Stepwise Approach for Detecting, Evaluating, and Treating Chronic Hepatitis B Virus Infection

Federal Bureau of Prisons
Clinical Practice Guidelines

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1. Purpose

The Federal Bureau of Prisons (BOP) *Stepwise Approach for Detecting, Evaluating, and Treating Chronic Hepatitis B Virus Infection* provides recommendations for the medical management of federal inmates with chronic hepatitis B, or who are otherwise at risk of infection. The treatment of chronic hepatitis B in pregnancy or with hepatocellular carcinoma is beyond the scope of this guideline. For a more in-depth discussion of vaccination strategies and management of blood and body fluid exposures, the reader should refer to the BOP Clinical Practice Guidelines for those topics.

2. Overview: Transmission and Natural History of Hepatitis B Virus Infection (HBV)

Hepatitis B virus is a DNA virus that replicates in the liver with hematologic dissemination systemically. It is a bloodborne and sexually transmitted pathogen that is spread through percutaneous and mucosal exposures to infected blood and body fluids.

Major modes of acquiring HBV infection: In low-prevalence areas such as the United States, injection drug use and sexual intercourse with an infected partner account for 50–80% of all new cases of HBV infection. Perinatal transmission from mother to child and household contact with a person infected with HBV are the primary modes of transmission in areas with intermediate- or high-prevalence of HBV such as Asia, the South Pacific, sub-Saharan Africa, and certain populations in the Arctic, South America, and the Middle East. Other less common modes of transmission include chronic hemodialysis, certain occupational exposures, blood transfusion, and organ transplant (rare). Tattooing with shared, contaminated needles or needle-like devices in jails and prisons is another potential mode of HBV transmission that specifically affects inmate populations. HBV is viable for at least seven days on environmental surfaces and can be transmitted by sharing contaminated household items such as razors and toothbrushes.

Incidence in the United States: In large part due to HBV vaccination strategies, the incidence of acute hepatitis B has declined markedly in the United States. Nevertheless, it is estimated that more than one million persons residing in the U.S. are infected with HBV, that half of these are from HBV-endemic areas outside the United States, and that 2,000 to 4,000 of them will die each year from complications of the disease.

3. Acute HBV Infection

A. Natural History and Diagnosis

Acute HBV infection may be subclinical, symptomatic but self-limited, or fulminant. Subclinical (asymptomatic) disease usually occurs when HBV is acquired perinatally or in early childhood or in the immunosuppressed. Mild to moderate symptoms occur in approximately 30–50% of persons infected as adults, and include fever, jaundice, anorexia, nausea, abdominal pain, and malaise. Arthritis, serum sickness, and a nonspecific rash may also occur with acute HBV infection and, when present, are helpful diagnostically. Fulminant hepatic failure is suggested by hemodynamic instability, vomiting and dehydration, encephalopathy,

coagulopathy, and bleeding. Death occurs in ≤ 1% of cases of acute HBV infection. The incubation period of HBV infection, from transmission of infection until the onset of symptoms, averages between 90–120 days (range: 45–180 days).

Acute HBV infection is confirmed by the serologic detection of IgM anti-HBc and HBsAg. The detection of HBsAg alone is not diagnostic for acute HBV infection, since persons with asymptomatic chronic HBV infection can be newly infected with other pathogens that cause acute hepatitis. IgM anti-HBc may persist at detectable levels for up to two years in a small subset of acutely infected persons.

➔ See Table 1, "Interpretation of HBV Serologic Markers."

B. Treatment

Although the majority of cases of acute HBV infection in adults are self-limited and resolve spontaneously, some cases may progress to fulminant hepatic failure, which requires hospitalization and intensive management. Supportive therapy is indicated for all cases of acute HBV. Currently, antiviral medications are not recommended for treatment of self-limited disease, and do not have a clearly established role in the treatment of fulminant hepatic failure caused by HBV. Inmates with acute hepatitis B should be monitored during convalescence and thereafter to determine whether they develop chronic HBV infection (persistently HBsAg-positive) or clear their infection (anti-HBs-positive).

4. Chronic HBV Infection

A. Natural History

The majority of adults acutely infected with HBV eventually clear HBsAg from the blood and develop antibodies to HBsAg (anti-HBs) that confer long-term protection from re-infection. Only a small subset of adults acutely infected with HBV develop chronic HBV infection (HBsAg-positive for six months or longer). The risk of chronic HBV infection is much greater for persons from parts of the world where HBV is endemic and acquired perinatally. Immunosuppressed individuals also are more likely to develop chronic HBV infection.

Chronic HBV Infection Course

The course of chronic HBV infection is varied and unpredictable and may result in one of three main presentations—chronic hepatitis B, inactive HBsAg carrier state, or resolved infection. Chronic hepatitis is associated with active hepatic necroinflammation and progressive fibrosis and is accompanied by a persistently positive HBsAg, serum HBV DNA > 20,000 IU/ml, and persistent or intermittent elevations in ALT levels. Despite a persistently positive HBsAg, the inactive carrier state is associated with relatively quiescent disease activity, a negative HBeAg and positive anti-HBe, HBV DNA level < 2,000 IU/ ml, and normal ALT levels, but may be accompanied by intermittent exacerbations or flares. Once established, chronic HBV resolves spontaneously with clearance of HBsAg and development of anti-HBs in less than 1–2% of patients per year.

➔ See *Appendix 1*, *Criteria for Determining HBV Disease State*.

Chronic Hepatitis B Flares

Clinically apparent flares of hepatitis B associated with ALT elevations > 10 times the upper limit of normal can occur in persons with chronic HBV infection during any of the following:

- Spontaneous clearance of HBeAg with development of anti-HBe antibodies
- Superinfection with HBV-HDV (hepatitis delta virus)
- Immunosuppression
- Initiation of antiviral therapy for chronic hepatitis B
- Discontinuation of certain antiviral therapies for chronic hepatitis B or HIV infection

Chronic Hepatitis B Complications

Individuals with chronic HBV infection are at increased risk of developing decompensated cirrhosis and hepatocellular carcinoma (HCC). Rates of progression to cirrhosis or HCC are increased by a variety of factors, including: HBeAg positivity; higher HBV DNA and ALT levels; HBV genotype C; co-infections with HCV, HDV, or HIV; immunosuppression; advanced age; duration of infection; alcohol ingestion; male gender; and family history of HCC. Some non-hepatic complications of HBV infection include membranous glomerulonephritis and polyarteritis nodosa.

B. Serologic Markers in the Diagnosis of HBV Infection

An array of HBV serologic markers are useful, alone or in combination, in characterizing various phases of HBV infection. These serologic markers are antigens produced by the hepatitis B virus or antibodies produced by the body against the various antigens.

➔ Table 1 below summarizes the interpretation of serologic markers for HBV.

Antigens

- ***Hepatitis B Surface Antigen (HBsAg)***, as the name indicates, is an antigen on the surface of the virus. Its presence indicates HBV infection. It is detectable within the first 10 weeks of initial infection and develops before the ALT becomes elevated or the patient develops liver-related symptoms. It becomes undetectable within 4 to 6 months in the majority of adult cases (95%) and indicates resolution of the infection. Persistence beyond 6 months indicates chronic infection. Subsequent loss of HBsAg occurs in < 1–2% of chronic cases per year. The diagnosis of chronic HBV infection is confirmed by the serologic detection of hepatitis B surface antigen (HBsAg) on two separate occasions, 6 months apart; or the one-time detection of HBsAg, if total anti-HBc-positive/IgM anti-HBc-negative.
- ***Hepatitis B Core Antigen (HBcAg)*** is found only within the infected hepatocyte and is not detectable in the blood, but may be detected through histologic analysis of infected cells.
- ***Hepatitis B e Antigen (HBeAg)*** is a protein associated with viral replication. In acute HBV infection, loss of HBeAg occurs early, before the loss of HBsAg. Persistence of HBeAg in chronic disease is associated with higher levels of HBV DNA and liver inflammation, and a greater risk for cirrhosis and hepatocellular carcinoma. Seroconversion to HBeAg-negative status is frequently associated with decreased or undetectable levels of HBV DNA, but HBV usually persists unless there is concomitant loss of HBsAg.

Antibodies

- ***Antibody to the hepatitis B surface antigen (anti-HBs)*** usually appears concomitantly with the loss of the hepatitis B surface antigen and indicates immunity to HBV.
- ***Antibody to the hepatitis B core antigen (anti-HBc)*** has both an IgM and an IgG component. Initial antibody to HBcAg is primarily IgM and, together with HBsAg, indicates acute infection. IgM may persist for up to 2 years following acute infection. IgG anti-HBc begins to develop as IgM anti-HBc wanes and persists in chronic, inactive, and resolved infections. Persistent titers of IgG anti-HBc with negative HBsAg and anti-HBs may have a number of different interpretations, as indicated below in Table 1.
- ***Antibody to hepatitis B e antigen (anti-HBe)*** in association with a seroconversion from HBeAg-positive to negative often is accompanied by diminished histologic and biochemical disease activity.

Table 1. Interpretation of HBV Serologic Markers[1]

HBsAg	Total Anti-HBc	IgM Anti-HBc	Anti-HBs	Interpretation
–	–	–	–	Susceptible (never infected)
+	–	–	–	Acute infection, early incubation[2]
+	+	+	–	Acute infection[3]
–	+	+	–	Acute resolving infection[3]
–	+	–	+	Past infection (recovered & immune)
+	+	–	–	Chronic infection
–	+	–	–	Multiple interpretations[4]
–	–	–	+ ≥ 10 mIU/ml	Immune from vaccination

Abbreviations:

HBsAg	hepatitis B surface antigen
Total anti-HBc	total antibody to hepatitis B core antigen
IgM anti-HBc	immunoglubulin M antibody to hepatitis B core antigen
Anti-HBs	antibody to hepatitis B surface antigen

[1] Adapted from CDC. Interpretation of Hepatitis B Serologic Test Results. Available at: http://www.cdc.gov/hepatitis/HBV/PDFs/SerologicChartv8.pdf. Accessed November 2010.

