

Hepatitis B Virus Infection

Updated: June 05, 2025

Reviewed: June 05, 2025

These recommendations are intended to focus on prepubertal children with HIV and hepatitis B virus (HBV) coinfection.

Panel's Recommendations

I. Should all pregnant women with HIV routinely undergo testing for hepatitis B virus (HBV) as part of antenatal care?

All pregnant women with HIV should be tested for HBV with hepatitis B surface antigen (HBsAg) as part of the pregnancy/obstetric panel during the first trimester of each pregnancy regardless of hepatitis B (HepB) vaccination history or prior testing. Testing should be repeated in late pregnancy or at the time of admission to the hospital for infant delivery for HBsAg-negative people at high risk of HBV infection (e.g., people who inject drugs, have intercurrent sexually transmitted infections, have multiple sex partners, or have clinical hepatitis). Pregnant women with HIV who do not have documentation of HepB vaccination should be vaccinated against hepatitis B (**strong, moderate**). Pregnant women who are HBsAg positive should also have an HBV DNA quantitative test and a hepatitis B e antigen (HBeAg) test and be referred to appropriate specialists for hepatitis B–related clinical management; HBV specialists can ensure essential follow-up of the pregnant woman and the hepatitis B–exposed infant(s), as well as provision of HepB vaccines for sexual and household contacts.

Prevention of hepatitis B in newborn infants relies on providing a birth dose (within 12 hours after birth is optimal) of the HepB vaccine to all infants. In addition to HepB vaccine, infants born to women known to be HBsAg positive should receive hepatitis B immune globulin (HBIG) within 12 hours of birth. Infants born to women with unknown HBsAg status should receive HepB vaccine within 12 hours of birth in conjunction with HBIG provided within 12 hours of birth (for infants <2,000 grams) or within 7 days (for infants $\geq 2,000$ grams) unless the pregnant woman is confirmed to be HBsAg negative by this time. When indicated, HBIG should be administered concurrently with the birth dose of HepB vaccine at a different anatomic site. Infants born to women who are HBsAg negative but who have other evidence of HBV infection (e.g., detection of HBV DNA HBeAg-positive, or known chronic HBV infection) should be managed as though they have been born to HBsAg-positive women.

See [Hepatitis B Virus/HIV Coinfection](#) in the Perinatal Guidelines for more information.

II. What is the optimal antiretroviral (ARV) regimen for people with HIV/HBV coinfection in the antenatal period?

Antiretroviral therapy (ART) that is active against both HIV and HBV is recommended; the preferred regimen should include tenofovir (tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide [TAF]) and either lamivudine (3TC) or emtricitabine (FTC) (**strong, high**). See [Hepatitis B Virus/HIV Coinfection](#) in the Perinatal Guidelines for more information.

IIIa. What is the optimal HBV prevention strategy for infants born to women with HIV/HBV coinfection?

All infants $\geq 2,000$ grams born to HBsAg-positive women should receive single-antigen HepB vaccine and HBIG within 12 hours after birth, a second dose of HepB vaccine at age 1 to 2 months, and a third dose of HepB vaccine at age ≥ 6 months. All infants <2,000 grams born to HBsAg-positive women should receive single-antigen HepB vaccine and HBIG within 12 hours after birth, a second dose of HepB vaccine at age 1 month, a third dose of HepB vaccine at age 2–3 months, and a fourth dose of HepB vaccine at age ≥ 6 months and not before 24 weeks (**strong, high**). See [Hepatitis B Virus/HIV Coinfection](#) in the Perinatal Guidelines for more information.

IIIb. What is the optimal initial HepB vaccination strategy for children with HIV?

Children with HIV should receive a standard dose of HepB vaccine at 0, 1, and 6 months (**strong, high**). A double dose at 0, 1, and 6 months may also be considered (**weak, moderate**).

IV. When should infants born to women with HIV/HBV coinfection undergo post-HepB vaccination serologic testing after completion of the HepB vaccine series?

Infants born to women with HIV/HBV coinfection should have serologic testing for antibody to hepatitis B surface antigen (anti-HBs) and HBsAg at age 9 to 12 months (i.e., the next well-child visit after completion of the HepB vaccine series) or 1 to 2 months after completion of the vaccine series if the final dose is delayed to assess for vaccine response and failure of perinatal prophylaxis (**strong, moderate**).

V. When should children and adolescents with HIV have post-HepB vaccination serologic testing after completion of the HepB vaccine series?

Due to the high prevalence of HBV infection, all infants, children, and adolescents with HIV should be tested for HBsAg as soon as possible after HIV diagnosis (**strong, high**). If there is no documentation of routine infant/child vaccination for hepatitis B, initial screening with the triple panel consisting of HBsAg, anti-HBs, and total antibody to hepatitis B core antigen (anti-HBc) will determine infection and immune status and guide clinical management. In addition, individuals with the isolated anti-HBc serologic profile should also be vaccinated for hepatitis B.

Anti-HBs titers should be evaluated 4 to 6 weeks after completion of the vaccination series (**strong, moderate**). See Advisory Committee on Immunization Practices' (ACIP) recommendations on [eliminating transmission of HBV infection](#) and [preventing HBV infection](#) for more information.

VI. What is the best strategy for HepB revaccination of children with HIV who have not responded to the primary HepB vaccine series (anti-HBs <10 mIU/mL)?

If anti-HBs levels are <10 mIU/mL and the HBsAg result is negative, the Panel on Opportunistic Infections in Children With and Exposed to HIV now recommends that children should be revaccinated with a single dose of HepB vaccine and receive postvaccination serologic testing 1 to 2 months later. Infants whose anti-HBs remains <10 mIU/mL following single-dose revaccination should receive two additional doses of HepB vaccine to complete the second series, followed by postvaccination serologic testing 1 to 2 months after the final dose. Alternatively, based on clinical circumstances or family preference, HBsAg-negative infants with anti-HBs <10 mIU/mL may instead be revaccinated with a second, complete three-dose series, followed by postvaccination serologic testing performed 1–2 months after the final dose of vaccine (**strong, moderate**). See ACIP's HBV [immunization strategy](#) for more information.

VII. Should individuals with HIV who have responded to HepB vaccination have ongoing assessment of hepatitis B immunity?

In individuals who respond to HepB vaccination (anti-HBs \geq 10 mIU/mL), periodic assessment of anti-HBs titers can be considered every 5 years. A booster dose should be provided if anti-HBs titer falls below 10 mIU/mL. Anti-HBs titers should be checked 4 to 6 weeks after a booster dose (**weak, very low**). If anti-HBs is still <10 mIU/mL, the standard three-dose series should be completed. See ACIP's [recommendations on hepatitis B prevention](#) for more information.

VIII. What ART regimens should be considered for ARV-naïve children with HIV/HBV coinfection who are immunotolerant to HBV?

- For children aged <2 years, a [standard preferred ART regimen](#) should be provided. Although there is a risk for development of 3TC-resistant HBV, the need to provide optimal HIV therapy outweighs this risk (**strong, high**).
- For children aged \geq 2 years to <12 years, a standard preferred ART regimen should be provided. If feasible (weight \geq 14 kg), the ART regimen should include TDF (or TAF) + 3TC or FTC (**strong, low**).
- For children aged \geq 12 years, a standard preferred ART regimen including TDF (or TAF) + 3TC or FTC should be provided (**strong, low**).

IX. Should 3TC or FTC be the only HBV therapy for children with HIV/HBV coinfection who require treatment of both infections?

- Children with HIV/HBV coinfection who require treatment of both infections should not be treated with 3TC or FTC as the only HBV-active agent in the regimen (**strong, moderate**). In addition to 3TC or FTC, inclusion of tenofovir (TDF or TAF) in the ART regimen is recommended for most children with HIV/HBV coinfection.

X. What treatment regimens should be considered for children with HIV/HBV coinfection who require treatment of both infections?

- For children aged ≥ 2 years who require treatment for both infections, a combination ARV regimen that includes TDF (or TAF) and an anti-HBV nucleoside (either 3TC or FTC) should be considered for treatment (**strong, low**).
- For children aged ≥ 2 years, if TDF (or TAF) is not available or not tolerated, entecavir can be added to a fully suppressive ARV regimen for HBV treatment (**weak, low**).

XI. How often should children with HIV/HBV coinfection be monitored for HBV status and disease activity?

Children with HIV/HBV coinfection who are not receiving HBV-directed treatment should have disease monitoring (alanine aminotransferase [ALT] for inflammation, complete blood count for platelet count and leukopenia, HBeAg/anti-HBe serostatus, HBV DNA, and HBsAg/anti-HBs serostatus) like children with HBV mono-infection (**strong, moderate**). The value of intermittent noninvasive assessment of hepatic fibrosis with such techniques as transient elastography is unclear (see the [Phases of Chronic Hepatitis B Infection table](#)).

XII. How should children with HIV/HBV coinfection be monitored for hepatocellular carcinoma?

There is no difference in screening recommendations for hepatocellular carcinoma (HCC) in children with HIV/HBV infection compared to children with HBV mono-infection. Surveillance of chronic HBV infection using abdominal ultrasound every 6 months should be performed to detect early HCC in people at risk: people with cirrhosis and those with HBsAg positivity without cirrhosis but with active hepatitis or family history of HCC. Children with a lower risk of HCC should be screened every 1 to 2 years with alpha-fetoprotein (AFP) and every 1 to 2 years with ultrasound, or sooner if AFP is >10 mcg/mL (**weak, low**).

XIII. How should children with HIV who are anti-HBc positive be monitored for reactivation of HBV infection?

Children with HIV who are anti-HBc positive are at risk for reactivation of HBV infection if HIV-related immunodeficiency worsens or if they are treated with agents associated with a risk of HBV reactivation (cancer chemotherapy, biologics such as anti-tumor necrosis factor-alpha, and direct-acting antivirals [DAAs] for hepatitis C curative treatment). For children initiating rituximab or other B-cell-depleting agents who are not on HBV-active ART, HBV antiviral therapy should be initiated. For children experiencing worsening HIV-related immunodeficiency or who are receiving cancer chemotherapy or high-dose steroids, periodic ALT and HBV DNA monitoring should be considered. For children receiving DAAs for hepatitis C curative treatment, HBsAg-positive children should receive prophylactic HBV treatment as part of HIV ART, and HBV DNA should be assessed at regular intervals to monitor for hepatotoxicity (**weak, very low**).

