Hepatitis B Virus Infection

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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 people with HIV have evidence of chronic HBV infection.[6-8]

Transmission routes vary geographically, with perinatal and early-childhood exposures responsible for most HBV transmission in higher-prevalence regions.[9] In low-prevalence regions—such as Europe and North America—a large proportion of transmission is through sexual contact and injection drug use, but perinatal transmission is becoming prevalent due to the increasing foreign-born population.[10] Although the general modes of transmission are similar to those of HIV, HBV is transmitted more efficiently than HIV.[1,2] The risk of progression to chronic HBV infection decreases with age and is 90% among those with HBV infection before 1 year of age, 25% to 50% among those with HBV infection between 1 year and 5 years of age, and <5% among those infected with HBV as adults.[10,11] People with HIV are at increased risk for developing chronic HBV infection.[12] Genotypes of HBV (A–J) have been identified, and their geographic distributions differ.[13] Genotype A is most common among people with HBV infection in North America and Western Europe and genotypes B and C among people with HBV infection in Asia.[14]

Clinical Manifestations

Acute HBV infection is asymptomatic in approximately 70% of people infected; <1% of people with HBV infection develop fulminant hepatic failure.[3,15] 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 people with chronic HBV infection are asymptomatic or have nonspecific symptoms, such as fatigue. Between 15% and 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.[16]

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 people with HIV for chronic HBV infection.[17-19] Initial testing should include serologic testing for HBV 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 two occasions at least 6 months apart.[19] People with chronic HBV infection should be tested further 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.[19] People 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.[3,20] With cccDNA in hepatocyte nuclei, a person with severe immune suppression—such as seen with anti-CD20 therapy or after stem cell transplant—may become serum HBsAg positive again with HBV viremia.[21,22]

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 people with HIV.[23-27] Incidence of HBV viremia among people with HIV and isolated anti-HBc ranges from 1% to 36%.[23,25,28-30] The clinical significance of isolated anti-HBc is unknown,[23,27,30-32] but in people with HIV, it may indicate chronic or, more likely, resolved HBV infection.[26,33,34] In a low-prevalence country—such as the United States—isolated anti-HBc also may represent a false-positive result.[26,33,35,36] People with HIV—particularly those with underlying hepatitis C virus (HCV) coinfection—have a higher frequency of isolated anti-HBc.[26,37,38]

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

Compared with people with HBV mono-infection, those with HIV/HBV coinfection have higher levels of HBV viremia and lower likelihood of resolved infection following acute HBV infection.[39] Among people with HBV mono-infection, 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 and HCC[40-42] and improved survival.[43-46] In comparison, people with HIV/HBV coinfection are usually more likely to have detectable HBeAg,[39,47] lower rates of seroconversion to anti-HBe, and increased risk of HCC and liver-related mortality and morbidity.[48,49]

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 following: the immune-tolerant phase (normal ALT [upper limits of normal 19–25 U/L for women and 29–33 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).[19] Duration of disease phases is different in those who acquire infection as neonates or young children than in those who acquire infection as adults. The immune-tolerant phase occurs primarily among people who acquired HIV perinatally. Clinicians should be knowledgeable about these phases among people with HBV mono-infection to determine who needs treatment and who should be monitored (see the AASLD 2018 Hepatitis B Guidance). In HIV/HBV coinfection, monitoring and treatment also are focused on the simultaneous treatment of both viruses.

People with anti-HBe seroconversion and HBeAg loss usually transition into the inactive hepatitis B phase.[16] 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.[50] However, such spontaneous HBeAg conversion rates appear to be lower among people with HIV/HBV coinfection than among people with HBV mono-infection. People in the inactive state remain at risk of reactivation of HBV infection and development of HCC, but the risk is lower than for people with active HBV replication. In any person, the reemergence of abnormal liver enzyme tests may reflect HBeAg-negative chronic HBV disease, a result of mutations in the basal core and precore promoter regions of the virus.[16] Although people who are HBeAg negative usually have lower levels of HBV DNA, they experience unrelenting but fluctuating disease progression, with changing HBV DNA

levels.[51] People 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.[51]