[2] Note: Transient HBsAg positivity (lasting < 21 days) might be detected in some patients during vaccination.

[3] IgM usually wanes after 5 months post-infection, but may persist longer.

[4] Multiple interpretations: May be recovering from acute HBV infection; may be distantly immune and the test not sensitive enough to detect low level of anti-HBs in serum; may be susceptible with a false positive anti-HBc; or may be undetectable level of HBsAg present in the serum and the person is actually a carrier. Most persons positive for anti-HBc alone are unlikely to be infectious, except in certain exposures involving very large amounts of blood.

C. Treatment Considerations

Treatment options and strategies for chronic HBV infection continue to evolve. Two general classes of medications have demonstrated efficacy in the treatment of chronic HBV infection: interferon alfa and nucleoside/nucleotide analogues (NAs). While treatment with antiviral medications is unlikely to completely eradicate HBV, it is possible to suppress viral replication and induce seroconversion to HBeAg-negative status, and thereby potentially prevent or reduce progression to cirrhosis or hepatocellular carcinoma (HCC)—which is the goal of treatment at present. However, the medications approved for treatment of HBV infection may cause significant adverse effects and toxicities (e.g., interferon alfa) or may require many years of treatment (NAs). Therefore, the decision to recommend antiviral treatment should be based on a variety of factors, including:

- The risk of disease progression and the severity of liver disease
- The likelihood of response to treatment
- ALT and HBV DNA levels
- HBeAg status
- Age of the patient and duration of infection
- Existing co-infections and co-morbid conditions
- The potential for adverse reactions
- Other relevant patient-specific factors

5. Stepwise Approach to Chronic HBV Infection

The BOP recommends a systematic, stepwise approach to Hepatitis B detection, evaluation, and treatment. These steps are outlined below in Table 2 and discussed on the pages that follow.

➔ See *Appendix 2* for a quick-reference summary table and algorithm for the stepwise process.

Table 2. Steps in Detecting, Evaluating, and Treating Chronic HBV Infection

STEP 1:	Appropriately screen for HBV infection based on risk factors.
STEP 2:	Provide initial follow-up for HBsAg-positive inmates.
STEP 3:	Assess the need for liver biopsy.
STEP 4a:	Determine if HBV treatment is NOT indicated.
STEP 4b:	Monitor HBV patients who are not on treatment.
STEP 5:	Determine if treatment is indicated.
STEP 5a:	Determine the preferred treatment regimen.
STEP 5b:	Determine the appropriate medication dose of therapy.
STEP 5c:	Determine the end points of treatment.
STEP 6:	Monitor patients on treatment.
STEP 7:	Manage treatment failure or virologic breakthrough.

STEP 1: Appropriately screen for HBV infection based on risk factors.

Inmate Education

Appropriately trained personnel should provide newly incarcerated inmates with educational information on the transmission, natural history, and medical management of HBV infection in accordance with BOP policy. The BOP peer-oriented video on infectious diseases, the attached information in *Appendix 6, Inmate Fact Sheet on Hepatitis B and Hepatitis C,* and other appropriate patient educational tools should be used to facilitate counseling efforts.

Screening Method

Several different screening strategies have been recommended, depending upon the clinical context and goal for screening, such as pre-vaccination screening and screening to detect chronic HBV. Various serologic markers, alone or in combination, have been proposed for this purpose, including: anti-HBc alone or in combination with HBsAg, and HBsAg alone or in combination with anti-HBs. For the purpose of screening federal inmates for HBV infection, the combination of HBsAg and anti-HBs should be performed. Additional HBV serologic tests may be warranted depending on the inmate's medical history. In order to detect occult infection, inmates who have HIV infection, but negative HBsAg and anti-HBs, should also be tested for anti-HBc. If the anti-HBc is positive, an HBV DNA test should be ordered. Inmates with risk factors for HBV, but negative HBsAg and anti-HBs, should be considered for HBV vaccination in accordance with the BOP *Preventive Health* Clinical Practice Guideline.

➔ See Table 1 for information on interpreting the different serologic markers.

Clinical Indications

Inmates should be screened for hepatitis B regardless of sentencing status if any of the following clinical indications exist:

- Pregnant inmates (routine screening is medically imperative, regardless of previous screening results, due to the risk of perinatal transmission).
- Inmates on chronic hemodialysis who fail to develop antibodies after two series of vaccinations (should be screened monthly, i.e., measure HBsAg).
- Asymptomatic inmates with elevated ALT levels of unknown etiology.
- As clinically indicated (e.g., inmates with signs or symptoms of acute or chronic hepatitis, percutaneous blood exposure while incarcerated, or planned or current treatment with immune suppressants including chemotherapy or anti-tumor necrosis factor alfa medications).

Non-Sentenced Inmates

In the absence of clinical indications, screening for HBV infection is generally not indicated for non-sentenced inmates, except in the following situations:

- Asymptomatic non-sentenced inmates in BOP detention facilities, who have histories of injection drug use or other high-risk behaviors for HBV infection, should be counseled regarding their risk of acquiring HBV infection—as well as the behaviors that will reduce transmission of HBV infection to themselves and others during incarceration and upon release. Referrals to community testing sites should be made when appropriate.

- Long-term inmates in BOP detention facilities should be screened for HBV infection in accordance with the guidelines for sentenced inmates described below.

Sentenced Inmates

The following sentenced inmates should be screened for HBV infection at the prevention baseline visit within 6–12 months of incarceration:

- Inmates who have ever injected illegal drugs or shared equipment.
- Inmates who have received tattoos or body piercings while in jail or prison.
- Male inmates who have had sex with another man.
- Inmates with a history of chlamydia, gonorrhea, or syphilis.
- Inmates with HIV infection or HCV infection.
- Inmates from high-risk countries (i.e., Africa, Eastern Europe, Western Pacific, and Asia, with the exception of Japan).
- Inmates with a history of percutaneous exposure to blood.

Sentenced inmates who have risk factors for chronic HBV infection, but who initially refuse testing, should be counseled periodically regarding the need for testing during periodic prevention visits.

STEP 2: Provide initial follow-up for HBsAg-positive inmates.

Patient Counseling

Inmates diagnosed with chronic HBV infection should be counseled by a health care provider about the natural history of the infection, potential treatment options, and specific measures for preventing transmission of HBV infection to others (during incarceration and upon release), including the following information and recommendations:

- Most persons with HBV infection will remain healthy, but a small number of persons will develop serious liver disease. Talk to your health care provider about your personal health status.
- Drug treatment options for chronic hepatitis B are developing. Medications may or may not be appropriate for you at this time. Talk to your doctor about your specific treatment plan.
- Do not shoot drugs, have sex with other inmates, or get a tattoo or body piercing while in prison.
- Do not share personal items that might have your blood on them, such as toothbrushes, dental appliances, nail-grooming equipment, or razors.
- Cover your cuts and skin sores to keep your blood from contacting other persons.
- Before release, talk to a health care provider about specific ways you can reduce the risk of transmitting HBV infection to others after you are released.
- Upon release, markedly limit alcohol consumption or abstain altogether, and speak to a physician prior to taking any new medications, including over-the-counter drugs such as nonsteroidal anti-inflammatory agents and herbal remedies that may damage your liver.

- Upon release, do not donate blood, body organs, other tissue, or semen.
- Upon release, seek medical attention so that your condition is appropriately monitored and treated.

Baseline Evaluation

A baseline clinician evaluation is indicated for inmates who have chronic HBV infection (HBsAg-positive) and should include the following:

- Targeted history (assess age at initial infection, alcohol and substance abuse history, family history of hepatocellular carcinoma and chronic HBV infection, risks for gastrointestinal bleeding, and symptoms of decompensated cirrhosis).
- Targeted physical examination (assess for evidence of decompensated cirrhosis such as jaundice, ascites, encephalopathy, asterixis, and peripheral edema).
- HBeAg, anti-HBe.
- HBV DNA quantitative assay by polymerase chain reaction (HBV DNA assays are poorly standardized; therefore data should be interpreted cautiously).
- Screening for other bloodborne pathogens, e.g., anti-HIV, anti-HCV, and anti-HDV.
- Serum ALT, AST, bilirubin, alkaline phosphatase, albumin, prothrombin time, and further diagnostic evaluations as clinically warranted for other potential causes of liver disease, such as hemochromatosis, Wilson's disease, and autoimmune hepatitis.
- CBC with differential and platelet count, INR.
- Renal function assessment, i.e., serum creatinine / BUN / Basic Metabolic Panel (BMP).
- Consider hepatitis A vaccination in accordance with the BOP *Preventive Health* Clinical Practice Guideline, with priority given to inmates with underlying liver disease. (Prescreening for immunity to HAV, by detecting IgG (or total) anti-HAV, should be considered prior to vaccination for Native American populations and foreign-born inmates from Latin America, Africa, Southeast Asia, and China where HAV infection is endemic, and for inmates 50 years of age or older).

Although four different genotypes of HBV (A, B, C, D) have been identified, genotype testing is not yet a routine part of the diagnostic evaluation and treatment strategy for chronic HBV infection.

Hepatocellular Carcinoma (HCC) Screening

HCC occurs in persons with chronic HBV infection with or without cirrhosis. The goal of screening is to improve survival through early detection and treatment of HCC. However, there are only limited data that support screening as a means of accomplishing this goal. Although the optimal screening strategy is uncertain, the available data and statistical models suggest that the following groups of inmates with chronic HBV infection are most likely to benefit from screening, and should be screened at baseline and periodically by obtaining a liver ultrasound every six months:

- Inmates with cirrhosis

- Inmates with hepatitis B and one of the following characteristics: a family history of HCC, or country of origin that is endemic for hepatitis B (specifically Asian male > 40 years old, Asian female > 50 years old, or African-American / African ethnicity).