Rating of Evidence

Strength of Recommendation: Strong; Weak

Quality of Evidence: High; Moderate; Low; Very Low

Epidemiology

Hepatitis B virus (HBV) is a DNA virus that causes both acute and chronic hepatitis and is associated with an increased risk of hepatocellular carcinoma (HCC). Transmission is via exposure to bodily fluids from individuals with HBV infection. This guideline will focus on the issues related to children and prepubertal adolescents with or at risk for HIV/HBV coinfection. The reader is referred to recent reviews and guidelines on HBV infection in populations without HIV¹⁻⁹ and in sexually mature adolescents and adults with HIV.^{10,11}

HBV infection is a common worldwide infection for which prevalence varies from $<1\%$ in the United States and Europe to as much as 10% to 15% in areas of Africa, Southeast Asia, and Eastern Europe. However, prevalence in low- and middle-income countries is likely underestimated due to issues with diagnosis.¹² In 2022 there were an estimated 1.2 million new infections with HBV.¹²

Chronic HBV infection is often defined as persistence of serum hepatitis B surface antigen (HBsAg) for >6 months.¹³ The risk of developing chronic HBV infection after acute infection correlates inversely with age and immune competence at HBV exposure. Chronic HBV infection following acute infection develops in about 90% of infants, 25% to 50% of children aged 1 to 5 years, and 6% to 10% of older children and adolescents; individuals with immunocompromising conditions (e.g., renal failure) are also at increased risk of developing chronic HBV infection.^{7,14-18}

Infants and children most commonly acquire HBV infection perinatally or through postnatal household contact, particularly in areas of high HBV endemicity.¹⁹⁻²¹ HBV can also be acquired parenterally or through sexual transmission. Pregnant women with HIV/HBV coinfection can transmit HIV, HBV, or both perinatally; it is not known if maternal HIV coinfection modifies the risk of HBV perinatal transmission.²² Maternal HBV infection is not a contraindication to breastfeeding. Horizontal transmission of HBV can occur through interpersonal contact between non-intact skin or mucous membranes and blood or body fluids that contain HBV (e.g., injuries, wounds) or through sharing personal-care objects (e.g., toothbrushes, razors). Universal hepatitis B (HepB) vaccination of newborns has dramatically lowered chronic HBV infection in children and reduced the rates of HBV-related morbidity and mortality in the United States.²³ The risk from blood transfusions in countries with blood bank screening is estimated to be very low (1.37 per million donations).²⁴

Prevention of HBV transmission at birth among perinatally exposed infants is very effective.²⁵ A three-dose HepB vaccine regimen is 70% to 95% effective in preventing HBV infection in infants exposed to HBV and is 85% to 95% effective when combined with hepatitis B immune globulin (HBIG).²⁶ The level of antibody to hepatitis B surface antigen (anti-HBs) considered protective is ≥ 10 mIU/mL. There is an increased risk of perinatal transmission if the pregnant woman has a high circulating level of HBV DNA.

The local prevalence of HBV/HIV coinfection in children and adolescents varies widely; from 1% in one study of 371 transfused children in the Democratic Republic of Congo, to 45% in a study of 179 Romanian children with HIV diagnosed before 16 years of age, not due to perinatal transmission.^{27,28} Regional variation in the prevalence of HIV/HBV coinfection is the major determinant of risk to children from different regions. In the National Health and Nutrition Examination Survey, 2001 through 2018, the estimated antibody to hepatitis B core antigen (anti-HBc) prevalence among United States–born people aged 6 to 29 years was 0.7% (95% confidence interval [CI], 0.5% to 1.0%) during 2001 to 2006, 0.7% (95% CI, 0.5% to 1.0%) during 2007 to 2012, and 0.5% (95% CI, 0.3% to 0.8%) during 2013 to 2018.²⁹ A small case series among children with HIV at an urban hospital in the United States reported a 2.6% chronic HBV prevalence in 228 children with HIV.³⁰ A study of chronic HBV infection in children with HIV in Senegal reported a prevalence of 4.1% among 613 children.³¹

Most children who acquire HBV perinatally are initially immunotolerant to HBV (see [Phases of Chronic HBV Infection](#) for definitions) and may remain immunotolerant with chronic infection for a decade or more. Although these children have high HBV DNA levels, serum transaminase levels are usually normal, and necroinflammatory liver disease is minimal. Childhood-acquired HBV infection, in contrast, is characterized by lower HBV DNA levels, greater serum transaminase elevation, and higher necroinflammatory liver disease than in perinatally acquired HBV infection.^{8,32}

Clinical Manifestations

Most acute HBV infections in children are asymptomatic.³² Prodromal symptoms of lethargy, malaise, fatigue, nausea, and anorexia can occur. Jaundice and right-upper-quadrant pain can follow and, less commonly, hepatomegaly and splenomegaly. Gianotti-Crosti syndrome (papular acrodermatitis), urticaria, macular rash, or purpuric lesions may be seen in acute HBV infection. Extrahepatic manifestations associated with circulating immune complexes that have been reported in children with HBV infection include arthralgias, arthritis, polyarteritis nodosa, thrombocytopenia, and glomerulonephritis. However, rare cases of acute hepatic failure have occurred during perinatal and childhood HBV infection.^{33,34}

Similar to children with isolated HBV infection, most children with HIV and chronic HBV infection do not experience HBV-related symptoms related. Infants and children with chronic HBV are at an increased risk of developing cirrhosis or HCC over the course of their life, which is dependent on HBV genotype and other factors.^{35,36} However, these sequelae usually develop over two to three decades and rarely occur during childhood.^{37,38} Development of HCC correlates with HBV DNA levels, HBV genotype, and duration of HBV infection, with the highest risk in people infected in early life.³⁹ There are no data on HCC outcomes in children with HIV/HBV coinfection. However, adults with HIV/HBV coinfection are at increased risk of cirrhosis, end-stage liver disease, and liver-related mortality.^{11,40,41}

In people with HIV/HBV coinfection starting combination antiretroviral therapy (ART), serum transaminase elevations (flares) can occur as part of immune reconstitution inflammatory syndrome (IRIS)⁴² or secondary to ART-associated hepatotoxicity. HBV-associated liver injury is thought to be immune-mediated, and restoration of immunocompetence with antiretroviral (ARV) treatment may reactivate liver inflammation and damage. Initiation of ART without anti-HBV therapy can lead to reactivation of HBV. This does not represent a failure of ART but rather a sign of immune reconstitution. IRIS manifests by an increase in serum transaminase levels as the CD4 T lymphocyte (CD4) cell count increases during the first 6 to 12 weeks of ART. Thus, serum transaminase levels should be monitored closely after introduction of ART. In such situations, ART should be continued and treatment for HBV infection initiated if it is not included in the ART (see [Treatment Recommendations](#) below). The prognosis in individuals with IRIS is generally favorable because a robust inflammatory response may predict an excellent response to ART in terms of immune reconstitution, and perhaps, improved survival.⁴³ In people experiencing hepatic flare, differentiating between IRIS and drug-induced liver toxicity may be difficult, and no reliable clinical or laboratory predictor exists to distinguish between the two. Close collaboration of an HIV specialist with a specialist in hepatic disease is recommended for such scenarios; a hepatologist should be consulted promptly if elevated aminotransferase levels are associated with clinical jaundice or other evidence of liver dysfunction (e.g., low serum albumin).

Diagnosis

All children with a new HIV diagnosis should be tested for HBV infection,⁴⁴ as the HBV status could impact ARV management and monitoring.⁴⁴

HBsAg is the first detectable serologic marker, appearing 30 days after HBV infection; HBsAg precedes the elevation of serum aminotransferase levels and the onset of symptoms. Necroinflammatory liver disease can then occur, during which serum transaminase levels increase, along with high HBV DNA levels and hepatitis B e antigen (HBeAg) positivity.

HBeAg correlates with viral replication, DNA polymerase activity, infectivity, and increased severity of liver disease.

Serologic Markers for HBV

HBsAg (Hepatitis B Surface Antigen)

- **Self-limited infections:** Usually eliminated in 1 to 2 months
- **Chronic infections:** Persistently positive beyond 6 months, with no detectable anti-HBs in individuals who have never been vaccinated

Anti-HBc (Antibody to Hepatitis B Core Antigen) Immunoglobulin M

- Appears **1 to 2 weeks after HBsAg**²⁵

Anti-HBc Immunoglobulin G (IgG)

- **Persists for life**
- **Passively transferred maternal anti-HBc IgG:** Detectable in infants up to 24 months after birth²⁵

Anti-HBs (Antibody to Hepatitis B Surface Antigen)

- Develops during **convalescence** in self-limited infections
- **Indicates immunity** from HBV infection
- **Post-recovery from natural infection:** Both anti-HBs and anti-HBc IgG are present.
- **Postvaccination without prior infection:** Detectable anti-HBs but no anti-HBc or HBsAg.
- **Inadvertent vaccination after recovery from HBV infection:** Detectable anti-HBs and anti-HBc upon postvaccination testing. (See [Table 1 from the Advisory Committee on Immunization Practices' \(ACIP\) Recommendations on Hepatitis B Immunization](#) for review of interpretation of serologic test results for HBV infection.)

