Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

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Epidemiology

Hepatitis B virus (HBV) is the leading cause of chronic liver disease worldwide.1-5 Globally and in North America, approximately 10% of HIV-infected patients have evidence of chronic HBV infection.6-8

In countries with a low prevalence of endemic chronic HBV infection, the virus is transmitted primarily through sexual contact and injection drug use, whereas perinatal and early childhood exposures are responsible for most HBV transmission in higher prevalence regions.9 Although the general modes of transmission are similar to HIV, HBV is transmitted more efficiently than HIV.1,2 The risk of progression to chronic HBV infection varies with age and is 90% among those infected before 1 year of age, 20% to 50% among those infected at 1 to 5 years of age, and <5% among those infected as adults.9,10 Persons with HIV infection are at increased risk for developing chronic HBV infection.11 Genotypes of HBV (A–J) have been identified with different geographic distributions.12 Genotype A is most common among patients in North America and Western Europe.13

Clinical Manifestations

Acute HBV infection is asymptomatic in approximately 70%, and <1% of patients develop fulminant hepatic failure.3,14 When symptoms manifest, they may include right upper quadrant abdominal pain, nausea, vomiting, fever, and arthralgias with or without jaundice. HBV has an average incubation period of 90 days (range 60–150 days) from exposure to onset of jaundice and 60 days (range 40–90 days) from exposure to onset of abnormal liver enzymes. Most patients with chronic HBV infection are asymptomatic or have nonspecific symptoms, such as fatigue. Between 15% to 40% of people with chronic HBV infection will develop cirrhosis, hepatocellular carcinoma (HCC), or liver failure and up to 25% of people will die prematurely from complications of chronic HBV infection.15

Diagnosis

The Centers for Disease Control and Prevention, United States Preventive Services Taskforce, and the American Association for the Study of Liver Disease (AASLD) recommend screening for chronic HBV infection among HIV-infected patients.9,16,17 Initial testing should include serologic testing for surface antigen (HBsAg), hepatitis B core antibody (anti-HBc total), and hepatitis B surface antibody (anti-HBs). In acute infection, HBsAg can be detected 4 weeks (range 1–9 weeks) after exposure and anti-HBc immunoglobulin M is usually detectable at the onset of symptoms.

Chronic HBV infection is defined as persistent HBsAg detected on 2 occasions at least 6 months apart.9 Patients with chronic HBV infection should be further tested for HBV e-antigen (HBeAg), antibody to HBeAg (anti-HBe), and HBV DNA. Active disease, which can be HBeAg-negative or HBeAg-positive, can be distinguished from inactive disease by the presence of serum HBV DNA and persistent or fluctuating alanine transaminase (ALT) elevations.3 Patients whose past infection has resolved are HBsAg-negative with positive anti-HBs and/or anti-HBc, although cccDNA may remain in hepatocyte nuclei3,18 (with the patient becoming serum HBsAg-positive again) or HBV viremia may occur under severe immune suppression, as is seen with rituximab therapy or after stem cell transplant.19,20

The presence of an isolated anti-HBc test result usually signifies infection with HBV in the past with subsequent loss of anti-HBs and occurs in 7% to 19% of HIV-infected patients.21-25 Incidence of HBV viremia in HIV-infected patients with the isolated anti-HBc pattern ranges from 1% to 36%.21,23,26-28 The clinical significance of isolated anti-HBc is unknown21,25,28,30 but it may indicate chronic or, more likely, resolved infection in HIV-infected individuals.24,31,32 In a low-prevalence country such as the United States,
isolated anti-HBc may also represent a false-positive result.24,31,33 HIV-infected patients have a higher frequency of isolated anti-HBc, particularly those with underlying HCV coinfection.24,35,36

**Diagnosis HBV Disease Progression and the Role of Assessment of Liver Fibrosis**

Compared with HIV-uninfected individuals, those with HIV/HBV coinfection have higher levels of HBV viremia and lower likelihood of resolved infection following acute HBV infection.37 In HBV-monoinfected individuals, HBV DNA suppression, anti-HBe seroconversion (to anti-HBe-seronegativity), HBsAg loss, and acquisition of anti-HBs are all associated with a decreased incidence of cirrhosis, HCC,38-40 and improved survival.41-44 In comparison, the predictive value of these parameters in persons with HIV/HBV coinfection indicate they usually are more likely to have detectable HBeAg,37,45 lower rates of seroconversion to anti-HBe, and increased risk of HCC, liver-related mortality and morbidity.46,47

Chronic HBV infection is a dynamic disease with a number of phases that are associated with either active or inactive chronic hepatitis, and include: the immune tolerant phase (normal ALT, high HBV DNA), the immune active phase (HBeAg-positive or negative, detectable HBV DNA, elevated ALT), and the inactive hepatitis B phase (HBeAg-negative, anti-HBe, low or undetectable HBV DNA, normal ALT).15 Duration of disease phases is different in those who acquire infection as neonates and young children compared with those who acquire infection as adults. The immune tolerant phase occurs primarily after perinatal infection. Clinicians should be knowledgeable about these phases for HBV-monoinfected patients to determine who needs treatment and who should be monitored (see AASLD guidelines 2015 https://www.aasld.org/sites/default/files/guideline_documents/hep28156.pdf). In HIV/HBV coinfection, monitoring and treatment are also focused on the simultaneous treatment of both viruses.

