytes and serum creatinine checked every 3 to 6 months and urinalysis every 12 months. For patients with renal insufficiency, including those receiving renally dosed tenofovir DF, monitoring should be frequent and as often as indicated based on the stability of serum creatinine.
- **HIV Antiretroviral Therapy**: When using modern antiretroviral regimens to treat HIV, antiretroviral medication-related liver toxicity is uncommon. With current antiretroviral agents, an increase in aminotransferase levels that occurs in a patient with HBV coinfection who recently started on HIV antiretroviral therapy would most likely be a result of HBV-related immune reconstitution inflammation.[49]

## Management of Hepatitis B Treatment Failure

For the purposes of management, HBV treatment failure should be categorized as follows: (1) primary nonresponse after 12 weeks of therapy (less than 1 $\log_{10}$ decline in HBV DNA levels) or (2) an increase in HBV DNA of greater than 1 $\log_{10}$ above nadir.[1] It is important to recognize that HBV DNA levels may decline very slowly, especially in the setting of high pretreatment DNA levels and low CD4 cell counts, with some individuals taking a few years or more to completely suppress HBV DNA.[43,50] These slow kinetics in HBV

DNA level decreases are not necessarily associated with HBV drug resistance,[51,52] but when lamivudine or emtricitabine is used without another active agent against HBV, resistance frequently develops.[1,53,54] The Adult and Adolescent OI Guidelines recommend the following strategies for the management of HBV treatment failure in persons with HIV coinfection.[1]

- If a person has been receiving lamivudine (or emtricitabine) as the sole agent against HBV, then tenofovir DF or tenofovir alafenamide should be added.[1,30] This strategy should be used even if lamivudine (or emtricitabine) HBV drug resistance is not suspected or documented.[55]
- Because tenofovir has a high genetic barrier to HBV resistance, the development of HBV drug resistance to tenofovir alafenamide or tenofovir DF is uncommon.[56] Therefore, it is reasonable to continue tenofovir alafenamide or tenofovir DF in the setting of slowly declining HBV DNA levels, along with adherence assessment and close monitoring.[46,56,57,58]
- Because entecavir resistance can emerge more readily in persons with preexisting lamivudine resistance, entecavir is not generally recommended as the mainstay of HBV therapy if lamivudine resistance is present. If it is necessary to use entecavir in that setting, use of higher-dose entecavir (1.0 mg/day rather than 0.5 mg/day) and more frequent monitoring of HBV DNA levels is recommended.[1]

# Stopping HBV Treatment and Hepatic Flares

In persons receiving treatment with one or more antiviral agent(s) active against HBV, stopping therapy may result in HBV reactivation and potentially serious hepatic inflammation; this inflammatory is marked by a rise in serum hepatic aminotransferase levels and commonly referred to as a hepatic flare—defined as an ALT increase to at least 3 times greater than the baseline level or ALT greater than 100 U/L.[25] In one study involving 255 individuals with HIV and HBV coinfection, when lamivudine was discontinued, approximately 30% of the participants had increases in ALT levels, 5% had grade 3 or grade 4 elevations, and approximately 1% developed fulminant hepatitis and hepatic decompensation (Figure 11).[59] If a hepatic flare occurs after stopping antiviral therapy, the onset is typically within 6 months after the cessation of therapy.[60]

## Management of Hepatic Flare

Individuals with HIV and HBV coinfection who stop antiviral therapy should have monitoring of aminotransferase levels every 6 weeks for 3 months and then every 3 months thereafter.[1] If a flare develops after stopping HBV therapy, the appropriate course of management is to restart antiviral therapy using a regimen that is fully suppressive for both HIV and HBV. It is also important to note that persons with HIV and HBV coinfection who abruptly stop antiretroviral therapy can have an abrupt marked increase in HIV RNA levels and develop a clinical illness similar to that observed in persons with acute HIV.[61]

# HBV-Related Immune Reconstitution Syndrome (HBV-IRIS)

In persons with HIV and HBV coinfection, hepatic inflammation can occur after immune recovery in response to effective HIV antiretroviral therapy. This clinical scenario is commonly referred to as immune reconstitution inflammatory syndrome (IRIS).

## Risk Factors for Developing HBV-Related IRIS

Although the risk of HBV-related IRIS is highest if HIV is treated without effective therapy against HBV, it can occur even with regimens that are fully active against both HIV and HBV.[62,63] Baseline risk factors (prior to initiation of antiretroviral therapy) associated with HBV-related IRIS include low CD4 cell count, high HBV DNA level, and elevated baseline ALT level.[64]

## Timing and Differential Diagnosis with HBV-Related IRIS

The hepatitis flare is first detected as an increase in ALT levels, typically within 3 to 12 weeks after starting antiretroviral therapy. The differential diagnosis includes medication-related toxicity, alcohol hepatotoxicity, a new viral hepatitis infection (acute hepatitis A or C), or an opportunistic infection. To help distinguish between these conditions, a review of the medication history, prior hepatitis A immunization, and history of recent HCV exposure would be indicated, as well as measurement of serum HBV DNA, HIV RNA, and CD4 cell count.[1]

## Monitoring for HBV-Related IRIS

Recommended monitoring for HBV-related IRIS consists of checking ALT levels monthly for 3 to 6 months after initiating antiretroviral therapy, then every 3 months thereafter.[1] If, at 12 months after starting antiretroviral therapy, IRIS has not developed, it is reasonable to return to routine laboratory monitoring.

## Management of HBV-Related IRIS

For individuals who develop HBV-related IRIS (as indicated by rising ALT levels in the setting of immune recovery), existing guidelines recommend continuing therapy for HIV and HBV, unless the individual develops drug-induced hypersensitivity (e.g., Stevens Johnson Syndrome or Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS]), symptomatic hepatitis (nausea, vomiting, abdominal pain, or jaundice), or the ALT increases to greater than 10 times the upper limit of normal.[1] With severe IRIS, particularly in a person with cirrhosis, consultation with a hepatologist is recommended.[1] Although corticosteroids are used to manage some IRIS-related disorders, there are insufficient data to recommend for or against the use of corticosteroids in an individual with HIV who has hepatitis B-related IRIS.[1]

# Hepatitis D Virus

Hepatitis D virus (HDV), also known as hepatitis delta virus, is a defective satellite RNA virus that depends on HBsAg for the encapsulation of the HDV genome—it cannot exist or infect individuals in the absence of active HBV infection. The rate of triple infection with HIV, HBV, and hepatitis D virus is estimated to occur in about 4% of persons with HIV and HBV coinfection.[36,65,66] Screening for HDV antibody is recommended for all individuals with HIV who have chronic HBV infection, with reflex HDV RNA testing for those who have a reactive anti-HDV serology.[1] Among those with positive HIV, HBV, and HDV serology, approximately 40% have a positive HDV RNA test.[36] Although triple infection with HIV-HBV-HDV has no known adverse impact on clinical, virologic, or immunologic responses to antiretroviral therapy when compared with dual HIV and HBV infection, it accelerates progression of liver fibrosis, increases the risk of liver cirrhosis, and elevates the likelihood of developing hepatocellular carcinoma.[66,67]

## Treatment of Hepatitis D Virus

There are currently no FDA-approved treatment options for the treatment of HDV, other than suppressing HBV infection. Although peginterferon has been recommended as the mainstay of therapy for HDV, it is poorly tolerated and produces low cure rates.[65,68] Unfortunately, the suppression of HDV RNA levels is not reliably sustained with treatment of HBV.[69] Individuals with HIV-HBV-HDV triple infection should be referred to a specialist who has expertise in this area.[30]

# Preventing HBV Perinatal Transmission

The overall rate of transmission of HBV from an HBsAg-positive woman to her neonate during the perinatal period can be as high as 90% in the absence of immunoprophylaxis. The presence of HBeAg and the associated higher HBV DNA levels mediate this risk; mothers with a positive HBeAg test have a perinatal transmission rate of 70 to 90%, whereas those with a negative HBeAg test have a rate of transmission less than 10%.[21,22] When perinatal transmission of HBV occurs, it usually happens during or shortly before delivery, but can take place less frequently in utero. The exact rate of perinatal HBV transmission among pregnant women with HIV and HBV coinfection is not well established. Transmission of HBV through breast milk is not a significant source of perinatal HBV transmission in an infant who has received appropriate immune prophylaxis.