HBV Reactivation

- Despite immunity, HBV can be incorporated into the human genome and reactivate if a person becomes immunocompromised.⁴⁵

There are four recognized phases of chronic HBV infection. For individuals with chronic HBV infection, HBeAg seroconversion (defined as loss of HBeAg followed by HBeAg antibody [i.e., anti-HBe] production) usually marks the transition to the inactive carrier state, also known as chronic carrier state, where HBsAg remains positive. However, some people may develop HBeAg-negative chronic hepatitis. Variable rates of HBeAg seroconversion have been reported in children infected perinatally with HBV ranging from 10% to 75% in the first 2 to 4 decades, but HBeAg seroconversion is very infrequent in children aged <3 years.^{15,46} In contrast, higher rates of HBeAg seroconversion occur in childhood-acquired HBV infection, with 70% to 80% of children acquiring anti-HBe by the second decade of life.³⁷ HBeAg seroconversion usually is followed by a reduction in serum HBV DNA levels and an initial increase and then subsequent normalization of serum

transaminase levels, followed by resolution of necroinflammatory liver disease.³⁷ HBeAg seroconversion rates have not been reported for children with HIV/HBV coinfection. Development of cirrhosis and HCC is more common in patients with delayed HBeAg seroconversion.⁴⁷ HBeAg-negative infection (pre-core mutant) is uncommon in children.⁴⁸

HBV DNA is a marker for HBV replication. The immunotolerant phase is characterized by high levels of HBV replication without evidence of active liver disease. In the immunoactive phase of chronic HBV, high HBV DNA levels have been associated with necroinflammatory liver disease. Children who acquired HBV perinatally, however, may remain in an immunotolerant phase with high levels of HBV DNA without evidence of liver damage and with normal serum aminotransferase levels. Quantitative DNA assays may help determine the need for treatment and for evaluating treatment response. Although not necessary for diagnostic purposes, liver biopsy or transient elastography may be useful to assess the degree of liver damage and determine the need for treatment.^{49,50}

Phases of Chronic HBV Infection

State	HBeAg/Anti-HBe	HBV DNA ^a	ALT
Immunotolerant	Positive/Negative	>1,000,000 IU	Normal
Immunoactive	Positive/Negative	>20,000 IU	Elevated
Chronic Carrier	Negative/Positive	<2,000 IU	Normal
HBeAg-Negative Hepatitis	Negative/Positive	>10,000 IU	Elevated

^a Values are the typical ranges but can vary in specific patients.

Key: ALT = alanine aminotransferase; anti-HBe = antibody to hepatitis B e antigen; HBeAg = hepatitis B e antigen; HBV = hepatitis B virus

General Management Considerations

Children with HBV infection should be advised not to share toothbrushes or other personal-care articles that may be contaminated with blood (e.g., razors, tweezers, nail clippers) and to cover open or draining wounds.⁹ Safe sex practices should be encouraged for all sexually active adolescents and young adults with HIV; barrier precautions (e.g., latex condoms) are recommended to reduce the risk of exposure to sexually transmitted pathogens, including HBV. All children should receive hepatitis A (HepA) vaccination at age 12 to 23 months, with the two doses in the series administered at least 6 months apart.⁵¹ Children who are not fully vaccinated by age 2 years can be vaccinated at subsequent visits. The HepA vaccine is also recommended for children and adolescents aged ≥ 24 months who were not previously vaccinated; see the [Immunizations for Preventable Diseases in Children and Adolescents With HIV](#) section.²⁵ International travelers aged 6 months through 11 months are recommended for HepA vaccine if traveling internationally to areas endemic or epidemic for hepatitis A. Children and adolescents with HBV should be screened for hepatitis C virus (HCV) infection. Household contacts should have their HepB vaccination status reviewed and updated if they have not been vaccinated.

Prevention Recommendations

Preventing Exposure

I. Should all pregnant women with HIV routinely undergo testing for hepatitis B as part of antenatal care?

All pregnant women with HIV should be tested for HBV infection with HBsAg, anti-HBc, and anti-HBs during an early prenatal visit. Testing for HBsAg should be repeated in late pregnancy for HBsAg-negative people who are at high risk of HBV infection (e.g., people who inject drugs, people with intercurrent sexually transmitted infections, people with multiple sex partners). Pregnant women who do not have documentation of HepB vaccination, immunity to, or infection with HBV should be vaccinated against hepatitis B (**strong, moderate**). Evidence suggests that people with HIV are at equal or increased risk for infection with HBV compared to people without HIV.^{52,53} Multiple clinical guidelines, including the [Perinatal Guidelines](#), have addressed this issue.^{2,54}

Pregnancy is not a contraindication or precaution to HepB vaccination for people who have not previously been vaccinated; current HepB vaccines contain noninfectious HBsAg and should cause no risk to the fetus. Pregnant women who are identified as at risk of HBV infection during pregnancy should be promptly vaccinated.⁵⁵ Providers should vaccinate pregnant women needing HepB vaccination with Engerix-B, Heplisav-B, Recombivax HB, or Twinrix.⁵⁶

Preventing Disease

II. What is the optimal ARV regimen for people with HIV/HBV coinfection in the antenatal period?

ART active against both HIV and HBV is recommended; the preferred regimen should include tenofovir (tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide [TAF]) and either lamivudine (3TC) or emtricitabine (FTC) (**strong, high**).

Studies in HIV/HBV coinfection are sparse, but one small study of 35 pregnant women with HIV/HBV coinfection demonstrated a numerically higher proportion of women with undetectable HBV viral load at delivery in those who received TDF/3TC (11 of 15 participants; 73%) compared to 3TC alone (8 of 16 participants; 50%) ($P = 0.27$).⁵⁷ Studies in women with HBV mono-infection demonstrate that TDF and TAF, both approved by the U.S. Food and Drug Administration for HIV and HBV infection, can reduce HBV perinatal transmission.^{58,59} See [Intrapartum Care for People With HIV](#) in the Perinatal Guidelines for more details on prevention of HBV transmission in pregnant women with HIV/HBV coinfection.

IIIa. What is the optimal HBV prevention strategy for infants born to women with HIV/HBV coinfection?

All infants born to HBsAg-positive people should receive HepB vaccine and HBIG within 12 hours after birth, a second dose of HepB vaccine at age 1 to 2 months, and a third dose at age ≥ 6 months but not before 24 weeks (see text below for adjustments for infants $< 2,000$ grams) (**strong, high**). Infants who test negative for HIV and who do not have a response on postvaccination serologic testing (see Question IV below) to the initial vaccine series may receive a challenge dose. If the anti-HBs titer is ≤ 10 mIU/mL, then revaccination with the standard series should be performed.

The initial recommendation for vaccination of infants born to women with HIV/HBV coinfection is not different from the initial recommendation for infants born to women with HBV mono-infection (Figure 1).^{25,54} See [Hepatitis B Virus/HIV Coinfection](#) in the Perinatal Guidelines for more information. In preterm infants weighing <2,000 g, the initial vaccine dose (birth dose) should not be counted as part of the vaccine series because of the potentially reduced immunogenicity of HepB vaccine in these infants. Therefore, three additional doses of vaccine (for a total of four doses) should be administered beginning when the infant reaches 1 month of age.⁶⁰ In addition, term (birth weight $\geq 2,000$ g) and preterm (birth weight <2,000 g) infants born to women with HIV whose HBsAg status is unknown at delivery should receive the first dose of HepB vaccine within 12 hours of birth. Infants weighing <2,000 g should also receive HBIG within 12 hours of birth. Pregnant women with HIV and unknown HBsAg status should be tested as soon as possible. If the pregnant woman is determined to be HBsAg positive, infants weighing $\geq 2,000$ grams should also receive HBIG as soon as possible but no later than age 7 days. The three-dose series of HepB vaccine is also recommended for *all* children and adolescents with HIV who were not previously vaccinated (**strong, high**).

All infants >2,000 grams born to women with HIV who are HBsAg negative should also receive the HepB vaccine series, with a first dose administered during the birth hospitalization, a second dose at age 1 to 2 months, and a third dose at 6 to 18 months of age.⁶⁰⁻⁶² Dosing adjustments for infants $\leq 2,000$ grams as detailed above are similarly recommended. (**strong, high**). The third dose must be given at 24 weeks or after. The minimal interval between vaccine doses are 4 weeks between doses 1 and 2, 8 weeks between doses 2 and 3, and 16 weeks between doses 1 and 3. Although longer intervals in the last two doses result in higher antibody levels, following minimum intervals is recommended, as longer intervals may increase the risk of infection in those who have a delayed response to vaccination.⁶³

IIIb. What is the optimal initial vaccination strategy in children with HIV?

Children with HIV should receive a standard dose of HepB vaccine at 0, 1, and 6 months (**strong, high**). A double dose at 0, 1, and 6 months may also be considered (**weak, moderate**).

Children with HIV should receive the HepB vaccine series. Two randomized trials have evaluated different strategies of vaccination, with the standard dose at 0, 1, and 6 months, demonstrating response rates of 60% to 92%.^{64,65} Individuals with higher CD4 counts and HIV viral suppression are more likely to have a vaccine response. In another randomized controlled trial, higher dose of HepB vaccine or use of Twinrix (combination HepA/HepB vaccine) had a higher response rate in children with HIV compared to standard dose of HepB vaccine.⁶⁶

IV. When should infants born to women with HIV/HBV coinfection undergo post-HepB vaccination serologic testing after completion of the HepB vaccine series?

Infants born to women with HIV/HBV coinfection should have anti-HBs and HBsAg testing performed at age 9 to 12 months or 1 to 2 months after completion of the vaccine series if the final dose is delayed (**strong, moderate**) to assess for vaccine response and failure of perinatal prophylaxis.

Recent data in infants born to women without HIV has shown that the optimum time for postvaccination testing is 1 to 2 months after the last dose of a three-vaccine series.^{67,68} Testing for vaccine response should not be performed prior to 9 months of age to avoid detection of anti-HBs from neonatally administered HBIG.⁶⁰ Similar testing should be performed on children with HIV

who receive their primary HepB vaccination later. One study suggests that there is a lower response rate to HepB vaccination in HIV-exposed infants compared to non-HIV-exposed infants.⁶⁹

V. When should children and adolescents with HIV have post-HepB vaccination serologic testing after completion of the HepB vaccine series?

Due to the intermediate to high prevalence of HBV infection in people with HIV infection and clinical management implications, all infants, children, and adolescents with HIV should be tested for HBsAg as soon as possible after HIV diagnosis (**strong, high**).

In children and adolescents with HIV who receive HBV vaccination, anti-HBs testing should be performed 4 to 6 weeks after completion of the vaccine series (**strong, moderate**).

The reasoning for this testing schedule is similar to the reasoning behind the testing schedule for infants.⁶⁸ No data in individuals with HIV indicate a more delayed response to HepB vaccination. Response rates to HepB vaccination as determined by anti-HBs titers of >10 mIU/mL at 4 to 6 weeks after the last dose of vaccine have been reported to be between 29% and 71%.⁷⁰⁻⁷² Antibody responses to HepB vaccination may be diminished in children with HIV,⁷³ especially in older children, children with CD4 counts <200 cells/mm³, or children with higher HIV viral loads.⁷⁴⁻⁷⁶

VI. What is the best strategy for HBV revaccination of children with HIV who have not responded to the primary HepB vaccine series (anti-HBs <10 mIU/mL)?