When chronic HBV infection is diagnosed, a patient should be linked to care and have a complete history and physical examination for signs of cirrhosis or HCC. In addition, clinicians should perform HBV serologic testing (HBeAg/anti-HBe and HBV DNA) and other laboratory testing—complete blood count, ALT, aspartate aminotransferase (AST), albumin, total bilirubin, alkaline phosphatase, international normalized ratio (INR), and anti-hepatitis A virus—to determine the need for vaccination, abdominal ultrasound, and liver fibrosis assessments at the initial visit and monitor these every 6 to 12 months.[3] People with chronic HBV infection are at increased risk of HCC; therefore, HCC surveillance every 6 months is required for people who are cirrhotic and for people 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.[52] People with HIV/HBV coinfection are at increased risk of HCC,[53] and some experts recommend screening people who have HIV/HBV coinfection and who are older than 40 years of age for HCC. Assessment of the patient's liver fibrosis stage is important. Increasing evidence indicates that noninvasive methods (i.e., elastography and serum markers) to evaluate liver fibrosis can be used to determine fibrosis in HBV infection.[54] The decision to perform a liver biopsy should be individualized, but the procedure is rarely necessary.[3]

Preventing Exposure

HBV infection is transmitted primarily through percutaneous or mucosal exposure to infectious blood or body fluids. Therefore, people with HIV should be counseled about transmission risks for HBV infection 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

Recommendations for Preventing Hepatitis B Virus Infection
Indications for HepB Vaccination
• People without chronic HBV infection and without immunity to HBV infection (anti-HBs <10 mIU/mL) (AII).
• People with isolated anti-HBc (BII). Recommend one standard dose of HepB 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 HepB vaccine should be completed (see below for Vaccination Schedule), followed by anti-HBs testing (BII). If anti-HBs quantitative titer is not available, then recommend a complete HepB vaccine series followed by qualitative anti-HBs testing (BII).
• Although vaccine response is better in people with CD4 >350 cells/mm^3, vaccination should not be deferred in people with a lower CD4 count because some people with CD4 <350 cells/mm^3 do respond to vaccination (AII).
Vaccination Schedule
• HepB vaccine IM (Engerix-B 40 mcg [2 injections of 20 mcg each] or Recombivax HB 20 mcg [2 injections of 10 mcg each]) at 0, 1, and 6 months (these doses are considered a "double-dose," three-dose series) (AII); *or*
• Combined HepA and HepB vaccine (Twinrix) 1 mL IM as a three-dose series (at 0, 1, and 6 months) (AII); *or*

- Vaccine conjugated to CpG (Heplisav-B) IM at 0 and 1 months for vaccine-naive patients (AII)
- Anti-HBs should be obtained 1 to 2 months after completion of the vaccine series.

For Vaccine Nonresponders

- Response to HepB vaccination, defined as anti-HBs ≥10 mIU/ml, should be documented 4 weeks after the last dose of vaccine (AII).
- Revaccinate with a second double-dose, three-dose series of recombinant HBV vaccine (Engerix-B 40 mcg [2 injections of 20 mcg each] or Recombivax HB 20 mcg [2 injections of 10 mcg each]) (BIII);* *or*
- Revaccinate with two-dose series of HepBCpG (Heplisav-B) (BIII).
- For people with low CD4 count at the time of first vaccination series, some experts might delay revaccination until after a CD4 count ≥200 is achieved and sustained with ART (CIII).

* Some experts consider that a double-dose, four-dose series of recombinant HepB vaccine (Engerix-B 40 mcg or Recombivax 20 mcg at 0, 1, 2, and 6 months) may produce a better immunologic response, but this approach has not been demonstrated to be superior to a double-dose, three-dose series.

Other Considerations

- HepA vaccination is recommended for all people who are total HAV antibody negative and have chronic liver disease, are men who have sex with men, or are injection drug users (AIII).
- Antibody response to HepA vaccine should be assessed 1 month after completion of vaccination series. If total anti-HAV (IgG and IgM) is negative, people should be revaccinated when the CD4 count is >200 cells/mm^3 (BIII).
- Pregnant people with chronic HBV infection who have not already received the HepA vaccine series should be screened for immunity to HAV infection. If they screen negative for total anti-HAV, they should receive the HepA vaccine series (AIII).

