CLINICAL GUIDELINES PROGRAM
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Prevention and Management of Hepatitis B Virus Infection in Adults With HIV

Updates, Authorship, and Related Guidelines

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Contents

Purpose of This Guideline

Purpose: This guideline on prevention and management of hepatitis B virus (HBV) infection in adults with HIV has been developed by the New York State Department of Health AIDS Institute (NYSDOH AI) to guide clinicians in New York State who provide medical care for adults (≥18 years old) with HIV who are at risk of acquiring HBV or have HBV coinfection.

The goals of this guideline are to:

- Raise awareness among clinicians about the prevalence and associated risks of chronic HBV in patients with HIV.
- Increase screening for and vaccination against HBV in adults with HIV.
- Provide up-to-date, evidence-based recommendations on diagnosis, assessment, treatment, and monitoring of chronic HBV infection in patients with HIV, with emphasis on the essential components of antiretroviral therapy to treat coinfection.

HBV transmission: There are an estimated 1.25 to 2.49 million people with chronic HBV in the United States [Lim, et al. 2020] and thousands of deaths annually from HBV-related complications, including cirrhosis and hepatocellular carcinoma (HCC) [CDC(b) 2020]. The primary routes of HBV transmission are perinatal transmission to the child, blood exposure, and sexual exposure. HBV DNA has been detected in various bodily secretions, including tears, urine, and saliva, but there is no firm evidence of HBV transmission via body fluids other than blood, semen, or vaginal secretions [StatPearls 2022; Komatsu, et al. 2012].

Approximately 95% of individuals who acquire HBV in adulthood will mount an immune response, resulting in spontaneous recovery and production of protective HBV antibodies (anti-HBs). However, some individuals will develop persistent HBV due to failure of the initial immune response to clear the virus, which results in chronic HBV infection [Bennett, et al. 2019]. Chronic HBV infection is defined as circulating hepatitis B surface antigen (HBsAg) in the blood for ≥6 months [Terrault, et al. 2018].

HIV/HBV coinfection: HIV and HBV share similar transmission routes and both infections are often diagnosed in the same patients. Individuals with HIV born in the United States generally acquire HBV through sexual contact and injection drug use. In contrast, people with HIV born in HBV-endemic regions most commonly acquire the infection at birth or in early childhood [Alter 2006].

In a large U.S. cohort study of individuals with HIV, from 1996 to 2007, 8.4% overall tested positive for HBsAg or detectable HBV DNA; prevalence was higher (10.3%) among men who have sex with men than among individuals who inject drugs (8.5%) and heterosexual individuals with risk factors (5.2%) [Spradling, et al. 2010].

HIV/HBV coinfection can significantly influence the natural history, progression, management, morbidity, and mortality associated with both infections. HBV viremia and the risk of chronic HBV are increased in people with HIV [Thio 2009]. In addition, HIV infection is associated with decreased clearance of HBV e antigen. Individuals with HIV who acquire protective anti-HBs through HBV infection remain at risk of developing low antibody levels and subsequent reactivation of HBV (reverse seroconversion). Individuals with HIV/HBV coinfection also tend to have a decreased inflammatory response to chronic HBV, indicated by decreased serum alanine transaminase levels, an increased risk of progression to cirrhosis and HCC, and increased mortality compared with individuals with HBV monoinfection [Sun, et al. 2021; Pinato, et al. 2019; Singh, et al. 2017; Thio 2009].

Post-exposure prophylaxis: For recommendations on HBV post-exposure prophylaxis, see the NYSDOH AI guideline PEP to Prevent HIV Infection > Management of Potential Exposure to Hepatitis B Virus.

Note on "experienced" and "expert" HIV care providers: Throughout this guideline, when reference is made to "experienced HIV care provider" or "expert HIV care provider," those terms are referring to the following 2017 NYSDOH AI definitions:

- Experienced HIV care provider: Practitioners who have been accorded HIV Experienced Provider status by the American Academy of HIV Medicine or have met the HIV Medicine Association's definition of an experienced provider are eligible for designation as an HIV Experienced Provider in New York State. Nurse practitioners and licensed midwives who provide clinical care to individuals with HIV in collaboration with a physician may be considered HIV Experienced Providers as long as all other practice agreements are met (8 NYCRR 79-5:1; 10 NYCRR 85.36; 8 NYCRR 139-6900). Physician assistants who provide clinical care to individuals with HIV under the supervision of an HIV Specialist physician may also be considered HIV Experienced Providers (10 NYCRR 94.2)
- Expert HIV care provider: A provider with extensive experience in the management of complex patients with HIV.

HBV Screening and Diagnosis

☑ RECOMMENDATIONS

Screening Tests

- Clinicians should determine the HBV vaccination and immune status of patients with HIV by performing laboratory testing for HBsAg, anti-HBs, and anti-HBc (total). (A*) See Table 1: Interpretation of HBV Screening Test Results.
- Clinicians should repeat laboratory screening annually in patients who are not immune to HBV, choose not to be vaccinated, and are at ongoing risk of acquiring HBV. (A3)

☑ RECOMMENDATIONS

Diagnosis

- In patients with positive baseline (screening) HBsAg test results, clinicians should perform HBeAg, anti-HBe, and HBV DNA testing to diagnose the phase of HBV infection. (B2†) See Table 2: Serologic and Virologic Responses to HBV Infection.
- If a patient with HIV and unknown HBsAg status has signs or symptoms of acute hepatitis (i.e., elevated ALT), the clinician should perform HBsAg, anti-HBc IgM**,** HBeAg, anti-HBe (A*), and HBV DNA (A3) testing along with other diagnostic testing for acute hepatitis.

Acute HBV Infection

- If acute HBV infection is confirmed and the patient is asymptomatic, the clinician should repeat ALT testing within 2 to 4 weeks to assess for symptoms of liver disease progression (B3) and repeat HBsAg, HBeAg, anti-HBe, and HBV DNA testing 6 months later to determine whether infection has cleared. (A3)
- If a patient with HIV and acute HBV is not taking ART, the clinician should recommend ART initiation. (A1)

Transmission Prevention

- Clinicians should advise patients who have a positive HBsAg test result that they can transmit HBV (A*) and encourage sexually active patients to use effective barrier protection to reduce the risk of HBV transmission. (A2†)
- Clinicians should inform patients with HBV that their household contacts should be vaccinated and counsel the patients to avoid sharing items such as razors or toothbrushes that could expose others to HBV-contaminated blood. (A2†)
- For individuals who inject drugs, clinicians should offer or refer for substance use treatment, ensure access to clean needles and syringes, and provide harm reduction counseling. (A2†)
  - See NYSDOH Drug Use Resources.

Abbreviations: ALT, alanine transaminase; anti-HBc, hepatitis B core antibody; anti-HBe, antibody to HBeAg; anti-HBs, hepatitis B surface antibody; ART, antiretroviral therapy; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IgG, immunoglobulin G; IgM, immunoglobulin M.

☆ NEW YORK STATE LAW: REPORTING HBV INFECTION

- Clinicians must report all suspected or confirmed HBV infections, and specify acute or chronic, to the local health department of the area where the individual resides according to NYSDOH Communicable Diseases Reporting Requirements.

Screening Tests

Clinicians should screen all patients with HIV for HBV risk, vaccination history, and infection upon entry into medical care and perform baseline testing to determine HBV immune status. Initial laboratory testing includes serologic testing for HBsAg, anti-HBc total, and anti-HBs, with results interpreted as detailed in Table 1, below. Patients with anti-HBs levels of ≥10 IU/mL are considered immune to HBV [DHHS 2022]. If a patient with HIV decides against HBV vaccination and remains at risk, annual laboratory screening is recommended (see guideline section HBV Vaccination) [Terrault, et al. 2018].

Table 1: Interpretation of HBV Screening Test Results

HBsAg	Anti-HBs	Anti-HBc		Interpretations
		IgG	IgM	
Negative	Negative	Negative	Negative	Susceptible to HBV infection
Negative	Positive	Negative	Negative	Immune due to HBV vaccination
Negative	Positive	Positive	Negative	Immune due to natural HBV infection
Positive	Negative	Positive	Positive	Acute HBV infection

Table 1: Interpretation of HBV Screening Test Results				
		Anti-HBc		
HBsAg	Anti-HBs	IgG	IgM	Interpretations
Positive	Negative	Positive	Negative/Positive	Chronic HBV infection
Negative	Negative	Positive	Negative/Positive	Isolated anti-HBc positivity. Possible interpretations: • Resolved HBV infection with waning anti-HBs titers • False-positive result • Occult HBV infection • Resolving acute HBV infection
Abbreviations: anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IgG, immunoglobulin G; IgM, immunoglobulin M.				

Diagnosis

For patients with positive HBsAg screening test results, follow-up laboratory testing should be performed to confirm HBV status (see Table 2, below). If a patient with HIV and unknown HBsAg status presents with signs or symptoms of acute hepatitis (i.e., elevated ALT), the clinician should perform HBsAg, anti-HBc IgM**,** HBeAg, anti-HBe, and HBV DNA testing to confirm a diagnosis.