The baseline evaluation should provide sufficient information to determine which of the following three management options are most appropriate, based primarily on the likelihood of active hepatitis, disease progression, or response to treatment:

- *A liver biopsy is indicated (see Step 3), or*
- *Treatment with antiviral medication is NOT indicated (see Step 4), or*
- *Treatment with antiviral medication IS indicated (see Step 5).*

STEP 3: Assess the need for liver biopsy.

In some cases, the likelihood of active hepatitis or disease progression is uncertain, as follows:

- HBeAg-negative *and* HBV DNA ≥ 20,000 IU/ml *and* ALT < 2x ULN
- HBeAg-negative *and* HBV DNA = 2,000–19,999 IU/ml
- HBeAg-positive *and* HBV DNA ≥ 20,000 IU/ml *and* ALT < 2x ULN *and* age ≥ 40

In such cases, a liver biopsy will provide additional clinical information that will determine whether treatment is indicated or not.

STEP 4: Determine if HBV treatment is NOT indicated (4a) and Monitor HBV patients who are not on treatment (4b).

4a: Determine if HBV Treatment is NOT indicated.

The likelihood of active disease or disease progression is relatively low in the following cases:

- HBeAg-negative *and* HBV DNA < 2,000 IU/ml
- HBeAg-positive *and* HBV DNA < 20,000 IU/ml
- HBeAg-positive *and* HBV DNA > 20,000 IU/ml *and* ALT < 2x ULN and age < 40
- Liver biopsy with stage 0–1 fibrosis

4b. Monitor HBV patients who are not in treatment.

Although the risk for disease progression is low in these cases, it is not non-existent; as noted earlier, chronic hepatitis B can follow a variable and unpredictable course. Therefore, periodic monitoring is indicated through routine follow-up in a chronic care clinic, as appropriate. A reasonable approach to monitoring is as follows:

HBeAg(+) and treatment not indicated:

- ALT every 3–6 months if WNL; ALT every 1–3 months if 1–2x ULN.
- HBV DNA viral load every 6–12 months.
- Liver biopsy if ALT ≥ 2x ULN for 6 months, *or* if ALT 1–2x ULN for 6 months and age ≥ 40.

HBeAg(–) and treatment not indicated:

- ALT every 3 months for 1 year; then every 6–12 months.
- HBV DNA viral load if ALT > 1–2x ULN.
- Liver biopsy if persistent ALT elevation *or* HBV DNA ≥ 2,000 IU/ml.

STEP 5: Determine if treatment is indicated.

Treatment Considerations

A thoughtful, case-by-case approach to initiating antiviral therapy for chronic hepatitis B is warranted, in consultation with a clinician experienced in the management of this condition, for the following reasons:

- The risks and benefits of long-term treatment are unknown.
- The potential for drug resistance is of concern with some treatments.
- Discontinuing therapy in some persons who are responding to treatment may result in relapse.
- A subset of infected persons spontaneously clear HBV infection without therapy or have inactive disease that may not progress.
- Future treatment options may be more effective, better tolerated, and more easily administered.

The decision to recommend antiviral treatment should be based on the severity of liver disease, the likelihood of response, existing co-morbid conditions, the potential for adverse reactions, and other relevant patient-specific factors.

Treatment Indications

Current indications for treating chronic hepatitis B with antiviral therapy include *any* of the following:

- HBV DNA ≥ 20,000 IU/ml *and* ALT ≥ 2x ULN.
- Liver biopsy with ≥ stage 2 / 4 (more than portal) fibrosis or moderate/severe inflammation.

- Cirrhosis, compensated or decompensated.

  Patients with decompensated cirrhosis have evidence of severe liver disease such as markedly impaired synthetic function and signs of portal hypertension. Interferon preparations are contraindicated in these patients due to an increased risk of inducing hepatic failure. Treatment with an NA is indicated since these agents may reduce the incidence of hepatic failure and hepatocellular carcinoma. Once instituted, these agents should ordinarily not be discontinued, due to the risk of precipitating hepatic failure.

- HIV co-infection

  In general with HBV and HIV co-infection, when criteria for treatment of either HBV or HIV infection are met, both conditions should be treated with an appropriate regimen developed in consultation with an experienced clinician.

- Hepatocellular carcinoma (HCC)

  Treatment for HBV with co-morbid HCC should be developed in consultation with an experienced clinician.

- Planned treatment with immunosuppressant therapy, including chemotherapy or anti-tumor necrosis factor alfa agents, and organ transplant recipients.

STEPS 5a, 5b, 5c: Determine the preferred antiviral medication (5a), dose of therapy (5b), and end points of treatment (5c).

Steps 5a and 5b: Determine preferred antiviral medication and dose of therapy.

Approved antiviral therapies for chronic hepatitis B include certain interferon preparations, and the nucleoside/nucleotide analogues (NAs).

➔ Dosing, potential side effects, and monitoring parameters are outlined in *Appendix 5*, *Antiviral Medications for Chronic Hepatitis B.*

- ***Interferon preparations:*** Interferon preparations exert antiviral effects by binding to interferon receptors and activating the body's own immune system. Interferon alfa-2b and pegylated interferon alfa-2a are approved for treatment of chronic HBV infection. They can be administered for a shorter duration (≤12 months) and are less likely to promote resistance compared to other therapies. Pegylated interferon alfa-2a is preferred because it is just as effective as interferon afla-2b, but is more conveniently administered once weekly, rather than daily or three times a week. Disadvantages of interferon therapy include its subcutaneous administration, the risk of hepatic decompensation when treating persons with cirrhosis, and the potential for serious side effects including neuropsychiatric symptoms, bone marrow suppression, and thyroid disease. Ribavirin is not effective against HBV.

  Predictors of a favorable response to interferon therapy include the following factors:

  - HBeAg-positive
  - High pretreatment ALT levels
  - Low serum HBV DNA levels
  - Liver necroinflammation on biopsy

- Genotypes A or B
- Absence of renal failure, HIV infection, or other serious co-morbidity

Interferon may also be a preferred treatment in the context of HCV or HDV co-infection.

Pegylated interferon dose and duration: Pegylated interferon alfa 2a (Pegasys) is administered 180 micrograms subcutaneously once weekly for 1 year. Monitoring of this treatment should be conducted according to the schedule outlined in the BOP *Guidelines for the Prevention and Treatment of Hepatitis C and Cirrhosis*. If treatment goals are not achieved with pegylated interferon alfa-2a after one year and treatment is still indicated, consideration should be given to treatment with an NA.

- ***Nucleoside/Nucleotide Analogues:*** NAs interrupt viral replication by blocking the DNA polymerase that converts HBV RNA into DNA. All are oral antiviral agents that are easy to administer, have limited toxicities, and can be effective in suppressing hepatitis B viral replication. They have several disadvantages including the difficulty in determining optimal treatment duration. Long-term treatment is likely required for many patients, but can result in resistance to some of the NAs. In addition, cessation of therapy can result in viral relapse or hepatitis exacerbation in certain patients.

  Preferred NA treatment options: Five NAs are FDA-approved for treatment of chronic HBV—adefovir, entecavir, lamivudine, telbivudine, and tenofovir. Emtricitabine is similar to lamivudine, but is FDA-approved only for the treatment of HIV infection. Determining which NA to use is based on the medication's efficacy (ability to suppress HBV DNA, to seroconvert to HBeAg-negative status, to normalize ALT levels, and to improve hepatic fibrosis), and its barrier to resistance. In general, entecavir and tenofovir have the greatest efficacy and lowest rates of resistance and are preferred as initial monotherapy for treatment-naïve patients. Emtricitabine and lamivudine have the highest rates of resistance (up to 90% after four years) and are not recommended as initial therapy or monotherapy. They are used in combination with another NA in certain circumstances. Telbivudine is an effective antiviral agent, but has an intermediate rate of resistance. Adefovir has the lowest potency and an intermediate rate of resistance. Cross resistance can develop among the NAs. In particular, lamivudine, emtricitabine, and telbivudine are likely to develop cross resistance. A number of cumulative genetic mutations are required to create cross resistance of these three NAs with entecavir. As a result, a higher dose of entecavir is recommended when entecavir is used to treat patients with prior exposure to these medications. Although adefovir resistant strains are not resistant to tenofovir, these strains do have a decreased rate of response to tenofovir.

  Appropriate NA dosing: All NAs are administered orally, once daily, and require dose adjustment with reduced GFR or dialysis. Standard dosing of the NAs in the treatment-naïve patient is as follows.

  - *Adefovir:* 10 mg P.O. once daily
  - *Emtricitabine:* 200 mg P.O. once daily in combination with tenofovir in HIV co-infection

- *Entecavir:* 0.5 mg P.O. once daily (NA naïve)
  or
  1 mg P.O. once daily (prior lamivudine treatment, or known lamivudine or telbivudine resistance)
- *Lamivudine:* 100 mg P.O. once daily
- *Telbivudine:* 600 mg P.O. once daily
- *Tenofovir:* 300 mg P.O. once daily

Steps 5c: Determine the end points of treatment.

The end point for treatment of patients treated with NAs is less clearly defined than for patients treated with interferon and is determined by the HBeAg status at the start of treatment, and the presence of co-mordities such as cirrhosis, co-infections, or HCC.

