

## HEPATITIS B VIRUS

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Key to Abbreviated Terms	
<b>AFP</b>	$\alpha$ -Fetoprotein
<b>ALT</b>	Alanine aminotransferase
<b>AST</b>	Aspartate aminotransferase
<b>HBcAb</b>	Hepatitis B core antibody
<b>HBeAb</b>	Hepatitis B envelope antibody
<b>HBeAg</b>	Hepatitis B envelope antigen
<b>HBsAb</b>	Hepatitis B surface antibody
<b>HBsAg</b>	Hepatitis B surface antigen
<b>HAV</b>	Hepatitis A virus
<b>HBV</b>	Hepatitis B virus
<b>HCC</b>	Hepatocellular carcinoma
<b>HCV</b>	Hepatitis C virus
<b>HDV</b>	Hepatitis delta virus
<b>IFN</b>	Interferon
<b>PegIFN</b>	Pegylated IFN
<b>PT/INR</b>	Prothrombin time international normalized ratio

### What's New — June 2008 Update

The committee recommends:

- Administering the HBV vaccination series to HIV-infected patients who are negative for HBsAb, unless they are chronically infected (see Figure 3).
- Testing for HBsAb between 4 and 12 weeks after vaccination. Nonresponders (HBsAb <10 IU/L) should be revaccinated with another three-dose hepatitis B vaccine series (see Figure 3). If a patient's CD4 count is <200 cells/mm<sup>3</sup> or the patient has symptomatic HIV disease, revaccination may be deferred until several months after initiation of ARV therapy in an attempt to maximize the antibody response to the vaccine. However, revaccination should not be deferred in pregnant patients or patients who are unlikely to achieve an increased CD4 count (see Figure 3).
- Initiating treatment active against HBV when HBV DNA levels are >2000 IU/mL.
- Initiating ARV therapy when initiating treatment against HBV in HIV/HBV co-infected patients.

## I. INTRODUCTION

Hepatitis B virus (HBV) is a double-stranded DNA, enveloped virus that replicates in hepatocytes. Its primary routes of transmission are vertical (mother-to-child), blood exposure, and sexual exposure. It is significantly more transmissible than HIV via blood-borne exposure, and some fluids that do not normally transmit HIV, such as saliva and sweat, contain infectious

HBV but at much lower levels than blood. In many cases, a patient's route of infection is not identified.

Approximately 1 to 1.25 million people are HBV carriers in the United States,<sup>1</sup> and four to five thousand deaths due to HBV-related cirrhosis or hepatocellular carcinoma (HCC) occur annually in the US. HBV infection resolves spontaneously in 90% to 95% of immunocompetent adults who are infected<sup>2</sup>; however, 5% to 10% develop chronic HBV infection that is characterized by persistence of circulating hepatitis B surface antigen (HBsAg) in the blood. Individuals with chronic hepatitis B are at risk for progression to cirrhosis or HCC. The similar routes of transmission for HIV and HBV place patients with either infection at greater risk for HIV/HBV co-infection. The rate of HBV infection in HIV-infected patients varies widely depending on the population. The highest rates of HIV/HBV co-infection (5% to 10% in the United States) are generally in men who have sex with men and injection drug users.<sup>3,4</sup> HIV-infected women in the US have co-infection rates of 3% to 4%.<sup>5</sup> HIV-infected patients in the EuroSIDA cohort had a co-infection rate of 9%.<sup>6</sup>

HIV-infected patients have lower rates than non-HIV-infected patients of hepatitis B envelope antibody (HBeAb) and hepatitis B surface antibody (HBsAb) seroconversion, resulting in higher rates of chronic HBV. HIV-infected individuals also have increased rates of HBV replication and accelerated disease progression, with increased incidence of liver fibrosis, cirrhosis, end-stage liver disease, HCC, and liver-related deaths compared with HBV mono-infected patients.<sup>7</sup> In the MACS cohort, HIV/HBV co-infected patients had a risk of liver-related mortality that was 13 times higher than HIV mono-infected patients.<sup>8</sup>

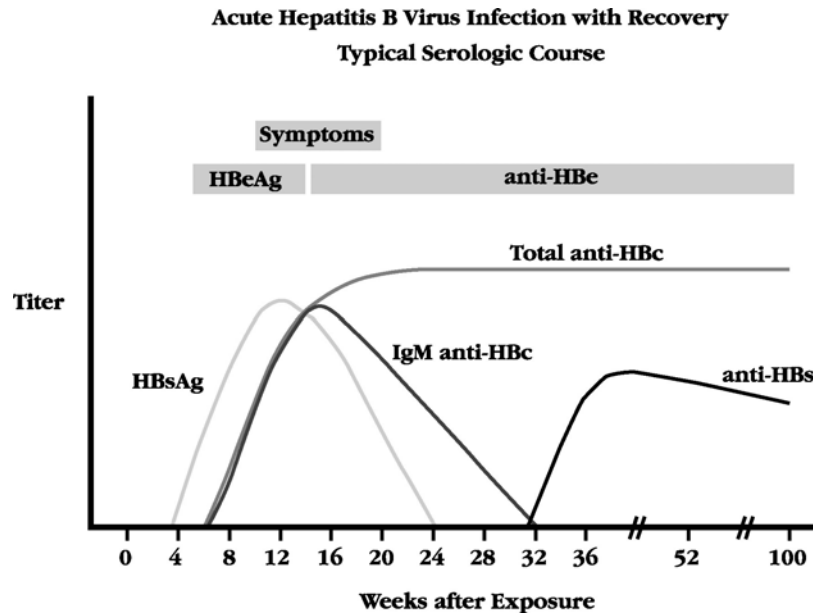
Assessment for HBV infection is part of the baseline evaluation of all HIV-infected patients (see [Primary Care Approach to the HIV-Infected Patient](#)), and treatment of HBV in HIV-infected patients requires consideration of both infections (see Section VI. Treatment of HBV Infection in the Setting of HIV).

## II. CLINICAL SYNDROMES

### A. Acute Hepatitis B Infection

The incubation period for HBV is 30 to 180 days (mean, 90 days), and acute infections may vary from asymptomatic or mild to severe jaundice and, rarely, fulminant hepatic failure. Fever, right upper-quadrant abdominal pain, headache, and malaise are common, as are elevated serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. Up to 20% of patients may develop arthralgias or arthritis. Symptoms resolve in 4 to 6 weeks, and 90% to 95% of non-HIV-infected patients develop HBsAb and are considered HBV-immune.<sup>2</sup> However, the rate of HBsAb development in HIV-infected individuals is lower.<sup>9</sup>

During acute infection, hepatitis B core antibody (HBcAb) IgM (IgM anti-HBc) appears within 4 weeks of HBsAg and is sometimes used as a marker for acute infection (although it can sometimes reappear during a reactivation of chronic infection). The emergence of HBsAb (anti-HBs) signals resolving infection (see Figure 1).