Key: anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; CpG = cytosine phosphoguanine; HAV = hepatitis A virus; HBV = hepatitis B virus; HepA = hepatitis A; HepB = hepatitis B; IgG = immunoglobulin G; IgM = immunoglobulin M; IM = intramuscular; mIU/mL = milli-international units per milliliter

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

All people with HIV should be screened for HBV infection, and screening should include HBsAg, anti-HBs, and anti-HBc.[17,18,51] A person 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 mIU/mL after completion of the vaccine series is consistent with seroprotection,[55] and no further vaccinations are required.[56] The interpretation is less clear among people 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.[57] Most people with HIV with isolated anti-HBc are HBV DNA negative and not immune to HBV infection[38]; therefore, routinely checking HBV DNA is not recommended. However, such people should be vaccinated with one standard dose of HepB vaccine (Engerix-B or Recombivax HB) or one dose of Heplisav-B, and anti-HBs titers should be checked 1 to 2 months after vaccination **(BII).** 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 the same HepB vaccine should be completed and followed by anti-HBs testing **(BII).**[58] The cutoff of 100 mIU/mL is used in this situation because one study demonstrated that 100% of people with isolated anti-HBc who achieved a titer of 100 mIU/mL after a booster dose maintained an anti-HBs response for >18 months compared with only 23% of those who achieved a titer of 10 to 100 mIU/mL.[58] If anti-HBs quantitative titers are not available, then the complete series of HepB vaccine should be completed followed by qualitative anti-HBs testing **(BII).**

Available adult single-antigen HepB 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 9 agonist (Heplisav-B). The magnitude and duration of immunogenicity to HepB vaccination with the recombinant vaccines in adults with HIV are significantly lower than in healthy adults who are HIV seronegative.[56,59-61] Factors associated with poor response to recombinant vaccines include low CD4 T lymphocyte (CD4) cell counts,[59,62-67] presence of detectable HIV RNA,[63,67,68] coinfection with HCV, occult HBV infection, and the general health status of the host.[25,38,69-73] Although vaccine response is better when CD4 counts are >350 cells/mm^3, vaccination should not be deferred until CD4 counts increase to >350 cells/mm^3 because some people with HIV with CD4 counts <350 cells/mm^3 do respond to vaccination **(AII).**

The Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV (the Panel) recommends hepatitis B vaccination for all non-immune patients either with double-dose vaccine Engerix-B or Recombivax HB as the primary series **(AII),** combined HepA and HepB as a three-dose series **(AII),** or, for vaccine-naive patients, Heplisav-B as a two-dose series **(AII).** A meta-analysis of 10 studies of people with HIV demonstrated that compared to a single dose, a double dose of Engerix-B or Recombivax HB had better response rates at 4 to 6 weeks (odds ratio [OR] 1.76; 95% confidence interval [CI], 1.36–2.29) and at >12 months (OR 2.28; 95% CI, 1.73–3.01) after vaccine completion.[74] A double dose of Engerix-B is 40 mcg (two injections of the 20-mcg dose). A double dose of Recombivax HB is 20 mcg (two injections of the 10-mcg dose). In four randomized controlled trials, a regimen of two doses of Heplisav-B was superior to three doses of Engerix-B in people without HIV.[75-77] In the largest trial, the protection rate was 95% for Heplisav-B and 81% for Engerix-B.[77] An increase in the number of cardiovascular events that was not statistically significant was observed in the Heplisav-B group. In a multicenter trial of the safety and efficacy of Heplisav-B in people with HIV naive to vaccine, the vaccine achieved a 98.5% seroprotective response rate after two doses (administered at 0 and 1 months) and evaluated 6 months after the first dose. The study found a 100% seroprotective rate 4 weeks after a third dose.[78] If Heplisav-B is used, the vaccine should not be interchanged with either of the other recombinant vaccines for the second dose.

Recommendations provided by the Advisory Committee on Immunization Practices state that the two-dose vaccine series is appropriate only when both doses are Heplisav-B. In other situations, three total doses of vaccine should be given.

Response to HepB vaccination, defined as anti-HBs ≥10 mIU/ml, should be documented 4 weeks after the last dose of vaccine **(AII).** In an observational study of 409 people with HIV who received the HepB vaccine, those with anti-HBs ≥10 mIU/mL were less likely to develop acute HBV infection compared to those who did not achieve that level (5% vs. 11%, hazard ratio 0.51; 95% CI 0.3–1.0).[79] In addition, among those who were acutely HBV infected, 0% of those with anti-HBs ≥10 mIU/mL developed chronic infection compared to 35% of those with anti-HBs <10 mIU/mL (P = 0.02).

Because of waning immunity, some experts would check anti-HBs annually and a booster dose would be given if levels fall below 10 mIU/mL, particularly if a person has ongoing risk factors for acquiring HBV and is not receiving tenofovir.