Persons with anti-HBe seroconversion and HBeAg loss usually transition into the inactive hepatitis B phase.15 This transition can be spontaneous or associated with effective HBV treatment. In some instances, increased levels of ALT may precede a decline in HBV DNA that is accompanied by anti-HBe seroconversion, that is, loss of HBeAg and development of anti-HBe.48 However, such spontaneous HBeAg conversion rates in HIV-infected patients appear to be lower than in monoinfected patients. The inactive chronic HBV state is characterized by a negative HBeAg, normal ALT levels, and an HBV DNA level <2,000 IU/mL.48 Patients in the inactive state remain at risk of reactivation of HBV and development of HCC, but the risk is lower than for individuals with active HBV replication. In any patient, the re-emergence of abnormal liver enzyme tests may reflect HBeAg-negative chronic HBV disease, a result of mutations in the basal core and precore promoter regions.15 Although levels of HBV DNA are usually lower, HBeAg-negative patients experience an unrelenting but fluctuating course of disease progression, with fluctuating HBV DNA levels.17 Patients in the inactive phase still require HBeAg, ALT, and HBV DNA monitoring. Persistent low-level serum ALT abnormalities may be associated with significant liver disease, although normal ALT levels also may be seen in the setting of cirrhosis.17

Patients diagnosed with chronic HBV infection should be linked to care and have a complete history and physical examination for signs of cirrhosis or HCC. In addition, patients should receive a complete blood count, ALT, aspartate aminotransferase (AST), albumin, total bilirubin, alkaline phosphatase, INR, HBeAg/ anti-HBe, HBV DNA, anti-HAV to determine need for vaccination, abdominal ultrasound, and liver fibrosis assessment at initial visit, and be monitored every 6 to 12 months.3 Patients with chronic HBV are at increased risk of HCC and therefore require HCC surveillance every 6 months in those who are cirrhotic, and in individuals in the following groups who are at increased risk of disease progression: Asian males older than age 40; Asian females older than age 50; and males older than age 20 who are from sub-Saharan Africa.49 Patients co-infected with HIV are at increased risk of HCC,50 and some experts perform HCC screening on HIV/HBV infected patients over 40 years of age. Assessment of the patient’s liver fibrosis stage is important to or serum biomarkers. There is increasing evidence that noninvasive methods (i.e., elastography and serum markers) to evaluate liver fibrosis can be used to determine fibrosis in HBV.51 The decision to perform a liver biopsy should be individualized and is rarely necessary.3
Preventing Exposure

HBV is primarily transmitted through percutaneous or mucosal exposure to infectious blood or body fluids. Therefore, HIV-infected patients should be counseled about transmission risks for HBV and encouraged to avoid behaviors associated with such transmission (AIII). Such counseling should emphasize sexual transmission as well as the risks associated with sharing needles and syringes, tattooing, or body-piercing.

Preventing Disease

All family members and sexual contacts of patients with HBV should be screened and all susceptible contacts should receive HBV vaccines regardless of whether they are HIV-infected (AII). Hepatitis B vaccination is the most effective way to prevent HBV infection and its consequences. All HIV-infected patients susceptible to HBV should receive hepatitis B vaccination (AII) or with the combined hepatitis A and hepatitis B vaccination (AII).

All HIV-infected patients should be screened for hepatitis B, and screening should include HBsAg, anti-HBs, and anti-HBc.9,16,17 A patient who is seropositive for anti-HBc and anti-HBs has resolved infection and does not need vaccination. Similarly, the presence of anti-HBs alone at levels ≥10 IU/mL is consistent with seroprotection, usually from vaccination,52 and no further vaccinations are required.53 The interpretation is less clear in individuals with the isolated anti-HBc pattern (HBsAg negative, anti-HBc positive, anti-HBs negative). Aside from false-positive results, this pattern may signify infection in the distant past with subsequent loss of anti-HBs.54 Most HIV-infected patients with isolated anti-HBc are HBV DNA-negative and not immune to HBV infection;55 therefore, routinely checking HBV DNA is not recommended. However, they should be vaccinated with one standard dose of HBV vaccine and anti-HBs titers should be checked 1 to 2 months afterward. If the anti-HBs titer is >100 IU/mL, no further vaccination is needed, but if the titer is <100 IU/mL, a complete series of HBV vaccine (single-dose or double-dose) should be completed followed by anti-HBs testing (BII).57 The cut-off of 100 IU/mL is used in this situation because one study demonstrated that patients with isolated anti-HBc who achieved a titer of 100 IU/mL after a booster dose maintained an anti-HBs response for >18 months compared to only 23% of those who achieved a titer of 10 to 100 IU/mL.55