**Figure 1.** Reprinted from Centers for Disease Control and Prevention. Available at: [www.cdc.gov/ncidod/diseases/hepatitis/slideset/hep\\_b/hep\\_b.pdf](http://www.cdc.gov/ncidod/diseases/hepatitis/slideset/hep_b/hep_b.pdf)

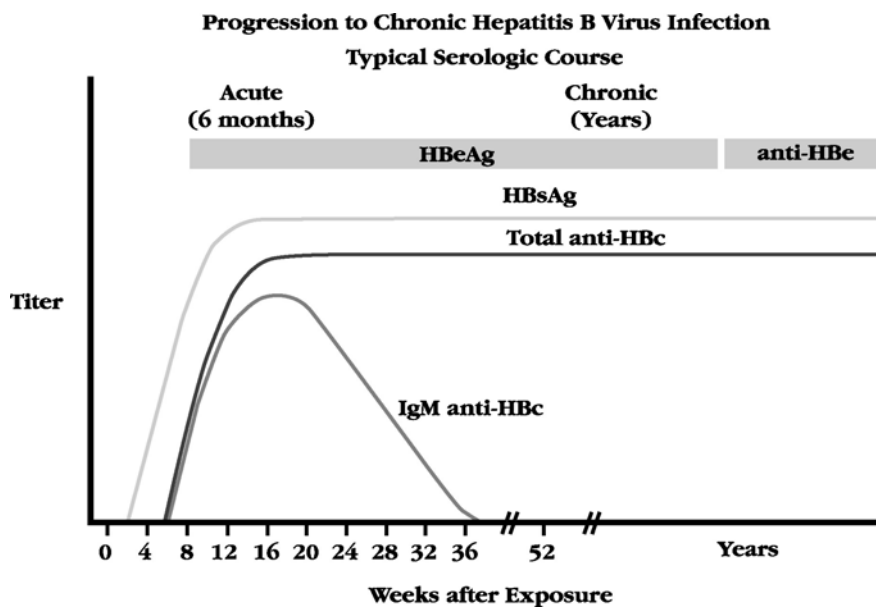
## B. Chronic Hepatitis B Infection

HIV/HBV co-infected patients are those who have HIV infection and chronic HBV, i.e., necroinflammatory disease of the liver caused by persistent infection with HBV. Chronic HBV infection can be subdivided into HBeAg-positive and HBeAg-negative HBV. Chronic hepatic inflammation, sometimes with elevated ALT, may progress to hepatic fibrosis and cirrhosis. In contrast to HCC in hepatitis C, HCC can develop in HBV infection without prior cirrhosis. Chronic HBV infection is often asymptomatic, although some patients experience periodic jaundice. In non-HIV-infected patients, HBsAg will clear in 2% of chronic carriers per year. HBeAg may often clear despite persistent HBsAg and is frequently associated with resolution of inflammation and hepatic recovery. This is attributable to continued expression of HBsAg from HBV DNA integrated into the hepatocyte genome with little viral replication.

Chronic HBV infection has been categorized into high and low replication:

- *High replication*—hepatitis B envelope antigen (HBeAg) positivity, high levels of HBsAg and HBV DNA, and elevated ALT
- *Low replication*—HBeAg negativity, low levels of HBsAg and HBV DNA, and low or normal ALT

This distinction is complicated by variants of HBeAg negativity in HBV infection, including the “precore” and “core promoter” mutants, which result in a state of high viral replication (i.e., >2000 IU/mL defined as significant). These mutations are present in up to 10% of HBeAg-negative patients. Identification of these cases is important because despite HBeAg negativity, liver disease progression is similar to that in patients who are positive for HBeAg (see Section IV. Evaluation of Patients with Chronic HBV). Figure 2 shows the serologic responses to chronic HBV infection.



**Figure 2.** Reprinted from Centers for Disease Control and Prevention. Available at: [www.cdc.gov/ncidod/diseases/hepatitis/slideset/hep\\_b/hep\\_b.pdf](http://www.cdc.gov/ncidod/diseases/hepatitis/slideset/hep_b/hep_b.pdf)

### C. Reactivation

Reactivation is defined as reappearance of active necroinflammatory disease of the liver in a person known to have the inactive HBsAg carrier state or resolved HBV (as defined in Table 1).<sup>10</sup> This is rare and is usually associated with severe immunosuppression but may be more common in HIV-infected patients, including those who experience immune reconstitution after initiation of ARV therapy.<sup>11</sup> Reactivation may result in severe hepatitis and should be considered as a potential cause of hepatitis in patients who have had previously resolved hepatitis B. During reactivation, ALT will be elevated and patients who were previously HBeAg- and/or HBsAg-negative may become both HBeAg-positive and HBsAg-positive. This requires confirmation by one of the appropriate serologic tests: HBeAg, HBeAb, or HBV DNA levels.

### D. Hepatitis Delta Virus (HDV)

HDV is a defective virus that requires active HBV infection for its replication and is associated with more severe liver disease, hepatic flares, and more rapid progression of liver disease when present in HBV-infected patients. Some clinicians assess for HDV with a serum total HDV IgM and IgG test in patients who are positive for HBsAg, particularly if the patient is from an HDV-endemic area. According to the Centers for Disease Control and Prevention, such areas include southern Italy, parts of Russia and Romania, and isolated regions of some South American countries in the Amazon River Basin.<sup>12</sup>

### E. HIV/HBV/HCV Tri-Infection

Hepatitis C virus (HCV) in the presence of HBV is of particular concern for clinicians treating HIV-infected patients. Studies have indicated that patients with chronic HBV/HCV co-infection have a significantly higher degree of liver fibrosis,<sup>13-15</sup> as well as hepatocellular apoptosis, bile duct damage, and ductular proliferation.<sup>14</sup>

These findings suggest more severe forms of HCV-related cirrhosis attributable to the presence of HBV.<sup>14</sup> Furthermore, HBV/HCV co-infection may be associated with rapid progression to HCC.<sup>16</sup>

### **III. BASELINE EVALUATION, SCREENING, AND PREVENTION OF HIV/HBV CO-INFECTION**

#### **A. Baseline Hepatic Evaluation**

##### **RECOMMENDATION:**

**As part of the baseline assessment of HIV-infected patients, clinicians should evaluate liver function, including AST and ALT.**

Liver function, including AST and ALT, should be assessed at baseline in all HIV-infected patients. If AST or ALT is elevated, the clinician should assess for causes of hepatic inflammation. Although the patient's platelet count may decrease as a result of many factors, low platelet count could be an indication of cirrhosis. Low albumin, high cholesterol, and elevated PT/INR (prothrombin time international normalized ratio) may indicate cirrhosis or end-stage liver disease, although they remain insensitive for liver dysfunction.