Among people with HIV who did not respond (anti-HBs titers <10 mIU/mL) to a primary three-dose vaccine series with a single-dose recombinant vaccine, 25% to 50% responded to an additional vaccine dose, and 44% to 100% responded to a three-dose revaccination series.[80-83] As a result, people with HIV who do not respond to a complete HepB vaccination series with one of the recombinant vaccines should be revaccinated with three double doses of a recombinant HBV vaccine **(BIII)** or with Heplisav-B **(BIII),**[56] although some specialists might delay revaccination until antiretroviral therapy (ART) results in a sustained increase in CD4 count (CD4 ≥200 cells/mm^3) **(CIII).** Two randomized controlled trials have shown that giving four double doses of the recombinant vaccine produces higher anti-HBs titers than three doses of single-dose vaccine,[84,85] and one study also showed a higher overall response rate.[85] Some specialists consider that this approach—four doses—improves immunologic response in people with HIV either as an initial vaccination schedule or among people who are nonresponders. However, whether vaccination with a schedule of four double doses is superior to four single doses or three double doses is still unclear.

Preventing Other Liver Diseases

HepA vaccination is recommended for all people with HIV who are hepatitis A virus (HAV) antibody negative, particularly those who have chronic liver disease,[3] are injection and non-injection drug users, and men who have sex with men **(AIII).** Among people with HIV with CD4 counts <200 cells/mm^3, responses to the HepA vaccine are reduced.[86,87] Antibody response should be assessed 1 month after vaccination is complete. If total anti-HAV immunoglobulin (immunoglobulin G and immunoglobulin M) is negative, people should be revaccinated when their CD4 count is >200 cells/mm^3 **(BIII).**

People with chronic HBV infection should be advised to avoid alcohol consumption **(AIII).**

Treating Disease

Recommendations for Treating Hepatitis B Virus Infection
Indication for Therapy • For all people with HIV/HBV coinfection, including pregnant people, regardless of CD4 count and HBV DNA level (AIII), therapy should be selected that includes drugs active against both HIV and HBV infections (AIII). *Preferred Therapy (CrCl ≥60 mL/min)* • The ART regimen must include two drugs active against HBV, preferably with (TDF 300 mg plus [FTC 200 mg or 3TC 300 mg]) or (TAF [10 or 25 mg][a] plus FTC 200 mg) PO once daily (AII). *Preferred Therapy (CrCl 30–59 mL/min)* • The ART regimen must include two drugs active against HBV, preferably with TAF (10 or 25 mg)[a] plus FTC 200 mg PO once daily (AII). *Preferred Therapy (CrCl <30 mL/min, Not Receiving HD)* • Renally dosed entecavir (in place of TDF or TAF), *or*

- ART with renally dose-adjusted TDF and FTC (BIII) when recovery of renal function is unlikely (see Table 6 for dosing recommendation for TDF and FTC or 3TC for people with renal impairment). Guidance for TAF use in people with CrCl <30 is not yet established.

Preferred Therapy (Receiving HD)

- (TDF or TAF) plus (FTC or 3TC) can be used. Refer to Table 6 for dosing recommendation.

Duration of Therapy

- People on treatment for HBV and HIV should receive therapy indefinitely (BIII).

Alternative Therapy

For People Not on ART

- Anti-HBV therapy is indicated for all those who meet criteria for treatment according to the AASLD 2018 Hepatitis B Guidance.
- 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)
- Anti-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

- Because people 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.
- Because HBV reactivation can occur during treatment for HCV with direct-acting antivirals in the absence of anti-HBV therapy, all people with HIV/HBV coinfection who will be treated for HCV infection 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 (AIII).
- 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 reinstituted because it can be potentially lifesaving (AIII).
- If immunosuppressive therapy is given, HBV reactivation can occur. For people who are HBsAg positive, treatment for HBV infection should be administered (AII). People 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).

Pregnancy Considerations

- TAF or TDF given in combination with 3TC or FTC is the preferred dual-NRTI backbone for pregnant people with chronic HBV infection (AIII).
- A person with HBV/HIV coinfection who becomes pregnant while virally suppressed on an ARV regimen that includes TAF can be offered the choice of continuing TAF or switching from TAF to TDF (BIII).
- 3TC has been well tolerated by pregnant people and is a recommended NRTI for use in pregnancy (AII).
- FTC is a recommended NRTI and is used commonly in pregnancy (BII).
- 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 people because of their direct antigrowth and antiproliferative effects (AII).

- Infants born to people who are HBsAg positive should receive HBIG and HepB vaccine (first dose of three) within 12 hours of delivery (AI). The second and third doses of vaccine should be administered at 1 month and 6 months of age, respectively (AI).