The magnitude and duration of immunogenicity to hepatitis B vaccination in HIV-infected adults is significantly lower than in HIV-seronegative healthy adults.53,56-58 Factors associated with poor response to vaccine include low CD4 cell counts,56,59-64 presence of detectable HIV RNA,60,64,65 coinfection with HCV, occult HBV infection, and the general health status of the host.23,36,66-70 Based on these data, early vaccination is recommended in HIV-infected patients before CD4 cell counts decline to <350 cells/mm³ (AII). However, in patients who present to care at a lower CD4 cell count, vaccination should not be deferred until CD4 counts increase to >350 cells/mm³ because some HIV-infected patients with CD4 counts <200 cells/mm³ do respond to vaccination (AII). Of HIV-infected persons who did not respond (anti-HBs titers <10 IU/mL) to a primary 3-dose vaccine series, 25% to 50% responded to an additional vaccine dose, and 44% to 100% responded to a 3-dose revaccination series.71-74 As a result, HIV-infected persons who did not respond to a complete hepatitis B vaccination series should receive a 3-dose revaccination series (BIII),53 although some specialists might delay revaccination until after a sustained increase in CD4 cell count is achieved on ART (CIII). Two randomised controlled trials have shown that using 4 doses of double-dose vaccine produces higher anti-HBs titers than 3 doses of standard-dose vaccine.75,76 and 1 study also showed a higher overall response rate.78 Some specialists consider that this approach—4 vaccinations—improves immunologic response in HIV-infected individuals either as an initial vaccination schedule or in patients who are non-responders (BII). However, whether a schedule of 4 double-dose vaccines is superior to 4 single-dose or 3 double-dose vaccines is still unclear. Another study suggested that HIV-infected patients with CD4 counts >350 cells/mm³ had improved responses when vaccinated with a double-dose vaccine on a 0-, 1-, and 6-month schedule.49 Although other approaches have been investigated to improve responses, such as the use of combined hepatitis A and B vaccine77,78 or the use of adjuvants,79 data are insufficient to support a broad recommendation for these approaches at this time. While additional studies are needed to determine optimal vaccination strategies in patients with advanced immunosuppression, the vaccination series for HBV should...
be initiated at first visit regardless of CD4 cell count.\textsuperscript{80}

**Preventing Other Liver Diseases**

HAV vaccination is recommended for all HAV antibody-negative patients who have chronic liver disease;\textsuperscript{3} for patients who are injection and non-injection drug users; and for men who have sex with men (AIIII). Responses to the HAV vaccine are reduced in HIV-infected patients with CD4 counts <200 cells/mm\textsuperscript{3}.\textsuperscript{81,82} Antibody response should be assessed 1 month after vaccination is complete. If HAV antibody immunoglobulin (HAV Ab IgG) is negative, patients should be revaccinated when the CD4 cell count is >200 cells/mm\textsuperscript{3} (BIIII).

Patients with chronic HBV disease should be advised to avoid alcohol consumption (AIIII).

**Treating Disease**

The ultimate treatment goals in HIV/HBV coinfection are the same as for HBV monoinfection: to prevent disease progression and to reduce HBV-related morbidity and mortality. HIV/HBV coinfected patients should receive tenofovir disoproxil fumarate (TDF)- or tenofovir alafenamide (TAF)-based ART.

**Special Considerations with Regard to Starting ART**

**Preferred Regimen**

The Department of Health and Human Services guidelines for treatment of HIV infection recommend the fixed-dose coformulation of tenofovir/emtricitabine or abacavir/lamivudine as recommended nucleoside reverse transcriptase inhibitor (NRTI) backbones for ART-naive patients\footnote{https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-ART-guidelines/25/hbv-hiv} regardless of CD4 cell count or need for HBV treatment.\textsuperscript{83} Because both tenofovir and emtricitabine have anti-HBV activity, the combination is also the treatment of choice for HIV/HBV coinfected patients (AIIII) regardless of CD4 (AI) and HBV DNA level (AIII). TDF and TAF are both active against wild-type and lamivudine-resistant HBV strains. Studies in HBV/HIV-coinfected patients (most of them carrying lamivudine-resistant HBV) have shown, on average, 4 log\textsubscript{10} declines in HBV DNA levels.\textsuperscript{84-89} TDF and TAF have a high genetic barrier for development of resistance mutations (AI).\textsuperscript{3,90}

The decision to use TAF/emtricitabine versus TDF/emtricitabine should be based upon creatinine clearance (CrCl) and an assessment of risk for nephrotoxicity and for acceleration of bone loss. In patients with CrCl $\geq 60$ mL/min, either TAF/emtricitabine or TDF/emtricitabine can be considered. In patients with a CrCl 30 to 59 mL/min, a TAF/emtricitabine regimen is preferred. Currently approved TAF/emtricitabine-containing regimens for the treatment of HIV infection are not recommended for use in patients with CrCl <30 mL/min, so in those situations renally dosed entecavir with a fully suppressive ART regimen is recommended (BIII). In HIV/HBV-coinfected patients, switching from a primarily TDF-based ART regimen to single tablet TAF/emtricitabine/elvitegravir/cobicistat maintained or achieved HBV suppression, with improved estimated glomerular filtration rate (eGFR) and bone turnover markers.\textsuperscript{91} In HBV-monoinfected patients, TAF 25 mg was non-inferior to TDF 300 mg based on the percentage of patients with HBV DNA levels <29 IU/mL at 48 weeks of therapy (94\% for TAF vs. 93\% for TDF; $P = 0.47$). Patients on TAF also experienced significantly smaller mean percentage decreases from baseline in hip and spine bone mineral density at 48 weeks compared to patients receiving TDF ($P < 0.0001$). Furthermore, the median change in eGFR from baseline to 48 weeks also favored TAF ($P = 0.004$).\textsuperscript{92,93}

Chronic administration of lamivudine or emtricitabine as the only active drug against HBV should be avoided because of the high rate of selection of HBV drug-resistance mutations (AI).