#### **B. Hepatitis Screening**

##### **RECOMMENDATIONS:**

**As part of the baseline assessment, clinicians should ask HIV-infected patients about their HBV vaccination history and should obtain the following:**

- **HBV serologies: HBsAg, HBsAb, and HBcAb (IgG or total)**
- **Hepatitis A IgG and hepatitis C IgG**

**Clinicians should obtain an HBV DNA test for patients with negative HBsAb, negative HBsAg, and positive HBcAb to determine whether the patient has occult HBV infection (see Figure 3).**

Screening for HBV should include obtaining HBsAb, HBsAg, and HBcAb. Patients with HBsAb levels of  $\geq 10$  IU/L are considered to be immune to HBV. Patients who are positive for HBcAb but are negative for HBsAb and HBsAg may have: 1) resolved HBV infection with  $< 10$  IU/L HBsAb; 2) acute HBV infection; 3) occult HBV infection and thus will be positive for HBV DNA; or 4) a false-positive result. Table 1 shows the serologic and virologic responses to HBV, and Table 2 shows interpretation of HBV serologies.

TABLE 1 SEROLOGIC AND VIROLOGIC RESPONSES TO HBV							
Stage of Infection	HBsAg	HBsAb	HBcAb IgG	HBcAb IgM	HBeAg	HBeAb	HBV Viral Load
Incubation	+	-	-	-	+ or -	-	Low
Acute hepatitis B	+	-	+	+	+	-	High
HBsAg-negative acute hepatitis B	-	-	+	+	+/-	-	High
Inactive HBsAg carrier	+	-	+++	+ or -	-	+	Low
Precore mutant	+	-	+ or -	+ or -	-	+	High
Occult infection*	-	-	+	+ or -	-	-	High or low
Chronic hepatitis B	+	-	+++	+ or -	+ or -	-	High or low
Resolved HBV infection†	-	++	++	+ or -	-	+	Undetectable
HBV vaccination	-	++	-	-	-	-	Undetectable

\* Studies have found occult HBV infection in approximately 10% of HBcAb-positive and HBsAg- and HBsAb-negative HIV-infected patients.<sup>17,18</sup> Occult infection may be associated with greater immunosuppression (<200 cells/mm<sup>3</sup>) and higher HIV DNA levels.<sup>19</sup>

† Formerly known as convalescent.

TABLE 2 INTERPRETATION OF THE HEPATITIS B PANEL		
Tests	Results	Interpretation
HBsAg HBcAb* HBsAb	Negative Negative Negative	Susceptible to infection
HBsAg HBcAb HBsAb	Negative Negative or positive Positive	Immune
HBsAg HBcAb IgM HBcAb HBsAb	Positive Positive Positive Negative	Acutely infected
HBsAg HBcAb IgM HBcAb HBsAb	Positive Positive Negative Negative	Chronically infected
HBsAg HBcAb HBsAb	Negative Positive Negative	Four interpretations possible†

\* Note about HBcAb: in the context of chronic infection, IgG is the applicable HBcAb marker. Therefore, references to HBcAb in these guidelines and elsewhere in the literature indicate IgG HBcAb, *not* IgM HBcAb, unless otherwise specified.

† 1) May be recovering from acute HBV infection; 2) may be distantly immune with test not sensitive enough to detect very low level of HBsAb in serum (<10 IU/L); 3) may be susceptible with a false-positive HBcAb; and 4) may be a carrier with an undetectable level of HBsAg, although HBV DNA may be detectable in this setting.

### C. Prevention of HIV/HBV Co-Infection

#### RECOMMENDATIONS:

**Clinicians should counsel patients about behavior modifications that decrease their risk of acquiring HBV infection through unprotected sexual activity and injection drug use.**

#### Vaccination:

**Clinicians should administer the HBV vaccination series to HIV-infected patients who are negative for HBsAb, unless they are chronically infected (see Figure 3).**

**Clinicians should test for HBsAb between 4 and 12 weeks after vaccination. Nonresponders (HBsAb <10 IU/L) should be revaccinated with another three-dose hepatitis B vaccine series (see Figure 3). If a patient's CD4 count is <200 cells/mm<sup>3</sup> or the patient has symptomatic HIV disease, revaccination may be deferred until several months after initiation of ARV therapy in an attempt to maximize the antibody response to the vaccine. However, revaccination should not be deferred in pregnant patients or patients who are unlikely to achieve an increased CD4 count (see Figure 3).**

Patients who are negative for HBsAb (who are not HBsAg-positive) should receive the HBV vaccination series and should be counseled to prevent HBV infection through avoidance of high-risk sexual behaviors and needle-sharing. Quantitative HBsAb levels should be obtained between 4 and 12 weeks after vaccination, and nonresponders (HBsAb <10 IU/L) should be revaccinated. *Revaccination* can be deferred for patients initiating ARV therapy until CD4 count is  $\geq 200$  cells/mm<sup>3</sup> because response rates to HBV vaccination in immunocompromised patients is low, whereas vaccination may be more than 60% effective in patients with CD4 counts of  $\geq 200$  cells/mm<sup>3</sup>.<sup>20</sup> Double-dose HBV revaccination has shown efficacy in some patients<sup>21</sup>; however, a previous study did not demonstrate similar results.<sup>22</sup>

#### **Key Point:**

Patients who are unlikely to achieve CD4 counts of  $\geq 200$  cells/mm<sup>3</sup> after ARV therapy (e.g., patients with HCV co-infection), as well as HIV-infected pregnant women, are at risk for severe complications resulting from HBV infection.