[a] 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 antiretrovirals, the dose is 25 mg.

Key: 3TC = lamivudine; AASLD = American Association for the Study of Liver Disease; anti-HBc = HBV core antibody; ARV = antiretroviral; ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; CrCl = creatinine clearance; FTC = emtricitabine; HBsAg = HBV surface antigen; HBV = hepatitis B virus; HBIG = hepatitis B immune globulin G; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HD = hemodialysis; HepB = hepatitis B; IFN = interferon; NRTI = nucleoside reverse transcriptase inhibitor; PO = orally; SQ = subcutaneous; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

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. People 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 U.S. Department of Health and Human Services Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV (Adult and Adolescent Antiretroviral Guidelines) recommend the fixed-dose coformulations of TDF/(emtricitabine [FTC] or lamivudine [3TC]), TAF/FTC, or abacavir/3TC as nucleoside reverse transcriptase inhibitor (NRTI) regimen backbones for most ART-naive people regardless of CD4 count.[88] Because both components of these tenofovir combinations (tenofovir and either FTC or 3TC) have anti-HBV activity, they are also the treatment of choice for people with HIV/HBV coinfection **(AIII)** regardless of CD4 count **(AI)** and HBV DNA level **(AIII)** (see Hepatitis B Virus/HIV Coinfection in the Adult and Adolescent Antiretroviral Guidelines). TDF and TAF are both active against wild-type and 3TC-resistant HBV strains. Studies among people with HIV/HBV coinfection (most of them carrying 3TC-resistant HBV) have shown, on average, 4 $\log_{10}$ declines in HBV DNA levels.[89-94] TDF and TAF have a high genetic barrier for development of resistance mutations **(AI).**[3,95]

The decision to use TAF/FTC versus TDF/FTC should be based upon creatinine clearance (CrCl) and an assessment of risk for nephrotoxicity and risk for acceleration of bone loss. Among people with CrCl ≥60 mL/min, either TAF/FTC or TDF/FTC can be considered. Among people with a CrCl 30 to 59 mL/min, a TAF/FTC regimen is preferred. Currently approved TAF/FTC-containing regimens for the treatment of HIV are not recommended for use among people with CrCl <30 mL/min who are not on hemodialysis. For these people, renally dosed entecavir with a fully suppressive ART regimen is recommended **(BIII).** Renally dosed TDF also can be used if recovery of renal function is unlikely **(BIII).** If renally dosed TDF is used, then the CrCl needs to be monitored carefully. Among people with HIV/HBV coinfection, switching from a primarily TDF-based ART regimen to single-tablet TAF/FTC/elvitegravir/cobicistat maintained or achieved HBV suppression, with improved estimated glomerular filtration rate (eGFR) and bone turnover markers.[96] Among people with HBV mono-infection, TAF 25 mg was non-inferior to TDF 300 mg based on the percentage of people with HBV DNA levels <29 IU/mL at 48 weeks of therapy (94% for TAF vs. 93% for TDF; $P = 0.47$). People on TAF also experienced significantly smaller mean percentage decreases from baseline in hip and spine bone mineral density at 48 weeks than people receiving

TDF ($P < 0.0001$). Furthermore, the median change in eGFR from baseline to 48 weeks also favored TAF ($P = 0.004$).[97,98]

Chronic administration of 3TC or FTC as the only active drug against HBV **should be avoided** because of the high rate of selection of HBV drug-resistance mutations **(AI).**

People receiving ART should continue HBV therapy indefinitely **(BIII)** because relapses after response can occur, particularly in those with lower CD4 counts.[3] Additionally, discontinuation of nucleos(t)ide analog therapy is associated with an HBV flare in approximately 30% of cases,[99,100] with loss of the benefit accrued from previous anti-HBV treatment and possible decompensation of liver disease.[59,101-103] In addition, switching to the one-pill regimen of dolutegravir/3TC should be avoided because 3TC is then the only active drug against HBV. 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 reinstituted and can be potentially lifesaving **(AIII).**

Some people with HIV/HBV coinfection also have chronic HCV infection. Scant information is available on the treatment of HBV/HCV/HIV coinfection. Because people with HBV/HCV/HIV coinfection appear to have accelerated progression of liver fibrosis, higher risk of HCC, and increased mortality,[104-106] 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 Virus) **(CIII).** Because HBV reactivation can occur during treatment for HCV infection with direct-acting antivirals in the absence of anti-HBV therapy, all people with HIV/HBV coinfection who will be treated for HCV infection should be on HBV-active ART at the time of HCV treatment initiation **(AIII).**[107-110]