If anti-HBs levels are <10 mIU/mL and the HBsAg result is negative, the Panel on Opportunistic Infections in Children With and Exposed to HIV (the Panel) now recommends that children should be revaccinated with a single dose of HepB vaccine and receive postvaccination serologic testing 1 to 2 months later. Infants whose anti-HBs remains <10 mIU/mL following single-dose revaccination should receive two additional doses of HepB vaccine to complete the second series, followed by postvaccination serologic testing 1 to 2 months after the final dose. Alternatively, based on clinical circumstances or family preference, HBsAg-negative infants with anti-HBs <10 mIU/mL may instead be revaccinated with a second, complete three-dose series, followed by postvaccination serologic testing performed 1 to 2 months after the final dose of vaccine (**strong, moderate**). See ACIP's HBV [immunization strategy](#) for more information. There are no randomized controlled trials of HBV revaccination strategies for children with HIV who had a nonresponse to the primary HepB vaccination series. A single booster vaccination only resulted in a 37% rate of protective antibody at 8 weeks in one study⁷⁷ and a 50% rate in another.⁷⁸ In contrast, several studies of revaccination with a second series demonstrated protective responses (anti-HBs titer >10 mIU/mL) in 52% to 92% of children, adolescents, and adults with HIV.⁷⁹⁻⁸³ One prospective trial of 63 Thai children with HIV on ART who were HepB vaccine nonresponders demonstrated that revaccination with a standard dose (10 mcg of recombinant vaccine) at 0, 2, and 6 months resulted in 92% of participants having anti-HBs titers ≥10 mIU/mL.⁷⁹ Limited data from studies that examined primary vaccination strategies in adolescents with HIV and revaccination strategies in adults with HIV suggest modified HepB vaccine dosing regimens—including a doubling of the standard antigen dose and use of combined HepA/HepB vaccine or using the HepB-CpG (Heplisav-b) vaccine—may increase response rates in nonresponders without HIV,⁸⁴ adult nonresponders with HIV, and adults and adolescents with HIV undergoing the primary vaccine series.^{66,85-89} Therefore, although off-label use of double-dose HepB vaccine or combination HepA/HepB vaccine may be considered for HepB vaccination or HepB-CpG in adolescents (aged ≥14 years) with HIV who are nonresponders, further studies are needed in children.⁹⁰ In the ART era, HIV virologic suppression and high CD4 counts have been associated

with higher vaccine responses in children with HIV^{77,79,80} during revaccination strategies in those who did not respond to the primary HepB vaccine series.

VII. Should individuals with HIV who have responded to HepB vaccination have ongoing assessment of HBV immunity?

In individuals who have a response to HepB vaccination (anti-HBs ≥ 10 mIU/mL), assessment of anti-HBs titers approximately every 5 years can be considered.^{91,92} If anti-HBs titers fall below 10 mIU/mL, they should be provided a booster. Anti-HBs titers should be checked 4 to 6 weeks after a booster dose (**weak, very low**). If anti-HBs is still < 10 mIU/mL, completion of the standard three-dose series should be done.⁹³

Waning of anti-HBs levels below 10 mIU/mL after HBV immunization in children with HIV is common.⁸⁰ Unlike immunocompetent individuals who have robust B and T cell immune memory, immunocompromised individuals may not mount an anamnestic response. Of individuals with HIV and the isolated HBcAb serologic profile, only 24% to 46% of patients developed an anamnestic response, as defined as an anti-HBs titer ≥ 10 mIU/mL 4 weeks after one vaccine.^{94,95} However, the need for booster doses of HepB vaccine in individuals with HIV has not been determined.⁸⁰ The American Academy of Pediatrics Committee on Infectious Disease recommends annual anti-HBs testing and booster doses when the anti-HBs levels decline to < 10 mIU/mL for hemodialysis patients and other immunocompromised people if they have an ongoing risk for HBV exposure.⁹⁶ One study of nonresponders demonstrated that 92% of children had anti-HBs titers of ≥ 10 mIU/mL after completion of the vaccine series; the population consisted of either those with primary vaccine nonresponse or waned anti-HBs titers who did not respond to a booster.⁹⁷ One study in 10 children with HIV who responded to HepB vaccine found that B-cell memory decreased after 4 years and were below appropriate levels by 6 years post-vaccine.⁹⁸ Thus, assessment of anti-HBs approximately every 5 years can be considered in children.

Treatment Recommendations

Treatment Issues in Children and Adolescents With HIV/HBV Coinfection

General Issues: There are excellent reviews of treatment of HBV infection in children.⁹⁹ The main difference in children and adolescents with HIV/HBV coinfection is that they will almost always be receiving anti-HIV treatment. This treatment generally will include an agent or agents that have antiviral activity against HBV in addition to antiviral activity against HIV. Understanding the various phases of HBV infection (see the [Phases of Chronic HBV Infection table](#) above) is important when considering choices of anti-HIV treatment and in decisions about directed anti-HBV treatment in children and adolescents with HIV/HBV coinfection. Specific directed HBV therapy in children and adolescents with HIV/HBV coinfection is restricted to those individuals in the chronic immunoactive state (HBsAg+, HBeAg+, elevated alanine aminotransferase [ALT], and HBV DNA $> 20,000$ IU for ≥ 6 months) or with HBeAg-negative chronic hepatitis (HBsAg+, HBeAg-, elevated ALT, and HBV DNA $> 10,000$ IU for ≥ 6 months). The goals of therapy are generally to normalize ALT, reduce HBV DNA, and in HBeAg-positive individuals, clear HBeAg.⁹

VIII. What ART regimens should be considered for ARV-naive children with HIV/HBV coinfection who are immunotolerant to HBV?

As most children and adolescents with HIV/HBV coinfection will be in the immunotolerant phase, the major issue is what ART regimen is appropriate for HIV/HBV coinfection for those in the immunotolerant phase.

Given the differences in medications currently available for HIV treatment and the desire to include medications with anti-HBV activity, when possible, the Panel recommends the following to minimize the development of resistance in the HBV virus:

- For children aged <2 years, a standard preferred ART regimen should be initiated. While there is a risk for development of 3TC-resistant HBV, the need to provide optimal HIV therapy outweighs this risk (**strong, high**).
- For children aged ≥2 years to <12 years, a standard preferred ART regimen should be initiated. If feasible (weight ≥14 kg), the ART regimen should include tenofovir (TDF or TAF) plus either 3TC or FTC (**strong, low**).
- For children aged ≥12 years, a standard preferred ART regimen including tenofovir (TDF or TAF) plus either 3TC or FTC should be initiated (**strong, low**).

Children with immunotolerant HBV have high HBV DNA levels but no evidence of liver damage. They respond less favorably to HBV treatment, and treatment in this stage of infection is generally not indicated.⁹ For children with HIV/HBV coinfection, this presents a dilemma. ART is recommended for all children with HIV, and medications with anti-HBV activity (e.g., 3TC or FTC) are included in the nucleoside reverse transcriptase inhibitor backbone of all regimens recommended as first-line ART, with coadministration of TDF or TAF in children weighing ≥14 kg.¹⁰⁰ However, treatment of HBV with 3TC or FTC as the only HBV-active agent (primarily in children <14 kg) is likely to lead to 3TC/FTC-resistant HBV,¹⁰¹⁻¹⁰³ which may affect future treatment options.

Inclusion of 3TC in an ART regimen has not shown clear benefit in adults with HBV/HIV,¹⁰⁴ and 3TC resistance mutations have been demonstrated in up to 50% of adults with coinfection and continued HBV viremia within 2 years of 3TC monotherapy, and increased to greater than 90% at 4 years.^{102,105,106} In a cohort of Thai adolescents with coinfection, 69% had HBV DNA levels above 10⁵ copies/mL despite 3TC therapy, and the 3TC resistance mutation rtM204V/I was found in 75% of the adolescents tested.¹⁰¹ Similarly, in a cohort of children with HIV/HBV coinfection from the Ivory Coast, 6 of 11 (55%) treated with ART containing 3TC failed to show a response to therapy based on continued high HBV DNA levels and/or persistent HBeAg, suggesting a high likelihood of 3TC resistance developing in these children.¹⁰⁷ Studies in children with HBV mono-infection have demonstrated only modest success with 3TC monotherapy, even in children with active HBV disease. In one study, only 23% of children randomized to HBV treatment with 3TC demonstrated suppression of HBV DNA and loss of HBeAg compared to 13% of those treated with placebo.¹⁰⁸ Of the nonresponders to 3TC monotherapy, 64% developed 3TC mutations after 3 years.¹⁰³ Therefore, treatment of children with HBV coinfection in the immunotolerant phase with 3TC or emtricitabine as the only HBV-active agent of the ART regimen will likely result in the development of 3TC-resistant HBV, potentially limiting future treatment options.^{109,110}

The risk of including 3TC or FTC as the only HBV-active agent in an ART regimen for children must be weighed against the need for optimal HIV treatment. ART should be initiated in infants with

HIV as soon as possible after HIV diagnosis, which would likely be prior to an HBV diagnosis. Given the limited options for ART in children <2 years of age, a standard preferred ART regimen should be provided. The goal for children with coinfection and immunotolerant HBV who are aged ≥ 2 years should also be optimal HIV treatment. Therefore, a standard preferred ART regimen should be provided. A regimen including TAF and 3TC or FTC should be considered, particularly for children ≥ 14 kg, based on extrapolation from evidence in adults with HIV/HBV coinfection^{109,111,112} and adolescents with HBV mono-infection,¹¹³ but this suggestion is limited by minimal data evaluating the use of TAF for treatment of HBV infection in children or adolescents with HBV mono-infection or HIV/HBV coinfection.¹¹⁴⁻¹¹⁶ An ongoing clinical trial of TAF in children and adolescents with HBV infection (NCT02932150) should further clarify this issue in the future.

If a child with coinfection is receiving HIV-suppressive ART including 3TC or FTC and plasma HBV DNA is detectable, HBV 3TC resistance can be assumed, particularly if they have received 3TC for 2 or more years.^{101-103,106}

IX. Should 3TC or FTC be the only HBV therapy in children with HIV/HBV coinfection who require treatment of both infections?