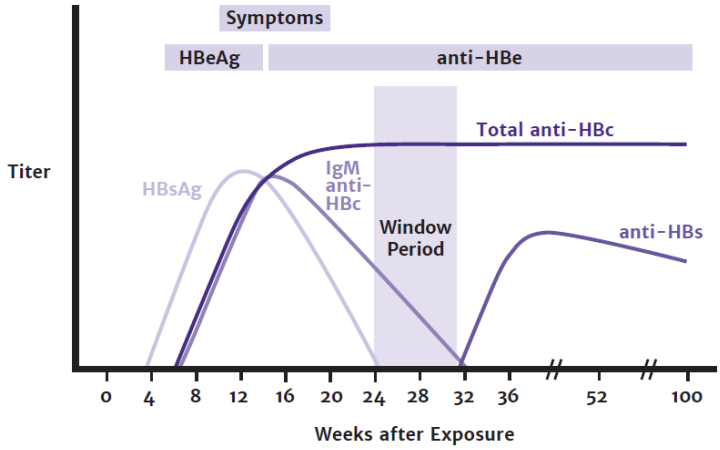
Table 2: Serologic and Virologic Responses to HBV Infection							
Stage of Infection	HBsAg	Anti-HBs	Anti-HBc IgG	Anti-HBc IgM	HBeAg	Anti-HBe	HBV DNA Level
Incubation	+	–	–	–	+ or –	–	Low
Acute HBV infection	+	–	+	+	+	–	High
HBs-negative acute HBV	–	–	+	+	+ or –	–	High
Inactive HBsAg carrier	+	–	+++	+ or –	–	+	Low
Precore mutant [a]	+	–	+ or –	+ or –	–	+	High
Occult infection	–	–	+	+ or –	–	–	High or low
Chronic HBV infection	+	–	+++	+ or –	+ or –	–	High or low
Abbreviations: anti-HBc, hepatitis B core antibody (IgG or IgM); anti-HBe, antibody to HBeAg; anti-HBs, hepatitis B surface antibody; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IgG, immunoglobulin G; IgM, immunoglobulin M. **Note:** a. For more information, see Medscape: Precore Mutant Chronic Hepatitis B -- Approach to Management.							

Acute HBV infection: Following exposure, HBV enters the bloodstream and circulates to the liver. The post-exposure time to the onset of abnormal liver enzymes averages 60 days (range, 40 to 90 days), and the onset of jaundice averages 90 days (range, 60 to 150 days). Acute HBV infection is asymptomatic in approximately 70% of patients, and <1% of patients develop fulminant hepatic failure. When symptoms manifest, they may include anorexia, malaise, nausea, vomiting, arthralgias, and right upper quadrant abdominal pain. Symptoms generally resolve within 4 weeks, with normalization of transaminase levels in 2 to 8 weeks.

Acute HBV infection is diagnosed through the detection of HBsAg and anti-HBc IgM. During the initial phase of infection, HBeAg and HBV DNA are also present (see Figure 1, below). Recovery is marked by the disappearance of HBV DNA and seroconversion of HBeAg to anti-HBe and of HBsAg to anti-HBs [Shiffman 2010].

Figure 1: Typical Serologic Course of Acute Hepatitis B Virus Infection With Recovery

Reprinted from Centers for Disease Control and Prevention Recommendations for Identification and Public Health Management of Persons with Chronic Hepatitis B Virus Infection



Abbreviations: anti-HBc, hepatitis B core antibody; anti-HBe, antibody to HBeAg; anti-HBs, hepatitis B surface antibody; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; IgM, immunoglobulin M.

The ideal management strategy for symptomatic acute HBV infection in patients with HIV is not clear. Treatment with entecavir (ETV), tenofovir alafenamide (TAF), or tenofovir disoproxil fumarate (TDF) outside of a fully active anti-HIV regimen could lead to HIV resistance, but initiation of a fully active ART regimen may worsen acute liver disease due to immune reconstitution inflammatory syndrome (IRIS). For most patients with acute HBV, treatment is mainly supportive. Antiviral therapy is generally not indicated in patients with symptomatic acute HBV because most immunocompetent adults with acute HBV recover spontaneously.

However, antiviral treatment is indicated for patients with acute liver failure or a protracted, severe course of HBV, as indicated by a total bilirubin level >3 mg/dL (or direct bilirubin level >1.5 mg/dL), an international normalized ratio >1.5, encephalopathy, or ascites. ETV, TAF, and TDF are the preferred antiviral agents for these patients. Treatment should be continued until HBsAg clearance is confirmed or should be continued indefinitely in patients who undergo liver transplantation [Terrault, et al. 2018]. Patients with HIV who are already taking a fully active ART regimen that includes TAF or TDF should continue with the regimen.

If acute HBV infection is confirmed in an asymptomatic patient, the clinician should repeat ALT testing within 2 to 4 weeks to assess for symptoms of liver disease progression and repeat HBsAg, HBeAg, anti-HBe, and HBV DNA testing in 6 months to determine whether infection has cleared. Patients with symptomatic acute HBV require more frequent monitoring tailored to the patient's condition.

Chronic HBV infection: HBV infection is a dynamic disease, and individuals can transition through the defined clinical phases with variable levels of serum ALT activity, HBV DNA, and HBV antigens. See the guideline sections Assessment Before HBV Treatment and HBV Treatment and Monitoring for recommendations on the management of chronic HBV infection in patients with HIV.

Reactivation: Chronic HBV can resolve in some patients, and tests will indicate a sustained loss of HBsAg, undetectable serum HBV DNA levels, and absence of clinical or histologic evidence of active viral infection. However, reactivation of HBV replication, characterized by the reappearance of HBeAg and HBsAg and a rise in serum HBV DNA, can occur. Reactivation is usually seen in patients taking immunosuppressive therapy for a concurrent medical condition; in rare instances, patients with prior resolved HBV infection who are anti-HBs-positive can have reactivation of HBV during subsequent immunosuppressive therapy. For a list of medications associated with increased risk for HBV reactivation, see Medscape > Hepatitis B Treatment & Management. Reactivation of HBV can also occur in individuals with HIV, including those who experience immune reconstitution after initiation of ART. HBV reactivation may result in severe hepatitis and should be considered a potential cause of hepatitis in patients with previously resolved HBV infection. During reactivation, serum ALT levels will be elevated, and patients who were HBeAg- or HBsAg-negative may become both HBeAg- and HBsAg-positive. HBV reactivation can vary from mild and asymptomatic to severe with possible fulminant hepatic failure.

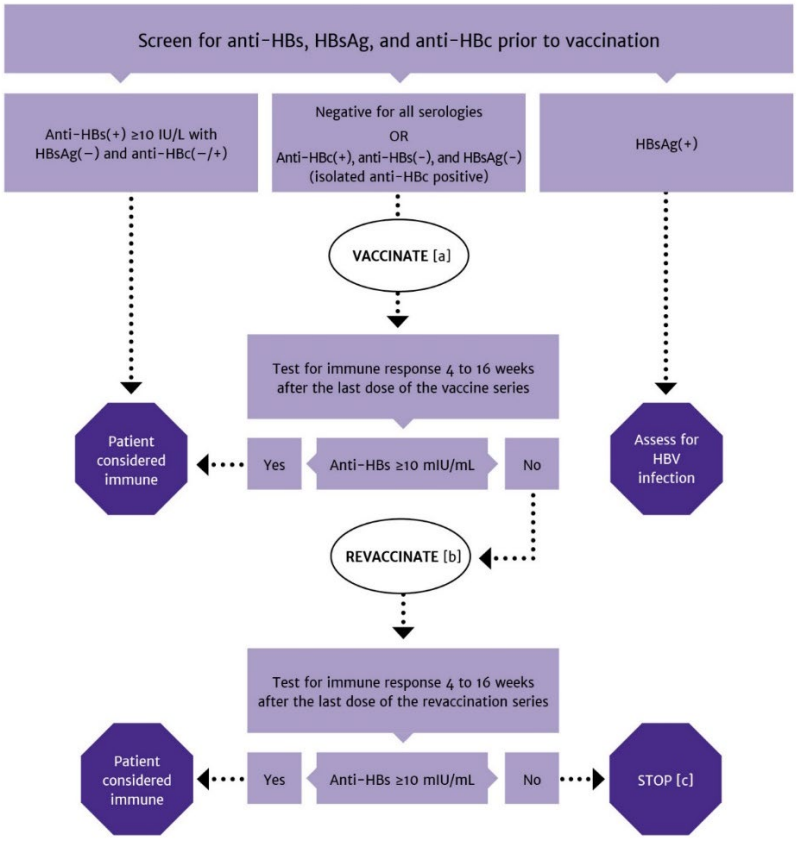
Occult HBV infection is defined as detectable HBV DNA in HBsAg-negative patients. Most patients with occult HBV have very low or undetectable serum levels, but HBV DNA is often detected in the liver. Patients with occult infection are at risk of HBV reactivation if they receive potent immunosuppressive therapy or chemotherapy. Occult HBV infection has been associated with chronic liver disease and increased risk of hepatocellular carcinoma [Raimondo, et al. 2007].