## Strategy for Preventing HBV Perinatal Transmission

In a pregnant woman with HIV and HBV coinfection, the following strategies should be used to effectively prevent the maternal-to-child transmission of HBV and HIV: (1) suppression of maternal HIV RNA and HBV DNA to undetectable levels during pregnancy and delivery and (2) administration of prophylaxis to the infant after birth (antiretroviral medication for HIV and immunoglobulin and HBV vaccine for HBV). For persons with HBV monoinfection, there is no contraindication to breastfeeding.[22,70] Therefore, decisions regarding breastfeeding should be based on shared decision-making regarding the risk of HIV transmission via breastfeeding.[71] The mode of delivery in pregnant women with HIV and HBV coinfection should be based on standard obstetrical and HIV-related indications, as there is no indication that cesarean section impacts the risk of vertical HBV transmission.[72,73] Women who are pregnant and have HIV and HBV coinfection, should receive hepatitis A vaccination during pregnancy if not already immune.

## Treatment of HBV and HIV Coinfection in Pregnant Women

Unfortunately, even with fully suppressed HBV DNA levels, the risk of HBV perinatal transmission is not completely eliminated.[74] Lamivudine, emtricitabine, tenofovir DF, and tenofovir alafenamide have been studied in pregnancy and can be used safely.[38] According to the Perinatal HIV Clinical Guidelines, the preferred dual NRTI backbone of antepartum antiretroviral therapy for pregnant women with HIV and HBV coinfection is either (1) tenofovir DF-emtricitabine, (2) tenofovir DF plus lamivudine, or (3) tenofovir alafenamide-emtricitabine.[72] An additional third antiretroviral medication is needed to complete the regimen for HIV therapy, and this medication can be determined based on recommended HIV antiretroviral regimens for use during pregnancy.[75] Peginterferon alfa is an abortifacient at high doses and should not be used in pregnancy.[30]

## HBV Prevention Measures for Neonates

Infants weighing greater than 2,000 grams who are born to HBsAg-positive mothers, regardless of HBV treatment status during pregnancy, should receive one dose of hepatitis B immune globulin and the first dose of the HBV vaccine series within 12 hours of birth. The second and third doses of vaccine should be administered at 1 and 6 months of age, respectively.[1] Management of infants weighing less than 2,000 grams is the same, except that the initial vaccine dose (at birth) should not be counted as part of the vaccine series due to potentially lower immunogenicity in these infants; three additional doses of vaccine (for a total of four doses) should be administered beginning at age 1 month, then at age 2-3 months, and then again at age 6 months.[22] Postvaccination testing for both anti-HBs and HBsAg should be performed in all infants after completion of the vaccine series at age 9 to 18 months (but not before 9 months of age or earlier than 4 weeks after the last vaccine dose); this regimen is greater than 95% effective in preventing HBV infection in these infants.[72]

# Surveillance for Hepatocellular Carcinoma

In persons with HIV and HBV coinfection, hepatocellular carcinoma usually develops at an earlier age and progresses faster than in persons with HBV monoinfection.[40,76] For persons with HBV and HIV coinfection, the risk of HCC is significantly increased with persistently elevated HIV RNA levels and with low CD4 cell counts.[77,78] Paradoxically, the overall incidence of hepatocellular carcinoma in people with HIV and HBV coinfection has increased in the modern antiretroviral era, primarily due to a longer overall lifespan and more years to develop hepatocellular cancer.[78] For individuals who have evidence of cirrhosis, including those with HIV and HBV coinfection, screening for hepatocellular carcinoma is strongly recommended.[1,79] In general, persons diagnosed with hepatocellular carcinoma have a poor prognosis, but survival may be improved if the cancer is detected at a very early stage. There is one randomized controlled trial, as well as observational data, to support HCC screening in all people with HIV and chronic HBV infection.[80,81]

## Indications for HCC Surveillance with HIV and HBV Coinfection

For persons with HIV and HBV coinfection, the 2025 AASLD/IDSA HBV Treatment Guideline recommends hepatocellular carcinoma surveillance in the following groups.[82]

- All individuals with cirrhosis
- All men 18 years of age and older
- All women 40 years of age and older
- Some experts recommend for all persons with HIV and HBV who are 40 years of age and older

## HCC Surveillance after Clearance of HBsAg

For persons with chronic HBV infection who experience spontaneous or treatment-related clearance of HBsAg, the risk of developing liver disease progression declines considerably, as does the risk of hepatocellular carcinoma. The risk of hepatocellular carcinoma, however, is thought to persist, particularly in older individuals and those who have cirrhosis. The 2025 AASLD/IDSA HBV Treatment Guideline recommends continued HCC surveillance for persons who have achieved HBsAg loss for any of the following:[4]

- Cirrhosis,
- Family history of HCC,
- Loss of HBsAg after 40 years of age for men,
- Loss of HBsAg after 50 years of age for women.

## Method of Hepatocellular Carcinoma Surveillance

The AASLD 2023 Guidance for HCC Surveillance recommends performing hepatic ultrasound and serum alpha-fetoprotein (AFP), every 6 months for hepatocellular carcinoma surveillance.[83] The hepatocellular carcinoma surveillance methods are the same for persons with HIV and HBV coinfection as with HBV monoinfection.

# Managing Advanced Liver Disease

The management of persons with HIV and HBV coinfection who develop cirrhosis and/or end-stage liver disease is the same as in patients with HBV monoinfection and involves close clinical monitoring.

- **Screening for Gastroesophageal Varices**: Patients with HBV and cirrhosis should undergo baseline screening with an esophagogastroduodenoscopy (EGD) to determine whether they have gastroesophageal varices large enough to warrant variceal bleed prophylactic therapy.[84] Patients with varices should undergo evaluation by a medical provider or specialist experienced with management of cirrhosis and prevention of variceal bleeding. If no substantial varices are observed, then EGD should be repeated every 2 years or sooner if liver decompensation occurs (progression from Child-Turcotte-Pugh class A to Child-Turcotte-Pugh class B/C cirrhosis).
- **Liver Transplantation**: Liver transplantation is not readily available for many patients with HIV, but has been shown to have favorable outcomes in persons with HIV and HBV coinfection.[85] The management of decompensated cirrhosis or end-stage liver disease in a person with HIV and HBV coinfection should be done by or under the guidance of a hepatologist.[1]

## Summary Points

- In the United States, approximately 10% of persons with HIV have HBV coinfection; these individuals have a higher risk of liver-related morbidity and mortality when compared to those with HBV monoinfection.
- The long-term treatment goals are the same for persons with HIV and HBV coinfection as for those with HBV monoinfection: delay progression of liver disease, reduce the risk of hepatocellular carcinoma, and improve survival.
- The recommended antiretroviral regimens for treating persons with HIV and HBV coinfection should include three medications that are active against HIV and two medications that are active against HBV. The preferred regimens should include tenofovir alafenamide-emtricitabine, tenofovir DF-emtricitabine, or tenofovir DF plus lamivudine as part of a fully suppressive antiretroviral regimen.
- People with chronic HBV can have hepatic flares when discontinuing antiretroviral therapy. People with chronic HBV can have immune reconstitution syndrome with hepatic inflammation after initiating antiretroviral therapy.
- Persons with HIV and HBV coinfection should undergo screening for HDV.
- Management of pregnant women with HIV and HBV coinfection requires antepartum, intrapartum, and postpartum interventions to reduce the risk of perinatal transmission of both HIV and HBV.
- For persons with chronic HBV infection and HIV coinfection, hepatocellular carcinoma surveillance is indicated in all individuals with cirrhosis, men 18 years of age and older, and women 30 years of age and older. Some experts recommend HCC screening for HCC in all persons with HBV and HIV coinfection who are 40 years of age and older.
- The management of individuals with HIV and HBV coinfection who develop cirrhosis and/or end-stage liver disease is generally the same as persons with HBV monoinfection and involves close clinical monitoring and the assistance of a hepatologist when indicated.