- **If HBeAg(+) at start of treatment:** Treat for 6 months beyond seroconversion to HBeAg(–) status.*****
- **If HBeAg(–) at start of treatment:** Treat indefinitely or until seroconversion to HBsAg(–) status.*****
- **Compensated cirrhosis:** Treat indefinitely or until seroconversion as above.
- **Decompensated cirrhosis:** Treat indefinitely.
- **HBV/HIV co-infection:** The end point of treatment in HBV/HIV co-infection is not yet known, but is likely to be indefinite in most cases. Due to the risk of hepatitis exacerbation, discontinuation of HBV treatment should be done only in consultation with an experienced clinician.
- **Immunosuppressant therapy** (e.g., chemotherapy or anti-tumor necrosis alfa medications)**:** If standard HBV treatment criteria *are* met, then the end point of treatment is the same as for those not receiving immunosuppressant therapy. If standard criteria *are not* met, e.g., due to low HBV DNA levels < 2,000 IU/ml, then treatment usually is continued for six months beyond completion of the chemotherapy. When long-term immunosuppressant therapy is needed, HBV treatment usually is continued for at least as long as the immunosuppressant therapy.

***** *Ongoing monitoring following discontinuation of therapy in a patient with a sustained response is necessary because relapse may occur. The optimal monitoring strategy has not been established.*

STEP 6: Monitor patients on treatment.

Monitoring Treated Inmates

Once antiviral medication is initiated, ongoing monitoring is required to assess response to therapy, and the development of side effects or adverse events. It is also required following discontinuation of antiviral medication in those patients for whom treatment goals are met. While the optimal monitoring strategy has not been established, the following monitoring strategy is reasonable.

The effectiveness of antiviral therapy for chronic hepatitis B is determined by monitoring the following parameters:

- ALT and AST levels every 3–6 months
- HBeAg every 3–6 months in patients who are HBeAg(+) at start of treatment
- HBsAg every 6–12 months in patients who are HBeAg(–) at start of treatment
- HBV DNA viral load every 3 months during first year of therapy; then every 6 months

In addition, serum creatinine should be monitored periodically during treatment with NAs. Inmates receiving interferon therapy for chronic hepatitis B should receive clinician evaluations in accordance with the monitoring schedule described in the BOP *Guidelines for the Prevention and Treatment of Hepatitis C and Cirrhosis*, in addition to monitoring the hepatitis B parameters described above.

Evaluating Treatment Response

One of the primary goals of treatment is suppression of viral replication, which forms the basis for defining treatment response:

- **Virologic response** is defined as an undetectable HBV DNA by PCR assay while on treatment, and seroconversion to HBeAg negative in those who were HBeAg positive.
- **Primary treatment failure/non-response** refers to *less than* a 2-log decrease in serum HBV DNA IU/ml after 24 weeks of NA therapy.
- **Virologic breakthrough** refers to greater than a 10-fold (1-log) increase in HBV DNA IU/ml from the treatment nadir in a patient with an initial treatment response.
- **Biochemical response** refers to normalization of serum ALT.
- **Biochemical breakthrough** refers to an increase in ALT above the upper limits of normal following a biochemical response on treatment.

➔ See also *Appendix 4, Definition of Terms Relating to Antiviral Resistance to Nucleoside Analogue (NA) Treatment*.

The clearance of HBeAg in persons with chronic HBeAg-positive hepatitis is associated with improved clinical outcomes. HBeAg may not disappear, however, for months or longer after the completion of effective antiviral therapy. HBsAg may remain positive, and HBV DNA may remain detectable, for years after completion of treatment. The long-term clinical consequences of persistent viremia are uncertain. Monitoring treatment response is even more difficult in persons with HBe-negative hepatitis. Clearance of viremia and normalization of ALT with treatment are helpful signs, but relapse is common in these patients despite an initial favorable response.

Transient increases in aminotransferase levels are common during therapy and correlate with immune system clearance of HBV and the disappearance of HBeAg. Mild to moderate increases in liver enzymes should not be an indication for reducing or discontinuing interferon therapy, unless associated with deteriorating liver synthetic function or jaundice.

STEP 7: Manage treatment failure or virologic breakthrough.

Virologic failure after one year of interferon, or six months of NA or virologic breakthrough, should prompt an assessment for medication adherence and viral resistance. Once medication adherence is confirmed, patents who continue to meet criteria for treatment should be considered for a change of medication in consultation with an experienced clinician because of the potential for cross-resistance among some of the NAs. However, in the context of primary treatment failure or virologic breakthrough, HBV genotype and phenotype testing are not routinely performed.

6. References

Belongia EA, Costa J, Gareen IF, et al. National Institutes of Health Consensus Development Conference Statement: management of hepatitis B. *Ann Intern Med*. 2009;150:104–110. Available at: http://consensus.nih.gov/2008/hepbstatement.pdf. Accessed November 2010.

Bhattacharya D, Thio CL. Review of hepatitis B therapeutics. *CID*. 2010;51:1201–1208.

Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology*. July 2010;1–35. Available at: www.aasld.org/practiceguidelines/Pages/NewUpdatedGuidelines.aspx. Accessed November 2010.

Centers for Disease Control and Prevention. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part II: immunization of adults. *MMWR*. 2006;55(RR-16): 1–40.

Centers for Disease Control and Prevention. Interpretation of Hepatitis B Serologic Test Results. Available at: http://www.cdc.gov/hepatitis/HBV/PDFs/SerologicChartv8.pdf. Accessed November 2010

European Association for the Study of the Liver. EASL clinical practice guidelines: management of chronic hepatitis B. *J Hepatol.* 2009;50:227–242.

Keeffe EB, Dieterich DT, Han S-H B, et al. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: 2008 update. *Clin Gastroenterol Hepatol*. 2008;6(12):1314–1340.

Lok ASF, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology*. 2009;50(3):1–36. Available at: http://www.aasld.org/practiceguidelines/Documents/Bookmarked%20Practice%20Guidelines/Chronic_Hep_B_Update_2009%208_24_2009.pdf. Accessed November 2010.

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009; 1–161. Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed November 2010.

Appendix 1. Criteria for Determining HBV Disease State[1]

Disease State	Description/Discussion	Diagnostic Criteria
Chronic Hepatitis B Chronic necroinflammatory disease of the liver caused by persistent infection with HBV	Chronic hepatitis B can be characterized as HBeAg-positive or HBeAg-negative: ◆ Persons with HBeAg-positive hepatitis have an increased risk of progressive liver disease. ◆ Persons with negative HBeAg may have chronic hepatitis B with elevated ALT levels, and necroinflammation on liver biopsy, but often have lower levels of HBV DNA (2,000–19,999 IU/ml or 10^4–10^5 cps/ml) than those with HBeAg-positive disease. HBeAg-negative chronic hepatitis has a fluctuating, less predictable course, compared to HBeAg-positive hepatitis, and occurs more commonly in persons from Asia and Mediterranean countries.	**1.** HBsAg-positive > 6 months **2.** Serum HBV DNA > 20,000 IU/ml (>10^5 cps/ml) The diagnostic threshold of serum HBV DNA of 10^5 cps/ml or greater is somewhat arbitrary, but helps to identify patients with significant infection that is usually associated with liver inflammation. **3.** Persistent or intermittent elevation in ALT/AST levels **4.** Liver biopsy (when performed) showing chronic hepatitis with moderate or severe necroinflammation
Inactive HBsAg Carrier State Persistent HBV infection of the liver without significant, ongoing necroinflammatory disease	Certain persons with chronic HBV infection are able to clear HBeAg, with an associated decrease in detectable serum HBV DNA, while remaining HBsAg-positive. These persons still have persistent infection, but are at lower risk of developing cirrhosis, and have the diagnostic criteria listed in the next column. Those with an inactive carrier state can revert back to an HBeAg-positive status. Similarly, liver inflammation and damage may develop in the inactive carrier state and is referred to as reactivation of hepatitis B. *The inactive carrier must therefore be monitored periodically to detect reactivation of chronic disease.*	**1.** HBsAg-positive > 6 months **2.** HBeAg-negative/anti-HBe-positive (a/k/a HBeAg seroconversion) **3.** Serum HBV DNA < 2,000 IU/ml **4.** Persistently normal ALT/AST levels **5.** Liver biopsy (when performed) without significant hepatitis or necroinflammation
Resolved Hepatitis B (anti-HBs-positive) Previous HBV infection without further virologic, biochemical, or histological evidence of active virus infection or disease	A certain proportion of persons with chronic HBV infection spontaneously clear their infection (approximately 1% yearly). Serum HBV DNA levels decrease to undetectable levels (although very low levels may be detectable by PCR), ALT levels normalize, and serum HBsAg disappears.	**1.** Previous known history of acute or chronic hepatitis B or the presence of anti-HBc ± anti-HBs **2.** HBsAg– **3.** Undetectable serum HBV DNA* **4.** Normal ALT levels * *Very low levels may be detectable using sensitive PCR assays.*

Adapted from:

[1] Lok ASF, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology*. 2009;50(3):1–36. Available at: http://www.aasld.org/practiceguidelines/Documents/Bookmarked%20Practice%20Guidelines/Chronic_Hep_B_Update_2009%208_24_2009.pdf. Accessed November 2010.

Appendix 2. Stepwise Approach for Detecting, Evaluating, and Treating Chronic HBV Infection[1]

STEP 1: Appropriately screen for HBV infection based on risk factors.

Assess for presence of HBV risk factors:

- Born in a country or region where HBV is endemic
- Ever injected drugs
- Multiple sexual partners or a history of STIs
- Men who have sex with men
- Chronically elevated ALT or AST
- Infection with HCV or HIV
- Renal dialysis
- Pregnancy
- Immunosuppression

Screen for HBV with HBsAg and anti-HBs:

- Anti-HBs-positive indicates immunity, while HBsAg-positive for greater than 6 months indicates chronic infection.
- If HBsAg and HBsAb are negative:
  - Refer to BOP Clinical Practice Guidelines for *Preventive Health Care* for indications for HBV vaccination.
  - If HIV co-infection, test for anti-HBc; if positive, order HBV DNA viral load.

➔ *For a more thorough discussion, see the Step 1 section in these guidelines.*

STEP 2: Provide initial follow-up for HBsAg-positive inmates.

