

# Hepatitis B Virus Infection (Last updated November 13, 2018; last reviewed October 13, 2021)

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**NOTE: Update in Progress**

## Epidemiology

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

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.<sup>9</sup> Although the general modes of transmission are similar to those for HIV, HBV is transmitted more efficiently than HIV.<sup>1,2</sup> The risk of progression to chronic HBV infection varies with age and is 90% among those infected before 1 year of age, 25 to 50% among those infected at 1 to 5 years of age, and <5% among those infected as adults.<sup>9,10</sup> Persons with HIV infection are at increased risk for developing chronic HBV infection.<sup>11</sup> Genotypes of HBV (A–J) have been identified, and their geographic distributions differ.<sup>12</sup> Genotype A is most common among patients in North America and Western Europe and genotypes B and C among patients from Asia.<sup>13</sup>

## Clinical Manifestations

Acute HBV infection is asymptomatic in approximately 70% of patients, and <1% of patients develop fulminant hepatic failure.<sup>3,14</sup> 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.<sup>15</sup>

## Diagnosis

The Centers for Disease Control and Prevention, the United States Preventive Services Taskforce, and the American Association for the Study of Liver Disease (AASLD) recommend testing patients with HIV infection for chronic HBV.<sup>9,16,17</sup> Initial testing should include serologic testing for surface antigen (HBsAg), hepatitis B core antibody (anti-HBc total), and hepatitis B surface antibody (anti-HBs) (**AI**). 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.<sup>9</sup> 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.<sup>3</sup> Patients whose past infection has resolved are HBsAg-negative with positive anti-HBs and/or anti-HBc, although covalently closed circular DNA (cccDNA) may remain in hepatocyte nuclei.<sup>3,18</sup> With cccDNA in hepatocyte nuclei, a patient with severe immune suppression, such as seen with rituximab therapy or after stem cell transplant, may become serum HBsAg-positive again with HBV viremia.<sup>19,20</sup>

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 patients with HIV infection.<sup>21-25</sup> Incidence of HBV viremia in patients with HIV infection and isolated anti-HBc ranges from 1% to 36%.<sup>21,23,26-28</sup> The clinical

significance of isolated anti-HBc is unknown<sup>21,25,28-30</sup> but in individuals with HIV infection, it may indicate chronic or, more likely, resolved HBV infection.<sup>24,31,32</sup> In a low-prevalence country such as the United States, isolated anti-HBc may also represent a false-positive result.<sup>24,31,33,34</sup> Patients with HIV infection have a higher frequency of isolated anti-HBc, particularly those with underlying HCV coinfection.<sup>24,35,36</sup>

### ***Diagnosing HBV Disease Progression and the Role of Assessment of Liver Fibrosis***

Compared with individuals with HBV monoinfection, those with HIV/HBV coinfection have higher levels of HBV viremia and lower likelihood of resolved infection following acute HBV infection.<sup>37</sup> In individuals with HBV monoinfection, 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,<sup>38-40</sup> and improved survival.<sup>41-44</sup> In comparison, persons with HIV/HBV coinfection are usually more likely to have detectable HBeAg,<sup>37,45</sup> lower rates of seroconversion to anti-HBe, and increased risk of HCC and liver-related mortality and morbidity.<sup>46,47</sup>

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 [upper limits of normal 19-25 U/L for women and 29-44 U/L for men], HBeAg-positive, 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 positive, low or undetectable HBV DNA, normal ALT).<sup>15</sup> Duration of disease phases is different in those who acquire infection as neonates and young children than in those who acquire infection as adults. The immune tolerant phase occurs primarily after perinatal infection. Clinicians should be knowledgeable about these phases in patients with HBV monoinfection to determine who needs treatment and who should be monitored (see AASLD guidelines 2018 <https://aasldpubs.onlinelibrary.wiley.com/doi/10.1002/hep.29800>). 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.<sup>15</sup> 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.<sup>48</sup> However, such spontaneous HBeAg conversion rates appear to be lower in patients with HIV/HBV coinfection than in patients with HBV monoinfection. The inactive chronic HBV state is characterized by a negative HBeAg, normal ALT levels, and an HBV DNA level <2,000 IU/mL.<sup>48</sup> 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.<sup>15</sup> Although levels of HBV DNA are usually lower, patients who are HBeAg-negative experience an unrelenting but fluctuating course of disease progression, with fluctuating HBV DNA levels.<sup>17</sup> 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.<sup>17</sup>