Children with HIV/HBV coinfection who require treatment of both infections should not be treated with 3TC or FTC as the only HBV-active agent in the regimen (**strong, moderate**).

The indications for targeting treatment for HBV infection remain the same in individuals with HIV/HBV coinfection as in HBV mono-infection. Treatment directed specifically at HBV is indicated in those children with immunoactive disease and HBeAg-negative chronic hepatitis (see the [Phases of Chronic HBV Infection table](#) above).^{3,6,99} For all the reasons given in Question VIII, the high risk of development of resistance^{102,103,105,106,110} and the impact of resistance on subsequent treatment options,^{109,110} 3TC or FTC should not be used alone in an ARV regimen for children who require treatment for both HIV and HBV infection.

X. What treatment regimens should be considered for children with HIV/HBV coinfection who require treatment of both infections?

- For children aged ≥ 2 years who require treatment for both infections, a combination ARV regimen that includes TDF (or TAF) and an anti-HBV nucleoside (either 3TC or FTC) should be considered for treatment (**strong, low**).
- For children aged ≥ 2 years, if TDF (or TAF) is not available or not tolerated, entecavir can be added to a standard ARV regimen for HBV treatment (**weak, low**).

If both HBV and HIV treatment are indicated, an ART regimen containing both tenofovir (TAF or TDF) and 3TC or FTC should be considered for use in children aged ≥ 2 years, based on extrapolation from the evidence in adults^{111,112,117,118} and adolescents^{116,119} with coinfection and in children^{114,115} and adolescents^{113,120} with HBV mono-infection. Improved virologic outcomes have been demonstrated in adults with HIV/HBV coinfection treated with tenofovir with and without 3TC or FTC with 77% to 96% achieving suppressed HBV DNA.^{111,117,121} Treatment with tenofovir resulted in HBV DNA suppression after 72 weeks of therapy in 89% of adolescents with HBV mono-infection¹¹³ and after 48 weeks in 61% of adolescents with HIV/HBV coinfection,¹¹⁶ despite prior 3TC exposure. Results of a recently completed clinical trial of TDF in children 2 to 12 years of age with HBV infection (NCT01651403) are available on [clinicaltrials.gov](#).¹¹⁵ In this study, children (mean 6 years of age) with chronic active HBV were randomized to TDF (n = 60) versus placebo

(n = 30). At Week 48, the percentage of participants treated with tenofovir with a serum HBV DNA level of <400 copies/mL was 83.6% (95% CI, 71.2–92.2) versus 7.7% (95% CI, 0.9–25.1) in those randomized to placebo ($P < 0.001$). More children in the TDF-treated group had $\geq 4\%$ decrease from baseline in spine bone mineral density at Week 48 compared to those in the placebo group (18.3% vs. 6.9%).

HBV DNA, HBeAg, and liver function should be monitored for response, as in one large study, previous 3TC therapy did affect virologic response to tenofovir in adults with HIV/HBV coinfection.¹⁰⁹

If tenofovir is not available or not tolerated, addition of entecavir to a fully suppressive ART regimen could be considered. Entecavir has been shown to be effective in children with HBV mono-infection, with HBV suppression achieved in 64% of 120 children treated with entecavir at 96 weeks.¹²⁰ However, entecavir should not be used in children with 3TC-resistant HBV, as it only has partial activity, and its use can result in development of entecavir resistance.¹¹⁰

While there are limited data on the use of TAF for treatment of HBV in young children (≤ 6 years of age),¹²² no evidence suggests TAF should be less effective than TDF. Additional options for treatment of chronic HBV in children are discussed in the [American Association for the Study of Liver Diseases Chronic Hepatitis B guidelines](#).

Agents that also have HIV activity (3TC, FTC, tenofovir, entecavir) should not be used alone without additional antiretroviral agents due to the risk of developing HIV resistance. These agents should only be used in children with HBV/HIV coinfection as a part of or in addition to a fully suppressive ART regimen. See the [Antiretroviral Therapy–Associated Adverse Effects and Management Recommendations — Hepatic Events table](#) in the Pediatric Antiretroviral Guidelines. The dose of 3TC required to treat pediatric HIV is higher than that used to treat pediatric chronic HBV infection; therefore, the higher dose of 3TC should be used in children with HIV/HBV coinfection to avoid development of 3TC-resistant HIV. If there is a need to alter the ART regimen due to HIV resistance, care must be taken to not discontinue effective anti-HBV treatment, even if it is ineffective for HIV, as a hepatitis flare may ensue. In other words, the alternative regimen must continue to have effective anti-HBV therapy in the regimen.

The goals of treatment for children with chronic HBV infection are identical to those for adults: suppression of HBV replication; normalization of serum transaminase levels; acceleration of HBeAg seroconversion (in those who are HBeAg positive); preservation of liver architecture; and prevention of long-term sequelae, such as cirrhosis and HCC.^{3,6,99} Treatment of chronic HBV infection is evolving; consultation with providers with expertise in treating chronic HBV infection in children is recommended.

Children and adolescents with HIV/HBV coinfection are at risk for long-term complications due to the coexistent HBV infection. Monitoring of HBV status and for complications should be part of ongoing care for these individuals.

XI. How often should children with HIV/HBV coinfection be monitored for HBV status and disease activity?

Children with HIV/HBV coinfection who are not receiving HBV-directed treatment should have disease monitoring (ALT for inflammation, complete blood count for platelet count and leukopenia, HBeAg/anti-HBe serostatus, HBV DNA and HBsAg/anti-HBs serostatus) like children with HBV

mono-infection (**strong, moderate**). The value of intermittent noninvasive assessment of hepatic fibrosis with techniques such as transient elastography is unclear.

Proposed Monitoring Based on Phases of Chronic HBV Infection

Status	ALT and CBC	HBeAg/Anti-HBe	HBV DNA	HBsAg/Anti-HBs
Immunotolerant	1–2 times per year	Annually	N/A	N/A
Immunoactive	Every 2 months ×3 ^a	Every 6 months	Every 6 months	N/A
Chronic Carrier	1–2 times per year	N/A	N/A	Every 2–3 years
HBeAg-Negative Chronic Hepatitis	Every 2 months ×3 ^a	N/A	Every 6 months	N/A

^a If abnormal ALT persists for 6 months, HBV treatment should be considered.⁹

Key: ALT = alanine aminotransferase; anti-HBe = antibody to hepatitis B e antigen; anti-HBs = antibody to hepatitis B surface antigen; CBC = complete blood count; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus

HBV disease activity should be closely monitored in children with HIV/HBV coinfection, with determination of serum ALT every 6 to 12 months depending on disease status. If serum transaminase levels are persistently elevated (more than twofold the upper limit of normal for ≥6 months), HBeAg, anti-HBe, and HBV DNA levels should be obtained before the initiation or escalation of anti-HBV therapy. Assessment of serum transaminases and HBV DNA levels over time can identify individuals who may be in the process of spontaneous HBeAg seroconversion and who would thus not require treatment. Liver biopsy is not required before treatment but may help to determine the severity of hepatic inflammation and fibrosis and to exclude other causes of liver disease.^{5,6}

Clinical and laboratory exacerbations of hepatitis and hepatic flare also can occur in children with HIV/HBV coinfection receiving ART if agents with anti-HBV activity are discontinued. Generally, once ARV drugs with anti-HBV activity are begun in children with HIV/HBV coinfection, they should be continued indefinitely unless contraindicated. If discontinuation of therapy for chronic HBV infection results in hepatic flare, therapy for chronic HBV should be reinstated.

The other major risk of chronic HBV infection is the development of HCC. There are conflicting data on whether the risk of HCC is elevated in individuals coinfecting with HIV/HBV. As anti-HIV regimens have improved, the risk of HCC does not seem to be increased in individuals coinfecting with HIV/HBV above the risk to individuals with chronic HBV infection. However, chronic HBV infection is associated with a lifetime incidence of HCC of 10% to 25%.¹²³

XII. How should children with HIV/HBV coinfection be monitored for HCC?

There is no difference in screening for HCC in children with HIV/HBV coinfection compared to children with HBV mono-infection. Surveillance of chronic HBV infection using abdominal ultrasound every 6 months should be performed to detect early HCC in people who have increased (e.g., people with cirrhosis or family history of HCC). Children with a lower risk for HCC should be screened every 1 to 2 years with alpha-fetoprotein (AFP) and every 1 to 2 years with liver ultrasound, or sooner if AFP is >10 mcg/mL (**weak, low**).

There is an increased risk of HCC in individuals with chronic HBV infection.¹²⁴ The risk is highest in those who have been infected for more than 40 years and have chronic hepatitis and those with cirrhosis and a family history of HCC.¹²⁴ There are no evidence-based guidelines for HCC screening in individuals with HIV/HBV coinfection.¹²⁵ There are data showing that adherence to current screening guidelines for individuals with HIV/HBV coinfection is poor.¹²⁶ Gelu-Simeon et al. have suggested that specific strategies should be determined for the group with HIV/HBV coinfection,¹²⁷ but there are no specific guidelines to date.

There has been only one study of HCC screening that included a significant number of children and adolescents with HBV.¹²⁸ That study suggested that screening with twice-yearly AFP with further evaluation, including ultrasound for AFP >15 ng/mL, improved outcomes.¹²⁸ They did not use ultrasound screening, as this study predated evidence supporting ultrasound as a preferred tool for HCC screening. A subsequent follow-up study from the same group using ultrasound and AFP >10 ng/mL demonstrated improved detection with combination screening but a higher cost.¹²⁹ HCC is also linked to presence of cirrhosis¹³⁰ and HBV genotype with genotypes C, D, and F associated with a lifetime higher risk of HCC.^{36,124} Thus, some authors have suggested genotype should also influence who is screened for HCC.