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# Figures

**Figure 1 Prevalence of Chronic HBV in Persons with HIV, the HIV Outpatient Study, 1996-2007**

These data are from the HIV Outpatient Study (HOPS), 1996-2007

Source: Spradling PR, Richardson JT, Buchacz K, Moorman AC, Brooks JT; HIV Outpatient Study (HOPS) Investigators. Prevalence of chronic hepatitis B virus infection among patients in the HIV Outpatient Study, 1996-2007. J Viral Hepat. 2010;17:879-86.

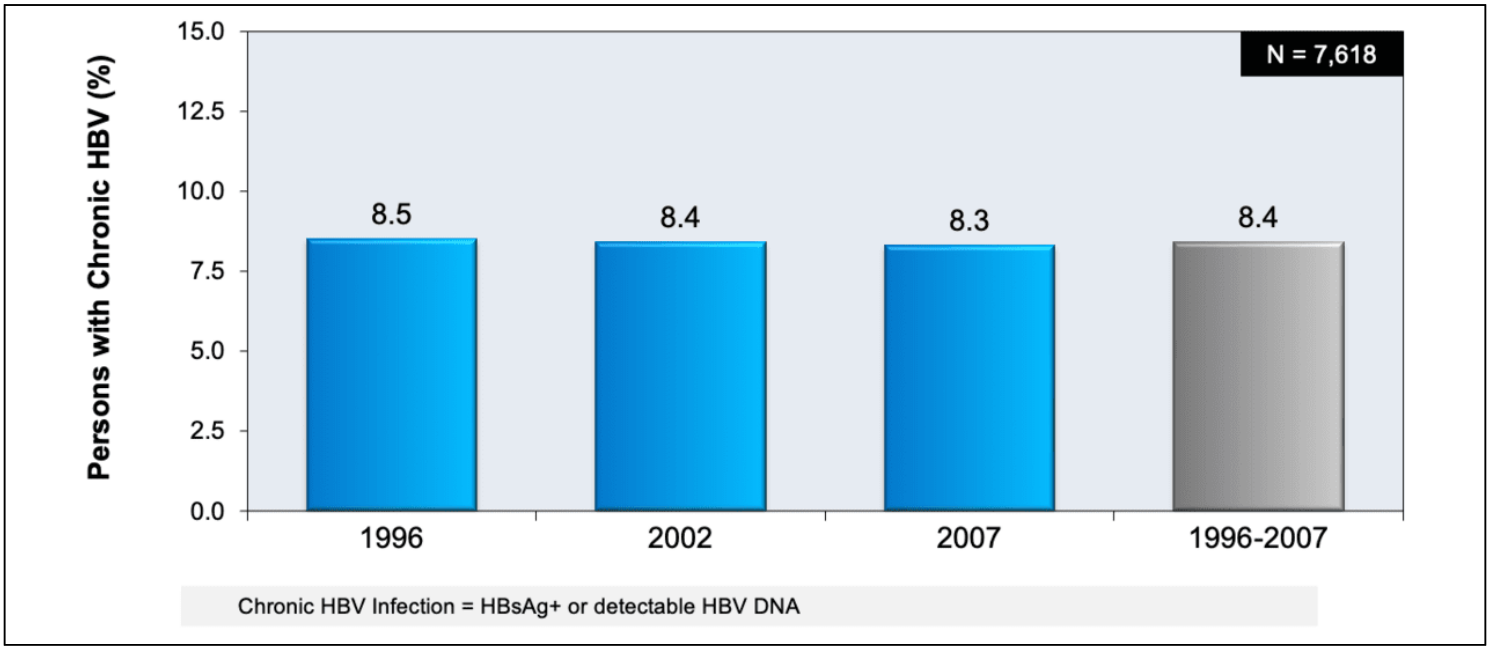

**Figure 2 Liver-Related Mortality Based on HBV and HCV Coinfection Status, 2004–2012**

These data are from 25 ,486 individuals with HIV enrolled in the UK Collaborative HIV Cohort (UK CHIC) Study during the years 2004-2012. Coinfection with HBV and/or HCV increased liver-related mortality.

Source: Thornton AC, Jose S, Bhagani S, et al. Hepatitis B, hepatitis C, and mortality among HIV-positive individuals. AIDS. 2017;31:2525-32.

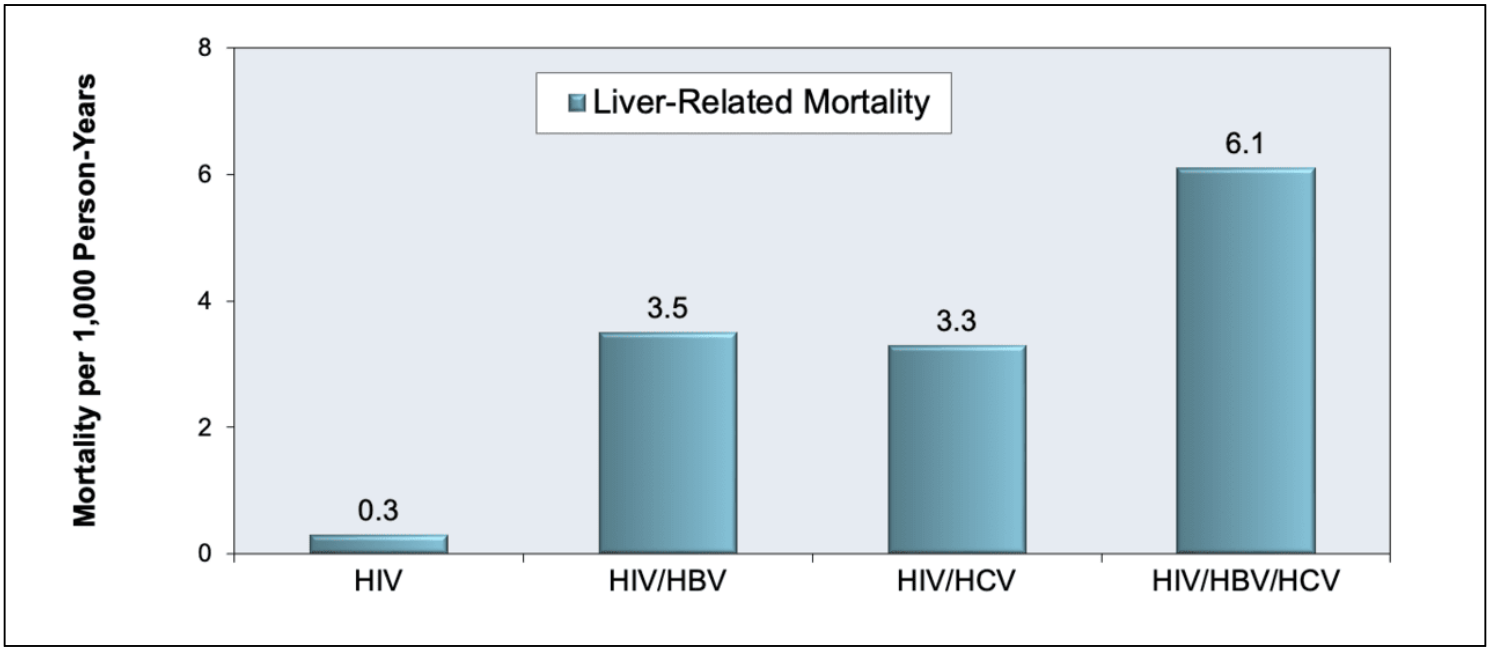

**Figure 3 Approach to Isolated Anti-HBc in Persons with HIV**

*The full vaccine series options include the 2-dose series using standard-dose *Heplisav-B* or the 3-dose series with double-dose vaccine using *Engerix-B* or *Recombivax HB*.

Source: 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.