Patients receiving ART should continue HBV therapy indefinitely (AIIII) because relapses after response occur, particularly in those with lower CD4 cell counts.\textsuperscript{3} Additionally, discontinuation of nucleos(t)ide analogue therapy is associated with a HBV flare in approximately 30\% of cases,\textsuperscript{84,95} with loss of the benefit accrued from previous anti-HBV treatment and possible decompensation of liver disease.\textsuperscript{56,96-98} If anti-HBV
therapy and ART must be discontinued, transaminase levels should be monitored every 6 weeks for 3 months and every 3 to 6 months thereafter. If a flare occurs, anti-HBV therapy and ART should be reinstated and can be potentially lifesaving (AIII).

**Alternative Treatment of HBV in HIV-Infected Patients Who Are Not Receiving ART**

HBV and HIV co-treatment is essential and recommended. There are few options that can be used for treatment of HBV alone in the coinfected patient. Directly acting HBV drugs must not be given in the absence of a fully suppressive ART regimen (AII). Only pegylated interferon-alfa-2a monotherapy may be considered for HIV/HBV-coinfected patients who are not receiving ART and who meet criteria for HBV therapy as described (see AASLD 2015 guidelines) (CIII).

Some HIV/HBV-coinfected patients also have chronic HCV infection. There is scant information on the treatment of HBV/HCV/HIV co-infection. Because patients with HBV, HCV, and HIV appear to have accelerated progression of liver fibrosis, higher risk of HCC, and increased mortality, attempts should be made to treat both hepatitis viruses, if feasible. If ART is administered, then anti-HBV therapy must be included as part of the regimen (as above) and anti-HCV therapy can be introduced as needed (see Hepatitis C Infection) (CIII). As HBV reactivation can occur during treatment for HCV with directly active agents (DAAs) in the absence of HBV-active drugs, all HIV-HBV-coinfected patients who will be treated for HCV should be on HBV-active ART at the time of HCV treatment initiation (AII).

**Regimens that are Not Recommended**

Tenofovir (TDF and TAF), entecavir, lamivudine, emtricitabine, and telbivudine should not be used alone in the absence of a fully suppressive ART regimen because of the development of HIV-resistance mutations (AI). Other HBV treatment regimens include adefovir in combination with lamivudine or emtricitabine or telbivudine in addition to a fully suppressive ART regimen; however, data on these regimens in persons with HIV/HBV coinfection are limited. In addition, compared to TDF or TAF or entecavir, these regimens are associated with higher incidence of toxicity, including renal disease with adefovir and myopathy and neuropathy with telbivudine, as well as higher rates of HBV treatment failure. Therefore, Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents (the Panel) does not recommend these drugs/regimens for HIV/HBV coinfected patients (AI).

**Monitoring of Response to Therapy and Adverse Events (Including IRIS)**

In order to prevent emergence of drug-resistant variants and evaluate response for patients on nucleos(t)ide analogues, treatment response should be monitored by testing for HBV DNA at 3 to 6 month intervals (AI). Treatment responses are defined as follows:

- **Primary non-response** is an HBV DNA <1 log₁₀ decline at 12 weeks.
- **A complete virologic response** is an undetectable HBV DNA by real-time polymerase chain reaction at 24 to 48 weeks.
- **A partial virologic response** is ≥1 log₁₀ decline but still detectable HBV DNA at 24 weeks.
- **A maintained virologic response** is a response that continues while on therapy, and a sustained virologic response is one that is still present 6 months after stopping therapy.

For patients who are HBeAg-positive, loss of HBeAg is also a measure of virologic response. Other markers that indicate treatment success include improvement in liver histology based on biopsy, transient elastography or noninvasive markers, normalization of serum aminotransferases, and, in those with loss of HBeAg, the development of anti-HBe. Sustained loss of HBsAg is considered by some to be a complete response; however, this desirable serologic response is uncommon (<1% per year).