XIII. How should children with HIV who are anti-HBc positive be monitored for reactivation of HBV?

Children with HIV who are anti-HBc positive are at risk for HBV reactivation with worsening immunodeficiency or if they are treated with agents associated with a risk of HBV reactivation (e.g., cancer chemotherapy, biologics such as anti-tumor necrosis factor-alpha and direct-acting HCV antiviral therapy). For children initiating rituximab or other B-cell-depleting agents who are not on HBV-active ART, HBV antiviral therapy should be initiated. For children experiencing worsening HIV-related immunodeficiency or who are receiving cancer chemotherapy or high-dose steroids, periodic ALT and HBV DNA monitoring should be considered. For children receiving HCV therapy with direct-acting antiviral (DAA) therapy, children who are HBsAg positive should receive prophylactic HBV treatment as part of their HIV ART, and their HBV DNA should be assessed in the event of hepatotoxicity (**weak, very low**).

Individuals who are HBsAg negative and anti-HBc positive have a risk of latent HBV infection or reactivation of HBV in the setting of increased immunosuppression or with treatment of coexistent HCV with DAAs.¹³¹ Recent guidelines suggest evaluating HBV DNA among individuals who are HBsAg negative and anti-HBc positive, and that administration of a single dose of HepB vaccine should be considered.⁹ For those with undetectable HBV DNA, monitoring with ALT and HBV DNA in the setting of increased immunosuppression or treatment of coexistent HCV with DAAs is recommended.² An exception is made for those individuals receiving rituximab or B-cell-depleting agents where prophylactic treatment with HBV antiviral therapy is recommended in adults.⁹ Those with detectable HBV DNA should be managed as if they have active HBV infection. Consideration should be given to HBV prophylaxis in those at high risk for HBV reactivation.⁹

Dosing Recommendations for Prevention and Treatment of HBV in Children With HIV/HBV Coinfection

Indication	First Choice	Alternative	Comments/Special Issues
Primary Prophylaxis	<p>All Children</p> <ul style="list-style-type: none"> HepB vaccine <p>Infants Born to Women With HBV</p> <ul style="list-style-type: none"> HepB vaccine plus HBIG 	HBIG following exposure	<p>See Figure 1 for detailed vaccine recommendations.</p> <p>Primary Prophylaxis Indicated for—</p> <ul style="list-style-type: none"> All individuals who are not infected with HBV <p>Criteria for Discontinuing Primary Prophylaxis</p> <ul style="list-style-type: none"> N/A <p>Criteria for Restarting Primary Prophylaxis</p> <ul style="list-style-type: none"> N/A
Secondary Prophylaxis	HepA vaccine	N/A	<p>Secondary Prophylaxis Indicated for—</p> <ul style="list-style-type: none"> Individuals with chronic HBV infection to prevent further liver injury <p>Criteria for Discontinuing Secondary Prophylaxis</p> <ul style="list-style-type: none"> N/A <p>Criteria for Restarting Secondary Prophylaxis</p> <ul style="list-style-type: none"> N/A
Treatment	<p>Treatment of Both HIV and HBV Required</p> <p><i>Child Not Already Receiving 3TC or FTC</i></p> <ul style="list-style-type: none"> 3TC 4 mg/kg body weight (maximum 150 mg) per dose by mouth twice daily as part of a fully suppressive ART regimen For children aged ≥ 2 years, TAF as part of ART regimen with 3TC or FTC For children aged ≥ 14 kg to < 25 kg, FTC 120 mg/TAF 15 mg FDC once daily For children ≥ 25 kg, FTC 200 mg/TAF 25 mg FDC once daily, or 3TC 300 mg plus 25 mg TAF daily 	Alternative for 3TC: FTC 6 mg/kg body weight (maximum 200 mg) once daily	<p>Indications for Treatment Include—</p> <ul style="list-style-type: none"> Detectable serum HBV DNA, irrespective of HBeAg status, for > 6 months; <i>and</i> Persistent (≥ 6 months) elevation of serum transaminases (\geq twice the upper limit of normal); <i>or</i> Evidence of chronic hepatitis on liver biopsy <p>Choice of HBV treatment options for children with HIV/HBV infection depends upon whether concurrent HIV treatment is warranted.</p> <p>3TC and FTC have similar activity (and have cross-resistance) and should not</p>

Dosing Recommendations for Prevention and Treatment of HBV in Children with HIV/HBV Coinfection

Indication	First Choice	Alternative	Comments/Special Issues
	<ul style="list-style-type: none"> • Note: For children weighing <35 kg, FTC/TAF combination should not be used with protease inhibitors for HIV therapy. <p><i>Child Already Receiving ART Containing 3TC or FTC, Suggesting 3TC/FTC Resistance</i></p> <ul style="list-style-type: none"> • For children aged ≥2 years, include TDF or TAF as part of ART regimen with 3TC or FTC. <ul style="list-style-type: none"> ○ For children aged <12 years, TDF 8 mg/kg body weight per dose once daily (maximum dose 300mg) ○ For children aged ≥12 years, TAF 25 mg once daily • For children aged ≥12 years, add entecavir 0.5 mg by mouth once daily in addition to ART regimen. 		<p>be given together. FTC is not FDA-approved for treatment of HBV.</p> <p>TAF is approved for use in treatment of HIV in children aged ≥2 years but it is not approved for treatment of HBV infection in children aged <12 years. It should only be used for HBV in children with HIV/HBV coinfection as part of an ART regimen.</p> <p>Entecavir is approved for use in children without HIV ≥2 years of age for treatment of chronic HBV. It should only be used for HBV in children with HIV/HBV coinfection who also receive an HIV-suppressive ART regimen but cannot use or access tenofovir.</p> <p>IRIS may be manifested by dramatic increase in transaminases as CD4 counts rise within the first 6–12 weeks of ART. It may be difficult to distinguish between drug-induced hepatotoxicity and other causes of hepatitis and IRIS.</p> <p>In children receiving TDF or TAF and 3TC or FTC, clinical and laboratory exacerbations of hepatitis (flare) may occur if the drug is discontinued; thus, once anti-HIV/HBV therapy has begun, it should be continued unless contraindicated or until the child has been treated for >12 months after HBeAg seroconversion and can be closely monitored on discontinuation.</p> <p>If anti-HBV therapy is discontinued and a flare occurs, reinstitution of therapy is recommended because a flare can be life threatening.</p>

Key: 3TC = lamivudine; ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; FDA = U.S. Food and Drug Administration; FDC = fixed dose combination; FTC = emtricitabine; HBeAg = hepatitis B antigen; HBIG = hepatitis B immune globulin; HBV = hepatitis B virus; HepA = hepatitis A [vaccine]; HepB = hepatitis B [vaccine]; IRIS = immune reconstitution inflammatory syndrome; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

References

1. Committee on Infectious Diseases, American Academy of Pediatrics. Hepatitis B. Red book: 2021–2024 report of the committee on infectious diseases (32nd edition). 2021:381–399. Available at: <https://publications.aap.org/redbook/book/347/chapter-abstract/5752538/Hepatitis-B?redirectedFrom=fulltext>.
2. Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int*. 2016;10(1):1-98. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26563120>.
3. Sokal EM, Paganelli M, Wirth S, et al. Management of chronic hepatitis B in childhood: ESPGHAN clinical practice guidelines: consensus of an expert panel on behalf of the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition. *J Hepatol*. 2013;59(4):814-829. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23707367>.
4. Sarri G, Westby M, Bermingham S, Hill-Cawthorne G, Thomas H, Guideline Development Group. Diagnosis and management of chronic hepatitis B in children, young people, and adults: summary of NICE guidance. *BMJ*. 2013;346:f3893. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23804177>.
5. Haber BA, Block JM, Jonas MM, et al. Recommendations for screening, monitoring, and referral of pediatric chronic hepatitis B. *Pediatrics*. 2009;124(5):e1007-1013. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19805457>.
6. Jonas MM, Block JM, Haber BA, et al. Treatment of children with chronic hepatitis B virus infection in the United States: patient selection and therapeutic options. *Hepatology*. 2010;52(6):2192-2205. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20890947>.
7. Indolfi G, Easterbrook P, Dusheiko G, et al. Hepatitis B virus infection in children and adolescents. *Lancet Gastroenterol Hepatol*. 2019;4(6):466-476. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30982722>.
8. Stinco M, Rubino C, Trapani S, Indolfi G. Treatment of hepatitis B virus infection in children and adolescents. *World J Gastroenterol*. 2021;27(36):6053-6063. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34629819>.
9. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology*. 2018;67(4):1560-1599. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29405329>.
10. Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: hepatitis B virus infection. 2023. Available at: <https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/hepatitis-b-0?view=full>.
11. Corcorran MA, Kim N. Chronic hepatitis B and HIV coinfection. *Top Antivir Med*. 2023;31(1):14-22. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/37018732>.

12. World Health Organization. Global hepatitis report 2024: action for access in low- and middle-income countries. World Health Organization. 2024. Available at: <https://www.who.int/publications/i/item/9789240091672>
13. Centers for Disease Control and Prevention. Hepatitis B, acute and chronic 2024 case definition. 2024. Available at: <https://ndc.services.cdc.gov/case-definitions/hepatitis-b-acute-and-chronic-2024/#print>.
14. Hyams KC. Risks of chronicity following acute hepatitis B virus infection: a review. *Clin Infect Dis*. 1995;20(4):992-1000. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7795104>.
15. Lee WM, King WC, Janssen HLA, et al. Hepatitis B e antigen loss in adults and children with chronic hepatitis B living in North America: a prospective cohort study. *J Viral Hepat*. 2021;28(11):1526-1538. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34355475>.
16. Mo S, Au L, Huang S, Malik P, Pan DH. Natural history of chronic hepatitis B infection among Chinese children and young adults: a single-center experience. *J Pediatr Gastroenterol Nutr*. 2021;73(2):150-155. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33661243>.
17. Yang Y, Huang A, Zhao Y. Spontaneous loss of chronic HBV infection markers in treatment-naïve children: a systematic review and pooled meta-analyses. *Expert Rev Anti Infect Ther*. 2021;19(5):649-660. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33164585>.
18. Takano T, Tajiri H, Hosono S, et al. Natural history of chronic hepatitis B virus infection in children in Japan: a comparison of mother-to-child transmission with horizontal transmission. *J Gastroenterol*. 2017;52(9):1041-1050. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28184998>.
19. Long SS PC, Fischer M, Kimberlin D, editors. Principles and practice of pediatric infectious diseases. 6th ed.: Elsevier Health Sciences. 2022. Available at: <https://www.sciencedirect.com/book/9780323401814/principles-and-practice-of-pediatric-infectious-diseases>
20. Bernier RH, Sampliner R, Gerety R, Tabor E, Hamilton F, Nathanson N. Hepatitis B infection in households of chronic carriers of hepatitis B surface antigen: factors associated with prevalence of infection. *Am J Epidemiol*. 1982;116(2):199-211. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/7114032>.
21. Gunardi H, Iskandar MY, Turyadi, et al. Hepatitis B virus infection in children of HBV-related chronic liver disease patients: a study of intra-familial HBV transmission. *Hepatol Int*. 2017;11(1):96-104. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27624502>.
22. Bhattacharya D, Guo R, Tseng CH, et al. Maternal HBV viremia and association with adverse infant outcomes in women living with HIV and HBV. *Pediatr Infect Dis J*. 2021;40(2):e56-e61. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33181788>.