Transmission Prevention

HBV is significantly more transmissible through exposure to blood and body fluid than HIV and requires more frequent assessment for behaviors that increase HIV/HBV transmission risk. Barrier protection, including latex or polyurethane condoms, should be recommended to decrease the risk of sexual transmission [Smith, et al. 2015; Weller and Davis 2002], and sexual partners should be vaccinated if possible. It is important to advise patients that household contacts should be vaccinated against HBV and that they should avoid sharing any objects that may be contaminated with blood, such as razors or toothbrushes.

All active injection drug users should be prescribed clean syringes and needles and offered referrals to substance use treatment, such as opioid substitution. Referral to needle-exchange programs should also be offered (see NYSDOH Drug Use Resources). Injection drug users should also receive information about safe disposal and storage of needles/syringes and safer injection techniques.

Figure 2: Algorithm for HBV Screening and Vaccination in Patients With HIV



Abbreviations: anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

Notes:

a. In patients with positive anti-HBc, negative anti-HBs, and negative HBsAg test results, vaccinate with 1 standard dose of HBV vaccine and check anti-HBs titer after 8 weeks. If titer is <100 mIU/mL, complete remaining doses in the vaccine series and recheck titer 8 weeks after the last vaccine.
b. In patients with anti-HBs levels <10 mIU/mL (vaccine nonresponse), revaccination is recommended with the Heplisav-B vaccine series or a double dose of the vaccine series previously administered.
c. A patient who is negative for all serologies and who does not respond to revaccination may have a primary nonresponse or chronic infection. HBV DNA testing may be used to detect the presence of chronic HBV infection.

HBV Vaccination

☑ RECOMMENDATIONS

Primary Vaccination

- Clinicians should offer HBV vaccination with the 3-dose Engerix-B or Recombivax HB vaccine series (A1) or the 2-dose Heplisav-B vaccine series (A2†) to patients with negative test results for HBsAg, anti-HBs, and anti-HBc.
- Clinicians should not defer initial HBV vaccination in patients with a CD4 count <200 cells/mm^3 who are at risk for HBV infection. (A2)
- Clinicians should repeat anti-HBs testing 4 to 16 weeks, based on the patient's visit schedule, after completion of the vaccination series to ensure immunity (anti-HBs ≥10 mIU/mL). (A3)
- In a patient with negative HBsAg, negative anti-HBs, and positive anti-HBc test results (isolated anti-HBc positive), the clinician should offer a 1-time dose of HBV vaccine. (A2)
  - Repeat anti-HBs testing 8 weeks after vaccination, and if the anti-HBs titer is <100 mIU/mL, complete the HBV vaccine series and repeat anti-HBs testing 8 weeks after the last vaccine. (A2)
  - If vaccination is refused or if follow-up anti-HBs titer testing cannot be assured, perform HBV DNA testing to evaluate for occult HBV infection. (A2)
- Clinicians should not defer initial vaccination or revaccination in pregnant patients with HIV who do not have immunity to HBV. (A3)

Revaccination

- In previously vaccinated patients with anti-HBs levels <10 mIU/mL (vaccine nonresponse), clinicians should recommend revaccination with the Heplisav-B vaccine series or a double dose of the vaccine series previously administered. (A2)

Abbreviations: anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

Vaccination effectively prevents HBV infection. Patients with HIV with negative anti-HBs, anti-HBc, and HBsAg test results have no evidence of immunity and should be offered vaccination against HBV [DHHS 2022]; see Figure 2: Algorithm for HBV Screening and Vaccination in Patients With HIV and Table 1: Interpretation of HBV Screening Test Results. Conversely, patients with positive anti-HBc and anti-HBs test results have resolved HBV infection and do not require vaccination.

Primary Vaccination Strategies

The single-antigen HBV vaccines currently approved by the U.S. Food and Drug Administration (FDA) for individuals ≥18 years old are Engerix-B, Recombivax HB, and Heplisav-B. Prehevbrio, a new 3-antigen recombinant HBV vaccine, was approved in 2021 by the FDA for use for individuals ≥18 years old [FDA 2021], but experience regarding its use in patients with HIV is lacking at this time.

The level of immune response to HBV vaccination in individuals with HIV can be lower than in adults who are HIV seronegative [Mast, et al. 2006; Rey, et al. 2000; Tayal and Sankar 1994; Loke, et al. 1990]. Many studies have shown that the presence of detectable HIV RNA [Overton, et al. 2005; Tedaldi, et al. 2004] and low CD4 cell counts [Veiga, et al. 2006; Fonseca, et al. 2005; Tedaldi, et al. 2004; Keet, et al. 1992] correlates with a poor immune response to vaccination. Ideally, based on the data, the HBV vaccine should be administered before a patient's CD4 count declines to <350 cells/mm^3 to improve immunogenicity; however, vaccination should not be deferred in patients who have CD4 counts <350 cells/mm^3.

The initial vaccine series using conventional HBV vaccines (Engerix-B, Recombivax HB) is typically administered intramuscularly as 3 standard doses at 0, 4, and 24 weeks (see Table 3, below). Whether patients with HIV should receive a standard or double dose of these vaccines is still being debated. This committee and the DHHS Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV recommend administering the

standard 3-dose regimen. If the patient does not respond, a higher dose can be administered when the patient is revaccinated [DHHS 2022].

Heplisav-B, a 2-dose (4 weeks apart) recombinant HBsAg vaccine with a novel adjuvant, is also available for individuals ≥18 years old [FDA 2020]. In 3 randomized controlled trials among individuals without HIV, administration of 2 doses of Heplisav-B was associated with a higher seroprotection rate than 3 doses of Engerix-B [FDA 2020].

A recent retrospective cohort study among individuals with HIV found seroprotection rates were increased with the Heplisav-B vaccine compared with other previously used HBV vaccines [Schnittman, et al. 2021]. In addition, a recent modeling study determined that use of Heplisav-B among individuals with HIV results in lower costs and increased benefits compared with Engerix-B [Rosenthal, et al. 2020]. A 2-dose series may increase adherence because it requires fewer follow-up visits and a shorter wait time between doses than the 3-dose vaccines. No data are available to support use of other recombinant vaccines for the second dose if Heplisav-B is used for the initial dose.

Combined HBV and hepatitis A virus (HAV) vaccine: Twinrix is a combination vaccine that includes recombinant HBV and HAV vaccines; it is approved by the FDA for use in individuals ≥18 years old in the United States. For individuals with HIV who are not immune to both HAV and HBV, Twinrix may be administered as an initial series and administered in 3 doses at 0, 4, and 24 weeks. No data are available to support the administration of this vaccine as a double-dose or 4-dose series, so these strategies are not recommended in patients with HIV.

Table 3: HBV Vaccine Dosing Schedule

Vaccine	Dosing	Notes
Engerix-B	**Single dose:** 20 µg as one 1 mL dose containing 20 µg/mL vaccine administered as follows: • 3 IM injections at weeks 0, 4, and 24 ***OR*** • 4 IM injections at weeks 0, 4, 8, and 24 **Double dose:** 40 µg as two 1 mL doses of 20 µg/mL vaccine administered as follows: • 3 IM injections at weeks 0, 4, and 24 ***OR*** • 4 IM injections at weeks 0, 4, 8, and 24	**Patients with ESRD or other immunocompromising conditions** [a]**:** 40 µg/mL as two 1 mL doses of 20 µg/mL vaccine administered in 3 IM injections at weeks 0, 4, 8, and 24
Recombivax HB	**Single dose:** 10 µg as one 1 mL dose containing 10 µg/mL vaccine administered as follows: • 3 IM injections at weeks 0, 4, and 24 ***OR*** • 4 IM injections at weeks 0, 4, 8, and 24 **Double dose** [b]**:** 20 µg as two 1 mL doses containing 10 µg/mL vaccine administered as follows: • 3 IM injections at weeks 0, 4, and 24 ***OR*** • 4 IM injections at weeks 0, 4, 8, and 24	**Patients with ESRD or other immunocompromising conditions** [a]**:** 40 µg/mL as 1 mL of higher-strength vaccine administered in 4 IM injections at weeks 0, 4, and 24
Heplisav-B [c]	**Single dose:** 20 µg as one 0.5 mL dose containing 20 µg/mL vaccine administered as follows: • 2 IM injections at weeks 0 and 4	• **Patients with ESRD:** Standard dosing [Awad, et al. 2021] • **Pregnant patients:** Insufficient data to recommend use
Twinrix [d]	**Single dose:** 1 mL administered as follows: • 3 IM injections at weeks 0, 4, and 24	For patients who are not immune to either HBV or HAV

Abbreviations: ESRD, end-stage renal disease; HAV, hepatitis A virus; HBV, hepatitis B virus; IM, intramuscular.