- Targeted history and physical
- Additional diagnostic testing:
  - Anti-HBe, HBeAg, HBV DNA viral load
  - HCV Ab, HIV Ab, hepatitis D virus Antibody (Total anti-HDV)
  - CBC w/ differential, BUN/Creatinine/BMP, liver panel, INR
  - Abdominal U/S
- Consider hepatitis A vaccination in accordance with the BOP *Preventive Health* Clinical Practice Guideline

➔ *For more detailed information, see the Step 2 section in these guidelines.*

STEP 3: Assess the need for liver biopsy.

A liver biopsy is indicated in the following scenarios:

- HBeAg-negative *and* HBV DNA ≥ 20,000 IU/ml *and* ALT < 2x ULN
- HBeAg-negative *and* HBV DNA = 2,000–19,999 IU/ml
- HBeAg-positive *and* HBV DNA ≥ 20,000 IU/ml *and* ALT < 2x ULN *and* age ≥ 40

STEP 4a: Determine if HBV treatment is NOT indicated.

Treatment for chronic hepatitis B is *not* indicated in the following scenarios:

- HBeAg-negative *and* HBV DNA < 2,000 IU/ml
- HBeAg-positive *and* HBV DNA < 20,000 IU/ml
- HBeAg-positive *and* HBV DNA > 20,000 IU/ml *and* ALT < 2x ULN *and* age < 40
- Liver biopsy with stage 0–1 fibrosis

STEP 4b: Monitor HBV patients who are not on treatment.

HBeAg(+) and treatment not indicated:

- ALT every 3–6 months if WNL; ALT every 1–3 months if 1–2x ULN
- HBV DNA viral load every 6–12 months
- Liver biopsy if ALT ≥ 2x ULN for 6 months *or* if ALT 1–2x ULN for 6 months and age ≥ 40

HBeAg(–) and treatment not indicated:

- ALT every 3 months for 1 year; then every 6–12 months
- HBV DNA viral load if ALT > 1–2x ULN
- Liver biopsy if persistent ALT elevation *or* HBV DNA ≥ 2,000 IU/ml

STEP 5: Determine if treatment is indicated.

Indications for treatment of chronic HBV infection:

- HBV DNA ≥ 20,000 IU/ml *and* ALT ≥ 2x ULN
- Liver biopsy with ≥ stage 2 fibrosis or moderate/severe inflammation
- HIV co-infection
- Cirrhosis or HCC
- Planned treatment with chemotherapy or anti-tumor necrosis factor alfa, or organ transplant recipients

➔ *For a more thorough discussion, see the sections on Step 5 and Steps 5a, 5b, and 5c in these guidelines.*

STEP 5a: Determine the preferred treatment regimen.

Chronic HBV with no prior HBV treatment and no cirrhosis or co-infections:

- *Preferred tx options:* tenofovir or entecavir, or pegylated IFNa (certain cases)

Chronic HBV with cirrhosis (compensated or decompensated):

- *Preferred tx options:* monotherapy with tenofovir or entecavir

Chronic HBV with HCV or HDV co-infection:

- *Preferred tx options:* Data are insufficient to establish a preferred treatment option or guideline. In many cases of HBV co-infection with HCV or HDV, treatment with pegylated interferon will be preferred due to interferon's activity against both viruses. Treatment decisions should be made on a case-by-case basis in consultation with a clinician experienced in managing these cases.

(Step 5a continues on next page.)

Chronic HBV with HIV co-infection:[2]

- *HIV and HBV tx naïve for whom either HBV treatment or HAART therapy is indicated/planned:* tenofovir + (emtricitabine *or* lamivudine) + (either darunavir *or* atazanavir boosted with ritonavir, or raltegravir).
- *In HBV / HIV co-infection, antiretroviral therapy may result in elevated transaminase levels* and must be interpreted cautiously because they may indicate hepatotoxicity from the medication, exacerbation of HBV activity, or seroconversion from HBeAg positive to negative.
- *A number of clinical scenarios may complicate treatment decisions for patients with HBV and HIV co-infection and should prompt a consultation with an experienced clinician.* Such cases include HIV patients already on an effective HAART regimen not including HBV-active NAs, HBV resistance to one of the HBV-active NAs, HIV resistance to one of the HBV-active NAs or to the NRTIs as part of a HAART regimen, and the need to change a HAART regimen that contains effective HBV-active NAs.

Note: *Consultation with an infectious disease specialist, Regional HIV Pharmacy Consultant, or Central Office Physician is recommended prior to initiating therapy in patients with HBV and HIV co-infection.*

STEP 5b: Determine the appropriate medication dose of therapy.

Nucleos(t)ide Analogues:

Dose adjustment required for all Neucleoside/Nucleotide Analogues (NAs) in patients on dialysis or with a decreased GFR.

- *Adefovir:* 10 mg P.O. once daily
- *Emtricitabine:* 200 mg P.O. once daily in combination with tenofovir in HIV co-infection
- *Entecavir:* 0.5 mg P.O. once daily (NA naïve)
  or
  1 mg P.O. once daily (prior lamivudine treatment, or known lamivudine or telbivudine resistance)
- *Lamivudine:* 100 mg P.O. once daily
- *Telbivudine:* 600 mg P.O. once daily
- *Tenofovir:* 300 mg P.O. once daily

Interferon alfa:

- Pegylated interferon alfa-2a 180 micrograms subcutaneously once weekly for 1 year duration; see BOP *Guidelines for the Prevention and Treatment of Hepatitis C and Cirrhosis* for additional information on treatment with interferon.

➔ *For more complete information, see Appendix 5, Antiviral Medications for Chronic Hepatitis B.*

STEP 5c: Determine the end points of treatment.

- *If HBeAg(+) at start of treatment:* Treat for 6 months beyond seroconversion to HBeAg(–) status.*
- *If HBeAg(–) at start of treatment:* Treat indefinitely or until seroconversion to HBsAg(–) status.*
- *Compensated cirrhosis:* Treat indefinitely or until seroconversion as above.
- *Decompensated cirrhosis or HCC:* Treat indefinitely.
- *HBV/HIV co-infection:* The end point of treatment in HBV/HIV co-infection is not yet known, but is likely to be indefinite in most cases. Due to the risk of hepatitis exacerbation, discontinuation of HBV treatment should be done only in consultation with an experienced clinician.

(Step 5c continues on next page.)

- *Chemotherapy, anti-tumor necrosis factor alfa, or immunosuppressed organ transplant recipients:* If standard HBV treatment criteria *are* met, then the end point of treatment is the same as for those not receiving immunosuppressant therapy. If standard criteria *are not* met, e.g., due to low HBV DNA levels < 2,000 IU/ml, then treatment usually is continued for 6 months beyond completion of the chemotherapy. When long-term immunosuppressant therapy is needed, HBV treatment usually is continued for at least as long as the immunosuppressant therapy.

* *Ongoing monitoring following discontinuation of therapy in a patient with a sustained response is necessary because relapse may occur. The optimal monitoring strategy has not been established.*

STEP 6: Monitor patients on treatment.

Monitoring schedule for Nucleos(t)ide Analogues:

- ALT and AST levels every 3–6 months
- HBeAg every 3–6 months (in patients who are HBeAg(+) at start of treatment)
- HBsAg every 6–12 months (in patients who are HBeAg(–) at start of treatment)
- HBV DNA viral load every 3 months during first year of therapy; then every 6 months
- Serum creatinine every 12 weeks while taking adefovir or tenofovir

Monitoring schedule for Interferon alfa:

- See BOP *Guidelines for the Prevention and Treatment of Hepatitis C and Cirrhosis.*

➔ *For a more thorough discussion, see the Step 6 section in these guidelines.*

STEP 7: Manage treatment failure or virologic breakthrough.

Definitions:

- *Primary treatment failure/non-response:* Less than a 2-log decrease in serum HBV DNA IU/ml after 6 months of NA therapy.
- *Partial virologic response:* HBV DNA via PCR assay that is < 20,000 IU/ml but still detectagle after 6 months or more of continuous therapy.
- *Virologic breakthrough:* Greater than a 10-fold (1-log) increase in HBV DNA IU/ml from the treatment nadir in a patient with an initial treatment response.