When chronic HBV infection is diagnosed, patients should be linked to care and have a complete history and physical examination for signs of cirrhosis or HCC. In addition, patients should have a complete blood count, ALT, aspartate aminotransferase (AST), albumin, total bilirubin, alkaline phosphatase, international normalized ratio (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.<sup>3</sup> Patients with chronic HBV infection are at increased risk of HCC; therefore, HCC surveillance every 6 months is required for patients who are cirrhotic, and for 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.<sup>49</sup> Patients with HIV/HBV coinfection are at increased risk of HCC,<sup>50</sup> and some experts screen patients with HIV/HBV coinfection over 40 years of age for HCC. Assessment of the patient's liver fibrosis stage is important. 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

infection.<sup>51</sup> The decision to perform a liver biopsy should be individualized and is rarely necessary.<sup>3</sup>

## Preventing Exposure

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

## Preventing Disease

All family members and sexual contacts of patients with HBV infection should be tested, and all susceptible contacts should receive HBV vaccines regardless of whether they have HIV infection (**AII**). Hepatitis B vaccination is the most effective way to prevent HBV infection and its consequences. All patients with HIV infection who are susceptible to HBV infection should receive hepatitis B vaccination with one of the available vaccines (see below) (**AII**) or with the combined hepatitis A and hepatitis B vaccine (**AII**).

All patients with HIV infection should be screened for hepatitis B, and screening should include HBsAg, anti-HBs, and anti-HBc.<sup>9,16,17</sup> 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  $\geq 10$  mIU/mL, after completion of the vaccine series, is consistent with seroprotection,<sup>52</sup> and no further vaccinations are required.<sup>53</sup> 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.<sup>54</sup> Most patients with HIV infection with isolated anti-HBc are HBV DNA-negative and not immune to HBV infection;<sup>36</sup> therefore, routinely checking HBV DNA is not recommended. However, such patients should be vaccinated with one standard dose of HBV vaccine and anti-HBs titers should be checked 1 to 2 months after vaccination. If the anti-HBs titer is  $>100$  mIU/mL, no further vaccination is needed, but if the titer is  $<100$  mIU/mL, a complete series of HBV vaccine should be completed followed by anti-HBs testing (**BII**).<sup>55</sup> The cut-off of 100 mIU/mL is used in this situation because one study demonstrated that 100% of patients with isolated anti-HBc who achieved a titer of 100 mIU/mL after a booster dose maintained an anti-HBs response for  $>18$  months as compared to only 23% of those who achieved a titer of 10 to 100 mIU/mL.<sup>55</sup>

Available adult single-antigen hepatitis B vaccines include two recombinant HBsAg vaccines (Engerix-B and Recombivax-HB) and a recombinant HBsAg vaccine conjugated to a cytosine phosphoguanine oligonucleotide (CpG 1018) adjuvant, which is a toll-like receptor (TLR) 9 agonist (Heplisav-B). The magnitude and duration of immunogenicity to hepatitis B vaccination with the recombinant vaccines in adults with HIV infection is significantly lower than in healthy adults who are HIV seronegative.<sup>53,56-58</sup> Factors associated with poor response to vaccine include low CD4 cell counts,<sup>56,59-64</sup> presence of detectable HIV RNA,<sup>60,64,65</sup> coinfection with HCV, occult HBV infection, and the general health status of the host.<sup>23,36,66-70</sup> Based on these data, early vaccination is recommended in patients with HIV infection before CD4 cell counts decline to  $<350$  cells/mm<sup>3</sup> (**AII**). However, in patients who present to care with a lower CD4 cell count, vaccination should not be deferred until CD4 counts increase to  $>350$  cells/mm<sup>3</sup> because some patients with HIV infection with CD4 counts  $<200$  cells/mm<sup>3</sup> do respond to vaccination (**AII**). Among persons with HIV infection who did not respond (anti-HBs titers  $<10$  mIU/mL) to a primary 3-dose vaccine series with a recombinant vaccine, 25% to 50% responded to an additional vaccine dose, and 44% to 100% responded to a 3-dose revaccination series.<sup>71-74</sup> As a result, persons with HIV infection who do not respond to a complete hepatitis B vaccination series with one of the recombinant vaccines should receive a 3-dose revaccination series (**BIII**),<sup>53</sup> although some specialists might delay revaccination until antiretroviral therapy (ART) results in a sustained increase in CD4 cell count (**CIII**). Two randomised controlled trials have shown that using 4 doses of double-dose of the recombinant vaccine produces higher anti-HBs titers than 3 doses of standard-dose vaccine,<sup>75,76</sup> and one study also showed a higher overall response rate.<sup>76</sup> Some specialists consider that