Notes:

a. Higher-strength regimens of both Engerix-B and Recombivax HB are approved by the U.S. Food and Drug Administration for use in patients with ESRD; these higher-strength regimens may also be considered for patients with other immunocompromising conditions.
b. Double dosing with Recombivax HB has not been as well studied as double dosing with Engerix-B. However, Recombivax HB may be the only formulation available at some institutions.
c. Double dosing and an accelerated schedule with Heplisav-B have not been well studied.
d. Double dosing and use of a 4-dose series with Twinrix have not been well studied in patients with HIV and are not recommended.

Double-dose and 4-dose strategies: Other vaccination approaches are to administer a double dose of vaccine on a standard 3-dose schedule or to add a fourth dose at 2 months to a 3-dose vaccine series. Several studies have shown improved immune response to double-dose vaccinations given in a 3-dose schedule [Psevdos, et al. 2010; de Vries-Sluijs, et al. 2008; Fonseca, et al. 2005]. A 2013 meta-analysis (5 studies, n=883) found that increasing the vaccine dosage may significantly improve immune responses in participants with HIV [Ni, et al. 2013]. A 2015 multicenter, open-label, randomized controlled trial (RCT) compared standard-dose (20 µg) with double-dose (40 µg) HBV revaccination in adults who did not respond to primary vaccination [Rey, et al. 2015]. In this study, double-dose revaccination was not associated with a higher response rate than revaccination with a standard single-dose regimen at week 4 after vaccination. However, the proportion who responded to the vaccine and the geometric mean titers at week 4 after vaccination were higher in the double-dose group than in the standard-dose group. Seroprotective responses at week 72 were greater in the double-dose group than in the standard-dose group. The safety profile was similar between the groups [Rey, et al. 2015].

An RCT conducted in 2013 compared the immunogenicity and safety of 4 standard doses and 4 double doses with 3 standard doses of HBV vaccination in adults with HIV [Chaiklang, et al. 2013]. Response rates were higher in the 4-dose group than in the standard 3-dose group, but the difference was not statistically significant. Local adverse effects were more common with increased frequency and dosage of vaccine, but systemic and serious adverse effects were extremely rare [Chaiklang, et al. 2013]. Based on these data, it is reasonable to consider an alternative primary HBV vaccination approach with a 3- or 4-injection double-dose vaccine series in patients with HIV.

Accelerated vaccination: An RCT using the standard-dose HBV vaccine compared an accelerated schedule (0, 1, and 3 weeks) with the standard schedule (0, 4, and 24 weeks) and demonstrated a noninferior response rate for participants with CD4 counts >500 cells/mm^3; this schedule may increase patient adherence to the full vaccine series [de Vries-Sluijs, et al. 2011]. However, the accelerated schedule was inferior in patients with CD4 counts of 200 to 500 cells/mm^3. Because of the low number of participants with CD4 counts <200 cells/mm^3, the results were inconclusive for this population.

Based on these findings, the accelerated schedule may be considered for patients with CD4 counts ≥500 cells/mm^3 but is not recommended for patients with CD4 counts <500 cells/mm^3 [de Vries-Sluijs, et al. 2011]. If an accelerated HBV vaccination schedule is used, the patient should also receive a fourth-dose booster at least 6 months after initiation of the vaccine series.

Pregnancy: Clinicians should not defer initial vaccination or revaccination in pregnant patients with HIV who do not have immunity to HBV. There are no well-controlled studies designed to evaluate the recommended anti-HBV vaccines during pregnancy. However, available data do not suggest an increased risk of miscarriage or major congenital disabilities in individuals who received Engerix-B, Twinrix, Recombivax HB, or Heplisav-B vaccines during pregnancy compared with individuals in the general U.S. population who were not vaccinated during pregnancy [FDA 2020; FDA(a) 2018; FDA(b) 2018; FDA(c) 2018].

Isolated anti-HBc positivity: Defined as having negative HBsAg, negative anti-HBs, and positive anti-HBc test results, isolated anti-HBc positivity has been reported in 0.4% to 1.7% of blood donors in low prevalence areas and 10% to 20% of the population in endemic countries [Lok, et al. 1988]. It has been estimated that 17% to 41% of patients with HIV have isolated anti-HBc positivity [Bhattacharya, et al. 2016; Witt, et al. 2013; Neau, et al. 2005]. As shown in Table 1: Interpretation of HBV Screening Test Results, there are 4 possible interpretations of this result: resolved HBV infection with waning anti-HBs titers, false-positive result, occult HBV infection, or resolving acute HBV infection [Mast, et al. 2006].

Most patients with HIV and isolated anti-HBc positivity are HBV DNA-negative, not immune to HBV [Gandhi, et al. 2005], and routinely checking HBV DNA is no longer recommended. Clinicians should offer patients with HIV and isolated anti-HBc a single standard dose of HBV vaccine [DHHS 2022]. Anti-HBs testing should be performed 8 weeks after the first dose. If the anti-HBs titer is <100 mIU/mL, the remaining vaccines in the series should be administered, and anti-HBs testing should be repeated 8 weeks after the vaccine series is complete [DHHS 2022; Piroth, et al. 2016]. In a prospective study of 54 patients with HIV and isolated anti-HBc, 46% responded to a single dose of vaccine. Of those who did not respond to a single dose, 89% developed immunity after a 3-dose series of double-dose vaccine [Piroth, et al. 2016]. For patients with an anti-HBs titer ≥100 mIU/mL, clinicians may opt to discontinue the vaccine series. There are few data to guide the optimal number of vaccine doses for these patients but no evidence of harm in completing the full vaccination series.

However, if patients with HIV and isolated anti-HBc refuse vaccination or if post-vaccination anti-HBs testing cannot be assured, then a reasonable approach is to perform HBV DNA testing [Chang, et al. 2018]. HBV DNA testing may also be performed in patients with isolated anti-HBc who do not respond to the full vaccine series. A positive HBV DNA test result in a patient with isolated anti-HBc test results indicates occult HBV infection (see guideline section HBV Screening and Diagnosis > Diagnosis > Reactivation).

Follow-up Testing

Clinicians should repeat anti-HBs testing 4 to 16 weeks, based on the patient's visit schedule, after vaccination to ensure immunity [Rubin, et al. 2014]. If the anti-HBs titer is ≥10 mIU/mL, the patient is considered immune to HBV. If the anti-HBs titer is <10 mIU/mL, the patient may have primary nonresponse to the vaccine and require revaccination, or the patient may have chronic HBV infection. HBV DNA testing may be used to detect chronic HBV.

→ KEY POINT

- Patient education regarding HBV vaccination is important to ensure awareness of the continued risk of acquiring and subsequently transmitting HBV until adequate anti-HBs response is confirmed.

Revaccination

Individuals with HIV who do not respond (anti-HBs <10 mIU/mL) to the primary HBV vaccine series should be revaccinated with Heplisav-B or a double dose of the vaccine series previously administered. In a recent retrospective, cross-sectional study among individuals with HIV who failed to seroconvert after vaccination (HBsAg- and anti-HBs-negative) with Engerix-B or Recombivax HB, revaccination with Heplisav-B was highly effective in achieving seroprotection [Khaimova, et al. 2021]. If Heplisav-B is not administered as the initial HBV vaccination series, revaccination with the 2-dose series may be considered.

If the primary HBV vaccination was a 3-dose series, a 4-dose series may be considered. Compared with a single-dose vaccine series for revaccination, a double-dose HBV vaccine series for revaccination improved immune response in some individuals with HIV [Rey, et al. 2015; Chaiklang, et al. 2013; Launay, et al. 2011; de Vries-Sluijs, et al. 2008].

Revaccination can be deferred for patients initiating ART until the CD4 count is ≥200 cells/mm^3; response rates to vaccination may be higher in patients with CD4 counts ≥200 cells/mm^3 than those with lower CD4 cell counts [Gandhi, et al. 2005].

Assessment Before HBV Treatment

☑ RECOMMENDATIONS

Liver Disease Assessment

- Before initiating HBV treatment in patients with HIV, clinicians should obtain a complete physical examination and medical history, including the use of hepatoxic medications (A*); noninvasive fibrosis evaluation (A2†); baseline ultrasonography for HCC [a] (A2†); and the following laboratory testing: CBC, albumin, bilirubin, alkaline phosphatase, PT/INR, ALT, AST, and a basic metabolic panel. (A*)
- Clinicians should refer patients with HIV/HBV coinfection and cirrhosis to a gastroenterologist or hepatologist to assess and manage complications of portal hypertension. (A3)
- In patients with HIV/HBV coinfection and cirrhosis, clinicians should screen for HCC with ultrasound every 6 months. (A2†)
  - See the guideline section HBV Treatment and Monitoring > Ongoing Screening for Hepatocellular Carcinoma regarding screening for patients without cirrhosis.