23. Wasley A, Kruszon-Moran D, Kuhnert W, et al. The prevalence of hepatitis B virus infection in the United States in the era of vaccination. *J Infect Dis.* 2010;202(2):192-201. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20533878>.
24. Brant LJ, Reynolds C, Byrne L, Davison KL. Hepatitis B and residual risk of infection in English and Welsh blood donors, 1996 through 2008. *Transfusion.* 2011;51(7):1493-1502. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21470235>.
25. Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep.* 2018;67(1):1-31. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29939980>.
26. Chen ZX, Zhuang X, Zhu XH, et al. Comparative effectiveness of prophylactic strategies for perinatal transmission of hepatitis B virus: a network meta-analysis of randomized controlled trials. *Open Forum Infect Dis.* 2017;4(4):ofx225. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29181424>.
27. Katabuka M, Mafuta ME, Ngoma AM, et al. Prevalence and risk factors for hepatitis C virus, hepatitis B virus, and human immunodeficiency virus in transfused children in Kinshasa. *Indian J Pediatr.* 2013;80(8):659-662. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23180402>.
28. Arbune M, Georgescu C. Characteristics of hepatitis B co-infection and disease evolution in HIV-positive paediatric patients in Romania. *Balkan Med J.* 2013;30(3):263-267. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25207116>.
29. Ly KN, Xing J, Spradling PR. Trends in prevalence and characteristics of resolved and current hepatitis B among US-born persons: National Health and Nutrition Examination Survey, 2001–2018. *J Infect Dis.* 2021;224(5):804-812. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33903902>.
30. Toussi SS, Abadi J, Rosenberg M, Levanon D. Prevalence of hepatitis B and C virus infections in children infected with HIV. *Clin Infect Dis.* 2007;45(6):795-798. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17712766>.
31. Toyé RM, Lo G, Diop-Ndiaye H, et al. Prevalence and molecular characterization of hepatitis B virus infection in HIV-infected children in Senegal. *Clin Res Hepatol Gastroenterol.* 2021;45(2):101502. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32828748>.
32. McMahon BJ, Alward WL, Hall DB, et al. Acute hepatitis B virus infection: relation of age to the clinical expression of disease and subsequent development of the carrier state. *J Infect Dis.* 1985;151(4):599-603. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3973412>.
33. Tovo PA, Lazier L, Versace A. Hepatitis B virus and hepatitis C virus infections in children. *Curr Opin Infect Dis.* 2005;18(3):261-266. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15864105>.

34. Delaplane D, Yogev R, Crussi F, Shulman ST. Fatal hepatitis B in early infancy: the importance of identifying HBsAg-positive pregnant women and providing immunoprophylaxis to their newborns. *Pediatrics*. 1983;72(2):176-180. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/6683400>.
35. Huang YT, Jen CL, Yang HI, et al. Lifetime risk and sex difference of hepatocellular carcinoma among patients with chronic hepatitis B and C. *J Clin Oncol*. 2011;29(27):3643-3650. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21859997>.
36. Lin CL, Kao JH. Natural history of acute and chronic hepatitis B: The role of HBV genotypes and mutants. *Best Pract Res Clin Gastroenterol*. 2017;31(3):249-255. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28774406>.
37. Bortolotti F, Guido M, Bartolacci S, et al. Chronic hepatitis B in children after e antigen seroclearance: final report of a 29-year longitudinal study. *Hepatology*. 2006;43(3):556-562. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16496323>.
38. Chang MH, You SL, Chen CJ, et al. Decreased incidence of hepatocellular carcinoma in hepatitis B vaccinees: a 20-year follow-up study. *J Natl Cancer Inst*. 2009;101(19):1348-1355. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19759364>.
39. Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA*. 2006;295(1):65-73. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16391218>.
40. Koziel MJ, Peters MG. Viral hepatitis in HIV infection. *N Engl J Med*. 2007;356(14):1445-1454. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17409326>.
41. Thio CL, Seaberg EC, Skolasky R, Jr., et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet*. 2002;360(9349):1921-1926. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12493258>.
42. Iannetta M, Crea AMA, Di Lorenzo A, et al. Hepatitis B-related hepatic flare during immune reconstitution syndrome after antiretroviral treatment initiation in an HBV surface antigen-positive patient with HIV: viroimmunological and histological characterization. *Open Forum Infect Dis*. 2022;9(9):ofac451. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/36092833>.
43. Yoshikawa S, Yoshio S, Yoshida Y, et al. Impact of immune reconstitution-induced hepatic flare on hepatitis B surface antigen loss in hepatitis B virus/human immunodeficiency virus-1 coinfecting patients. *J Infect Dis*. 2021;223(12):2080-2089. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33073291>.
44. Connors EE, Panagiotakopoulos L, Hofmeister MG, et al. Screening and testing for hepatitis B virus infection: CDC recommendations - United States, 2023. *MMWR Recomm Rep*. 2023;72(1):1-25. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/36893044>.
45. Lok AS, Ward JW, Perrillo RP, McMahon BJ, Liang TJ. Reactivation of hepatitis B during immunosuppressive therapy: potentially fatal yet preventable. *Ann Intern Med*. 2012;156(10):743-745. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22586011>.

46. Chang MH, Hsu HY, Hsu HC, Ni YH, Chen JS, Chen DS. The significance of spontaneous hepatitis B e antigen seroconversion in childhood: with special emphasis on the clearance of hepatitis B e antigen before 3 years of age. *Hepatology*. 1995;22(5):1387-1392. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7590652>.
47. Chu CM, Hung SJ, Lin J, Tai DI, Liaw YF. Natural history of hepatitis B e antigen to antibody seroconversion in patients with normal serum aminotransferase levels. *Am J Med*. 2004;116(12):829-834. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15178498>.
48. Arnone OC, Serranti D, Bartolini E, et al. Chronic hepatitis B in children, report of a single-centre longitudinal study on 152 children. *J Viral Hepat*. 2020;27(12):1344-1351. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32853482>.
49. Merchante N, Tellez F, Rivero-Juarez A, et al. Progression of liver stiffness predicts clinical events in HIV/HCV-coinfected patients with compensated cirrhosis. *BMC Infect Dis*. 2015;15:557. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26643257>.
50. Fitzpatrick E, Quaglia A, Vimalasvaran S, Basso MS, Dhawan A. Transient elastography is a useful noninvasive tool for the evaluation of fibrosis in paediatric chronic liver disease. *J Pediatr Gastroenterol Nutr*. 2013;56(1):72-76. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22922372>.
51. Nelson NP, Weng MK, Hofmeister MG, et al. Prevention of hepatitis A virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices, 2020. *MMWR Recomm Rep*. 2020;69(5):1-38. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32614811>.
52. Zaongo SD, Ouyang J, Chen Y, Jiao YM, Wu H, Chen Y. HIV infection predisposes to increased chances of HBV infection: current understanding of the mechanisms favoring HBV infection at each clinical stage of HIV infection. *Front Immunol*. 2022;13:853346. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35432307>.
53. Mayaphi SH, Roussow TM, Masemola DP, Olorunju SA, Mphahlele MJ, Martin DJ. HBV/HIV co-infection: the dynamics of HBV in South African patients with AIDS. *S Afr Med J*. 2012;102(3 Pt 1):157-162. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22380911>.
54. Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission. Recommendations for the use of antiretroviral drugs during pregnancy and interventions to reduce perinatal HIV transmission in the United States. 2023:193. Available at: <https://clinicalinfo.hiv.gov/en/guidelines/perinatal/whats-new?view=full>.
55. Centers for Disease Control and Prevention. Guidelines for vaccinating pregnant women. 2024. Available at: <https://www.cdc.gov/vaccines-pregnancy/hcp/vaccination-guidelines/index.html>.
56. Sandul AL, Rapposelli K, Nyendak M, Kim M. Updated recommendation for universal hepatitis B vaccination in adults aged 19–59 years - United States, 2024. *MMWR Morb Mortal Wkly Rep*. 2024;73(48):1106. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/39636783>.

57. Wang L, Wiener J, Bulterys M, et al. Hepatitis B virus (HBV) load response to 2 antiviral regimens, tenofovir/lamivudine and lamivudine, in HIV/ HBV-coinfected pregnant women in Guangxi, China: the Tenofovir in Pregnancy (TiP) Study. *J Infect Dis.* 2016;214(11):1695-1699. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27658693>.
58. Pan CQ, Duan Z, Dai E, et al. Tenofovir to prevent hepatitis B transmission in mothers with high viral load. *N Engl J Med.* 2016;374(24):2324-2334. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27305192>.
59. Zeng QL, Yu ZJ, Ji F, et al. Tenofovir alafenamide to prevent perinatal hepatitis B transmission: a multicenter, prospective, observational study. *Clin Infect Dis.* 2021;73(9):e3324-e3332. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33395488>.
60. Mast EE, Margolis HS, Fiore AE, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part 1: immunization of infants, children, and adolescents. *MMWR Recomm Rep.* 2005;54(RR-16):1-31. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16371945>.
61. American Academy of Pediatrics. Red Book: 2012 Report of the Committee on Infectious Diseases. 2015. Available at: <https://publications.aap.org/aapbooks/book/603/Red-Book-2012-Report-of-the-Committee-on->
62. Centers for Disease Control and Prevention. Implementation of newborn hepatitis B vaccination--worldwide, 2006. *MMWR Morb Mortal Wkly Rep.* 2008;57(46):1249-1252. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19023261>.
63. Jilg W, Schmidt M, Deinhardt F. Vaccination against hepatitis B: comparison of three different vaccination schedules. *J Infect Dis.* 1989;160(5):766-769. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2530289>.
64. Bunupuradah T, Ananworanich J, Pancharoen C, et al. Randomized study of intradermal compared to intramuscular hepatitis B vaccination in HIV-infected children without severe immunosuppression. *Vaccine.* 2011;29(16):2962-2967. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21329776>.
65. Jain P, Dewan P, Gomber S, Kashyap B, Raizada A. Three vs four dose schedule of double strength recombinant hepatitis-B vaccine in HIV-infected children: a randomized controlled trial. *Indian Pediatr.* 2021;58(3):224-228. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33713056>.
66. Flynn PM, Cunningham CK, Rudy B, et al. Hepatitis B vaccination in HIV-infected youth: a randomized trial of three regimens. *J Acquir Immune Defic Syndr.* 2011;56(4):325-332. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21350366>.
67. Ko SC, Schillie SF, Walker T, et al. Hepatitis B vaccine response among infants born to hepatitis B surface antigen-positive women. *Vaccine.* 2014;32(18):2127-2133. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24560676>.