this approach—4 vaccinations—improves immunologic response in individuals with HIV infection either as an initial vaccination schedule or in patients who are non-responders (**BI**). 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 patients with HIV infection with CD4 counts  $>350$  cells/mm<sup>3</sup> had improved responses when vaccinated with a double-dose recombinant vaccine on a 0-, 1-, and 6-month schedule.<sup>59</sup> Although other approaches have been investigated to improve responses, such as the use of combined hepatitis A and B vaccine<sup>77,78</sup> data are insufficient to support a broad recommendation for these approaches at this time.

In four randomized-controlled trials, Heplisav-B was superior to 3 doses of [Engerix-B](#) in HIV-negative individuals.<sup>79-81</sup> In the largest trial, the protection rate was 95% for Heplisav-B and 81% for Engerix-B.<sup>81</sup> There was an increase in the number of cardiovascular events in the Heplisav-B group that was not statistically significant. The safety and efficacy of Heplisav-B in individuals with HIV infection has not been studied. If a two-dose vaccine is preferred, Heplisav-B is an option (**CIII**). If Hepisav-B is used, the vaccine should not be interchanged with either of the other recombinant vaccines for the second dose. If the previously administered vaccine is unknown, then the Advisory Committee on Immunization Practices provides [recommendations](#), which state that the two-dose vaccine series only applies when both doses are Hepisav-B. In other situations, three total doses of vaccine should be given.

## Preventing Other Liver Diseases

HAV vaccination is recommended for all patients who are HAV antibody-negative and have chronic liver disease<sup>3</sup>; for patients who are injection and non-injection drug users; and for men who have sex with men (**AIII**). Responses to the HAV vaccine are reduced in patients with HIV infection with CD4 counts  $<200$  cells/mm<sup>3</sup>.<sup>82,83</sup> 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<sup>3</sup> (**BIII**).

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

## Treating Disease

The ultimate treatment goals in HIV/HBV coinfection are the same as for HBV mono-infection: to prevent disease progression and to reduce HBV-related morbidity and mortality. Patients with HIV/HBV coinfection 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 the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV](#) recommend the fixed-dose coformulations of TDF or TAF/emtricitabine or abacavir/lamivudine as nucleoside reverse transcriptase inhibitor (NRTI) regimen backbones for ART-naïve patients regardless of CD4 cell count.<sup>84</sup> Because both tenofovir and emtricitabine have anti-HBV activity, the tenofovir combinations are also the treatment of choice for patients with HIV/HBV coinfection (**AIII**) **regardless of CD4 count (AI) and HBV DNA level (AIII)**. (See [HBV/HIV Coinfection](#) in the Adult and Adolescents Guidelines.) TDF and TAF are both active against wild-type and lamivudine-resistant HBV strains. Studies in patients with HIV/HBV coinfection (most of them carrying lamivudine-resistant HBV) have shown, on average, 4 log<sub>10</sub> declines in HBV DNA levels.<sup>85-90</sup> TDF and TAF have a high genetic barrier for development of resistance mutations (**AI**).<sup>3,91</sup>

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 for these patients renally dosed entecavir with a fully suppressive ART is recommended (**BIII**). Renally-dosed TDF can also be used if recovery of renal function is unlikely (**BIII**). If renally-dosed TDF is used, then the CrCl needs to be monitored carefully. In patients with HIV/HBV coinfection, 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.<sup>92</sup> In patients with HBV monoinfection, 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 than patients receiving TDF ( $P < 0.0001$ ). Furthermore, the median change in eGFR from baseline to 48 weeks also favored TAF ( $P = 0.004$ ).<sup>93,94</sup>

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 (**CIII**) because relapses after response occur, particularly in those with lower CD4 cell counts.<sup>3</sup> Additionally, discontinuation of nucleos(t)ide analogue therapy is associated with a HBV flare in approximately 30% of cases,<sup>95,96</sup> with loss of the benefit accrued from previous anti-HBV treatment and possible decompensation of liver disease.<sup>56,97-99</sup> 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 Patients with HIV Infection Who Are Not Receiving ART***