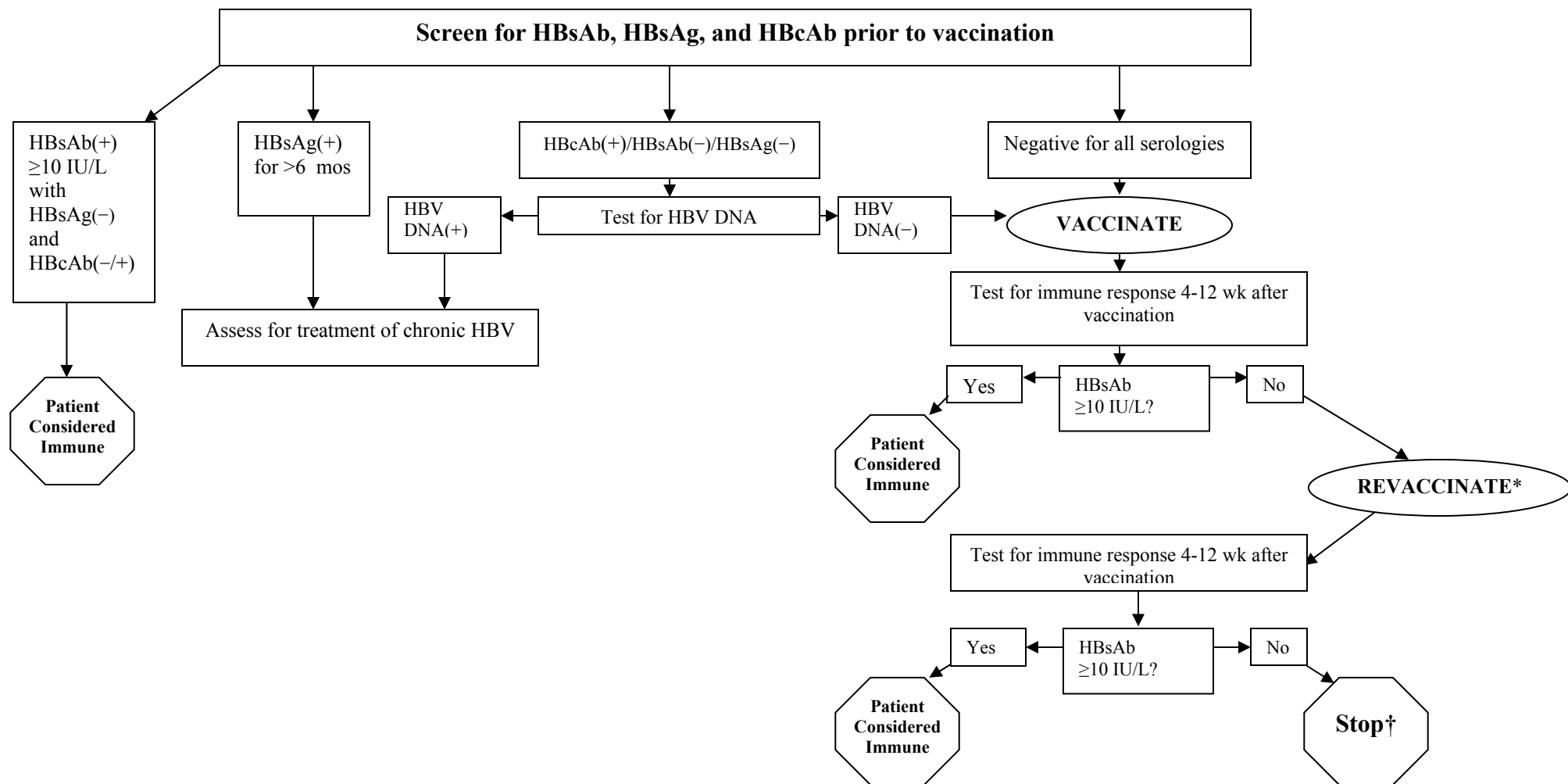
For information regarding perinatal HBV prophylaxis, see the Women's Health guidelines *Management of HIV-Infected Pregnant Women Including Prevention of Perinatal HIV Transmission*.

If HBsAb is not induced by primary vaccination and revaccination, then HBV DNA testing can be performed to determine whether the patient is a primary nonresponder or has chronic HBV infection (see Tables 1 and 2 and Figure 3). Primary nonresponders are individuals who are HBsAg-negative but are unable to develop immunity after receiving vaccinations that are administered according to standard protocols. Primary nonresponders are considered susceptible to HBV infection.<sup>23</sup>

#### **Key Point:**

Patient education regarding HBV vaccination is important to ensure awareness of the continued risk for acquiring HBV until adequate surface antibody response is documented.

**Figure 3. Algorithm for HBV prevaccination screening and vaccination in HIV-infected patients**



\* Revaccination can be deferred in patients initiating ARV therapy until CD4 count is  $\geq 200$  cells/mm<sup>3</sup>; revaccination should not be delayed in pregnant patients or those who are unlikely to experience immune reconstitution of  $\geq 200$  cells/mm<sup>3</sup>.

† A patient who is negative for all serologies and who does not respond to revaccination may be a primary nonresponder or have chronic infection. HBV DNA testing may be used to detect the presence of chronic HBV infection.

## HAV Co-Vaccination

### **RECOMMENDATION:**

**Clinicians should administer the HAV vaccine to HIV-infected patients who are negative for HAV IgG to prevent concurrent HAV infection (see [Hepatitis A Virus](#)).**

Hepatitis A virus (HAV) and HBV vaccines should be administered regardless of CD4 counts to patients who are all of the following: HAV IgG-, HBsAb-, and HBsAg-negative. A combined hepatitis A and B vaccine is available and can be used in persons susceptible to both HAV and HBV. Patients who do not require HBV vaccination may benefit from deferral of HAV vaccination until CD4 counts reach  $\geq 200$  cells/mm<sup>3</sup> (see [Hepatitis A Virus](#)).<sup>24</sup> Such deferral is not advisable in pregnant women or in patients who are not likely to achieve CD4 counts of  $\geq 200$  cells/mm<sup>3</sup>.

For additional information regarding prevention of viral hepatitis, refer to the Prevention guidelines [Viral Hepatitis](#). For information regarding post-exposure prophylaxis to hepatitis infection, refer to [HIV Prophylaxis Following Occupational Exposure](#) and [HIV Prophylaxis Following Non-Occupational Exposure Including Sexual Assault](#).