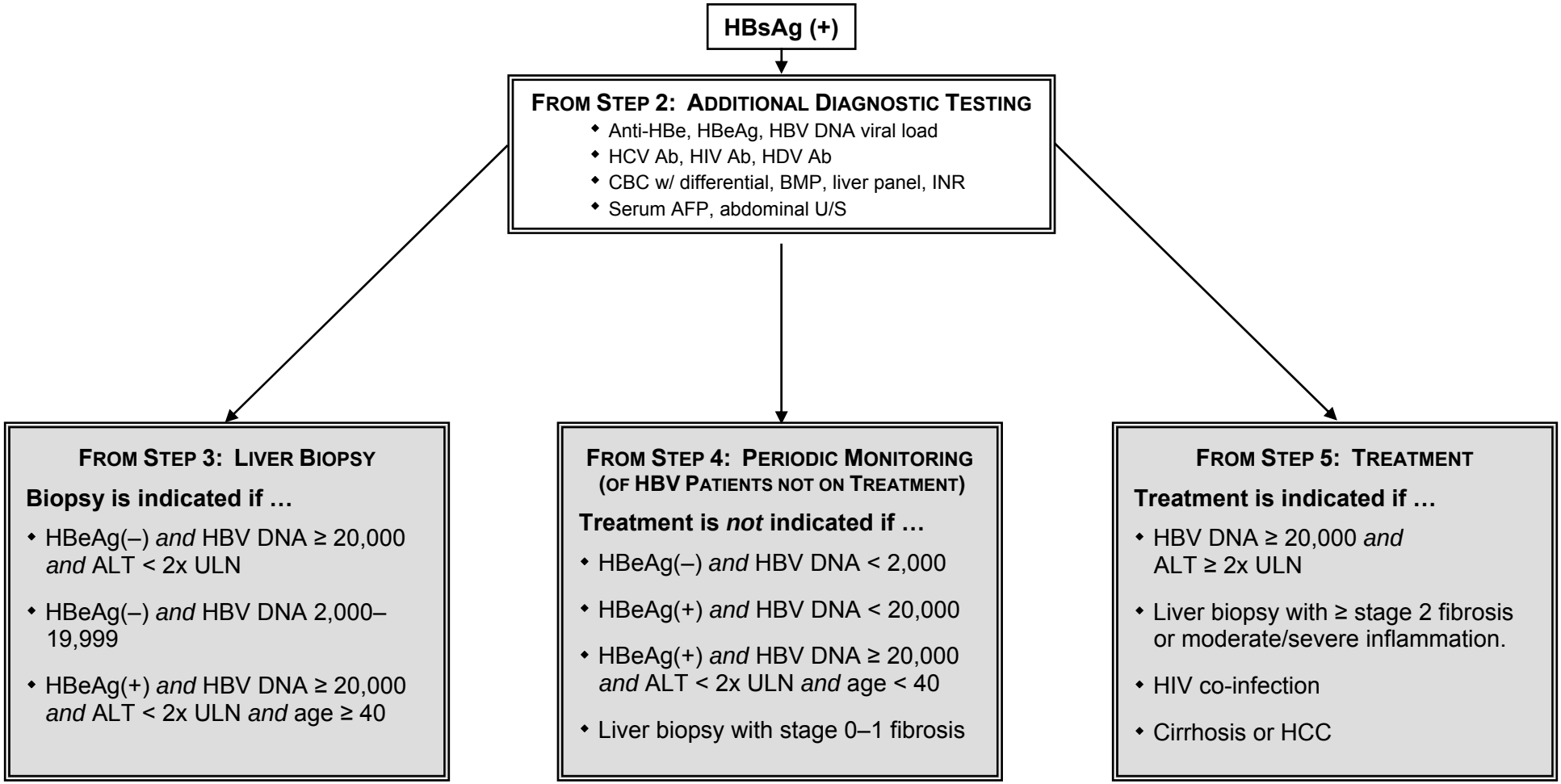
Treatment of resistant HBV (check for medication adherence first):

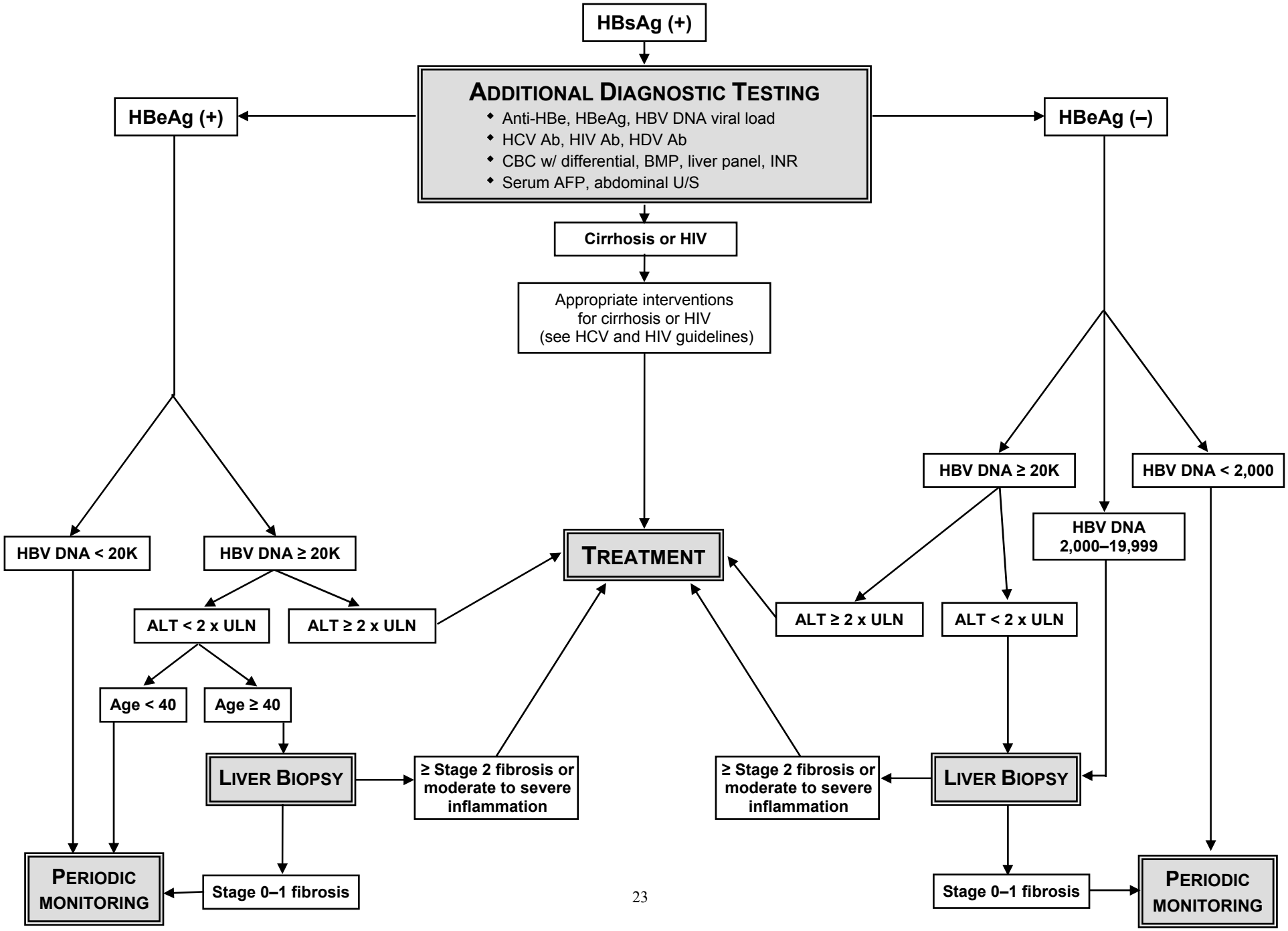
- *In the context of primary treatment failure or virologic breakthrough, HBV genotype and phenotype testing are not routinely performed.*
- Once medication adherence is confirmed, treatment with a different agent, either pegylated interferon alfa-2a or a different NA, should be considered in consultation with experienced clinician, because of the potential for cross-resistance among some of the NAs.

Adapted from:

1 Lok ASF, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology. 2009;50(3):661–662. Complete article available at: http://www.aasld.org/practiceguidelines/Documents/Bookmarked%20Practice%20Guidelines/Chronic_Hep_B_Update_2009%208_24_2009.pdf. Accessed November 2010.

2 Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009; 1–161. Available at: http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed November 2010.


HBsAg (+)
FROM STEP 2: ADDITIONAL DIAGNOSTIC TESTING
Anti-HBe, HBeAg, HBV DNA viral load
HCV Ab, HIV Ab, HDV Ab
CBC w/ differential, BMP, liver panel, INR
Serum AFP, abdominal U/S
FROM STEP 3: LIVER BIOPSY
Biopsy is indicated if …
HBeAg(–) and HBV DNA ≥ 20,000 and ALT < 2x ULN
HBeAg(–) and HBV DNA 2,000–19,999
HBeAg(+) and HBV DNA ≥ 20,000 and ALT < 2x ULN and age ≥ 40
FROM STEP 4: PERIODIC MONITORING (OF HBV PATIENTS NOT ON TREATMENT)
Treatment is not indicated if …
HBeAg(–) and HBV DNA < 2,000
HBeAg(+) and HBV DNA < 20,000
HBeAg(+) and HBV DNA ≥ 20,000 and ALT < 2x ULN and age < 40
Liver biopsy with stage 0–1 fibrosis
FROM STEP 5: TREATMENT
Treatment is indicated if …
HBV DNA ≥ 20,000 and ALT ≥ 2x ULN
Liver biopsy with ≥ stage 2 fibrosis or moderate/severe inflammation.
HIV co-infection
Cirrhosis or HCC


HBsAg (+)
ADDITIONAL DIAGNOSTIC TESTING
Anti-HBe, HBeAg, HBV DNA viral load
HCV Ab, HIV Ab, HDV Ab
CBC w/ differential, BMP, liver panel, INR
Serum AFP, abdominal U/S
HBeAg (+)
HBeAg (–)
Cirrhosis or HIV
Appropriate interventions for cirrhosis or HIV (see HCV and HIV guidelines)
HBV DNA < 20K
HBV DNA ≥ 20K
ALT < 2 x ULN
ALT ≥ 2 x ULN
Age < 40
Age ≥ 40
LIVER BIOPSY
≥ Stage 2 fibrosis or moderate to severe inflammation
Stage 0–1 fibrosis
PERIODIC MONITORING
TREATMENT
HBV DNA ≥ 20K
HBV DNA 2,000–19,999
HBV DNA < 2,000
ALT ≥ 2 x ULN
ALT < 2 x ULN
LIVER BIOPSY
≥ Stage 2 fibrosis or moderate to severe inflammation
Stage 0–1 fibrosis
PERIODIC MONITORING

Appendix 3. Definition of Response to Antiviral Therapy of Chronic Hepatitis B[1]

Category of Response	
Biochemical (BR)	Decrease in serum ALT to within the normal range
Virologic (VR)	Decrease in serum HBV DNA to undetectable levels by PCR assays, and loss of HBeAg in patients who were initially HBeAg-positive
Primary non-response (not applicable to interferon therapy)	Decrease in serum HBV DNA by < 2 $\log_{10}$ IU/ml after at least 24 weeks of therapy
Virologic relapse	Increase in serum HBV DNA of 1 log10 IU/ml after discontinuation of treatment in at least two determinations more than 4 weeks apart
Histologic (HR)	Decrease in histology activity index by at least 2 points and no worsening of fibrosis score compared to pre-treatment liver biopsy
Complete (CR)	Fulfill criteria of biochemical and virological response and loss of HBsAg
Time of Assessment	
On-therapy	During therapy
Maintained	Persists throughout the course of treatment
End-of-treatment	At the end of a defined course of therapy
Off-therapy	After discontinuation of therapy
Sustained (SR-6)	6 months after discontinuation of therapy
Sustained (SR-12)	12 months after discontinuation of therapy

Adapted from:

[1] Lok ASF, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology*. 2009;50(3):1–36. Available at: http://www.aasld.org/practiceguidelines/Documents/Bookmarked%20Practice%20Guidelines/Chronic_Hep_B_Update_2009%208_24_2009.pdf. Accessed November 2010.