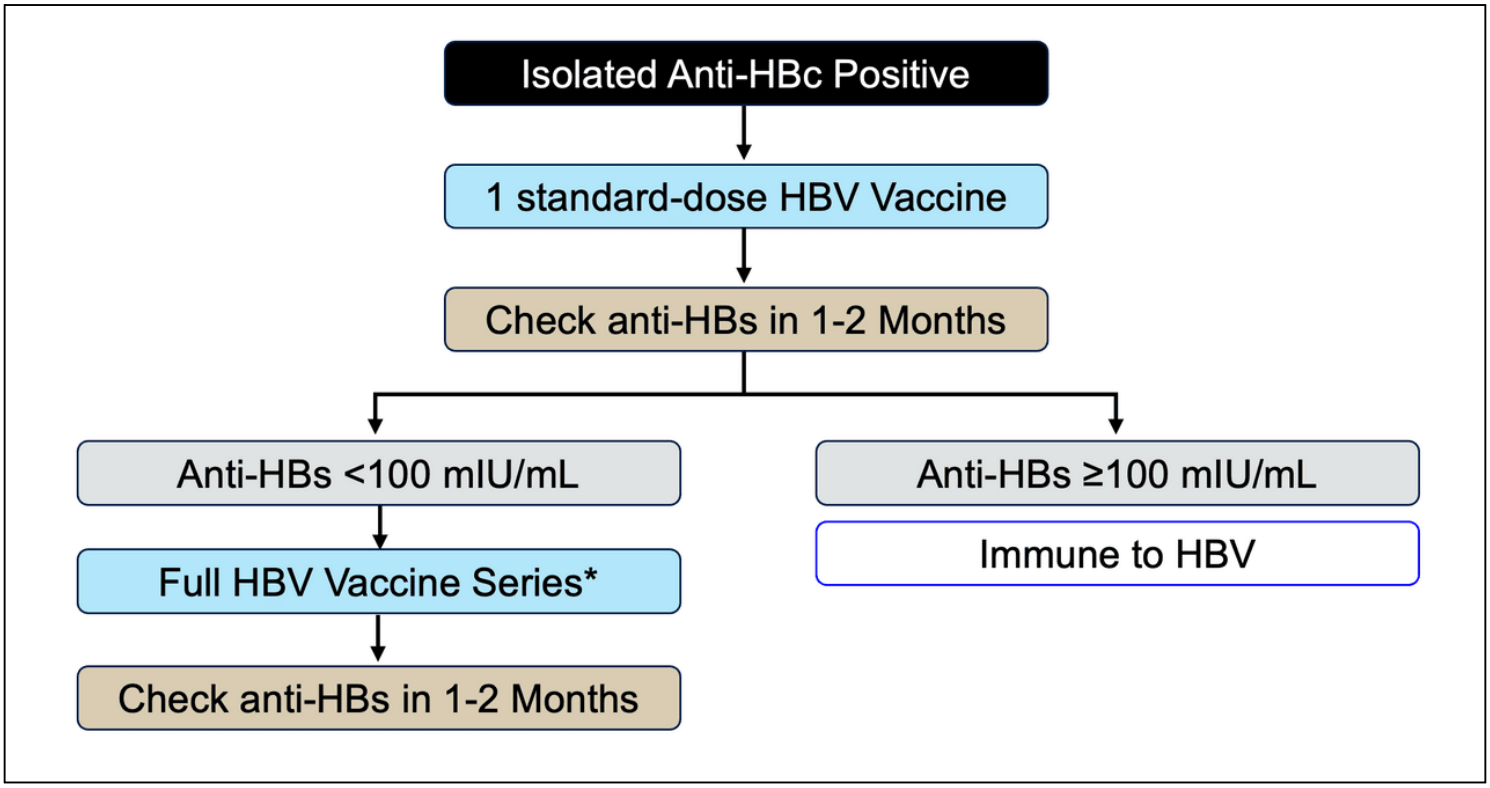

**Figure 4 Antiviral Agents with Activity Against HBV and HIV**

Note: in this table tenofovir includes tenofovir DF and tenofovir alafenamide.

Source: Iser DM, Sasadeusz JJ. Current treatment of HIV/hepatitis B virus coinfection. J Gastroenterol Hepatol. 2008;23:699-706.

| Medication | HBV Activity | HIV Activity | Selection of HIV Resistance Reported |
|---|---|---|---|
| Lamivudine | Yes | Yes | Yes |
| Adefovir | Yes | No[a] | No |
| Entecavir | Yes | Partial | Yes |
| Emtricitabine | Yes | Yes | Yes |
| Telbivudine | Yes | Partial[b] | No |
| Tenofovir alafenamide | Yes | Yes | Yes |
| Tenofovir disoproxil fumarate | Yes | Yes | Yes |

[a] = anti-HIV activity at higher doses; more potent against HBV
[b] = No in vitro activity observed against HIV, but HIV RNA decline reported

**Figure 5 HBV Therapy: Primary Virologic Nonresponse**

This graphic shows a less than 1 $\log_{10}$ IU/mL decline in HBV DNA levels 12 weeks after starting therapy

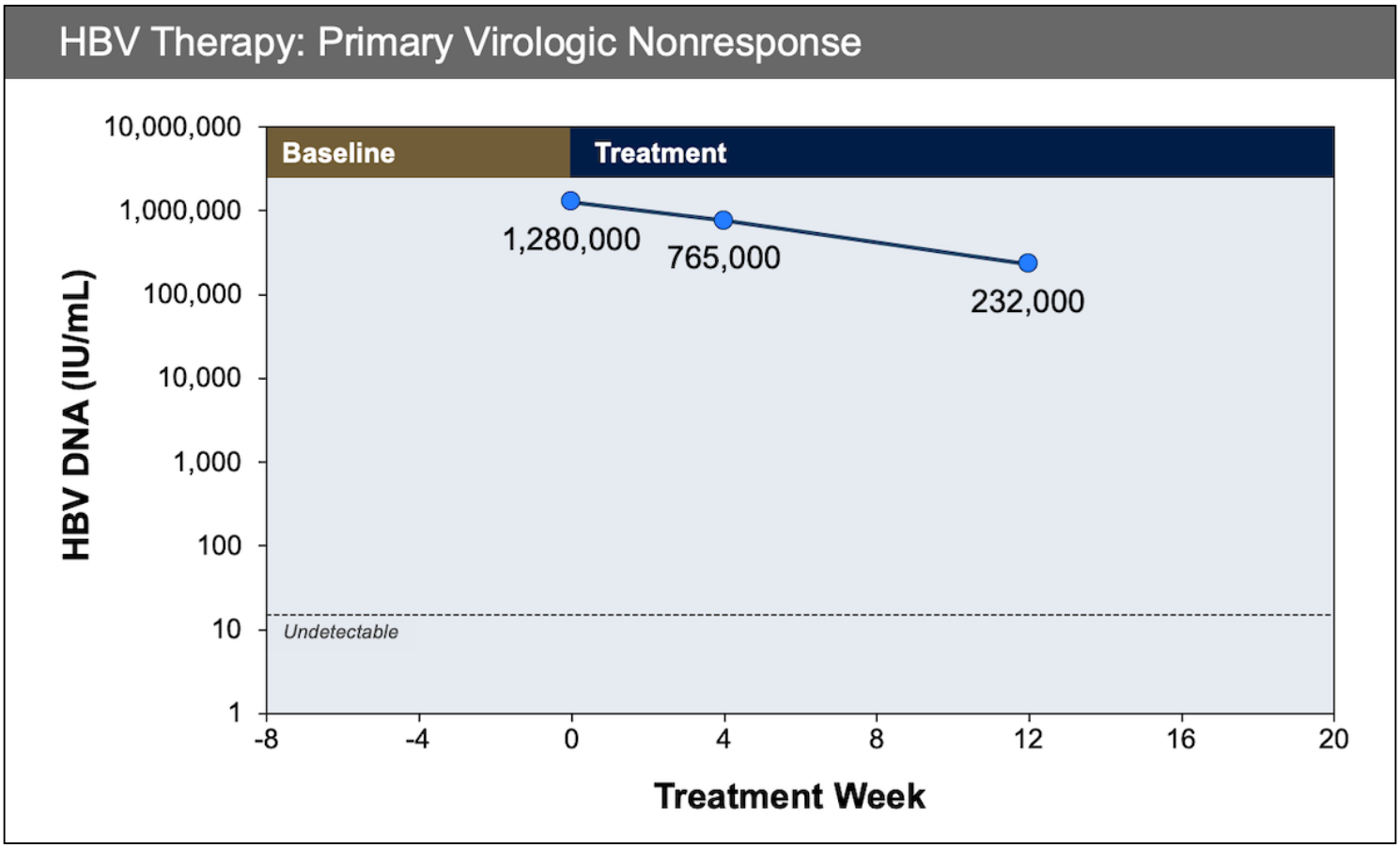

**Figure 6 HBV Therapy: Partial Virologic Response**

This graphic shows a greater than or equal to 1 $\log_{10}$ IU/mL decline in HBV DNA levels at 24 weeks, but HBV DNA remains detectable