## **IV. EVALUATION OF PATIENTS WITH CHRONIC HBV**

### **RECOMMENDATIONS:**

**Clinicians should evaluate the extent of liver disease in patients with chronic hepatitis by:**

- **Obtaining an HBV-related history**
- **Performing a physical examination for signs and symptoms of advanced liver disease**
- **Measuring serial ALT levels, PT/INR, albumin, and platelet count**
- **Assessing inflammation, fibrosis, HBV replication, and risk of HCC**
- **Obtaining HBeAg, HBeAb, and HBV DNA quantification (nucleic acid amplification)**

**If the baseline HBV DNA level is  $\leq 2000$  IU/mL in HBeAb-positive patients with elevated ALT, then clinicians should perform serial HBV DNA measurements at least annually.**

Patients who are positive for HBsAg should be evaluated for signs and symptoms of advanced liver disease. Serial ALT measurements should be obtained because of the possibility of significant fluctuation. Higher ALT levels do not directly correlate with liver disease, but they do increase the likelihood of significant liver disease with increased disease progression.

All patients with chronic hepatitis should be tested for HBeAg and HBeAb. Patients who are positive for HBeAg usually have higher HBV DNA levels and more rapid progression of liver disease. One of the goals of treatment for patients who are positive for HBeAg is seroconversion to HBeAg negativity and HBeAb positivity. HBe seroconversion is associated with decreased levels of HBV DNA and halted or reversed progression of liver disease.

**Key Point:**

HBeAg negativity can be associated with greater HBV DNA replication and more rapid disease progression in patients carrying mutations in either the precore or the basic core promoter region of the HBV genome.<sup>25</sup>

HBV DNA levels should be obtained at baseline in patients with chronic HBV. If the baseline HBV DNA level is  $\leq 2000$  IU/mL in HBeAb-positive patients with elevated ALT, then HBV DNA levels should be measured serially because wide fluctuation of ALT in these patients makes ALT an unreliable indicator. The laboratory that measures HBV DNA should participate in external quality control and use an assay with high sensitivity and a wide range (e.g., 80 to  $10^{10}$ /mL).

**Additional Evaluation**

Liver biopsy is considered the gold standard to assess fibrosis and inflammation and to stage chronic disease; however, treatment of HIV/HBV co-infected patients is often guided by elevated ALT and HBV DNA levels. Because HIV-infected patients are at higher risk for fibrosis, liver biopsy may be prudent for HIV/HBV co-infected patients with normal ALT or low HBV DNA levels who are considering deferral of treatment or who are also infected with HCV (see [Hepatitis C Virus](#)). Ultrasound of the liver can sometimes detect cirrhosis, steatosis, and HCC. If cirrhosis is identified, then triple-phase CT scan can be used for detecting HCC. Liver stiffness measurements and calculations of a fibrosis score from noninvasive tests, such as ALT and platelet count, can be used but have not yet been validated in HIV/HBV co-infected patients. A method for calculating liver stiffness, known as the elastography technique (FibroScan), has demonstrated promising results<sup>26</sup>; clinical trials in the US are ongoing.

**V. COUNSELING FOR HIV/HBV CO-INFECTED PATIENTS****1. Alcohol Consumption****RECOMMENDATIONS:**

**Clinicians should obtain a substance use and alcohol history for HIV/HBV co-infected patients and should refer patients with alcohol abuse or dependence for chemical dependency treatment.**

**Clinicians should educate HIV/HBV co-infected patients regarding the effects of alcohol on the course of HBV infection. Patients who have other underlying liver disease should be advised to abstain from alcohol.**

Alcohol consumption accelerates liver fibrosis and decreases response to treatment. Psychological, social, and medical support to decrease alcohol intake is strongly recommended. Although more than 50 g of ETOH per day has been shown to be detrimental, no safe threshold for alcohol consumption has been established.

## 2. Transmission

### RECOMMENDATIONS:

**Clinicians should assess for HBV transmission risk behaviors and advise household contacts of HBV carriers to be vaccinated for HBV and to avoid sharing objects that may be contaminated with blood, such as razors or toothbrushes, until their immunity has been confirmed.**

**Clinicians should encourage all sexually active patients who are positive for HBsAg to use effective barrier protection consistently and correctly, including latex or polyurethane condoms and dental dams, to reduce the risk of transmission of HIV and HBV.**

**Clinicians should refer active injection drug users for substance use treatment, including opioid substitution therapy. Active injection users who are not ready for treatment should be referred to needle exchange programs.**

HBV is significantly more transmissible through exposure to blood and body fluid than HIV and requires more frequent assessment for behaviors that increase risk of HIV/HBV transmission. Latex or, if one partner is allergic to latex, polyurethane condoms and dental dams should be recommended to decrease the risk of sexual transmission. Active drug users should be offered treatment programs, including opioid substitution. Needle exchange programs can decrease HBV and HIV transmission rates. New York State's two syringe access initiatives are the [Expanded Syringe Access Demonstration Program and Syringe Exchange Programs](#).

## VI. TREATMENT OF HBV INFECTION IN THE SETTING OF HIV

Few studies address HBV treatment recommendations in the setting of HIV. The recommendations provided in this section are based on this panel's expert opinion.

In HIV/HBV co-infected patients, options for effective treatment of HBV are limited without concurrent treatment of HIV. However, effective treatments for HBV are significantly increased when an HIV-infected patient is treated concomitantly with ARV therapy. Importantly, once treatment is initiated, the interruption of therapy for either infection should be avoided whenever possible. Treatment interruption of anti-HIV/HBV agents can cause transaminase flares.

HIV/HBV co-infected patients develop lamivudine-resistant HBV more rapidly than HBV mono-infected patients. HIV/HBV co-infected patients also respond less well to interferon (IFN)-alpha therapy than HBV mono-infected patients<sup>27,28</sup>; however, limited data are available regarding pegylated IFN (PegIFN) or IFN-alpha in the era of ARV therapy.

## A. Treatment of Acute HBV Infection

### RECOMMENDATIONS:

**Patients with acute HBV infection accompanied by fulminant liver disease should receive treatment with lamivudine. Initiation of ARV therapy is not recommended during fulminant hepatitic liver disease.**

**Clinicians should not treat patients with fulminant hepatitis with adefovir or tenofovir.**

Most cases of acute HBV infection resolve spontaneously without specific therapy, and there is no evidence that treatment in the acute phase improves the likelihood of development of HBsAb positivity.<sup>29</sup> In cases of fulminant liver disease resulting from acute HBV infection, lamivudine treatment has been shown to increase patient survival.<sup>30</sup> Therapy with lamivudine should be used in patients with fulminant hepatic failure despite the risk of developing lamivudine-resistant HIV. Patients with fulminant hepatitis should not be treated with adefovir or tenofovir because of the high concomitant rate of renal failure in fulminant hepatitis.