Appendix 4. Definition of Terms Relating to Antiviral Resistance to Nucleoside Analogue (NA) Treatment[1]

Term	Definition
Virologic breakthrough	Increase in serum HBV DNA by > 1 log10 (10-fold) above nadir after achieving virologic response, during continued treatment
Viral rebound	Increase in serum HBV DNA to > 20,000 IU/ml or above pretreatment level after achieving virologic response, during continued treatment
Biochemical breakthrough	Increase in ALT above upper limit of normal after achieving normalization, during continued treatment
Genotypic resistance	Detection of mutations that have been shown in *in vitro* studies to confer resistance to the NA that is being administered
Phenotypic resistance	*In vitro* confirmation that the mutation detected decreases susceptibility (as demonstrated by increase in inhibitory concentrations) to the NA administered

Adapted from:

[1] Lok ASF, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology*. 2009;50(3):1–36. Available at: http://www.aasld.org/practiceguidelines/Documents/Bookmarked%20Practice%20Guidelines/Chronic_Hep_B_Update_2009%208_24_2009.pdf. Accessed November 2010.

Appendix 5. Antiviral Medications for Chronic Hepatitis B

Adefovir dipivoxil (Hepsera®)

Medication /Dosage	Baseline Tests/Monitoring	Adverse Reactions/Comments
Dose:* ▸ 10 mg orally, daily ▸ ***Must adjust dose for renal impairment.*** **Duration:** Optimal treatment duration is unknown. For guidance in determining treatment duration, see Steps 6-7 in the text or Steps 6-7 in Appendix 2. ***See warning below.***	**Baseline Tests:** ▸ Anti-HIV, anti-HCV, anti-HDV ▸ HBeAg, anti-HBe, HBV DNA ▸ ALT/AST, liver function ▸ CBC with differential and platelets ▸ Chemistry panel ▸ Calculated creatinine clearance/ BUN ▸ Thyroid function studies* ▸ Mental health assessment* ▸ Pregnancy test * Thyroid studies and mental health assessment are necessary only if clinically indicated. **Monitoring:** ▸ ALT, liver function ▸ Renal function tests every 3 months ▸ Creatinine/BUN **Discontinue treatment if creatinine rises more than 0.5 above baseline.** ▸ See Step 6 in the text or Step 6 in Appendix 2 for other specific monitoring recommendations.	**Black Box Warnings:** ▸ **Use with caution with patients with renal dysfunction or patients at risk of nephrotoxicity (including nephrotoxic agents: NSAIDS).** ▸ **Lactic acidosis and severe hepatomegaly with steatosis have been reported.** ▸ **Acute exacerbations may occur (up to 25% of patients) following discontinuation.** **Adverse Reactions:** ▸ Lactic acidosis ▸ Hepatomegaly **Comments:** ▸ Medications are well tolerated, and rate of developing drug resistance is low. ▸ Low-level activity against HIV. ▸ Active against lamivudine-resistant mutants.

* ***Warning***: **Due to the risk of precipitating liver failure, do not discontinue nucleoside analogue therapy without consulting a physician expert.**

(Appendix 5 continued on next page)

Appendix 5. Antiviral Medications for Chronic Hepatitis B (page 2 of 7)

Emtricitabine (Emtriva®)

Medication /Dosage	Baseline Tests/Monitoring	Adverse Reactions/Comments
Dose:* ▸ 200 mg orally, daily (*normal renal function*) ▸ Not FDA indicated for chronic hepatitis B ▸ Can be used in combination with other NAs for resistant hepatitis B therapy or co-infected HIV patients ▸ *Recommended dose for HIV co-infection* is 200 mg daily, along with other anti-retroviral medications. ▸ ***Must adjust dose for renal impairment.*** **Duration:** Optimal treatment duration is unknown. For guidance in determining treatment duration, see Steps 6-7 in the text or Steps 6-7 in Appendix 2. ***See warning below.***	**Baseline Tests and Monitoring:** ▸ Anti-HIV, anti-HCV, anti-HDV ▸ HBeAg, anti-HBe, HBV DNA ▸ ALT/AST, liver function ▸ CBC with differential and platelets ▸ Chemistry panel ▸ Calculated creatinine clearance/ BUN* ▸ Thyroid function studies** ▸ Mental health assessment** ▸ Pregnancy test ▸ See Step 6 in the text or Step 6 in Appendix 2 for other specific monitoring recommendations. * Conduct renal function tests every 3 months. ** Thyroid studies and mental health assessment are necessary only if clinically indicated.	**Black Box Warnings:** ▸ **Lactic acidosis and severe hepatomegaly with steatosis have been reported.** ▸ **Monitor closely following discontinuation for clinical exacerbation in HIV/HBV co-infected patients.** **Adverse Reactions:** ▸ Lactic acidosis ▸ Hepatomegaly **Comments:** ▸ Not FDA indicated for treatment of HBV. ▸ Do not combine with interferon or other antiviral agents for hepatitis B. ▸ Common combination therapy with Tenofovir (Truvada®).

* ***Warning*: Due to the risk of precipitating liver failure, do not discontinue nucleoside analogue therapy without consulting a physician expert.**

(Appendix 5 continued on next page)

Appendix 5. Antiviral Medications for Chronic Hepatitis B (page 3 of 7)

Entecavir (Baraclude®)

Medication /Dosage	Baseline Tests/Monitoring	Adverse Reactions/Comments
Dose:* ▸ 0.5 mg orally, daily in nucleoside-treatment-naïve adults ▸ 1 mg orally, daily in lamivudine- or telbivudine-refractory adults ▸ ***Must adjust dose for renal impairment.*** **Duration:** Optimal treatment duration is unknown. For guidance in determining treatment duration, see Steps 6-7 in the text or Steps 6-7 in Appendix 2. ***See warning below.***	**Baseline Tests:** ▸ Anti-HIV, anti-HCV, anti-HDV ▸ HBeAg, anti-HBe, HBV DNA ▸ ALT/AST, liver function ▸ CBC with differential and platelets ▸ Chemistry panel ▸ Calculated creatinine clearance/ BUN ▸ Thyroid function studies ▸ Mental health assessment ▸ Pregnancy test **Monitoring**: ▸ ALT, liver function ▸ Renal function tests every 3 months ▸ Clinical and laboratory follow-up should continue for several months after treatment is stopped. ▸ See Step 6 in the text or Step 6 in Appendix 2 for other specific monitoring recommendations.	**Black Box Warnings:** ▸ **Lactic acidosis and severe hepatomegaly with steatosis have been reported.** ▸ **May cause the development of HIV resistance in chronic Hep B patients with unrecognized or untreated HIV.** **Adverse reactions**: ▸ Lactic acidosis ▸ Hepatomegaly **Comments**: ▸ Since entecavir is primarily eliminated by the kidneys, co-administration of drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of either entecavir or the co-administered drug. ▸ Effective against lamivudine-resistant HBV mutants; activity against dual mutants is significantly less than that of wild-type HBV. ▸ Not active against HIV.

* ***Warning***: **Due to the risk of precipitating liver failure, do not discontinue nucleoside analogue therapy without consulting a physician expert.**

(Appendix 5 continued on next page)

Appendix 5. Antiviral Medications for Chronic Hepatitis B (page 4 of 7)

Lamivudine (Epivir-HBV®)

Medication /Dosage	Baseline Tests/Monitoring	Adverse Reactions/Comments
Dose:* ▸ 100 mg orally (*normal renal function and HIV seronegative*) ▸ *Recommended dose for HIV co-infection* is 150 mg bid, along with other anti-retroviral medications. ▸ ***Must adjust dose for renal impairment.*** **Duration:** Optimal treatment duration is unknown. For guidance in determining treatment duration, see Steps 6-7 in the text or Steps 6-7 in Appendix 2. ***See warning below.***	**Baseline Tests and Monitoring:** ▸ Anti-HIV, anti-HCV, anti-HDV ▸ HBeAg, anti-HBe, HBV DNA ▸ ALT/AST, liver function ▸ CBC with differential and platelets ▸ Chemistry panel ▸ Calculated creatinine clearance/ BUN* ▸ Thyroid function studies** ▸ Mental health assessment** ▸ Pregnancy test ▸ See Step 6 in the text or Step 6 in Appendix 2 for other specific monitoring recommendations. * Conduct renal function tests every 3 months. ** Thyroid studies and mental health assessment are necessary only if clinically indicated.	**Black Box Warnings:** ▸ **Do not use Epivir-HBV for HIV.** ▸ **Lactic acidosis and severe hepatomegaly with steatosis have been reported. Monitor closely following discontinuation for clinical exacerbation.** **Adverse Reactions:** ▸ Lactic acidosis ▸ Hepatomegaly **Comments:** ▸ Lamivudine is a less attractive treatment option due to a lack of long-term efficacy and a strong association with drug-resistant mutants. ▸ Do not combine with interferon. ▸ Different formulation and lower therapeutic dose than HIV formulation Epivir.