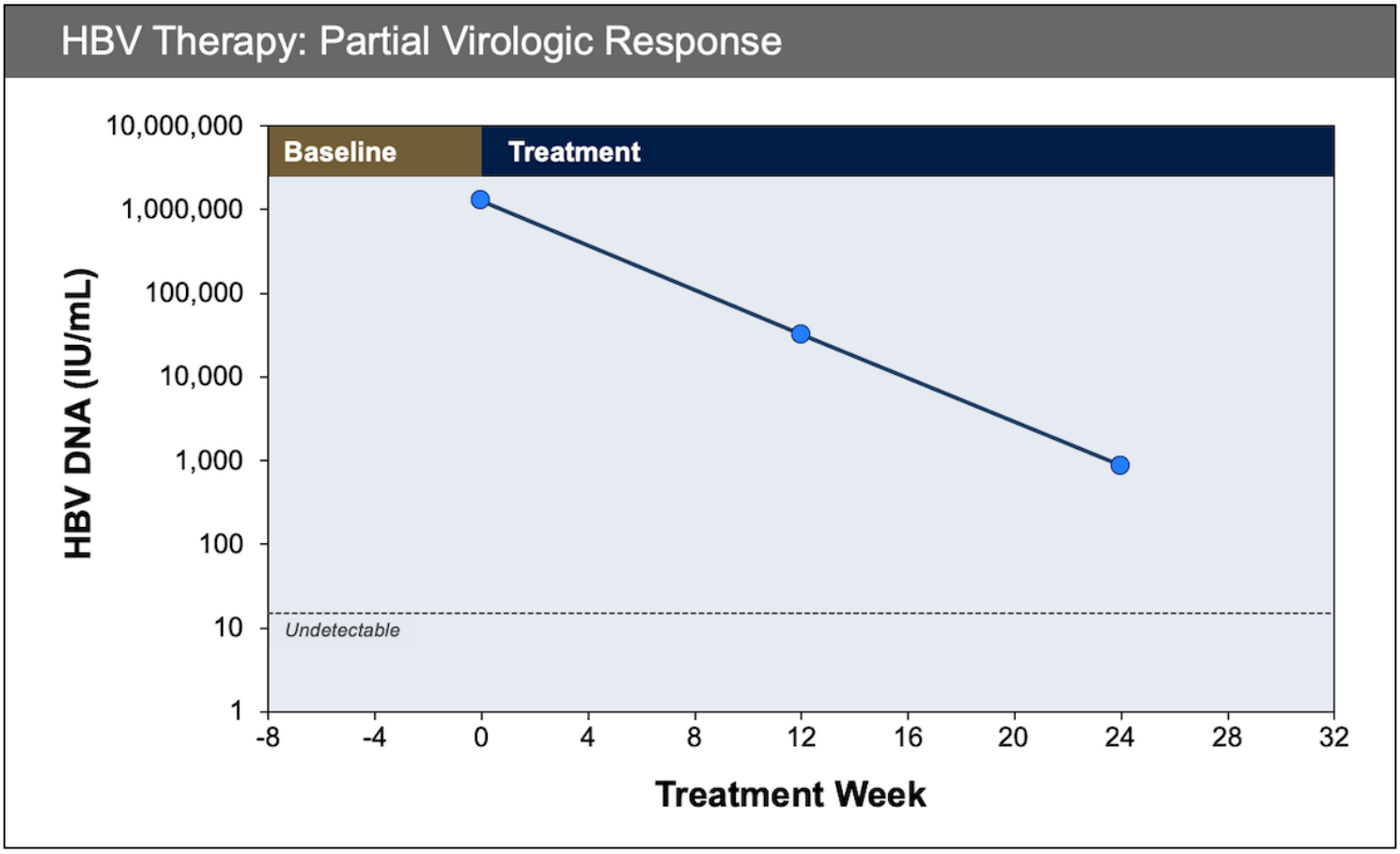

**Figure 7 HBV Therapy: Complete Virologic Response**

This graphic shows undetectable HBV DNA levels at 24 to 48 weeks using a real-time HBV DNA assay.

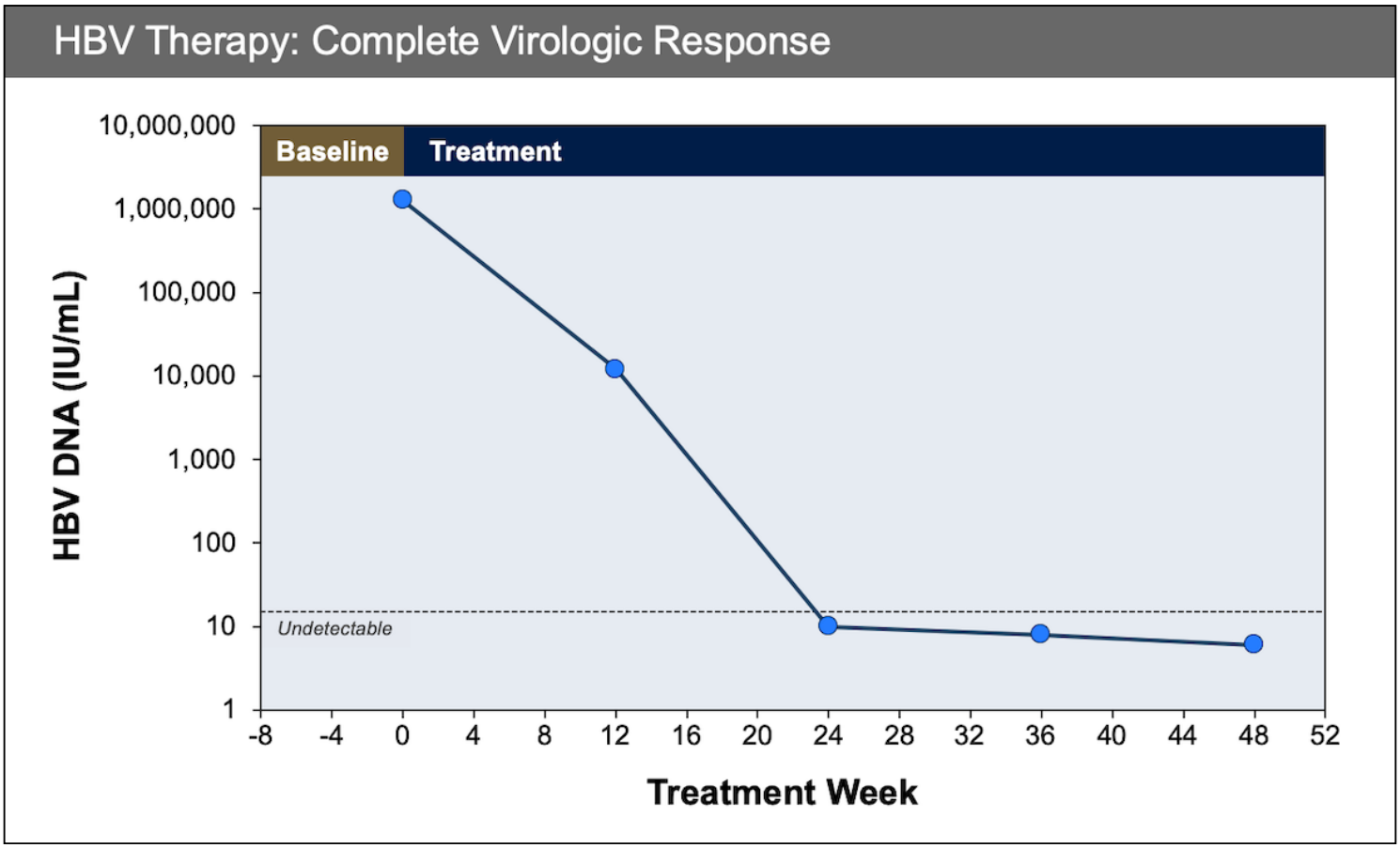

**Figure 8 HBV Therapy: Maintained Virologic Response**

This graphic shows a virologic response that continues while the patient is maintained on therapy for HBV.