Alcohol Use Screening and Education

- Clinicians should perform alcohol use screening in patients with HIV/HBV coinfection at baseline and at least annually and refer patients for treatment as needed. (A3)
  - See the NYSDOH AI guidelines Substance Use Screening and Risk Assessment in Adults and Treatment of Alcohol Use Disorder.
- Clinicians should educate patients about the detrimental effects of alcohol use on the course of HBV infection and counsel patients with underlying liver disease to abstain from or minimize alcohol use. (A*)

☑ RECOMMENDATIONS

HAV, HCV, and HDV Status

- Clinicians should perform anti-HAV IgG or total (IgM and IgG) serum testing and administer the full HAV vaccine series in patients who are not immune to HAV. (A3)
- Clinicians should determine patients' HCV status by medical history and serum testing and recommend treatment with DAA therapy if chronic HCV infection is diagnosed. (A1)
  - See the NYSDOH AI guidelines Hepatitis C Virus Screening, Testing, and Diagnosis in Adults and Treatment of Chronic Hepatitis C Virus Infection in Adults.
- Clinicians should perform anti-HDV total (IgM and IgG) serum testing to screen for HDV in all patients with HIV/HBV coinfection. (B2)

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CBC, complete blood count; DAA, direct-acting antiviral; HAV, hepatitis A virus; HBV, hepatitis B virus; HCC; hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; IgG, immunoglobulin G; IgM, immunoglobulin M; PT/INR, prothrombin time/international normalized ratio.

Note:

a. Baseline ultrasound for HCC is performed in all patients with HIV/HBV coinfection. In patients with HIV/HCV coinfection, an ultrasound is performed only in patients with cirrhosis.

Liver Disease Assessment

Initial assessment of patients with chronic HBV should include a detailed history and physical examination to evaluate for any signs of advanced liver disease, including bruising, jaundice, dark urine, light stools, history of gastrointestinal bleeding, and pruritus. A prior treatment history, including medication history, should be obtained to determine whether the patient has previously taken hepatotoxic medications or lamivudine or emtricitabine, which have been associated with HBV resistance when taken as monotherapy. On examination, identify any stigmata of advanced liver disease, such as spider angiomas, splenomegaly, palmar erythema, and asterixis. The presence of ascites or encephalopathy indicates decompensated liver disease. Baseline laboratory tests include CBC, albumin, bilirubin, alkaline phosphatase, prothrombin time, ALT, and AST. Low albumin levels or elevated prothrombin time may suggest advanced liver disease with hepatic decompensation. Leukopenia and thrombocytopenia may indicate the presence of portal hypertension.

All individuals should be evaluated for liver fibrosis using noninvasive methods, such as transient elastography (FibroScan), serum testing for biomarkers (FibroSure), or AST to platelet ratio index (APRI) calculation. Liver biopsy is no longer preferred because of the risk of complications (e.g., bleeding, infection) and the possibility of a sampling error when only a small portion of the liver is evaluated. All patients with HIV/HBV coinfection should have a baseline ultrasound to screen for HCC [Terrault, et al. 2018], and those with cirrhosis should be referred to a hepatologist to screen for esophageal varices [Garcia-Tsao, et al. 2017; de Franchis 2015].

Results of the liver disease assessment determine the phase of chronic HBV infection. Liver biopsy results are included below as part of the description of each stage. However, liver biopsy is rarely indicated in patients with HIV/HBV. The procedure can be considered in patients who have persistently elevated ALT but persistently low HBV DNA to exclude other causes of liver disease.

- **Immune tolerance:** Characterized by hepatitis B e antigen (HBeAg) positivity with elevated HBV DNA levels but normal or minimally elevated ALT levels. Liver biopsies are generally benign, without signs of necroinflammation or fibrosis [Tran 2011].
- **Immune active:** Subdivided into HBeAg-positive and HBeAg-negative. In HBeAg-positive patients, HBV DNA levels are typically >20,000 IU/mL, and serum ALT levels are elevated. In HBeAg-negative patients, HBV DNA levels tend to be lower (2,000 to 20,000 IU/mL) with low to normal serum ALT levels. Liver biopsy often reveals chronic hepatitis with variable signs of necroinflammation or fibrosis [Terrault, et al. 2018].
- **Inactive chronic HBV**: These patients are HBeAg-negative and antibody to HBeAg-positive. Serum HBV DNA is usually <2000 IU/mL or undetectable, and ALT levels are normal. Liver biopsy indicates an absence of significant necroinflammation and variable levels of fibrosis [Terrault, et al. 2018].

Alcohol Use Screening and Education

In 2020, there were an estimated 29,000 deaths from alcoholic liver disease and 51,000 deaths from chronic liver disease and cirrhosis in the general U.S. population [CDC(a) 2022; CDC(b) 2022]. Chronic alcohol use in patients with HBV infection results in increased oxidative stress and liver inflammation, which can progress to cirrhosis and lead to the development of HCC [Donato, et al. 1997; Nakanuma and Ohta 1983]. These effects are even more pronounced in patients with HIV/HBV coinfection in whom increased levels of liver inflammation, liver fibrosis, drug-induced hepatotoxicity, liver cirrhosis, and death from liver disease and HCC have been observed [Marcellin, et al. 2008; Poynard, et al. 2003; Núñez, et al. 2001]. Patient education is essential to helping patients understand the effects of alcohol use on the course of HBV infection, as is counseling for patients with underlying liver disease so that patients can make informed decisions regarding alcohol use or abstinence. Studies have shown that individual counseling and peer group education and support can be effective in reducing alcohol use in patients with HIV [Knox, et al. 2013; Velasquez, et al. 2009].

HAV, HCV, and HDV Status

HAV: For information on HAV/HIV coinfection, see the NYSDOH AI guideline Prevention and Management of Hepatitis A Virus Infection in Adults With HIV > Management of HAV/HIV Coinfection.

HCV: HBV/HCV coinfection is associated with higher rates of cirrhosis, increased severity of liver disease, and increased risk of HCC than HBV or HCV monoinfection [Mavilia and Wu 2018]. This is of particular concern in patients with HIV/HBV coinfection; patients with HIV infection have more severe liver disease and higher rates of liver complications than patients without HIV [Bräu, et al. 2007; Thio, et al. 2002]. For information on screening, diagnosis, and treatment of HCV in patients with HIV, see the NYSDOH AI guidelines Hepatitis C Virus Screening, Testing, and Diagnosis in Adults and Treatment of Chronic Hepatitis C Virus Infection in Adults.

HDV: Formerly known as hepatitis delta virus, HDV is a defective satellite RNA virus that requires active HBV infection to replicate. HIV/HBV/HDV tri-infection is associated with more rapid liver disease progression and higher rates of decompensated cirrhosis, HCC, and mortality than HIV/HBV coinfection [Béguelin, et al. 2017; Fernández-Montero, et al. 2014; Castellares, et al. 2008; Sheng, et al. 2007]. HDV infection is uncommon in the United States; it is not a reportable disease, and the prevalence is unknown [Patel, et al. 2019]. The majority of cases occur among people who migrate or travel to the United States from countries with high HDV endemicity (i.e., Eastern Europe, Southern Europe, the Mediterranean region, the Middle East, West and Central Africa, East Asia, and the Amazon River Basin in South America) [CDC(a) 2020].

Existing data indicate that pegylated interferon (PEG-IFN) is the only effective anti-HDV treatment [EASL 2012]. However, fewer than 30% of people without HIV who have HDV achieve sustained HDV suppression when treated with PEG-IFN [Wedemeyer, et al. 2011]. No data are available regarding the efficacy of PEG-IFN therapy in patients with HIV/HBV/HDV tri-infection. Because HDV depends on HBV to replicate, HBsAg seroconversion should be the primary goal for patients with HIV/HBV/HDV tri-infection. In patients with tri-infection, prompt initiation of anti-HBV and anti-HIV therapy should be strongly encouraged.

Little guidance is available on optimal monitoring strategies for patients with HIV/HBV coinfection and positive serum anti-HDV total (IgM and IgG) test results. It is reasonable to perform baseline HDV RNA testing and consult with an experienced care provider about ongoing HDV RNA and DNA testing [Farci and Niro 2018].

HBV Treatment and Monitoring

☑ RECOMMENDATIONS

Treatment

- Clinicians should recommend immediate ART initiation for any patient with HIV/HBV coinfection who is not taking ART. (A1)
- **Preferred:** In patients with HIV and chronic HBV, clinicians should recommend an ART regimen that includes 2 agents active against HBV (see Table 4: Available Medications for Treatment of HBV Infection in Adults With HIV). Preferred regimens include a backbone of either TAF/FTC, TDF/FTC, or TDF/3TC. (A2)

☑ RECOMMENDATIONS

- Clinicians should not prescribe a 2-drug regimen of TAF/FTC, TDF/FTC, or TDF/3TC alone to treat patients with HIV/HBV coinfection; a fully suppressive ART regimen is required. (A1)
- Nonadherence with or discontinuation of anti-HBV treatment may result in transaminase flares and hepatic damage. Clinicians should educate patients about the treatment adherence requirements (A*), and if treatment must be interrupted or discontinued, consult with a care provider experienced in HIV/HBV coinfection. (A3)
- **Alternative:** If a patient cannot or chooses not to take TDF or TAF, the clinician should initiate treatment with ETV and a fully suppressive ART regimen for HIV. (A3)

Pregnant Patients

- Clinicians should offer pregnant patients treatment with an ART regimen that includes 2 agents active against both HIV and HBV; 3TC, FTC, TAF, and TDF can be used safely during pregnancy at standard doses. (A2†)

Monitoring

- After HBV treatment initiation, clinicians should perform the laboratory testing listed in Table 6: Recommended Monitoring After HBV Treatment Initiation in Adults With HIV. (A3)
- If a patient being treated for chronic HBV develops signs or symptoms of acute hepatitis (nausea, vomiting, elevated ALT or bilirubin levels), the clinician should rule out HBV IRIS and HDV flare and consult with an HIV-experienced hepatologist. (A3)
  - See the NYSDOH AI guideline Management of IRIS.