* ***Warning***: **Due to the risk of precipitating liver failure, do not discontinue nucleoside analogue therapy without consulting a physician expert.**

(Appendix 5 continued on next page)

Appendix 5. Antiviral Medications for Chronic Hepatitis B (page 5 of 7)

Telbivudine (Tyzeka ®)

Medication /Dosage	Baseline Tests/Monitoring	Adverse Reactions/Comments
Dose:* ▸ 600 mg orally, daily ▸ ***Must adjust dose for renal impairment.*** **Duration:** Optimal treatment duration is unknown. For guidance in determining treatment duration, see Steps 6-7 in the text or Steps 6-7 in Appendix 2. ***See warning below.***	**Baseline Tests and Monitoring:** ▸ Anti-HIV, anti-HCV, anti-HDV ▸ HBeAg, anti-HBe, HBV DNA ▸ ALT/AST, liver function ▸ CBC with differential and platelets ▸ Chemistry panel ▸ Calculated creatinine clearance/ BUN* ▸ Thyroid function studies** ▸ Mental health assessment** ▸ Pregnancy test ▸ See Step 6 in the text or Step 6 in Appendix 2 for other specific monitoring recommendations. * Conduct renal function tests every 3 months. ** Thyroid studies and mental health assessment are necessary only if clinically indicated.	**Black Box Warnings:** ▸ **Lactic acidosis and severe hepatomegaly with steatosis have been reported.** ▸ **Monitor closely following discontinuation for clinical exacerbation in HIV/HBV co-infected patients.** **Adverse Reactions:** ▸ Lactic acidosis ▸ Hepatomegaly ▸ Myopathy ▸ Peripheral neuropathy **Comments:** ▸ Not recommended as first-line treatment of chronic HBV because of intermediate rate of resistance. ▸ Not active against HIV. ▸ Do not combine with interferon.
* ***Warning***: **Due to the risk of precipitating liver failure, do not discontinue nucleoside analogue therapy without consulting a physician expert.**		

(Appendix 5 continued on next page)

Appendix 5. Antiviral Medications for Chronic Hepatitis B (page 6 of 7)

Tenofovir (Viread ®)

Medication /Dosage	Baseline Tests/Monitoring	Adverse Reactions/Comments
Dose:* ▸ 300 mg orally, daily (*normal renal function*) ▸ Can be used in combination with other NAs for resistant hepatitis B therapy or co-infected HIV patients ▸ *Recommended dose for HIV co-infection* is 300 mg daily, along with other anti-retroviral medications. ▸ ***Must adjust dose for renal impairment.*** **Duration:** Optimal treatment duration is unknown. For guidance in determining treatment duration, see Steps 6-7 in the text or Steps 6-7 in Appendix 2. ***See warning below.***	**Baseline Tests and Monitoring:** ▸ Anti-HIV, anti-HCV, anti-HDV ▸ HBeAg, anti-HBe, HBV DNA ▸ ALT/AST, liver function ▸ CBC with differential and platelets ▸ Chemistry panel ▸ Calculated creatinine clearance/ BUN* ▸ Thyroid function studies** ▸ Mental health assessment** ▸ Pregnancy test ▸ See Step 6 in the text or Step 6 in Appendix 2 for other specific monitoring recommendations. * Conduct renal function tests every 3 months. ** Thyroid studies and mental health assessment are necessary only if clinically indicated.	**Black Box Warnings:** ▸ **Lactic acidosis and severe hepatomegaly with steatosis have been reported.** ▸ **Monitor closely following discontinuation for clinical exacerbation in HIV/HBV co-infected patients.** **Adverse Reactions:** ▸ Lactic acidosis ▸ Hepatomegaly **Comments:** ▸ FDA indicated and AASLD preferred treatment for chronic hepatitis B ▸ Common combination therapy with Emtricitabine (Truvada®)

* ***Warning***: **Due to the risk of precipitating liver failure, do not discontinue nucleoside analogue therapy without consulting a physician expert.**

(Appendix 5 continued on next page)

Appendix 5. Antiviral Medications for Chronic Hepatitis B (page 7 of 7)

Pegylated Interferon alfa 2a (Pegasys®)		
Medication /Dosage	**Baseline Tests/Monitoring**	**Adverse Reactions/Comments**
Dose: ▸ 180 mcg subcutaneously weekly **Duration:** ▸ One year of treatment is recommended, unless complications require discontinuation. Refer to BOP *Guidelines for the Prevention and Treatment of Hepatitis C and Cirrhosis* for a more detailed discussion and guidance on the use of interferon.	**Baseline Tests:** ▸ Anti-HIV, anti-HCV, anti-HDV ▸ HBeAg, anti-HBe, HBV DNA ▸ ALT/AST, liver function ▸ CBC with differential and platelets ▸ Chemistry panel ▸ Calculated creatinine clearance/ BUN ▸ Thyroid function studies ▸ Mental health assessment ▸ Pregnancy test **Monitoring:** ▸ Clinician evaluations every week x 1 month, then monthly ▸ CBC with differential and platelets ▸ ALT / liver function ▸ Creatinine/BUN ▸ Thyroid function studies ▸ Psychology/psychiatry monitoring, as necessary ▸ HIV evaluation throughout treatment ▸ Pregnancy evaluation and education up to 6 months post-treatment for female and male patients	**Black Box Warning:** ▸ **May cause or aggravate fatal or life threatening autoimmune disorders, neuropsychiatric symptoms, ischemic changes, or worsening hepatic function and or infectious disorders.** **Adverse Reactions:** ▸ Fever, fatigue, myalgias ▸ Nausea and diarrhea ▸ Alopecia ▸ Headache ▸ Psychiatric (depression, anxiety, irritability) ▸ Neutropenia and thrombocytopenia ▸ Thyroid dysfunction ▸ Renal failure ▸ Injection site irritation **Comments:** ▸ Contraindicated with decompensated cirrhosis ▸ High cost

Appendix 6. Inmate Fact Sheet on Hepatitis B and Hepatitis C

Am I at risk for infection with hepatitis B or hepatitis C?

You may be at risk for infection with hepatitis B or hepatitis C if you have ever injected drugs or had sex with an infected partner. People who received blood transfusions before 1992 may also be at risk. Talk to a health care provider about the risks of infection that affect you personally.

How can I prevent getting hepatitis B or hepatitis C while I am in prison?

- Do not have sex with other inmates, shoot drugs, or get a tattoo or body piercing.
- Do not share tooth brushes, razors, nail files or clippers, or other personal items that might have blood on them.

Why should I be tested for hepatitis B and hepatitis C?

You should be tested if you are at risk. That way, if tests show that you have hepatitis B or hepatitis C, doctors can monitor your health and decide whether you need treatment. It's also important for *you* to know if you are infected, so that you can take precautions to prevent infecting other people—including your unborn child if you or your partner become pregnant.

How do I get tested for hepatitis B and hepatitis C?

A simple blood test can determine if you are infected.

Are hepatitis B and hepatitis C dangerous to my health?

Most people with hepatitis B or hepatitis C can remain healthy. However, a small but significant number do develop serious liver disease. Treatments for hepatitis B and hepatitis C are fairly effective, and we expect that new medications in the future will work even better. Talk to a health care provider to better understand your level of risk for liver disease and to discuss your treatment plan.

How can I prevent giving hepatitis B or hepatitis C to others if I am infected?

- First, remember that you can spread this infection even if you feel fine!
- Do not shoot drugs or have sex with anyone.
- Do not share personal items that might have your blood on them, such as tooth brushes, nail files or clippers, or razors.
- Cover your cuts and skin sores to keep your blood from contacting other people.
- If you are being released, talk to a health care provider about specific ways you can reduce the risks of spreading the infection to others. For example, in addition to the precautions you are already taking, do not donate blood, semen, or body organs.

Appendix 7. Worksheet for Treatment of Hepatitis B / Approval Form

U.S. DEPARTMENT OF JUSTICE **FEDERAL BUREAU OF PRISONS**

Inmate Name:	Reg No:	Institution:
Date of Birth:	Projected Release Date:	

Test/Eval	Date	Findings/Result
HBsAg		(Circle result) positive / negative
HBeAg		(Circle result) positive / negative
HBV Viral Load		IU/ml
Liver biopsy (if indicated)		(Circle degree of fibrosis) none / portal / periportal / bridging / cirrhosis

Medical Clearance (Check all that apply)

☐ No evidence of decompensated cirrhosis (ascites, esophageal, varices, jaundice, encephalopathy)

☐ No contraindications to interferon (see guidelines)

☐ Contraindications to interferon: (list)

CURRENT OR PRIOR ANTI-VIRAL TREATMENT FOR HBV: (Circle one) No Yes

Drug(s) name and dose:

Start Date: Stop Date: Reason Stopped:

During/after prior treatment – HBV DNA: _____ Date: _____

Previous Treatment Response (circle one): Virologic Response / Failure / Breakthrough

Requested medication regimen:

Signature/Clinical Director:

INCLUDE COPIES OF THE FOLLOWING WITH THIS REQUEST

☐ CBC with diff (dated within 90 days) ☐ INR (dated within 90 days)

☐ Chem panel (dated within 90 days) ☐ Liver panel (dated within 90 days)

☐ Abdominal US or CT ☐ Liver Biopsy Report (if indicated)

☐ Hepatitis D serology ☐ TSH / Free T4 (if interferon tx)

☐ Hepatitis B serology – HBsAg, HBeAg, anti-HBe, and HBV DNA levels

☐ HCV Ab – if positive, HCV genotype and RNA viral load reports.

☐ HIV test – If HIV Ab +, include CD4, HIV viral load, and HAART regimen

PROCEDURE FOR SUBMITTING HBV TREATMENT REQUEST

- Complete/Scan Worksheet and all required documentation (see above). Save as pdf file.
- Attach to BEMR non-formulary request for Hepatitis B Treatment Algorithm.
- Requests for treatment of HBV and HCV co-infection should be requested as per Hepatitis C Treatment Algorithm.