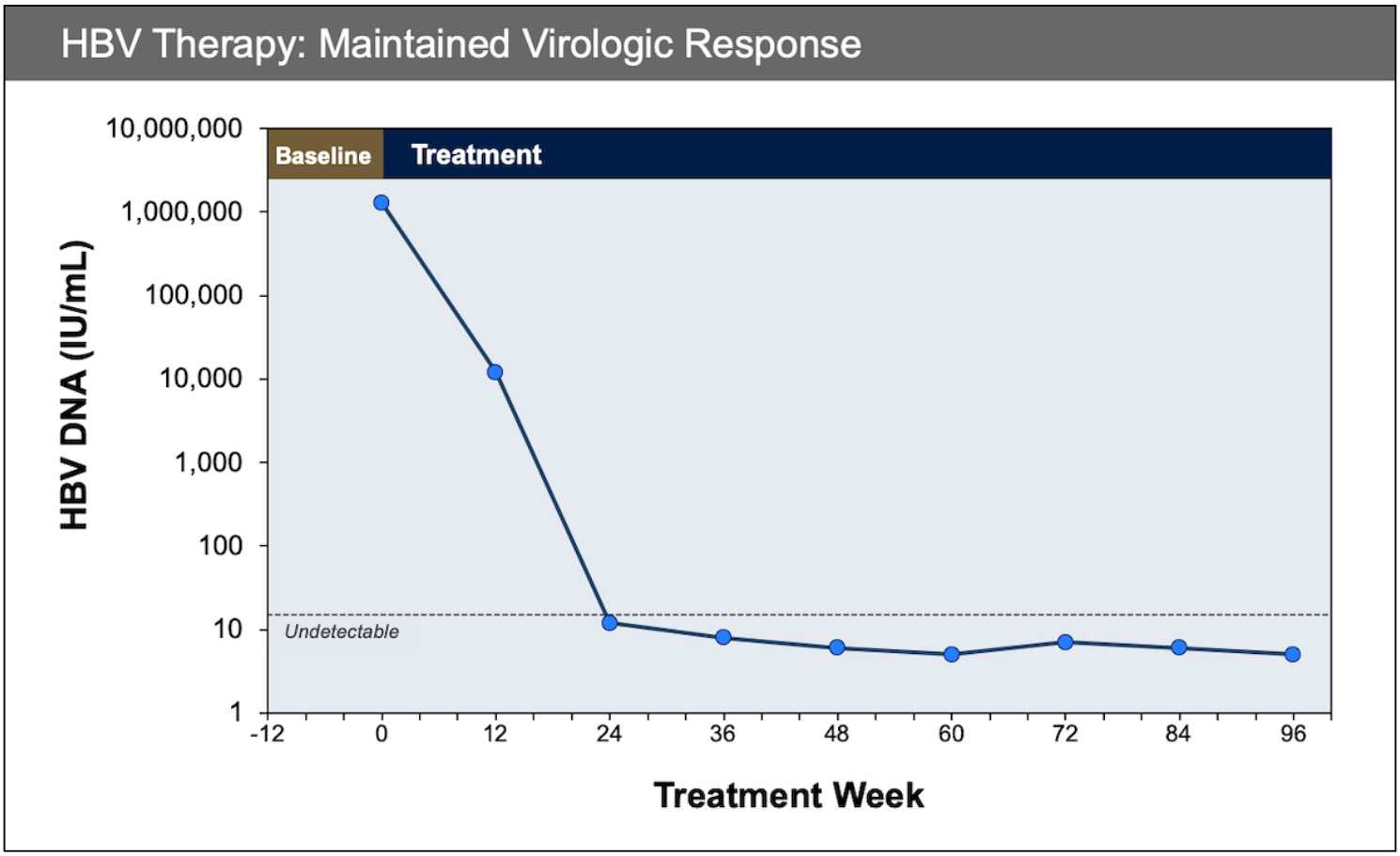

**Figure 9 HBV Therapy: Sustained Virologic Response**

In this example, HBV therapy is given for 120 weeks and the HBV DNA is maintained at undetectable levels for weeks 24 to 120. The HBV DNA levels remain undetectable for 48 weeks after discontinuing therapy.