Abbreviations: 3TC, lamivudine; ALT, alanine transaminase; ART, antiretroviral therapy; ETV, entecavir; FTC, emtricitabine; HBV, hepatitis B virus; HDV, hepatitis D virus; IRIS, immune reconstitution inflammatory syndrome; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Treatment

Goals: The goals of treatment for chronic HBV infection in adults with HIV are to reduce liver inflammation (as indicated by normalization of ALT), obtain seroconversion of hepatitis B e antigen (HBeAg) to antibody to HBeAg, and suppress HBV viral replication. These changes will help reduce the risk of hepatic decompensation, halt or reverse liver fibrosis, prevent the development of hepatocellular carcinoma (HCC), and decrease HBV-related mortality [Kim, et al. 2021; Terrault, et al. 2018; Soriano, et al. 2008].

As indicated in the NYSDOH AI guideline Rapid ART Initiation, clinicians should recommend ART to all patients diagnosed with HIV infection. For patients with HIV/HBV coinfection, the regimen should include medications that suppress both HIV and HBV (see Table 4, below). Optimal treatment for both viruses should be taken simultaneously to prevent the development of HIV and HBV drug resistance. Optimal treatment of both infections may also help reduce the risk of IRIS, which is increased in patients with high levels of HBV viremia (see guideline section Monitoring, below) [Avihingsanon, et al. 2012; Crane, et al. 2009].

Table 4: Available Medications for Treatment of HBV Infection in Adults With HIV

Medication	Clinical Comment
Tenofovir disoproxil fumarate (TDF)	• A prodrug of the NRTI tenofovir active against HIV and HBV, including 3TC-resistant HBV • A preferred agent for chronic HBV treatment because of its high virologic efficacy and low risk of HBV resistance [Terrault, et al. 2018] • Potential association with renal impairment and loss of bone density [McComsey, et al. 2011; Gupta 2008] • Initiate ***only*** in patients with CrCl ≥50 mL/min.
Tenofovir alafenamide (TAF)	• A prodrug of the NRTI tenofovir active against HIV and HBV that achieves higher intracellular concentrations in peripheral blood mononuclear cells and hepatocytes than TDF [Agarwal, et al. 2018] • Improved biomarkers for renal and bone safety compared with TDF while maintaining high rates of HIV and HBV viral suppression [Lampertico, et al. 2020; Gallant, et al. 2016; Callebaut, et al. 2015] • In HIV/HBV coinfection, switching from a TDF- to a TAF-containing regimen demonstrated similarly high levels of HBV virologic control [Gallant, et al. 2016]. • Initiate ***only*** in patients with CrCl ≥30 mL/min.

Table 4: Available Medications for Treatment of HBV Infection in Adults With HIV	
Medication	**Clinical Comment**
Lamivudine (3TC)	• An HBV reverse transcriptase inhibitor and HIV NRTI active against HIV and HBV • Has a low genetic barrier to HIV and HBV resistance and should not be used as the sole anti-HBV drug in an ART regimen. Studies found the rate of HBV resistance reached 90% after 4 years of 3TC monotherapy [Benhamou, et al. 1999]. Avoid 3TC monotherapy.
Emtricitabine (FTC)	• An NRTI similar to 3TC and active against HIV and HBV • 3TC-resistant isolates are also cross-resistant to FTC [Gallant 2006]. • Do not use as the sole anti-HBV drug in an ART regimen.
Entecavir (ETV)	• An NRTI active against HIV and HBV • May select for 3TC- and FTC-resistant HIV • ETV monotherapy for HBV is not recommended in patients with HIV unless combined with a fully active ART regimen to treat HIV.
Interferon (IFN)	• IFN alfa-2a or -2b or PEG-IFN alfa-2a is used as HBV treatment in patients with HBV monoinfection. • Contraindicated in patients with decompensated liver disease (Child-Turcotte-Pugh class B or C) • PEG-IFN alfa-2a monotherapy for up to 48 weeks may be considered for HBV treatment in patients with HIV/HBV coinfection if concurrent ART active against HIV and HBV is not possible. • PEG-IFN alfa-2a is not associated with HBV drug resistance [DHHS 2022].
Abbreviations: ART, antiretroviral therapy; CrCl, creatinine clearance; HBV, hepatitis B virus; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PEG-IFN, pegylated interferon.	

Preferred regimen: Because FTC, 3TC, TDF, and TAF all have activity against HIV and HBV, an ART regimen for a patient with HIV/HBV coinfection should include a nucleoside/nucleotide reverse transcriptase inhibitor backbone of either TAF/FTC, TDF/FTC, or TDF/3TC as part of a fully suppressive regimen. TDF or TAF should not be used alone in the absence of a fully suppressive ART regimen because resistance mutations may develop [DHHS 2022; DHHS 2019]. For the use of TDF or TAF in patients with reduced renal function, see the NYSDOH AI guideline Selecting an Initial ART Regimen > ARV Dose Adjustments for Hepatic or Renal Impairment.

Alternative regimen: If patients cannot or choose not to take TDF or TAF, the alternative recommended regimen is ETV in addition to a fully suppressive HIV ART regimen [DHHS 2022; DHHS 2019]. ETV should not be considered part of the HIV ART regimen. The ETV dose should be increased from 0.5 mg per day to 1.0 mg per day in patients with known or suspected 3TC-resistant HBV infection. However, ETV resistance may emerge rapidly in patients with 3TC-resistant HBV infection [Terrault, et al. 2018]. Therefore, ETV should be used with caution in patients with HIV/HBV coinfection who do not take TAF or TDF, and frequent monitoring (every 3 months) of HBV DNA levels should be performed to detect viral breakthrough (see guideline section Monitoring, below).

The anti-HBV activity of 3TC, FTC, TDF, and TAF warrants their continued use whenever possible, even when HIV resistance indicates that they should be discontinued as part of the ART regimen. These agents should be continued after an anti-HBV therapy response has been achieved, even if the ART regimen has to be changed. Patients should be advised against discontinuing HIV or HBV treatment because the cessation of therapy has been associated with reactivation of HBV leading to exacerbations of hepatitis and hepatic failure [DHHS 2022]. Hepatitis flares can occur in patients with HBV monoinfection and those with HIV/HBV coinfection, but the risk of hepatic injury and fulminant hepatic failure is greater in patients with HIV/HBV coinfection [Moreno-Cubero, et al. 2018; Boyd, et al. 2017; Dore, et al. 2010].

Two-drug regimens for HIV: For patients with HIV/HBV coinfection, a 2-drug ART regimen should not be used as initial ART unless combined with an additional agent(s) with activity against HBV (see Table 5, below, for recommended additions). The same is true for patients with controlled HIV/HBV coinfection who switch to a 2-drug regimen for HIV ART—an agent with anti-HBV activity is required. Patients switching to a 2-drug regimen for HIV plus the additional agent(s) to treat HBV should be closely monitored for potential HBV flare (see guideline section Monitoring, below).

Table 5: Recommended Additions to 2-Drug HIV ART Regimens for Patients With Chronic HBV	
2-Drug HIV ART Regimen	**Addition for HBV Treatment**
DTG/3TC	TAF, TDF, or ETV
DTG/RPV	TAF/FTC, TDF/FTC, or TDF/3TC
CAB/RPV	TAF/FTC, TDF/FTC, or TDF/3TC
Abbreviations: 3TC, lamivudine; ART, antiretroviral therapy; CAB, cabotegravir; DTG, dolutegravir; ETV, entecavir; FTC, emtricitabine; HBV, hepatitis B virus; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.	

HBV treatment during pregnancy: Clinicians should offer pregnant patients with HIV/HBV coinfection ART that includes agents active against HIV and HBV. 3TC, FTC, TAF, and TDF can be safely used during pregnancy [DHHS 2022; Terrault, et al. 2018]. The preferred regimen is DTG plus TDF or TAF in combination with either FTC or 3TC. An alternative regimen is ritonavir-boosted darunavir (DRV/r) plus TDF or TAF with FTC or 3TC [DHHS 2022].