### **Key Point:**

In an HIV-infected patient with fulminant hepatitic failure induced by acute HBV infection, treatment with lamivudine therapy alone is indicated. In patients with less severe hepatic injury from acute HBV infection, and for whom ARV therapy may be indicated, ARV therapy should be deferred until resolution of the acute hepatic insult.

## B. Treatment of Chronic HBV Infection

### RECOMMENDATIONS:

**Clinicians treating HIV/HBV co-infected patients should:**

- **Initiate treatment active against HBV when HBV DNA levels are >2000 IU/mL**
- **Consider HBV treatment in patients with detectable HBV DNA  $\leq$ 2000 IU/mL who also have elevated ALT levels above baseline or fibrosis or inflammation**
- **Consult with a specialist experienced in the treatment of hepatitis and HIV to discuss treatment decisions, including changes to a patient's existing ARV regimen when HBV treatment is indicated, and to establish a schedule for monitoring (see Table 3)**

**When initiating treatment against HBV in HIV/HBV co-infected patients, clinicians should:**

- **Initiate ARV therapy**
- **Use a standard ARV regimen that includes two drugs that are also active against HBV (see Figure 4)**

**Clinicians should avoid discontinuing either HBV or HIV treatment whenever possible and should monitor ALT closely if discontinuation of HBV treatment is unavoidable.**

**When ARV regimens need to be changed for HIV considerations, the agents active against HBV should be continued whenever possible to avoid risk of reactivation of HBV.**

No large controlled trials have been conducted to define efficacy of combination therapies in HIV/HBV co-infected patients. These guidelines are therefore extrapolated from the treatment of HBV mono-infected patients, limited data from co-infected patients, and best practices for HIV treatment.<sup>15,31-34</sup> Treatment goals and the agents used depend on the clinical status of the patient (see Figure 4). Initiation of ARV therapy is prudent when HBV treatment is indicated because resistance may result if an agent that is active against both viruses is used inadvertently to treat one or the other exclusively.

Timing of treatment initiation in patients with HBV mono-infection is based on HBV DNA level, liver disease (ALT, inflammation, fibrosis), and evaluation for cirrhosis. Patients at risk for HCC require additional monitoring (see Section VI. B. 5. Patients at Risk for Hepatocellular Carcinoma). Anti-HBV therapy is indicated for HIV/HBV co-infected patients with HBV DNA levels >2000 IU/mL because they have a greater risk of progression to HCC and cirrhosis.<sup>35,36</sup> ALT levels are often lower in HIV/HBV co-infected patients in comparison with HBV mono-infected patients.<sup>36</sup> As such, ALT levels above baseline, regardless of whether or not the levels exceed the upper limit of normal, may also be predictive of HBV disease progression. Although HBV DNA is a more definitive indication for treatment, HBV DNA levels that are ≤2000 IU/mL, but accompanied by elevated ALT levels above baseline or hepatic fibrosis or inflammation, may also warrant anti-HBV treatment. The primary goal of HBV treatment for HIV/HBV co-infected patients is HBsAg clearance with HBsAb seroconversion. However, because the rate of HBs seroconversion is low among HIV-infected patients,<sup>37</sup> and treatment should be considered chronic once it is initiated, the following secondary goals are reasonable:

- HBeAg to HBeAb seroconversion
- Suppression of HBV replication
- Reduction of liver inflammation
- Prevention or delay of progression of fibrosis, cirrhosis, and HCC

## **1. Patients Eligible for Both HBV and HIV Treatment**

### **RECOMMENDATIONS:**

**Clinicians should treat patients who are eligible for both HBV and HIV treatment with an ARV regimen that contains tenofovir plus lamivudine or emtricitabine if such treatment is not contraindicated because of renal insufficiency or fulminant hepatic disease. If the ARV regimen needs to be changed because of HIV resistance to any of these agents, then these agents should still be continued as part of anti-HBV treatment (see Figure 4).**

**Patients with lamivudine or emtricitabine resistance to HBV should receive an alternative ARV regimen with optimal combined anti-HBV activity (see Figure 4).**

**Clinicians should monitor ALT during initiation of or changes to the ARV regimen, especially in patients with cirrhosis.**

When ARV therapy is indicated and the patient has HBV DNA levels of >2000 IU/mL, a standard ARV regimen that includes two drugs that are also active against HBV should be used. Some experts would include dual anti-HIV/HBV agents in the ARV regimen regardless of HBV DNA levels.

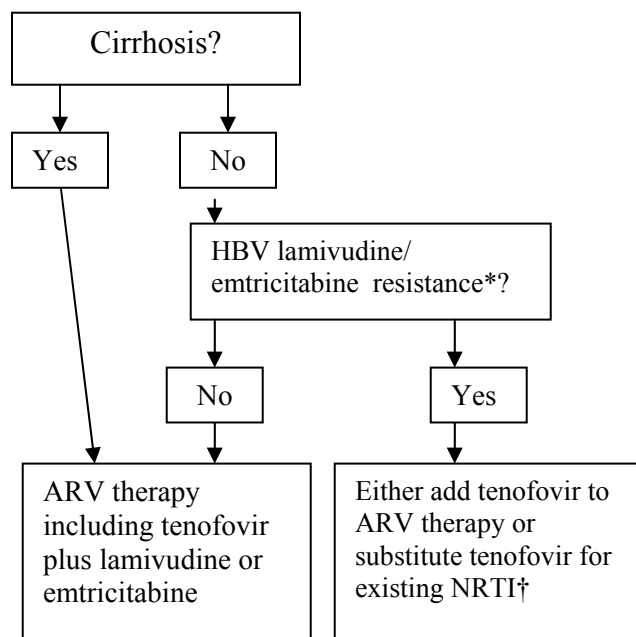
For patients already on successful ARV therapy, the benefits of adding anti-HBV agents to the existing ARV regimen are compared with the advantages of restructuring the ARV regimen to include medications that are active against both HIV and HBV. Currently, tenofovir plus lamivudine or emtricitabine provides a backbone active against both HIV and HBV for use with an NNRTI or boosted PI. For patients who have previously received lamivudine or emtricitabine, determination of lamivudine/emtricitabine HBV resistance, where available, can help guide the selection of an appropriate regimen (see Figure 4 and Appendix A). When assessment for HBV resistance is not an option, obtaining HBV DNA levels after 3 months can indicate treatment efficacy in these cases. Maintenance of suppression should be monitored every 3 to 6 months (see Section VII. Monitoring Treatment Response).