Major toxicities of IFN-alfa (pegylated or standard) are flu-like symptoms such as fatigue, pyrexia, myalgia, headache, and psychiatric reactions including depression, insomnia, irritability, anxiety. Other common toxicities include flu-like symptoms, headache, nausea, vomiting, pruritis, insomnia, depression, hypoactive sexual desire, weight loss, cough, sinusitis, pyrexia, and myalgia. In addition, IFN-alfa may cause significant hematologic toxicity.
reactions are anorexia, nausea and vomiting, diarrhea, arthralgias, injection site reactions, alopecia, and pruritus.3

**Nucleos(t)ide Analogs**

Renal toxicity with TDF, including increased serum creatinine or renal tubular dysfunction, has been observed; both are more frequent in HIV-infected patients with underlying renal insufficiency, older patients, or those treated for prolonged periods.111 These biochemical changes are usually reversible on discontinuation of TDF or change to TAF.112

Electrolytes and serum creatinine levels should be evaluated at baseline and every 3 to 6 months, and urinalysis every 6 months. Because renal toxicity may be reversible, alternative anti-HBV therapy should be used if renal toxicity occurs (AI). If TDF is used in patients with baseline renal insufficiency, either a dose adjustment as noted in the package insert or a change to TAF with appropriate dose adjustment is required.112 All nucleos(t)ides must be dose adjusted for renal dysfunction (see package insert) and TAF is not recommended in patients with CrCl <30 mL/min (AI).

Entecavir-associated lactic acidosis is uncommon but has been reported in HBV-monoinfected patients with advanced cirrhosis.113

**Immune Reconstitution Inflammatory Syndrome (IRIS)**

Return of immune competence after ART (or after steroid withdrawal or chemotherapy) can lead to reactivation of HBV-associated liver disease. Any immune reconstitution can lead to a rise in serum aminotransferases, so called “hepatitis flare,”114 which constitutes IRIS in HIV/HBV-coinfected persons. IRIS may manifest when serum aminotransferase levels dramatically increase as CD4 cell counts rise within the first 6 to 12 weeks after starting ART, with signs and symptoms characteristic of acute hepatitis and without another cause for the flare.115,116 After introduction of ART, serum ALT levels should be monitored closely; some experts recommend ALT testing at 6 and 12 weeks, then every 3 to 6 months thereafter. Any association between abnormal aminotransferases and clinical jaundice or synthetic dysfunction (elevated International Normalized Ratio and low serum albumin) should prompt consultation with a hepatologist (CI).112

Flares are worse in patients with more severe liver disease, especially in those with cirrhosis.117 Distinguishing between ART-associated hepatotoxicity or other causes of hepatitis (acute hepatitis A, C, D, or E virus, Epstein-Barr virus, herpes simplex virus, cytomegalovirus) and IRIS may be difficult. ART-associated hepatotoxicity may be dose-dependent or idiosyncratic. The risk of hepatotoxicity has been consistently associated with elevated pre-ART aminotransferases (ALT, aspartate aminotransferase) and the presence of HBV or HCV coinfection before initiation of ART. In HIV/HBV coinfection, baseline elevated HBV DNA levels are predictive of hepatotoxicity.118-121 However, despite this increased risk of hepatotoxicity in the setting of HCV or HBV coinfection, most (80% to 90%) coinfected patients do not have hepatotoxicity,122 and clinically significant hepatotoxicity (elevated direct bilirubin) is rare; aminotransferase levels return to baseline in most cases, even if the offending medication is continued.123,124 Therefore, discontinuing ART usually is not necessary in the presence of hepatotoxicity unless patients have symptoms of hypersensitivity (e.g., fever, lymphadenopathy, rash), symptomatic hepatitis (i.e., nausea, vomiting, abdominal pain, or jaundice), or elevations in serum aminotransferase levels >10 times the upper limit of normal. However, the development of jaundice is associated with severe morbidity and mortality and the offending drug(s) should be discontinued (AIII).125

The major problem in managing ALT flares is distinguishing between drug-induced liver injury and HBV reactivation, IRIS, emergence of HBV drug resistance, and HBeAg seroconversion. In drug-induced liver injury, determining the offending medication also can be challenging. A review of the medication history and testing for serum HBV DNA, HBeAg, HIV RNA levels, and CD4 cell count can help distinguish between these possibilities. Liver histology also may help to differentiate drug toxicity (e.g., increased eosinophils) from viral hepatitis (e.g., portal inflammation). If the flare is severe or HBV drug resistance is suspected, then consultation with a hepatologist is recommended. Other causes of abnormal liver tests should be sought, including use of drugs or alcohol, other viral hepatitis infections (hepatitis A, C, D, and E), and nonalcoholic fatty liver disease.
Managing Treatment Failure

HBV treatment failure on nucleos(t)ide analogues is defined as primary nonresponse after 12 weeks of therapy in patients who consistently adhere to HBV therapy or an increase in HBV DNA levels greater than 1 log₁₀ above nadir. In either situation, treatment failure is generally due either to drug-resistant HBV if on lamivudine/emtricitabine monotherapy or noncompliance.³ If drug-resistant HBV is present, a change in treatment needs to be made (AII). Distinct resistance patterns exist with the different groups of anti-HBV drugs: the L-nucleosides (telbivudine, lamivudine/emtricitabine); acyclic phosphonates/nucleotides (adefovir and tenofovir); and D-cyclopentane (entecavir), which shares some resistance mutations with the L-nucleosides. Many experts will obtain HBV-resistance testing because it has value in distinguishing between noncompliance and resistance, evaluating patients with unclear prior drug history, assessing different adefovir-resistance pathways, and predicting the level of resistance to entecavir.¹²⁶ However, TDF has not been associated with clinical resistance, although slow response has been noted as discussed above. Addition of entecavir has led to suppression of HBV DNA in these slow-to-respond patients.¹²⁷