Monitoring

Recommended clinical evaluation and laboratory monitoring are described in Table 6, below.

Table 6: Recommended Monitoring After HBV Treatment Initiation in Adults With HIV			
Laboratory Test	**Every 3 Months**	**Every 6 Months**	**Every 12 Months**
HBV DNA	Until HBV DNA is undetectable [a]	After HBV DNA is undetectable	
HBeAg			Check for HBeAg-negative result [b]
Electrolyte panel		X	
Serum creatinine		X	
Urinalysis [c]			X
Liver function panel [c]	Until HBV DNA is undetectable [a]	After HBV DNA is undetectable	
Abbreviations: HBeAg, hepatitis B e antigen; HBV, hepatitis B virus. **Notes:** a. Undetectable is defined as <10 IU/mL. b. Patients who have been taking anti-HBV treatment for several years may not convert to HBeAg-negative [Singh, et al. 2017]. c. See NYSDOH AI guideline Laboratory Monitoring for Adverse Effects of ART.			

Response to treatment: HBV viral load levels generally decline more slowly after treatment initiation than HIV viral load levels. Anti-HBV treatment responses are defined as follows [DHHS 2022]:

- Primary nonresponse: HBV DNA <1 $\log_{10}$ decline at 12 weeks
- Complete virologic response: Undetectable HBV DNA by polymerase chain reaction assay at 24 to 48 weeks
- Partial virologic response: ≥1 $\log_{10}$ decline but still detectable HBV DNA at 24 weeks
- Maintained virologic response: A response that continues while on therapy
- Sustained virologic response: A virologic response that is still present 6 months after cessation of therapy

Renal toxicity: Renal toxicity with increased creatinine or renal tubular dysfunction has been associated with tenofovir use, and the association is stronger with TDF than TAF [Gupta, et al. 2019]. This renal toxicity may be reversible with dose adjustments of TDF or switching to TAF. Clinicians should evaluate electrolytes, serum creatinine levels, and urinalysis every 6 months [DHHS 2022].

Cirrhosis: Patients with HIV/HBV coinfection and cirrhosis should be referred to a gastroenterologist or hepatologist to assess and manage complications of portal hypertension such as gastroesophageal varices and ascites. Patients with HIV/HBV coinfection and cirrhosis should undergo esophagogastroduodenoscopy at the time of chronic HBV diagnosis and every 1 to 2 years thereafter [DHHS 2022; Terrault, et al. 2018].

Acute flare: If a patient being treated for chronic HBV develops signs or symptoms of acute hepatitis (nausea, vomiting, elevated ALT or bilirubin levels), clinicians should evaluate the patient, rule out HBV IRIS and HDV flare among other potential causes, and consult with an HIV-experienced hepatologist. Hepatic flares are usually mild and self-limited but can result in decompensation in individuals with preexisting cirrhosis [Anderson, et al. 2010; Crane, et al. 2009; Perrella, et al. 2006; Konopnicki, et al. 2005; Drake, et al. 2004].

In patients with HIV, initiation of or a change in ART introduces the potential for IRIS, which may manifest as a worsening of previously diagnosed disease or the appearance of a previously undiagnosed disease. In patients with HIV/HBV coinfection, IRIS can present as an acute flare of HBV disease. It can often be difficult to distinguish HBV IRIS from other causes of an acute HBV flare, such as drug or alcohol hepatotoxicity or other viral infection (hepatitis A, C, D, or E virus, Epstein-Barr virus, herpes simplex virus, or cytomegalovirus). Reviewing medication history and testing for serum HBV DNA, HBeAg, HIV viral load, and CD4 cell count can help distinguish between these possibilities [DHHS 2022].

HBV IRIS is usually detected within the first 6 to 12 weeks after ART is initiated, based on a noticeable rise in ALT levels that coincides with rising CD4 cell counts (immune reconstitution) and signs and symptoms characteristic of acute hepatitis and with no other cause for the flare [DHHS 2022]. Risk factors for HBV IRIS include high HBV viral load, elevated ALT level, and low CD4 cell count at baseline [Singh, et al. 2017].

Ongoing Screening for Hepatocellular Carcinoma

Compared with HBV monoinfection, HIV/HBV coinfection is associated with an increased risk of developing HCC and increased mortality rates [Sun, et al. 2021; Pinato, et al. 2019; Singh, et al. 2017]. Patients with HIV/HBV coinfection and cirrhosis should be screened with ultrasound for HCC every 6 months [Terrault, et al. 2018].

There is no consensus on how frequently to screen for HCC in patients with HIV/HBV coinfection who do not have cirrhosis. In patients with HBV monoinfection, screening is recommended every 6 months for groups at increased risk for developing HCC, including Asian men >40 years old, Asian women >50 years old, Black men >40 years old, individuals with a first-degree family member who has a history of HCC, or individuals with HDV [Terrault, et al. 2018; Sarin, et al. 2016; Zhang, et al. 2004].

All Recommendations

☑ ALL RECOMMENDATIONS

Screening Tests

- Clinicians should determine the HBV vaccination and immune status of patients with HIV by performing laboratory testing for HBsAg, anti-HBs, and anti-HBc (total). (A*) See Table 1: Interpretation of HBV Screening Test Results.
- Clinicians should repeat laboratory screening annually in patients who are not immune to HBV, choose not to be vaccinated, and are at ongoing risk of acquiring HBV. (A3)

Diagnosis

- In patients with positive baseline (screening) HBsAg test results, clinicians should perform HBeAg, anti-HBe, and HBV DNA testing to diagnose the phase of HBV infection. (B2†) See Table 2: Serologic and Virologic Responses to HBV Infection.
- If a patient with HIV and unknown HBsAg status has signs or symptoms of acute hepatitis (i.e., elevated ALT), the clinician should perform HBsAg, anti-HBc IgM**,** HBeAg, anti-HBe (A*), and HBV DNA (A3) testing along with other diagnostic testing for acute hepatitis.

Acute HBV Infection

- If acute HBV infection is confirmed and the patient is asymptomatic, the clinician should repeat ALT testing within 2 to 4 weeks to assess for symptoms of liver disease progression (B3) and repeat HBsAg, HBeAg, anti-HBe, and HBV DNA testing 6 months later to determine whether infection has cleared. (A3)
- If a patient with HIV and acute HBV is not taking ART, the clinician should recommend ART initiation. (A1)

Transmission Prevention

- Clinicians should advise patients who have a positive HBsAg test result that they can transmit HBV (A*) and encourage sexually active patients to use effective barrier protection to reduce the risk of HBV transmission. (A2†)
- Clinicians should inform patients with HBV that their household contacts should be vaccinated and counsel the patients to avoid sharing items such as razors or toothbrushes that could expose others to HBV-contaminated blood. (A2†)
- For individuals who inject drugs, clinicians should offer or refer for substance use treatment, ensure access to clean needles and syringes, and provide harm reduction counseling. (A2†)
  - See NYSDOH Drug Use Resources.

Primary Vaccination

- Clinicians should offer HBV vaccination with the 3-dose Engerix-B or Recombivax HB vaccine series (A1) or the 2-dose Heplisav-B vaccine series (A2†) to patients with negative test results for HBsAg, anti-HBs, and anti-HBc.
- Clinicians should not defer initial HBV vaccination in patients with a CD4 count <200 cells/mm^3 who are at risk for HBV infection. (A2)
- Clinicians should repeat anti-HBs testing 4 to 16 weeks, based on the patient's visit schedule, after completion of the vaccination series to ensure immunity (anti-HBs ≥10 mIU/mL). (A3)
- In a patient with negative HBsAg, negative anti-HBs, and positive anti-HBc test results (isolated anti-HBc positive), the clinician should offer a 1-time dose of HBV vaccine. (A2)
  - Repeat anti-HBs testing 8 weeks after vaccination, and if the anti-HBs titer is <100 mIU/mL, complete the HBV vaccine series and repeat anti-HBs testing 8 weeks after the last vaccine. (A2)
  - If vaccination is refused or if follow-up anti-HBs titer testing cannot be assured, perform HBV DNA testing to evaluate for occult HBV infection. (A2)
- Clinicians should not defer initial vaccination or revaccination in pregnant patients with HIV who do not have immunity to HBV. (A3)

Revaccination

- In previously vaccinated patients with anti-HBs levels <10 mIU/mL (vaccine nonresponse), clinicians should recommend revaccination with the Heplisav-B vaccine series or a double dose of the vaccine series previously administered. (A2)

Liver Disease Assessment

- Before initiating HBV treatment in patients with HIV, clinicians should obtain a complete physical examination and medical history, including the use of hepatoxic medications (A*); noninvasive fibrosis evaluation (A2†); baseline ultrasonography for HCC [a] (A2†); and the following laboratory testing: CBC, albumin, bilirubin, alkaline phosphatase, PT/INR, ALT, AST, and a basic metabolic panel. (A*)

☑ ALL RECOMMENDATIONS

- Clinicians should refer patients with HIV/HBV coinfection and cirrhosis to a gastroenterologist or hepatologist to assess and manage complications of portal hypertension. (A3)
- In patients with HIV/HBV coinfection and cirrhosis, clinicians should screen for HCC with ultrasound every 6 months. (A2†)
  - See the guideline section HBV Treatment and Monitoring > Ongoing Screening for Hepatocellular Carcinoma regarding screening for patients without cirrhosis.