HBV and HIV co-treatment is essential and recommended.<sup>84</sup> There are few options that can be used for treatment of HBV alone in the patient with HIV/HBV coinfection. 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 patients with HIV/HBV coinfection who are not receiving ART and who meet criteria for HBV therapy as described in the [AASLD 2018 guidelines](#) (**CIII**).<sup>100</sup>

Some patients with HIV/HBV coinfection also have chronic HCV infection. There is scant information on the treatment of HBV/HCV/HIV coinfection. Because patients with HBV, HCV, and HIV appear to have accelerated progression of liver fibrosis, higher risk of HCC, and increased mortality,<sup>101-103</sup> 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 patients with HIV/HBV coinfection who will be treated for HCV should be on HBV-active ART at the time of HCV treatment initiation (**AIII**).<sup>104-107</sup>

### ***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**).<sup>108,109</sup> Other HBV treatment regimens include adefovir in combination with lamivudine or emtricitabine or telbivudine in addition to a fully suppressive ART regimen;<sup>90,110,111</sup> 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, the Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV (the Panel) does not recommend these drugs/regimens for patients with HIV/HBV coinfection (**AI**).

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

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  $<1 \log_{10}$  decline at 12 weeks.<sup>112</sup>
- A complete virologic response is an undetectable HBV DNA by real-time polymerase chain reaction at 24 to 48 weeks.<sup>112</sup>
- A partial virologic response is  $\geq 1 \log_{10}$  decline but still detectable HBV DNA at 24 weeks.<sup>112</sup>
- 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.<sup>112</sup>

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 ( $<1\%$  of HBsAg-positive patients per year).<sup>3</sup>

### **Adverse Events**

Renal toxicity with TDF, including increased serum creatinine or renal tubular dysfunction, has been observed; both are more frequent in patients with HIV infection who have underlying renal insufficiency, are older, or have been treated with TDF for prolonged periods.<sup>113</sup> These biochemical changes are usually reversible when TDF is discontinued or changed to TAF.<sup>114</sup>

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.<sup>114</sup> 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 patients with HBV monoinfection with advanced cirrhosis.<sup>115</sup>

Major toxicities of IFN- $\alpha$  (pegylated or standard) are flu-like symptoms such as fatigue, pyrexia, myalgia, and headache, and psychiatric reactions including depression, insomnia, irritability, and anxiety. Other common reactions are anorexia, nausea and vomiting, diarrhea, arthralgias, injection site reactions, alopecia, and pruritus.

### ***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,”<sup>116</sup> which constitutes IRIS in persons with HIV/HBV coinfection. IRIS may manifest when serum aminotransferase levels dramatically increase as CD4 cell counts rise within the first 6 to 12 weeks after ART is started, with signs and symptoms characteristic of acute hepatitis and without another cause for the flare.<sup>117,118</sup> 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 INR and low serum albumin) should prompt consultation with a hepatologist (**CI**).<sup>114</sup>

Flares are worse in patients with more severe liver disease, especially in those with cirrhosis.<sup>119</sup> Distinguishing between drug-induced liver injury or other causes of hepatitis (acute hepatitis with 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. In individuals with HIV, the risk of ART-associated 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.<sup>120-123</sup> However, despite this increased risk of hepatotoxicity in the setting of HCV or HBV coinfection, most (80% to 90%) patients with HIV/HBV coinfection do not have ART-associated hepatotoxicity,<sup>124</sup> and clinically significant hepatotoxicity (elevated direct bilirubin and INR) is rare; aminotransferase levels return to baseline in most cases, even if the offending medication is continued.<sup>125,126</sup> 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**).<sup>127</sup>

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 considered, 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 (HBV DNA <1 log<sub>10</sub> decline) after 12 weeks of therapy in patients who consistently adhere to HBV therapy or as an increase in HBV DNA levels >1 log<sub>10</sub> above nadir. In either situation, treatment failure is generally due either to drug-resistant HBV if the patient is on lamivudine/emtricitabine monotherapy or to non-adherence to therapy.<sup>3</sup> If drug-resistant HBV is present, a change in treatment is needed (**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 non-adherence and drug resistance, evaluating patients with unclear prior drug history, assessing different adefovir-resistance pathways, and predicting the level of resistance to entecavir.<sup>128</sup> 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 patients whose response to TDF is slow.<sup>129</sup>

Lamivudine (or emtricitabine) monotherapy for HBV leads to emergence of drug-resistant HBV, which increases with time on treatment; therefore, **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 patients with HIV/HBV coinfection treated with lamivudine alone.<sup>130</sup> If lamivudine resistance is suspected or documented, TDF or TAF should be added to the ART regimen (**BIII**).<sup>131-133</sup> 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**).<sup>134</sup> 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 HBV DNA levels may still be detectable for some years.<sup>3</sup> Thus, in a patient who is adherent to therapy with a partial virologic response to tenofovir, the drug should be continued with monitoring of HBV DNA levels (**BII**). Improved virologic response has been reported with the addition of entecavir to TDF; however, whether such “intensification therapy” is required is unclear.<sup>129</sup> 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 log<sub>10</sub> 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 on adefovir) because of the risk of development of drug resistance to the initial therapy (**BII**).