Lamivudine (or emtricitabine) monotherapy for HBV leads to emergence of drug-resistant HBV increasingly with time on treatment and should not be used as the sole anti-HBV drug in an ART regimen (AII). The rate of development of lamivudine-resistance is approximately 20% per year in HIV/HBV-coinfected patients treated with lamivudine alone.¹²⁸ If lamivudine resistance is suspected or documented, TDF or TAF should be added (BIII).¹²⁹⁻¹³¹ Because patients with lamivudine-resistant HBV will have cross-resistance to the other L-nucleosides (telbivudine, emtricitabine), and partial resistance to entecavir, those agents should not be used in patients found to have lamivudine-resistant HBV (AI).¹³² All nucleoside analogs must be dose adjusted for renal insufficiency per package insert guidelines and Table 8.

If treatment failure occurs on entecavir, then the only rational choice is replacement with TDF or TAF (with or without emtricitabine) because of the cross resistance that occurs with L-nucleosides (telbivudine, lamivudine, emtricitabine) (AI).

Patients whose HBV initially fails to respond to pegylated IFN-alfa can be given nucleos(t)ide analogue therapy following the recommendations previously described (CIII).

If treatment failure with TDF or TAF occurs, particularly in lamivudine- or emtricitabine-experienced patients, then entecavir may be an active alternative, especially if higher doses of entecavir can be used (CIII).

However, documented in vivo resistance to tenofovir has not yet been reported. Declines in HBV DNA levels can be slow, especially when pretherapy HBV DNA levels are very high. HBV DNA levels usually drop quickly in patients who are receiving an HBV drug with high potency and a high genetic barrier to resistance, such as tenofovir, but they may still be detectable for some years.³ Thus, in a compliant patient with a partial virologic response to tenofovir, the drug should be continued with monitoring of HBV DNA levels (BII). Improvement of response with the addition of entecavir has been reported, but whether such “intensification therapy” is required is unclear.¹²⁷ Nonetheless, patients on drugs that are less potent or that have a lower barrier to resistance, such as adefovir or L-nucleosides, who have partial virologic responses (<2 log₁₀ drop in HBV DNA levels from baseline at 24 weeks) should be switched to a more potent regimen such as tenofovir (TDF or TAF) with emtricitabine or entecavir (if treatment-naive) because of the risk of development of drug resistance to the initial therapy (BII).

Special Considerations for Treating End-Stage Liver Disease

Treatment of end-stage liver disease in HIV/HBV-coinfected patients should be managed as it is in HIV-seronegative patients. These patients should be referred to a hepatologist (CI). As with monoinfected patients, interferon-alfa is contraindicated in end-stage liver disease (AI), but nucleoside analogs are safe and efficacious (AI).¹²⁸,¹³³,¹³⁴ All patients with ascites should undergo paracentesis to exclude spontaneous bacterial peritonitis (SBP).¹³⁵,¹³⁶ Management of ascites includes sodium restriction (<2 g/day) and the recommended diuretic regimen is spironolactone combined with furosemide (ratio of 40 mg furosemide: 100 mg spironolactone) (AI). All patients who have had SBP and those with ascites total protein <1 g/dL should

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receive prophylaxis against SBP with administration of oral antibiotics such as norfloxacin (400 mg/day), ciprofloxacin (750 mg/week), or trimethoprim-sulfamethoxazole (one double-strength tablet/day) (AI).137

Esophagogastroduodenoscopy (EGD or upper endoscopy) should be performed on all patients with cirrhosis at the time of diagnosis and then every 1 to 2 years to identify substantial gastroesophageal varices (see AASLD guidelines). Patients with varices require non-selective beta blockers, such as nadolol or propranolol, that are the mainstay of both primary and secondary prevention of variceal hemorrhage. Esophageal variceal banding is another preventive option, particularly for those who cannot tolerate beta blockers. Hepatic encephalopathy is treated with a 40-g protein diet and the use of non-absorbable disaccharides such as lactulose and/or non-absorbable antibiotics such as rifaximin.3

Patients with HBV-related cirrhosis are at increased risk of HCC138 and should be screened every 6 to 12 months with imaging studies, as recommended in HBV monoinfection (AI).3 Choice of imaging (ultrasound, computed tomography, or magnetic resonance imaging) depends upon the expertise of the imaging center and whether the patient has cirrhosis. Usually ultrasound is the initial preferred imaging modality.3 HCC can occur without cirrhosis and HIV coinfection appears to increase the risk of HCC in HBV,139 but more frequent screening in HIV/HBV coinfection has not been studied, and so cannot be recommended due to insufficient evidence. HIV/HBV-coinfected patients with decompensated liver disease and/or early HCC are candidates for liver transplantation. HIV infection is not a contraindication to organ transplantation with the use of effective ART.140 Because transplantation does not cure HBV infection, post-transplant hepatitis B immune globulin (HBIG) and HBV treatment is required (AII).