The anti-HBV activity of lamivudine, emtricitabine, and tenofovir warrants the continuation of their use when HIV resistance requires a change in the ARV regimen. In addition, these agents should be continued after HBV treatment response has been achieved, even when the ARV regimen needs to be changed.

**Key Point:**

Agents with dual activity against both HBV and HIV can simplify treatment regimens because a single agent can be used as part of a regimen to treat both viruses.

**Figure 4. Initial Treatment for HIV/HBV Co-Infection**



\* When lamivudine and emtricitabine cease to be effective against HIV, but are still active against HBV, they should be continued as part of anti-HBV therapy.

† If HBV is also tenofovir-resistant, consult a specialist experienced in the treatment of hepatitis and HIV.

## 2. Patients With Co-Infection Receiving HBV Treatment but Not HIV Treatment

### RECOMMENDATION:

**Clinicians should use pegylated interferon-alfa 2a for the treatment of HBV in HIV-infected patients who decline ARV treatment. No drug other than interferon should be used alone for the treatment of chronic HBV in patients with HIV.**

If liver disease is active and the patient declines ARV treatment, then clinicians should initiate therapy with PegIFN alfa 2a (180 µg weekly for 48 weeks). The goal of IFN therapy is to achieve one of the following:

- A sustained seroconversion from HBsAg to HBsAb
- Seroconversion from HBeAg to HBeAb
- Normalization of ALT and sustained HBV DNA  $\leq 2000$  IU/mL

If patients are unable to tolerate IFN or do not respond, then concomitant treatment for HIV should be encouraged. No drug other than IFN should be used alone for the treatment of chronic HBV in patients with HIV. If used as monotherapy, tenofovir, lamivudine, emtricitabine, and telbivudine may select for HIV resistance. Entecavir can select for lamivudine/emtricitabine-resistant HIV.<sup>38</sup> Telbivudine and lamivudine are also likely cross-resistant.<sup>39</sup> Adefovir 10 mg daily is not active against HIV, but it is unclear whether it can induce HIV resistance to tenofovir or NRTIs. Although limited data do not show K65R mutations during treatment with adefovir 10 mg daily in HIV-infected patients,<sup>40</sup> the small but poorly defined rates of K65R mutation, as well as the manufacturer's warning against its use as monotherapy in HIV/HBV co-infected patients,<sup>41</sup> suggest that monotherapy with adefovir should be avoided.<sup>42</sup>

## 3. Patients With Co-Infection Eligible for HIV Treatment but Not HBV Treatment

### RECOMMENDATION:

**For patients who require HIV treatment and in whom HBV treatment is not indicated, lamivudine or emtricitabine should not be used without tenofovir.**

For HIV/HBV co-infected patients who meet the medical criteria for initiation of ARV therapy but have HBV DNA levels  $\leq 2000$  IU/mL, clinicians should generally follow guidelines established for patients with HIV mono-infection (see [Antiretroviral Therapy](#)). However, lamivudine or emtricitabine should not be used without tenofovir to avoid selecting for lamivudine/emtricitabine-resistant HBV.

## 4. Patients With Cirrhosis

### RECOMMENDATIONS:

**Patients with hepatitis who develop symptomatic cirrhosis should be managed by a clinician experienced in the management of cirrhosis, preferably a hepatologist.**

**Clinicians should refer HIV/HBV co-infected patients with known cirrhosis for endoscopy every 1 to 2 years to monitor for esophageal varices.**

HIV/HBV co-infected patients with cirrhosis are at increased risk for a life-threatening hepatitis flare during immune reconstitution after initiation of ARV therapy, particularly when their baseline CD4 count is  $<200$  cells/mm<sup>3</sup>. Reduction of HBV levels with adefovir, which does not inhibit HIV replication, prior to starting ARV therapy, may be beneficial but is controversial because most experts prefer initiating a full ARV regimen with monthly monitoring of transaminases. HBV-infected patients with known cirrhosis should be referred for endoscopy every 1 to 2 years to monitor for esophageal varices.

## 5. Patients at Risk for Hepatocellular Carcinoma

### RECOMMENDATION:

**In patients with chronic HBV who are at higher risk for HCC, clinicians should:**

- Screen serum  $\alpha$ -fetoprotein every 3 to 6 months
- Perform annual imaging with either a triple-phase CT scan of the abdomen, MRI scan of the abdomen, or hepatic ultrasound, depending on the imaging protocol of the institution
- Perform imaging every 6 months if cirrhosis is present

The decision to initiate treatment in patients at risk for HCC is established according to routine monitoring, including  $\alpha$ -fetoprotein (AFP) measurements every 3 to 6 months and annual imaging with triple-phase CT scan of the abdomen, MRI scan of the abdomen, or hepatic ultrasound. The choice of imaging technique will depend on the imaging protocol of the institution. Because the sensitivity of hepatic ultrasound is more variable in detecting small tumors, some experts alternate between CT and MRI every year and perform ultrasound at the 6-month interval between the annual scan. If cirrhosis is present, then imaging should be performed every 6 months.

## VII. MONITORING TREATMENT RESPONSE

### RECOMMENDATION:

**After initiation of HBV treatment, clinicians should obtain HBV DNA levels and should assess for HBeAg and HBsAg seroconversion every 3 to 6 months.**

An initial response of at least 1 log decrease in HBV DNA in 3 months for nucleoside or nucleotide analog regimens is considered a response to therapy. Clinically relevant responses to HBV therapy are a sustained seroconversion from HBsAg to HBsAb, from HBeAg to HBeAb, or normalization of ALT and sustained HBV DNA  $\leq 2000$  IU/mL. If HBV DNA level increases by more than 1 log in adherent patients after a decrease in therapy, then resistance should be suspected. Although the appropriate interval for monitoring HBV DNA and seroconversion to HBeAb positivity has not been established, monitoring every 3 to 6 months is a reasonable approach because of the risk of future virologic resistance and a subsequent hepatic flare. Transaminase flares are also possible when initiating ARV therapy.<sup>11,43</sup>

Detailed monitoring considerations are provided in Table 3.