### Special Considerations for Treating End-Stage Liver Disease

Patients with HIV/HBV coinfection who have end-stage liver disease should be managed as an HBV monoinfected patient with end-stage liver disease including referral to a hepatologist (**CI**). In patients with HIV/HBV coinfection in end-stage liver disease, interferon-alfa is **contraindicated (AI)**, but nucleoside analogs are safe and efficacious (**AI**).<sup>130,135,136</sup> All patients with ascites should undergo paracentesis to exclude spontaneous bacterial peritonitis (SBP).<sup>137,138</sup> 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 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**).<sup>139</sup>

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.<sup>3</sup>

Patients with HBV-related cirrhosis are at increased risk of HCC<sup>140</sup> and should have imaging studied performed every 6 to 12 months, as recommended in HBV monoinfection (**AI**).<sup>3</sup> 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.<sup>3</sup> HCC can occur without cirrhosis in HBV infection, and HIV/HBV coinfection appears to increase the risk of HBV-associated HCC,<sup>141</sup> but more frequent surveillance in HIV/HBV coinfection has not been studied, and so cannot be recommended given insufficient evidence. Patients with HIV/HBV coinfection with decompensated liver disease and/or early HCC are candidates for liver transplantation. HIV infection is not a contraindication to organ transplantation in patients on suppressive ART.<sup>142</sup> 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.<sup>97-99</sup>

### Special Considerations During Immunosuppressive Therapy

As patients with HIV infection live longer, treatment of individuals with HIV infection with immunosuppressive therapy, both in the context of malignancy and rheumatologic/autoimmune diseases is



becoming common. HBV reactivation in HIV-negative patients with HBsAg-positive/anti-HBc positive disease receiving immunomodulatory therapy is well described.<sup>143,144</sup> Even in patients with HBsAg-negative/anti-HBc positive disease, HBV reactivation occurs in 8% to 18% and 1.7% of patients receiving anti-cancer<sup>145</sup> and rheumatologic disease drugs,<sup>146</sup> respectively.

If not already performed, individuals with HIV infection undergoing immunosuppressive therapy should have HBsAg, anti-HBc and anti-HBs testing. Individuals who are HBsAg positive should receive treatment as detailed in *Special Considerations with Regard to Starting ART*. The optimal approach for those patients with HBsAg-negative/anti-HBc positive disease is unknown. However, since tenofovir/emtricitabine is a preferred backbone for ART, it is prudent to start or modify ART to include these drugs before initiating immunosuppressive, cytotoxic, or immunomodulatory therapy in patients with HBsAg-negative/anti-HBc positive disease (**BIII**). If tenofovir/emtricitabine cannot be used as part of their HIV regimen, these patients could either receive entecavir for anti-HBV prophylaxis or be monitored and given entecavir if signs of HBV reactivation occur (increase in HBV DNA or HBsAg seroreversion) (**BIII**). The option to give pre-emptive entecavir prophylaxis is preferred if HBV DNA is detectable or if immunosuppression is more severe, such as with anti-CD20 antibodies (**AII**).<sup>147</sup> There are no studies on the appropriate length of therapy but the Panel agrees with the AASLD 2018 guidance recommendation to continue treatment for 6 months after cessation of immunosuppressive therapy and for 12 months in the setting of anti-CD20 antibodies (**BIII**).<sup>100</sup>

## Special Considerations During Pregnancy

Pregnant women with HIV infection should be screened for HBsAg, and co-infection with HBV may be first diagnosed at this time. (**AI**).<sup>148</sup> 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.<sup>149-152</sup> See [HIV/Hepatitis B Virus Coinfection](#) in the Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States.