Preventing Recurrence

As previously indicated, most patients should continue HBV therapy (with the exception of pegylated IFN) indefinitely (CIII) because relapses after response occur, particularly in those with lower CD4 cell counts, and because reports of hepatitis flares after discontinuation of 3TC in those who have not reached treatment endpoints can be extrapolated to other HBV-active drugs.96-98

Special Considerations During Pregnancy

HIV-infected pregnant women should be screened for HBsAg, anti-HBc, and anti-HBs (AI).141 Those who are both HBsAg and anti-HBs-negative should be offered vaccination against HBV. Treatment of symptomatic acute HBV infection during pregnancy should be supportive, with special attention given to maintaining blood glucose levels and normal clotting status. Risk of pre-term labor and delivery may increase with acute HBV infection. High maternal HBV DNA levels correlate strongly with perinatal HBV transmission, including failures of HBV passive-active immunoprophylaxis.142-145 Perinatal guidelines are available at https://aidsinfo.nih.gov/guidelines/html/3/perinatal-guidelines/159/hiv-hepatitis-b-virus-coinfection.

ART including drugs active against both HIV and HBV is recommended for all individuals with HIV/HBV coinfection, including pregnant women (AIII). TDF given in combination with 3TC or FTC is the preferred dual-NRTI backbone for pregnant women with chronic HBV infection (AIII).146 There are no data on use of TAF in pregnancy, therefore it is not recommended.147 Once HBV therapy with nucleos(t)ide analogs is initiated, treatment is recommended to be continued indefinitely.

Cases of adverse events during pregnancy to any of the ARV or HBV drugs listed should be reported to the Antiretroviral Pregnancy Registry (800-258-4263; http://www.apregistry.com). As of January 2017, 4763 cases of pregnancy outcomes after first-trimester exposures to lamivudine have been reported to the Antiretroviral Pregnancy Registry, with no indication of an increased risk of birth defects after exposure (http://www.apregistry.com/forms/interim_report.pdf). Lamivudine has been well tolerated by pregnant women and is a recommended NRTI for use in pregnancy (AII).146 Similarly, no increase in birth defects has been noted in 2,523 cases of first-trimester exposure to emtricitabine. Emtricitabine is an alternative NRTI for use in pregnancy (http://www.apregistry.com) (BII).148 A total of 3229 cases of first-trimester exposure to tenofovir have been reported to the Antiretroviral Pregnancy Registry with no increase in birth defects.
noted. In a large HIV PMTCT trial examining different antenatal ART regimens, TDF/emtricitabine + lopinavir/ritonavir was associated with a higher infant mortality rate at 14 days when compared to zidovudine/lamivudine + lopinavir/ritonavir, 4.4% vs. 0.06% respectively. The mechanisms for this finding are unclear.149 Other studies of tenofovir use in pregnancy have not suggested increased risk of adverse pregnancy outcomes.150

Several other ART agents with activity against HBV, including adefovir and telbivudine, have been evaluated and found not to be teratogenic in animals, but experience in the first trimester with these agents in human pregnancy is limited. These drugs could be included in a regimen during pregnancy if other options are inappropriate. Each of these agents should be administered only in combination with a fully suppressive ART regimen because of the risk of development of ART drug resistance. Entecavir was associated with skeletal anomalies in rats and rabbits, but only at high, maternally-toxic doses (package insert). Data on use of entecavir and adefovir in human pregnancy are not available. Telbivudine given to HBV-seropositive, HIV-seronegative women during the second and third trimester was well-tolerated with no birth defects observed.151 Cases of exposure during pregnancy to any of the ART and HBV drugs listed should be reported to the Antiretroviral Pregnancy Registry (800-258-4263; http://www.apregistry.com).

IFN-alfa formulations are not recommended for use in pregnancy. Although these agents are not teratogenic, they are abortifacient at high doses in monkeys and should not be used in pregnant women because of their direct antigrowth and antiproliferative effects (AII).152

Infants born to HBsAg-positive women should receive hepatitis B immune globulin and hepatitis B vaccine within 12 hours of delivery (AI). The second and third doses of vaccine should be administered at 1 and 6 months of age, respectively (AI).

Recommendations for Preventing and Treating Hepatitis B Virus Infection (page 1 of 2)

Preventing HBV Infection

**Indications for HBV Vaccination:**
- Patients without chronic HBV infection or without immunity to HBV (anti-HBs <10 IU/mL) (AII)
- Patients with isolated anti-HBc (BII). Recommend 1-time dose followed by anti-HBs at 1-2 months. If the titer is >100 IU/mL, no further vaccination is needed, but if the titer is <100 IU/mL, a complete series of HBV vaccine (single-dose or double-dose) should be completed followed by anti-HBs testing (BII).
- Early vaccination is recommended before CD4 count falls below 350 cells/mm$^3$ (AII), as low CD4 count at time of vaccination has been associated with poor response to the vaccine.
- However, in a patient with low baseline CD4 cell count, vaccination should not be deferred until CD4 reaches >350 cells/mm$^3$, as some patients with CD4 <200 cells/mm$^3$ do respond to vaccination (AII).