Alternative Treatment of HBV Infection Among People with HIV Who Are Not Receiving HBV-Active ART

All people with HIV should receive ART. Among people with HBV infection and HIV, co-treatment is essential and recommended.[88] Few options exist that can be used for treatment of HBV alone in a person with HIV/HBV coinfection. Anti-HBV therapy must not be given in the absence of a fully suppressive ART regimen **(AII).** Only pegylated interferon (IFN)-alfa-2a monotherapy may be considered for people with HIV/HBV coinfection who are not receiving ART and who meet criteria for anti-HBV therapy as described in the AASLD 2018 Hepatitis B Guidance **(CIII).**[19]

Regimens That Are Not Recommended

Tenofovir (TDF and TAF), entecavir, 3TC, FTC, and telbivudine **should not be used alone** in the absence of a fully suppressive ART regimen because of the potential for development of HIV drug-resistance mutations **(AI).**[111,112] Other anti-HBV treatment regimens include adefovir in combination with 3TC or FTC in addition to a fully suppressive ART regimen[94,113,114]; however, data on this regimen among people with HIV/HBV coinfection are limited. In addition, compared with TDF or TAF or entecavir, adefovir is associated with higher incidence of toxicity, including renal disease, as well as higher rates of HBV treatment failure. Therefore, the Panel **does not recommend** adefovir-containing regimen for people with HIV/HBV coinfection **(AI).**

Monitoring of Response to Therapy and Adverse Events

To prevent emergence of drug-resistant variants and evaluate response for people on nucleos(t)ide analogs, treatment response should be monitored by testing for HBV DNA at 3- to 6-month intervals **(AI).** Treatment responses are defined as the following:

- Primary non-response: HBV DNA <1 $\log_{10}$ decline at 12 weeks.[115]
- Complete virologic response: undetectable HBV DNA by real-time polymerase chain reaction at 24 to 48 weeks.[116]
- Partial virologic response: ≥1 $\log_{10}$ decline, but still detectable HBV DNA at 24 weeks.[116]
- Maintained virologic response: response that continues while on therapy.[116]
- Sustained virologic response: one that is still present 6 months after stopping therapy.[116]

For people 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 people per year).[3]

Adverse Events

Renal toxicity with TDF, including increased serum creatinine or renal tubular dysfunction, has been observed; both increased serum creatinine and renal tubular dysfunction are more frequent among people with HIV who have underlying renal insufficiency, are older, or have been treated with TDF for prolonged periods.[117] These biochemical changes are usually reversible when TDF is discontinued or changed to TAF.[118]

Electrolytes and serum creatinine levels should be evaluated at baseline and every 3 to 6 months, with 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 among people 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.[118] All nucleos(t)ides must be dose adjusted for renal dysfunction (see package insert), and TAF with FTC or 3TC is not recommended for people with CrCl <30 mL/min unless they are on hemodialysis **(AI).**

TDF has been associated with a decrease in bone mineral density (BMD). TAF is associated with less of a decrease in BMD than TDF. TAF also has been associated with weight gain among people with HIV but has not been studied in HBV mono-infection.

See the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV for more information on adverse events related to TAF and TDF in Considerations for Antiretroviral Use in Patients with Coinfection: Hepatitis B Virus/HIV Coinfection.

Entecavir-associated lactic acidosis is uncommon but has been reported among people with HBV mono-infection with advanced cirrhosis.[119]

Major toxicities of IFN-alfa (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,"[120] which constitutes IRIS among people with HIV/HBV coinfection. IRIS may manifest when serum aminotransferase levels dramatically increase as CD4 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.[121,122] 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).**[118]

Flares are worse among people with more severe liver disease, especially those with cirrhosis.[123] Distinguishing between drug-induced liver injury or other causes of hepatitis (acute hepatitis caused by HAV, HCV, hepatitis D virus [HDV], hepatitis E virus [HEV], Epstein-Barr virus, herpes simplex virus, or cytomegalovirus infection) and IRIS may be difficult. ART-associated hepatotoxicity may be dose dependent or idiosyncratic. Among people with HIV, the risk of ART-associated hepatotoxicity has been associated consistently with elevated pre-ART aminotransferases (ALT, AST) 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.[124-127] However, despite this increased risk of hepatotoxicity in the setting of HCV or HBV coinfection, most (80% to 90%) people with HIV/HBV coinfection do not have ART-associated hepatotoxicity,[128] 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.[129,130] Therefore, discontinuing ART usually is not necessary in the presence of hepatotoxicity unless the following symptoms are observed: 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).**[131]

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, and CD4 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 (HAV, HCV, HDV, and HEV), and nonalcoholic fatty liver disease.