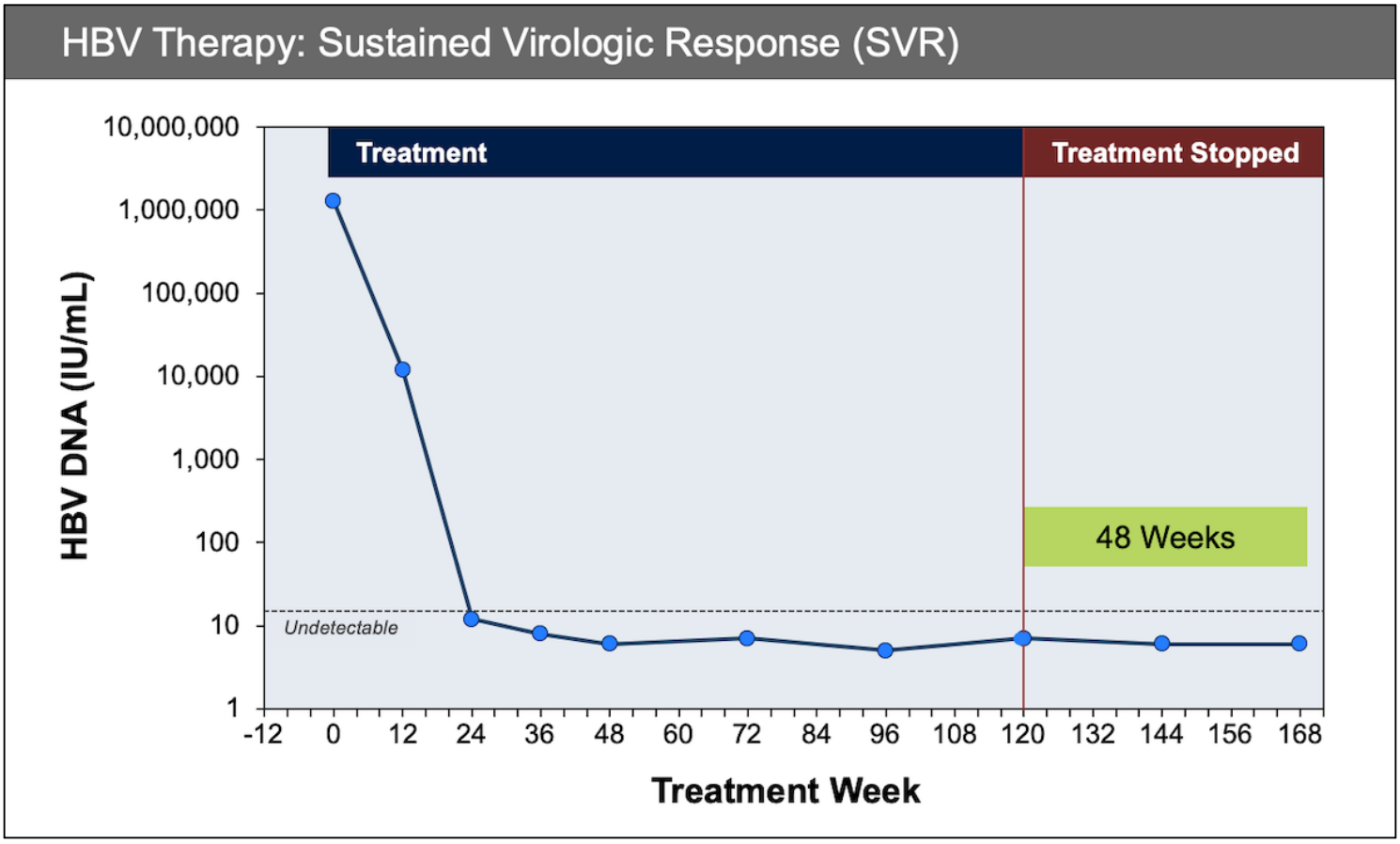

**Figure 10 Definitions for Hepatitis B Virologic Responses to Treatment**

**This is a dynamic visualization.** Please visit our website to experience this dynamic content.

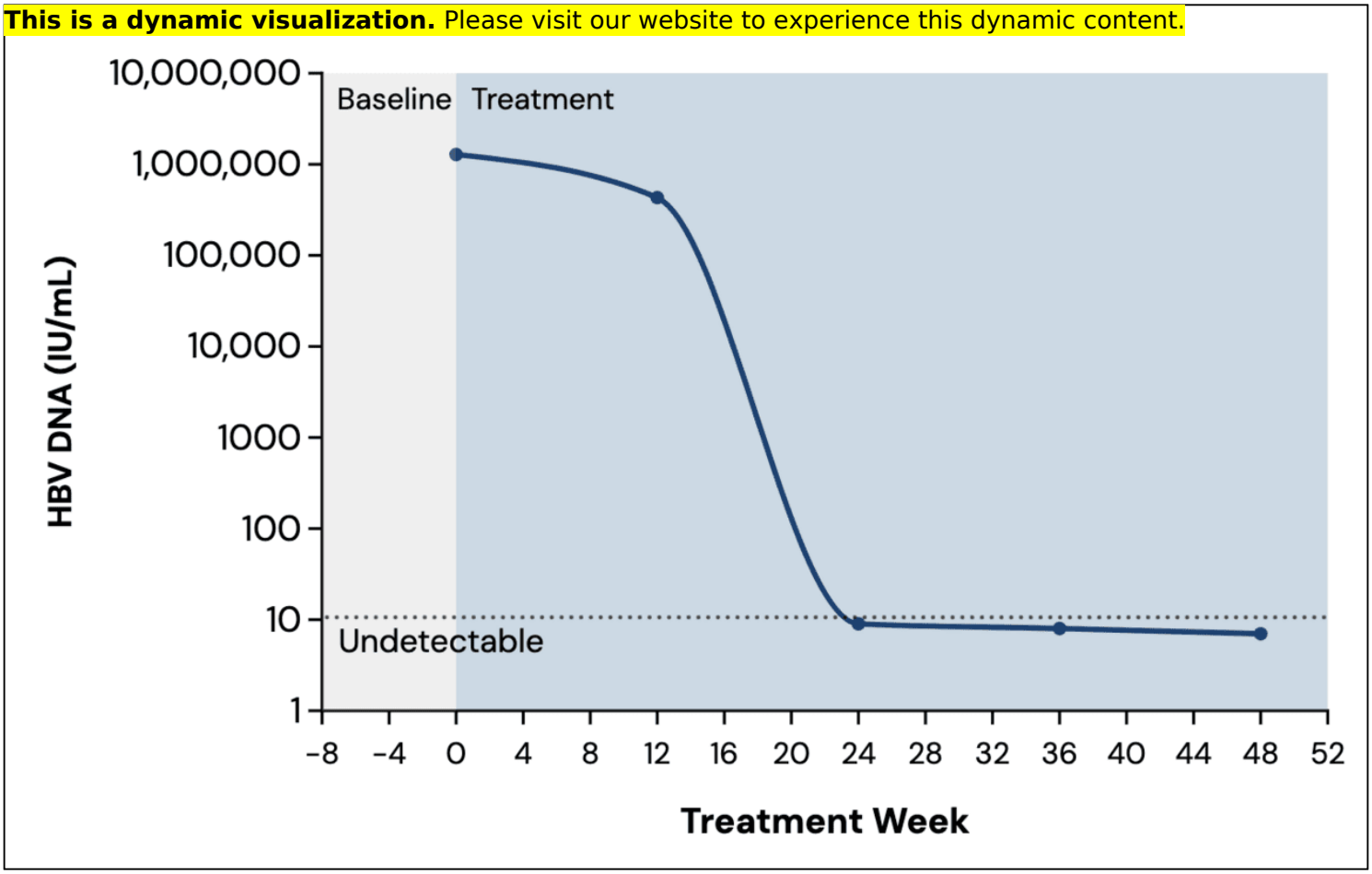

**Figure 11 Liver Enzyme Elevation after Lamivudine Discontinuation in Persons with HIV-HBV Coinfection**

This graph shows liver enzyme elevation after lamivudine discontinuation in persons with HIV-HBV coinfection who were enrolled in the Swiss HIV Cohort study. The graph shows the hepatotoxicity by grade severity (I-IV).

Source: Bellini C, Keiser O, Chave JP, et al. Liver enzyme elevation after lamivudine withdrawal in HIV-hepatitis B virus co-infected patients: the Swiss HIV Cohort Study. HIV Med. 2009;10:12-8.