**Vaccination Schedule:**
- HBV vaccine IM (Engerix-B® 20 mcg/mL or Recombivax HB® 10 mcg/mL) at 0, 1, and 6 months (AII); or
- HBV vaccine IM (Engerix-B® 40 mcg/mL or Recombivax HB® 20 mcg/mL) at 0, 1, 2 and 6 months (BII); or
- Combined HAV and HBV vaccine (Twinrix®) 1 mL IM as a 3-dose series (at 0, 1, and 6 months) or as a 4-dose series (at days 0, 7, 21 to 30, and 12 months) (AII)
- Anti-HBs should be obtained 1–2 months after completion of the vaccine series. Anti-HBs <10 IU/mL will be considered as non-responders (BIII).

**For Vaccine Non-Responders:**
- Revaccinate with a second vaccine series (BIII).
- For patients with low CD4 count at the time of first vaccination series, some experts might delay revaccination until after a sustained increase in CD4 count with ART (CIII).

**Alternative Vaccine Dose for Non-Responders:**
- HBV vaccine IM (Engerix-B® 40 mcg/mL or Recombivax HB® 20 mcg/mL at 0, 1, 2 and 6 months (BII).
### Treating HBV Infection

**Indication for Therapy:**
- All HIV/HBV coinfected patients, regardless of CD4 count and HBV DNA level (AII). Therapy should be selected to treat both HIV and HBV infections (AIII).
- HBV reactivation can occur during treatment of HCV infection in the absence of HBV-active drugs; therefore, all HBV patients who will be treated for HCV should be on HBV-active ART at the time of HCV treatment initiation (AII).

**Preferred Therapy (CrCl ≥ 60 mL/min):**
- The ART regimen must include 2 drugs active against HBV, preferably with [TDF 300 mg plus (FTC 200 mg or 3TC 300 mg)] or [TAF (10 or 25 mg)\* plus FTC 200 mg] PO once daily (AIII).

**Preferred Therapy (CrCl 30–59 mL/min):**
- The ART regimen must include 2 drugs active against HBV, preferably with TAF (10 or 25 mg)\* + FTC 200 mg PO once daily (AIII).

**Preferred Therapy (CrCl < 30 mL/min):**
- A fully suppressive ART regimen without tenofovir should be used, with the addition of renally dosed entecavir to the regimen or
- ART with renally dose adjusted TDF and FTC can be used (BIII) when recovery of renal function is unlikely (see Table 7 for dosing recommendation for TDF and FTC or 3TC for patients with renal impairment). Guidance for TAF with CrCl < 30 not yet approved.

**Duration of Therapy:**
- Patients on treatment for HBV and HIV should receive therapy indefinitely (AIII).

**Alternative Therapy If the Patient Refuses ART:**
- Anti-HBV therapy is indicated for elevated ALT, and HBV DNA > 2000 IU/mL, significant liver fibrosis, advanced liver disease, or cirrhosis (AII).
- Peg-IFN-alfa 2a 180 mcg SQ once weekly for 48 weeks (CIII), or
- Peg-IFN- alfa 2b 1.5 mcg/kg SQ once weekly for 48 weeks (CIII)
- Directly acting HBV drugs (such as 3TC, FTC, TAF, TDF, entecavir, adefovir, and telbivudine) must not be given in the absence of a fully suppressive ART regimen to avoid selection of drug resistant HIV (AII).

### Other Considerations:
- Hepatitis A vaccination is recommended for all HAV antibody-negative patients who have chronic liver disease, are men who have sex with men, or who are injection drug users (AIII).
- Antibody responses to HAV should be assessed 1 month after completion of vaccination series. If HAV Ab IgG is negative, patients should be revaccinated when the CD4 count is > 200 cells/mm\(^3\) (BII).
- As patients with HBV/HCV/HIV coinfection appear to have accelerated liver fibrosis progression, high risk of HCC, and increased mortality, treatment for both HBV and HCV infection should be initiated, if feasible.
- When changing ART regimens, it is crucial to continue agents with anti-HBV activity (BIII).
- If anti-HBV therapy must be discontinued, serum transaminase levels should be monitored every 6 weeks for 3 months, then every 3 to 6 months thereafter.
- If a hepatic flare occurs after drug discontinuation, HBV therapy should be re-instituted, as it can be potentially lifesaving (AIII).

\* TAF 10 mg dose is part of a combination tablet with elvitegravir/cobicistat/TAF/FTC; for use with other ART drugs, without cobicistat boosting, TAF dose is 25 mg

**Key to Acronyms:**
- 3TC = lamivudine; ab = antibody; anti-HBs = hepatitis B surface antibody; ALT = alanine transferase; ART = antiretroviral therapy; CD4 = CD4 T lymphocyte cell; FTC = emtricitabine; HAV = hepatitis A virus; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; IFN = interferon; IgG = immunoglobulin; IM = intramuscular; PO = orally; SQ = subcutaneous; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate
References


Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

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