Managing Treatment Failure

HBV treatment failure on nucleos(t)ide analogs is defined as primary non-response (HBV DNA <1 $\log_{10}$ decline) after 12 weeks of therapy among people who consistently adhere to HBV therapy or an increase in HBV DNA levels >1 $\log_{10}$ above nadir. In either situation, treatment failure generally is due to either drug-resistant HBV if the person is on 3TC/FTC monotherapy or to non-adherence to therapy.[3] 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, 3TC/FTC); 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 people with unclear prior drug history, assessing different adefovir-resistance pathways, and predicting the level of resistance to entecavir.[132] However, TDF is associated infrequently with clinical resistance, although slow response has been noted, as discussed above. Addition of entecavir has led to suppression of HBV DNA among people whose response to TDF is slow.[133]

3TC (or FTC) monotherapy for HBV infection leads to emergence of drug-resistant HBV, which increases with time on treatment; therefore, it **should not be used** as the sole anti-HBV drug in an ART regimen **(AII).** The rate of development of 3TC-resistance is approximately 20% per year among people with HIV/HBV coinfection treated with 3TC alone.[134] If 3TC resistance is suspected or documented, TDF or TAF should be added to the ART regimen **(BIII).**[135-137] Because people with 3TC-resistant HBV will have cross-resistance to the other L-nucleosides (telbivudine, FTC), and partial resistance to entecavir, those agents **should not be used** among people found to have 3TC-resistant HBV **(AI).**[138] All nucleoside analogs must be dose adjusted for renal insufficiency per package insert guidelines and Table 6.

If treatment failure occurs on entecavir, the only rational choice is replacement with TDF or TAF (with or without FTC) because of the cross-resistance that occurs with L-nucleosides (telbivudine, 3TC, FTC) **(AI).**

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

If treatment failure with TDF or TAF occurs, particularly in 3TC- or FTC-experienced people, entecavir may be an active alternative, especially if higher doses of entecavir can be used **(CIII).**

Declines in HBV DNA levels can be slow, especially when pretherapy HBV DNA levels are very high. HBV DNA levels usually drop quickly among people 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.[3] Thus, in a person 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.[139] Nonetheless, people 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 $\log_{10}$ drop in HBV DNA levels from baseline at 24 weeks) should be switched to a more potent regimen—such as tenofovir with FTC 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

People with HIV/HBV coinfection who have end-stage liver disease should be managed as a person with HBV mono-infection with end-stage liver disease, including referral to a hepatologist **(AIII).** Among people with HIV/HBV coinfection in end-stage liver disease, IFN-alfa is **contraindicated (AI),** but nucleoside analogs are safe and efficacious **(AI).**[134,140,141] All people with ascites should undergo paracentesis to exclude spontaneous bacterial peritonitis (SBP).[142,143] 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 people 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).**[144]

Esophagogastroduodenoscopy (EGD or upper endoscopy) should be performed on all people with cirrhosis at the time of diagnosis and then every 1 year to 2 years to identify substantial gastroesophageal varices (see the AASLD 2018 Hepatitis B Guidance). People with varices require nonselective 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]

People with HBV-related cirrhosis are at increased risk of HCC[145] and should have imaging studies performed every 6 months, as recommended in HBV mono-infection **(AI).**[3] Choice of imaging (ultrasound, computed tomography, or magnetic resonance imaging) depends upon the expertise of the imaging center and whether the person has cirrhosis. Usually, ultrasound is the initial preferred imaging modality.[3] HCC can occur without cirrhosis in HBV infection, and HIV/HBV coinfection appears to increase the risk of HBV-associated HCC,[146] but more frequent surveillance in HIV/HBV coinfection has not been studied, and so cannot be recommended given insufficient evidence. People 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 among people on suppressive ART.[147] 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 people should continue HBV therapy (with the exception of pegylated IFN-alfa) indefinitely **(AIII)** because relapses after response can occur, particularly in those with lower CD4 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.[101-103]

Special Considerations During Immunosuppressive Therapy

With immunosuppressive therapy, both in the context of malignancy and rheumatologic/autoimmune diseases, reactivation of HBV infection can occur. HBV reactivation in HIV-negative people with HBsAg-positive/anti-HBc-positive disease receiving immunomodulatory therapy is well described.[148,149] Even among people with HBsAg-negative/anti-HBc-positive disease, HBV reactivation occurs in 8% to 18% of people receiving anti-cancer drugs[150] and 1.7% of people receiving rheumatologic disease drugs.[151]