Alcohol Use Screening and Education

- Clinicians should perform alcohol use screening in patients with HIV/HBV coinfection at baseline and at least annually and refer patients for treatment as needed. (A3)
  - See the NYSDOH AI guidelines Substance Use Screening and Risk Assessment in Adults and Treatment of Alcohol Use Disorder.
- Clinicians should educate patients about the detrimental effects of alcohol use on the course of HBV infection and counsel patients with underlying liver disease to abstain from or minimize alcohol use. (A*)

HAV, HCV, and HDV Status

- Clinicians should perform anti-HAV IgG or total (IgM and IgG) serum testing and administer the full HAV vaccine series in patients who are not immune to HAV. (A3)
- Clinicians should determine patients' HCV status by medical history and serum testing and recommend treatment with DAA therapy if chronic HCV infection is diagnosed. (A1)
  - See the NYSDOH AI guidelines Hepatitis C Virus Screening, Testing, and Diagnosis in Adults and Treatment of Chronic Hepatitis C Virus Infection in Adults.
- Clinicians should perform anti-HDV total (IgM and IgG) serum testing to screen for HDV in all patients with HIV/HBV coinfection. (B2)

Treatment

- Clinicians should recommend immediate ART initiation for any patient with HIV/HBV coinfection who is not taking ART. (A1)
- **Preferred:** In patients with HIV and chronic HBV, clinicians should recommend an ART regimen that includes 2 agents active against HBV (see Table 4: Available Medications for Treatment of HBV Infection in Adults With HIV). Preferred regimens include a backbone of either TAF/FTC, TDF/FTC, or TDF/3TC. (A2)
- Clinicians should not prescribe a 2-drug regimen of TAF/FTC, TDF/FTC, or TDF/3TC alone to treat patients with HIV/HBV coinfection; a fully suppressive ART regimen is required. (A1)
- Nonadherence with or discontinuation of anti-HBV treatment may result in transaminase flares and hepatic damage. Clinicians should educate patients about the treatment adherence requirements (A*), and if treatment must be interrupted or discontinued, consult with a care provider experienced in HIV/HBV coinfection. (A3)
- **Alternative:** If a patient cannot or chooses not to take TDF or TAF, the clinician should initiate treatment with ETV and a fully suppressive ART regimen for HIV. (A3)

Pregnant Patients

- Clinicians should offer pregnant patients treatment with an ART regimen that includes 2 agents active against both HIV and HBV; 3TC, FTC, TAF, and TDF can be used safely during pregnancy at standard doses. (A2†)

Monitoring

- After HBV treatment initiation, clinicians should perform the laboratory testing listed in Table 6: Recommended Monitoring After HBV Treatment Initiation in Adults With HIV. (A3)
- If a patient being treated for chronic HBV develops signs or symptoms of acute hepatitis (nausea, vomiting, elevated ALT or bilirubin levels), the clinician should rule out HBV IRIS and HDV flare and consult with an HIV-experienced hepatologist. (A3)
  - See the NYSDOH AI guideline Management of IRIS.

Abbreviations: 3TC, lamivudine; ALT, alanine transaminase; anti-HBc, hepatitis B core antibody; anti-HBe, antibody to HBeAg; anti-HBs, hepatitis B surface antibody; ART, antiretroviral therapy; AST, aspartate transaminase; CBC, complete blood count; DAA, direct-acting antiviral; ETV, entecavir; FTC, emtricitabine; HAV, hepatitis A virus; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; IgG, immunoglobulin G; IgM, immunoglobulin M; IRIS, immune reconstitution inflammatory syndrome; PT/INR, prothrombin time/international normalized ratio; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Note:

a. Baseline ultrasound for HCC is performed in all patients with HIV/HBV coinfection. In patients with HIV/HCV coinfection, an ultrasound is performed only in patients with cirrhosis.

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Supplement: Guideline Development and Recommendation Ratings

Table S1: Guideline Development: New York State Department of Health AIDS Institute Clinical Guidelines Program	
Developer	New York State Department of Health AIDS Institute (NYSDOH AI) Clinical Guidelines Program
Funding source	NYSDOH AI
Program manager	Clinical Guidelines Program, Johns Hopkins University School of Medicine, Division of Infectious Diseases. See Program Leadership and Staff.
Mission	To produce and disseminate evidence-based, state-of-the-art clinical practice guidelines that establish uniform standards of care for practitioners who provide prevention or treatment of HIV, viral hepatitis, other sexually transmitted infections, and substance use disorders for adults throughout New York State in the wide array of settings in which those services are delivered.
Expert committees	The NYSDOH AI Medical Director invites and appoints committees of clinical and public health experts from throughout New York State to ensure that the guidelines are practical, immediately applicable, and meet the needs of care providers and stakeholders in all major regions of New York State, all relevant clinical practice settings, key New York State agencies, and community service organizations.
Committee structure	• Leadership: AI-appointed chair, vice chair(s), chair emeritus, clinical specialist(s), JHU Guidelines Program Director, AI Medical Director, AI Clinical Consultant, AVAC community advisor • Contributing members • Guideline writing groups: Lead author, coauthors if applicable, and all committee leaders
Disclosure and management of conflicts of interest	• Annual disclosure of financial relationships with commercial entities for the 12 months prior and upcoming is required of all individuals who work with the guidelines program, and includes disclosure for partners or spouses and primary professional affiliation. • The NYSDOH AI assesses all reported financial relationships to determine the potential for undue influence on guideline recommendations and, when indicated, denies participation in the program or formulates a plan to manage potential conflicts. Disclosures are listed for each committee member.
Evidence collection and review	• Literature search and review strategy is defined by the guideline lead author based on the defined scope of a new guideline or update. • A comprehensive literature search and review is conducted for a new guideline or an extensive update using PubMed, other pertinent databases of peer-reviewed literature, and relevant conference abstracts to establish the evidence base for guideline recommendations. • A targeted search and review to identify recently published evidence is conducted for guidelines published within the previous 3 years. • Title, abstract, and article reviews are performed by the lead author. The JHU editorial team collates evidence and creates and maintains an evidence table for each guideline.

Table S1: Guideline Development: New York State Department of Health AIDS Institute Clinical Guidelines Program	
Recommendation development	• The lead author drafts recommendations to address the defined scope of the guideline based on available published data. • Writing group members review the draft recommendations and evidence and deliberate to revise, refine, and reach consensus on all recommendations. • When published data are not available, support for a recommendation may be based on the committee's expert opinion. • The writing group assigns a 2-part rating to each recommendation to indicate the strength of the recommendation and quality of the supporting evidence. The group reviews the evidence, deliberates, and may revise recommendations when required to reach consensus.
Review and approval process	• Following writing group approval, draft guidelines are reviewed by all contributors, program liaisons, and a volunteer reviewer from the AI Community Advisory Committee. • Recommendations must be approved by two-thirds of the full committee. If necessary to achieve consensus, the full committee is invited to deliberate, review the evidence, and revise recommendations. • Final approval by the committee chair and the NYSDOH AI Medical Director is required for publication.
External reviews	• External review of each guideline is invited at the developer's discretion. • External reviewers recognized for their experience and expertise review guidelines for accuracy, balance, clarity, and practicality and provide feedback.
Update process	• JHU editorial staff ensure that each guideline is reviewed and determined to be current upon the 3-year anniversary of publication; guidelines that provide clinical recommendations in rapidly changing areas of practice may be reviewed annually. Published literature is surveilled to identify new evidence that may prompt changes to existing recommendations or development of new recommendations. • If changes in the standard of care, newly published studies, new drug approval, new drug-related warning, or a public health emergency indicate the need for immediate change to published guidelines, committee leadership will make recommendations and immediate updates and will invite full committee review as indicated.

Table S2: Recommendation Ratings and Definitions		
Strength	**Quality of Evidence**	
A: Strong B. Moderate C: Optional	1	Based on published results of at least 1 randomized clinical trial with clinical outcomes or validated laboratory endpoints.
	*	Based on either a self-evident conclusion; conclusive, published, in vitro data; or well-established practice that cannot be tested because ethics would preclude a clinical trial.
	2	Based on published results of at least 1 well-designed, nonrandomized clinical trial or observational cohort study with long-term clinical outcomes.
	2†	Extrapolated from published results of well-designed studies (including nonrandomized clinical trials) conducted in populations other than those specifically addressed by a recommendation. The source(s) of the extrapolated evidence and the rationale for the extrapolation are provided in the guideline text. One example would be results of studies conducted predominantly in a subpopulation (e.g., one gender) that the committee determines to be generalizable to the population under consideration in the guideline.
	3	Based on committee expert opinion, with rationale provided in the guideline text.