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**).<sup>153</sup> There are no data on use of TAF in pregnancy, therefore it is not recommended.<sup>154</sup> Once HBV therapy with nucleos(t)ide analogs and ART is initiated in patients with HIV/HBV coinfection, treatment should 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). As of January 2018, 5,008 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](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**).<sup>153</sup> Similarly, no increase in birth defects has been noted in 2,785 cases of first-trimester exposure to emtricitabine. Emtricitabine is a recommended NRTI and is commonly used in pregnancy (**BII**).<sup>155</sup> A total of 3,535 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 prevention of mother-to-child transmission (PMTCT) trial examining different antenatal ART regimens, TDF/emtricitabine + lopinavir/ritonavir was associated with a higher infant mortality rate at 14 days than zidovudine/lamivudine + lopinavir/ritonavir, 4.4% vs. 0.06% respectively. The mechanisms for this finding are unclear.<sup>156</sup> Other studies of tenofovir use in pregnancy have not suggested increased risk of adverse pregnancy outcomes.<sup>157</sup>

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 with these agents in the first trimester of 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 women who were HBV-seropositive, HIV-seronegative during the second and third trimester was well-tolerated with no birth defects observed.<sup>158</sup>

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**).<sup>159</sup>

Infants born to women who are HBsAg-positive 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**). For infants who weigh <2000g at birth, the birth dose should not be counted toward the 3 dose series.

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

### Preventing HBV Infection

#### Indications for HBV Vaccination:

- Patients without chronic HBV infection and without immunity to HBV (anti-HBs <10 mIU/mL) (**AII**)
- Patients with isolated anti-HBc (**BII**). Recommend one standard dose of HBV vaccine followed by anti-HBs at 1-2 months. If the titer is >100 mIU/mL, no further vaccination is needed, but if the titer is <100 mIU/mL, a complete series of HBV vaccine should be completed followed by anti-HBs testing (**BII**).
- Early vaccination is recommended before CD4 count falls below 350 cells/mm<sup>3</sup> (**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<sup>3</sup>, as some patients with CD4 <200 cells/mm<sup>3</sup> 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 (**BI**); *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**); *or*
- Vaccine conjugated to CpG (Heplisav-B®) IM at 0 and 1 months (**CIII**) – a 2-dose series can only be used when both doses given are Heplisav-B®.
- Anti-HBs should be obtained 1 to 2 months after completion of the vaccine series. Patients with anti-HBs <10 mIU/mL will be considered as vaccine 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 and Duration for Vaccine Non-Responders:

- Double dose, 4-dose series - HBV vaccine IM (Engerix-B® 40 mcg/mL or Recombivax HB® 20 mcg/mL at 0, 1, 2, and 6 months (**BI**).

### Treating HBV Infection

#### Indication for Therapy:

- All patients with HIV/HBV coinfection, regardless of CD4 count and HBV DNA level (**AII**). Therapy should be selected to treat both HIV and HBV infections (**AIII**).

#### Preferred Therapy (CrCl ≥60 mL/min):

- The ART regimen must include 2 drugs active against HBV, preferably with [TDF 300 mg + (FTC 200 mg or 3TC 300 mg)] or [TAF (10 or 25 mg)<sup>a</sup> + 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)<sup>a</sup> + FTC 200 mg PO once daily (**AIII**).

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

### *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 use in persons with CrCl <30 is not yet established.

### *Duration of Therapy:*

- Patients on treatment for HBV and HIV should receive therapy indefinitely (**CIII**).

### **Alternative Therapy**

#### If the Patient Refuses ART:

- Anti-HBV therapy is indicated for all those who meet criteria for treatment according to the [AASLD 2018 guidelines](#).
- 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, TDV, 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<sup>3</sup> (**BIII**).
- 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.
- As HBV reactivation can occur during treatment for HCV with directly active agents (DAAs) in the absence of HBV-active drugs, all patients with HIV/HBV coinfection who will be treated for HCV should be on HBV-active ART at the time of HCV treatment initiation (**AIII**).
- 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**).
- If immunosuppressive therapy is given, HBV reactivation can occur. For patients who are HBsAg positive, treatment for HBV should be administered (**AII**). Patients with isolated anti-HBc can either be monitored or be given prophylaxis to prevent reactivation depending on the degree of immunosuppression and whether HBV DNA is detectable (**AII**).

<sup>a</sup> TAF 10 mg dose is in the fixed dose combination tablets of elvitegravir/cobicistat/TAF/FTC and darunavir/cobicistat/TAF/FTC; when TAF is used with other ARVs, the dose is 25mg.

**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

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