If not already performed, people with HIV undergoing immunosuppressive therapy should have HBsAg, anti-HBc, and anti-HBs testing. People who are HBsAg positive should receive treatment with TDF or TAF plus 3TC or an FTC-based ART regimen (see Special Considerations with Regard to Starting ART above**)**. The optimal approach for those people with HBsAg-negative/anti-HBc-positive disease is unknown. However, because TDF or TAF plus FTC 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 among people with HBsAg-negative/anti-HBc-positive disease **(BIII).** If TDF or TAF/FTC cannot be used as part of their HIV regimen, these people either could receive entecavir for anti-HBV prophylaxis or could 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).**[152] No studies have been performed on the appropriate length of therapy, but the Panel agrees with the AASLD 2018 Hepatitis B 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).**[19]

Special Considerations During Pregnancy

Pregnant people with HIV should be screened for HBV infection, and coinfection with HBV may be first diagnosed at this time **(AI).**[153] People with HIV should be tested for HBsAg during each pregnancy, preferably in the first trimester, even if vaccinated or tested previously.[153] Those who are both HBsAg negative and anti-HBs negative should be offered vaccination against HBV. Pregnant people with chronic HBV infection who have not already received the HepA vaccine series should be screened for immunity to HAV infection. Those who screen negative for total anti-HAV should receive the HepA vaccine series **(AIII).**[154] 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 preterm 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.[155-158] See Hepatitis B Virus/HIV Coinfection in the Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Interventions to Reduce Perinatal HIV Transmission in the United States.

ART—including drugs active against both HIV and HBV—is recommended for all people with HIV/HBV coinfection, including pregnant people **(AIII).** TAF or TDF given in combination with 3TC or FTC is the preferred dual-NRTI backbone for pregnant people with chronic HBV infection **(AIII).**[154] A person with HBV/HIV coinfection who becomes pregnant while virally suppressed on an antiretroviral regimen that includes TAF can be offered the choice of continuing TAF or switching from TAF to TDF **(BIII).**[159] Several other antiviral agents have activity against HBV, including entecavir, adefovir, and telbivudine. However, these drugs have not been well evaluated in pregnancy, with too few exposures to assess overall risk. They **are currently not recommended** for pregnant people with HBV/HIV coinfection.[159] Once HBV therapy with nucleos(t)ide analogs and ART is initiated in people with HIV/HBV coinfection, treatment should be continued indefinitely.

Cases of adverse events during pregnancy related to any of the antiretroviral or anti-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 3TC have been reported to the Antiretroviral Pregnancy Registry, with no indication of an increased risk of birth defects after exposure (see The Antiretroviral Pregnancy Registry Interim Report). 3TC has been well tolerated by

pregnant people and is a recommended NRTI for use in pregnancy **(AII).**[154] Similarly, no increase in birth defects has been noted in 2,785 cases of first-trimester exposure to FTC. FTC is a recommended NRTI and is used commonly in pregnancy **(BII).**[160] 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.[160]

Several large studies have been conducted to evaluate the effect of tenofovir use in pregnancy. No evidence exists that the use of TDF increases the risk of birth defects. Overall, the available evidence does not indicate a link between maternal TDF use and infants who are low birth weight or small for gestational age. Some concern remains regarding a link between maternal TDF use and preterm birth, but the evidence is mixed; the role of concomitant medications and other cofactors and/or confounders requires further investigation.[154]

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 and if the benefits are thought to outweigh the risks. 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 (see package insert). Data on the use of entecavir and adefovir in human pregnancy are not available. Telbivudine given to pregnant people who were HBV seropositive/HIV seronegative during the second and third trimester was well tolerated, with no birth defects observed.[161]

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 people because of their direct antigrowth and antiproliferative effects **(AII).**[162]

Infants born to people who are HBsAg positive should receive HBIG and HepB vaccine (first dose of three) within 12 hours of delivery **(AI).** The second and third doses of vaccine should be administered at 1 month and 6 months of age, respectively **(AI).** Infants who weigh <2,000 g at birth should receive four doses of HepB vaccine; administer one dose of HepB vaccine within 12 hours of delivery and initiate the three-dose HepB vaccine series beginning at age 1 month (four doses total: birth, 1 month, 2–3 months, and 6 months).

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