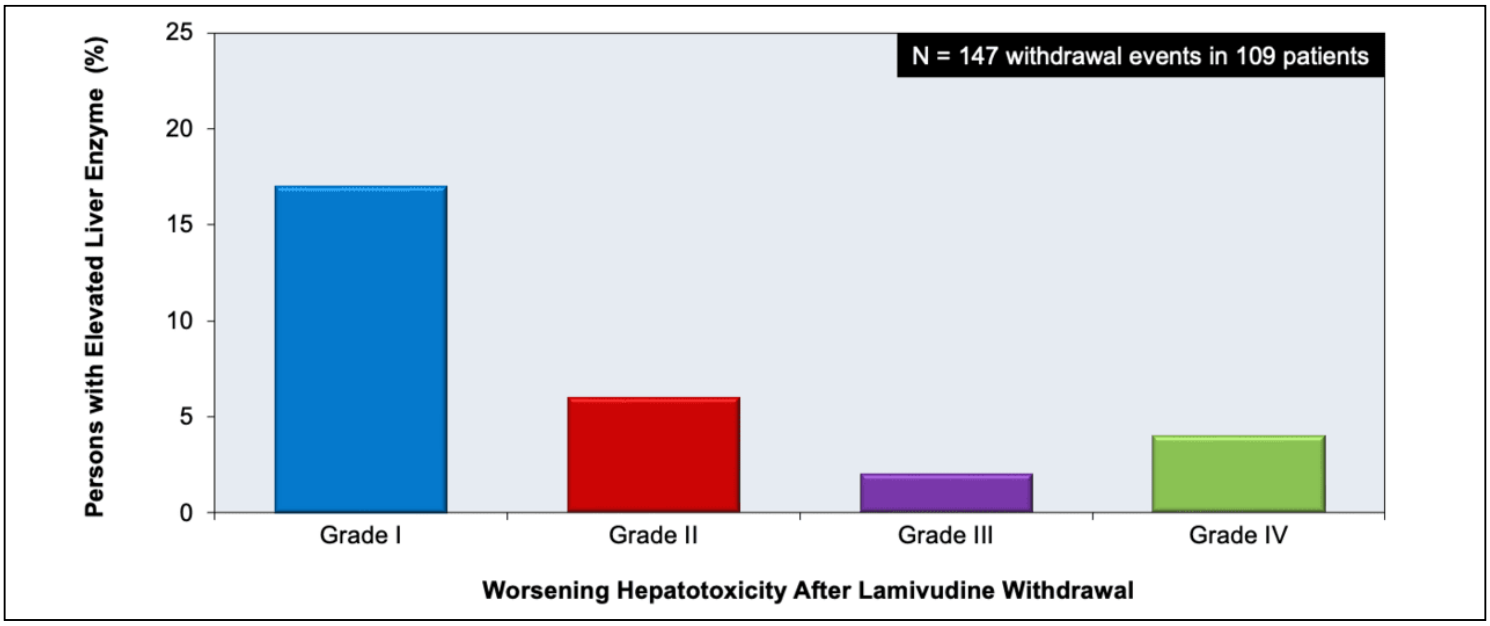

Table 1. Interpretation of Hepatitis B Triple Screen Serologic Test Results

| HBsAg | Anti-HBs | Total anti-HBc* | Interpretation |
|---|---|---|---|
| — | — | — | No prior exposure to hepatitis B virus, or<br>Prior vaccination with waning anti-HBs |
| — | + | + | Immune due to resolved natural hepatitis B infection |
| — | + | — | Immune due to hepatitis B vaccination (if anti-HBs ≥10 mIU/mL) |
| + | — | — | Very recent receipt of a hepatitis B vaccine dose, or<br>Very early acute HBV infection (prior to anti-HBc IgM) |
| + | — | + | Chronic hepatitis B infection, or<br>Acute HBV with reactive anti-HBc IgM |
| — | — | + | Interpretation unclear; four possibilities:<br>1. Resolved infection (most common)<br>2. False-positive anti-HBc, thus susceptible<br>3. “Low level” chronic infection (HBV DNA positive)<br>4. Resolving acute infection |

*Total anti-HBc is a measure of both IgM and IgG antibodies to HBcAg
Abbreviations: anti-HBc = antibody to hepatitis B core antigen; anti-HBs = antibody to hepatitis B surface antigen; HBsAg = hepatitis B surface antigen

Source:


- Schillie S, Vellozzi C, Reingold A, et al. Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep. 2018;67:1-31. [PubMed Abstract]

Table 2. Treatment of Chronic HBV Infection in People with HIV

| Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV | |
|---|---|
| Recommended Treatment of Chronic HBV in People with HIV | **Indication for Therapy**<br>• All people with HIV/HBV coinfection (HBsAg posi level **(AII),** should be treated with an antiretrov against both HIV and HBV infections **(AII).**<br>• Some experts recommend that people with isol therapy regimen that includes drugs active aga therapy regimen without HBV activity can be co benefits outweigh the risks of potential HBV rea below in the Special Considerations When Initia |
| | **Preferred Therapy (CrCl ≥60 mL/min)**<br>• The antiretroviral therapy regimen should inclu<br>◦ Tenofovir alafenamide (10 or 25 mg)[a] pl Tenofovir alafenamide 25 mg plus lamiv<br>◦ Tenofovir DF 300 mg plus (emtricitabine |
| | **Preferred Therapy (CrCl 30–59 mL/min)**<br>• The antiretroviral therapy regimen should inclu<br>◦ Tenofovir alafenamide (10 or 25 mg)[a] pl |
| | **Preferred Therapy (CrCl <30 mL/min, Not Receivi**<br>• Renally dosed entecavir (in place of [tenofovir D tenofovir alafenamide-emtricitabine) **(AIII),** wit<br>• Antiretroviral therapy with renally dose-adjuste lamivudine) **(AIII)** when recovery of renal functi<br>• If CrCl ≥ 15 to 29 mL/min, then antiretroviral th daily plus renally dose-adjusted emtricitabine o<br>◦ Some clinicians may choose to continue people with CrCl 15–29 mL/min to remai products. |
| | **Preferred Therapy (Receiving Hemodialysis)**<br>• Antiretroviral therapy with renally dose-adjuste lamivudine 300 mg once daily] **(AII)** *or*<br>• Antiretroviral therapy with tenofovir alafenamid hemodialysis on dialysis days) **(AII).** Tenofovir a dose adjustment in people receiving hemodialys emtricitabine products may be continued. |
| | **Duration of Therapy/Monitoring During Therapy**<br>• People on treatment for HBV and HIV should rec<br>• HBV DNA should be monitored at 6-month inter<br>• HBsAg should be monitored yearly **(AIII).** |
| | **Abbreviations**: CrCl = creatinine clearance; HBV = he<br>[a]Tenofovir alafenamide 10 mg dose is in the fixed-dose tenofovir alafenamide-emtricitabine and darunavir-cobi tenofovir alafenamide is used with other antiretrovirals<br><br>Rating of Recommendations: A = Strong; B = Moderate |

| | |
|---|---|
| | Rating of Evidence: I = Data from randomized controlle trials, observational cohort studies with long-term clinic studies, or regimen comparisons from randomized swit |

Source:

- Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV. National Institutes of Health, HIV Medicine Association, and Infectious Diseases Society of America. Hepatitis B virus infection. Last updated: December 16, 2024. [HIV.gov]

Table 3. Special Considerations when Initiating or Switching Nucleos(t)ide-Sparing Regimens

| Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV | |
|---|---|
| Special Considerations when Initiating or Switching Nucleos(t)ide-Sparing Regimens | • *In people without a histo*<br>sparing antiretroviral reg<br>unrecognized chronic HE |
| | • *In people with chronic H*<br>◦ Anti-HBV therapy<br>a switch to a nuc<br>◦ Switching to the<br>therapy (tenofov<br>lamivudine is the<br>◦ Switching to dolu<br>an anti-HBV drug |
| | • *In people with isolated a*<br>dolutegravir-lamivudine<br>therapy, but this could b<br>reactivation **(CIII).** |
| | • *In people with anti-HBc a*<br>regimen without additio |
| | **Abbreviations**: HBV = hepatiti<br>hepatitis B surface antigen; HBs<br>Rating of Recommendations: A =<br>Rating of Evidence: I = Data fro<br>trials, observational cohort stud<br>studies, or regimen comparison |

Source:

- Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV. National Institutes of Health, HIV Medicine Association, and Infectious Diseases Society of America. Hepatitis B virus infection. Last updated: December 16, 2024. [HIV.gov]

Table 4. Additional Considerations with Management of HBV and HIV Coinfection

| Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV<br>Additional Considerations with Management of HBV and HIV Coinfection | Other Considerations |
|---|---|
| | • Because people with HBV/HCV/HIV c high risk of hepatocellular carcinoma infection should be initiated, if feasib |
| | • Because HBV reactivation can occur absence of anti-HBV therapy, all peo infection should be on HBV-active ar |
| | • When changing antiretroviral therap due to risk of HBV reactivation with |
| | • If anti-HBV therapy must be discontin monitored every 6 weeks for 3 mont |
| | • If a hepatic flare occurs after drug di be potentially lifesaving **(AIII).** |
| | • If immunosuppressive therapy is giv<br>◦ People who are HBsAg positi of HBV DNA level **(AII).**<br>◦ For people who are HBsAg-ne tenofovir alafenamide given antiretroviral therapy regime<br>◦ For people who are HBsAg-ne cannot be given, then they c prevent reactivation dependi is detectable **(BIII)** (see Spec below)**.** If anti-CD20 is given, HBV DNA **(AII).**<br>◦ Treatment should be continu for 12 months after anti-CD2 |
| | **Pregnancy Considerations** |
| | • During pregnancy, tenofovir alafena emtricitabine is the preferred dual-N |
| | • Infants born to women who are HBsA HepB vaccine (first dose of three) wi vaccine should be administered at 1 |
| | **Abbreviations**: HBV = hepatitis B virus; an surface antigen; HCV = hepatitis C virus; NR<br>Rating of Recommendations: A = Strong; B<br>Rating of Evidence: I = Data from randomize trials, observational cohort studies with long studies, or regimen comparisons from randc |

Source:

- Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV. National Institutes of Health, HIV Medicine Association, and Infectious Diseases Society of America. Hepatitis B virus infection. Last updated: December 16, 2024. [HIV.gov]