<b>TABLE 3</b>	
<b>ROUTINE LABORATORY ASSESSMENT AND THERAPEUTIC MONITORING OF HIV-INFECTED PATIENTS WITH HBV*</b>	
<b>Diagnostic Screen</b>	<b>Frequency</b>
<b>Laboratory Testing</b>	
HBeAg and HBeAb	Baseline and every 3-6 months for patients receiving treatment who are HBeAg(+) and HBeAb(-)
ALT	Serial measurements every 3-6 months or more frequently if stopping HBV therapy
HBV DNA	Serial measurements if low ( $\leq 2000$ IU/mL) in HBeAb(+) patients with elevated ALT; every 3-6 months to monitor therapy
PT/INR, AST, platelets	Baseline and 6 months
AFP	Baseline and every 3-6 months in patients at risk for HCC†
<b>Imaging Studies</b>	
MRI, triple-phase CT, or alternation between the two	Annual triple-phase CT scan of the abdomen, MRI scan of the abdomen, or hepatic ultrasound, depending on the imaging protocol of the institution; if cirrhosis is present, then every 6 months
<b>Liver Biopsy‡</b>	Consider at baseline for the following: <ul style="list-style-type: none"> <li>• Patients who are considering deferring anti-HBV treatment <i>or</i></li> <li>• Patients who are HIV/HBV/HCV tri-infected</li> </ul>

\* These routine assessment and monitoring procedures are performed in conjunction with those recommended for all HIV-infected adults (see [Primary Care Approach to the HIV-Infected Patient](#)).

† HBV-infected patients at risk for HCC are those with cirrhosis, those who are HBsAg(+), those with high HBV DNA, and those with a family history of HCC.

‡ If HCC is suspected, refer to a hepatologist or oncologist. Monitoring considerations are different for patients with HCC.

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**APPENDIX A**  
**CURRENTLY AVAILABLE ANTI-HBV MEDICATIONS**

<p><b>Tenofovir disoproxil fumarate</b></p>	<p>Nucleotide reverse transcriptase inhibitor that inhibits both HIV and HBV (wild-type and lamivudine-resistant). It has been effective at decreasing the viral loads of both HIV and HBV when used in combination with lamivudine. In a small trial of HIV/HBV co-infected patients, many of whom had been receiving lamivudine, addition of tenofovir decreased HBV DNA level 4 logs vs. 3.2 logs with adefovir.<sup>44</sup> Tenofovir-resistant mutations have been described, but the rate of developing mutations is not defined.</p>
<p><b>Lamivudine</b></p>	<p>Nucleoside analog that is active against HIV and inhibits HBV replication in most HIV/HBV co-infected patients. It results in low (10%) seroconversion rates. It should always be used at its 300-mg daily or 150-mg twice-daily dose in HIV-infected patients. It should not be used as monotherapy for HBV in HIV-infected patients because HIV resistance will develop rapidly. Likewise, HBV resistance to lamivudine will develop in up to 30% of HIV-infected patients per year if used as the only active agent against HBV in a regimen.<sup>45</sup> ALT levels frequently increase 1 to 2 months after lamivudine is started, and this should not prompt discontinuation of the drug. ALT may also increase during seroconversion from HBeAg to HBeAb positive.</p>
<p><b>Emtricitabine</b></p>	<p>Emtricitabine is a nucleoside analog, similar to lamivudine, that is active against both HIV and HBV. HBV resistance also develops rapidly (12% in 1 year) if used as monotherapy, and lamivudine-resistant isolates are also cross-resistant to emtricitabine.<sup>46</sup></p>
<p><b>Entecavir</b></p>	<p>Nucleoside analog that is active against both HIV and HBV. It is approved in the US for use against HBV. In a small study, 84% of HIV/HBV co-infected patients failing lamivudine therapy achieved significant decrease in HBV DNA levels (vs. 0% of placebo) with entecavir.<sup>47</sup> However, it can select for lamivudine/emtricitabine-resistant HIV; therefore, it is not recommended for treatment of HBV in HIV-infected patients not receiving ARV therapy.<sup>38</sup> It is active against both wild-type and lamivudine-resistant HBV but more so against wild type.</p>
<p><b>Adefovir dipivoxil*</b></p>	<p>Nucleoside analog reverse transcriptase inhibitor active against HBV, including lamivudine-resistant strains. At the 10-mg daily dose, it does not appear to affect HIV replication, and, in one study, there was a negligible rate of selection for K65R mutant HIV, although the true rate is yet to be determined.<sup>40</sup> In a small trial of HIV/HBV co-infected patients, many of whom had lamivudine-resistant HBV, addition of adefovir decreased the HBV DNA level 3.2 log (vs. 4 log for tenofovir).<sup>48</sup> However, the manufacturer warns against its use as monotherapy in HIV/HBV co-infected patients.<sup>41</sup></p>

<p><b>Telbivudine</b></p>	<p>Telbivudine has not been studied in HIV/HBV co-infected patients. It is a nucleoside analog that, in contrast to other nucleoside analogs, has no antiviral activity against any known human viruses other than HBV.<sup>44</sup> Patients achieve normalization of transaminase levels at a higher rate with telbivudine than with lamivudine (86% vs. 63%).<sup>49</sup> Telbivudine and lamivudine share cross-resistance,<sup>39</sup> and combination of telbivudine and lamivudine is not more effective than telbivudine alone.<sup>49</sup> The rate of HBeAb seroconversion appears to be higher with telbivudine than with lamivudine (31% vs. 22%) but lower when telbivudine and lamivudine are combined (17%).<sup>49</sup> Rates of telbivudine resistance are high; therefore, it is not recommended as monotherapy.</p>
<p><b>Interferon-alfa</b></p>	<ul style="list-style-type: none"> <li>○ INF-alfa 2a or 2b or PegIFN alfa 2a are used as therapy for HBV mono-infected patients. PegIFN alfa 2a has been shown to be superior to the short-acting IFN. Some small studies suggest a lower response rate in HIV/HBV co-infected patients (approximately 10%), but it may be useful if an agent that is not active against HIV is desired. It has a higher success rate in HBeAg(+) patients and those with elevated ALT levels (&gt;200 IU/L) and with CD4 counts <math>\geq 200</math> cells/mm<sup>3</sup>.<sup>28</sup> Advantages include the following: <ul style="list-style-type: none"> <li>▪ A finite treatment duration—6 months for HBeAg(+) and 12 months for HBeAg(-)</li> <li>▪ Higher likelihood of HBeAg seroconversion</li> <li>▪ No activity against HIV to promote HIV resistance</li> </ul> </li> <li>○ IFNs have numerous side effects and toxicities that should be managed by a clinician experienced with its use. IFN-alfa cannot be used in patients with decompensated cirrhosis.</li> </ul>

\* A dose of >10 mg daily increases the likelihood of HIV resistance when used as HBV monotherapy. However, monotherapy with any agent other than IFN-alfa, regardless of dose, is not recommended.