68. Schillie S, Murphy TV, Fenlon N, Ko S, Ward JW. Update: shortened interval for postvaccination serologic testing of infants born to hepatitis B-infected mothers. *MMWR Morb Mortal Wkly Rep*. 2015;64(39):1118-1120. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26447601>.
69. Abramczuk BM, Mazzola TN, Moreno YM, et al. Impaired humoral response to vaccines among HIV-exposed uninfected infants. *Clin Vaccine Immunol*. 2011;18(9):1406-1409. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21775515>.
70. Mutwa PR, Boer KR, Rusine JB, et al. Hepatitis B virus prevalence and vaccine response in HIV-infected children and adolescents on combination antiretroviral therapy in Kigali, Rwanda. *Pediatr Infect Dis J*. 2013;32(3):246-251. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22976050>.
71. Pippi F, Bracciale L, Stolzuoli L, et al. Serological response to hepatitis B virus vaccine in HIV-infected children in Tanzania. *HIV Med*. 2008;9(7):519-525. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18554311>.
72. Haban H, Benchekroun S, Sadeq M, et al. Assessment of the HBV vaccine response in a group of HIV-infected children in Morocco. *BMC Public Health*. 2017;17(1):752. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28962610>.
73. Shaver ZM, Anderson M, Bhebhe L, et al. Decreased hepatitis B virus vaccine response among HIV-positive infants compared with HIV-negative infants in Botswana. *AIDS*. 2022;36(6):755-762. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35113045>.
74. Rutstein RM, Rudy B, Codispoti C, Watson B. Response to hepatitis B immunization by infants exposed to HIV. *AIDS*. 1994;8(9):1281-1284. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7802981>.
75. Siriaksorn S, Puthanakit T, Sirisanthana T, Sirisanthana V. Prevalence of protective antibody against hepatitis B virus in HIV-infected children with immune recovery after highly active antiretroviral therapy. *Vaccine*. 2006;24(16):3095-3099. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16488516>.
76. Aурpibul L, Kariminia A, Vibol U, et al. Seroprevalence of hepatitis B among HIV-infected children and adolescents receiving antiretroviral therapy in the TREAT Asia Pediatric HIV Observational Database. *Pediatr Infect Dis J*. 2018;37(8):788-793. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29846357>.
77. Abzug MJ, Warshaw M, Rosenblatt HM, et al. Immunogenicity and immunologic memory after hepatitis B virus booster vaccination in HIV-infected children receiving highly active antiretroviral therapy. *J Infect Dis*. 2009;200(6):935-946. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19663708>.
78. Giacomet V, Masetti M, Nannini P, et al. Humoral and cell-mediated immune responses after a booster dose of HBV vaccine in HIV-infected children, adolescents and young adults. *PLoS One*. 2018;13(2):e0192638. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29444185>.

79. Lao-araya M, Puthanakit T, Aурpibul L, Sirisanthana T, Sirisanthana V. Antibody response to hepatitis B re-vaccination in HIV-infected children with immune recovery on highly active antiretroviral therapy. *Vaccine*. 2007;25(29):5324-5329. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17566615>.
80. Lao-Araya M, Puthanakit T, Aурpibul L, Taecharoenkul S, Sirisanthana T, Sirisanthana V. Prevalence of protective level of hepatitis B antibody 3 years after revaccination in HIV-infected children on antiretroviral therapy. *Vaccine*. 2011;29(23):3977-3981. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21473954>.
81. de Vries-Sluijs TE, Hansen BE, van Doornum GJ, et al. A prospective open study of the efficacy of high-dose recombinant hepatitis B rechallenge vaccination in HIV-infected patients. *J Infect Dis*. 2008;197(2):292-294. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18177248>.
82. Cruciani M, Mengoli C, Serpelloni G, et al. Serologic response to hepatitis B vaccine with high dose and increasing number of injections in HIV infected adult patients. *Vaccine*. 2009;27(1):17-22. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18984022>.
83. Rey D, Krantz V, Partisani M, et al. Increasing the number of hepatitis B vaccine injections augments anti-HBs response rate in HIV-infected patients. Effects on HIV-1 viral load. *Vaccine*. 2000;18(13):1161-1165. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10649616>.
84. Cardell K, Akerlind B, Sallberg M, Fryden A. Excellent response rate to a double dose of the combined hepatitis A and B vaccine in previous nonresponders to hepatitis B vaccine. *J Infect Dis*. 2008;198(3):299-304. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18544037>.
85. Potsch DV, Oliveira ML, Ginuino C, et al. High rates of serological response to a modified hepatitis B vaccination schedule in HIV-infected adults subjects. *Vaccine*. 2010;28(6):1447-1450. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19995540>.
86. Pettit NN, DePestel DD, Malani PN, Riddell J. Factors associated with seroconversion after standard dose hepatitis B vaccination and high-dose revaccination among HIV-infected patients. *HIV Clin Trials*. 2010;11(6):332-339. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21239361>.
87. Rey D, Piroth L, Wendling MJ, et al. Safety and immunogenicity of double-dose versus standard-dose hepatitis B revaccination in non-responding adults with HIV-1 (ANRS HB04 B-BOOST): a multicentre, open-label, randomised controlled trial. *Lancet Infect Dis*. 2015;15(11):1283-1291. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26257021>.
88. Chaiklang K, Wipasa J, Chaiwarith R, Preparattapan J, Supparatpinyo K. Comparison of immunogenicity and safety of four doses and four double doses vs. standard doses of hepatitis B vaccination in HIV-infected adults: a randomized, controlled trial. *PLoS One*. 2013;8(11):e80409. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24265819>.

89. Launay O, van der Vliet D, Rosenberg AR, et al. Safety and immunogenicity of 4 intramuscular double doses and 4 intradermal low doses vs standard hepatitis B vaccine regimen in adults with HIV-1: a randomized controlled trial. *JAMA*. 2011;305(14):1432-1440. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21486976>.
90. Reilly-Evans B, Dudzik B, Costlow DJ, et al. Observational study evaluating the seroprotection of HepB-alum vaccine and HepB-CpG vaccine in people with HIV. *Open Forum Infect Dis*. 2023;10(6):ofad267. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/37389224>.
91. Ferdous S, Karim AB, Ahmmed MF, Azad AK. Immunity after primary hepatitis B vaccination in children 7 years or more attending a tertiary care hospital. *Mymensingh Med J*. 2022;31(2):385-394. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35383755>.
92. Salama I, Sami S, Saleh R, et al. Immunogenicity of compulsory and booster doses of hepatitis B vaccine among children in Cairo, Egypt. *J Egypt Public Health Assoc*. 2017;92(2):77-85. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30184404>.
93. Murthy N, Wodi AP, McNally V, Cineas S, Ault K. Advisory Committee on Immunization Practices recommended immunization schedule for adults aged 19 years or older - United States, 2023. *MMWR Morb Mortal Wkly Rep*. 2023;72(6):141-144. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/36757861>.
94. Gandhi RT, Wurcel A, Lee H, et al. Response to hepatitis B vaccine in HIV-1-positive subjects who test positive for isolated antibody to hepatitis B core antigen: implications for hepatitis B vaccine strategies. *J Infect Dis*. 2005;191(9):1435-1441. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15809901>.
95. Piroth L, Launay O, Michel ML, et al. Vaccination against hepatitis B virus (HBV) in HIV-1-infected patients with isolated anti-HBV core antibody: the ANRS HB EP03 CISOVAC prospective study. *J Infect Dis*. 2016;213(11):1735-1742. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26768256>.
96. American Academy of Pediatrics. Red Book: 2024–2027 Report of the Committee on Infectious Diseases. 33rd ed.: American Academy of Pediatrics. 2024. Available at: <https://publications.aap.org/redbook/book/755/Red-Book-2024-2027-Report-of-the-Committee-on>
97. Salama, II, Sami SM, Salama SI, et al. Immune response to second vaccination series of hepatitis B virus among booster dose non-responders. *Vaccine*. 2016;34(16):1904-1908. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26930367>.
98. Contreras GA, Rodriguez G, Del Bianco G, Perez N, Murphy JR, Heresi GP. Durability of cellular and humoral immunity after primary and booster hepatitis B vaccination of individuals living with perinatally acquired HIV. *Open Forum Infect Dis*. 2023;10(2):ofad070. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/36846609>.
99. Terrault NA, Bzowej NH, Chang KM, et al. AASLD guidelines for treatment of chronic hepatitis B. *Hepatology*. 2016;63(1):261-283. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26566064>.

100. Panel on Antiretroviral Therapy and Medical Management of Children Living With HIV. Guidelines for the use of antiretroviral agents in pediatric HIV infection. What to start: regimens recommended for initial therapy of antiretroviral-naive children. 2024. Available at: <https://clinicalinfo.hiv.gov/en/guidelines/pediatric-arv/regimens-recommended-initial-therapy-antiretroviral-naive-children?view=full>.
101. Aurpibul L, Lumbiganon P, Kolasaraksa P, et al. HIV and hepatitis B coinfection among perinatally HIV-infected Thai adolescents. *Pediatr Infect Dis J*. 2012;31(9):943-947. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22592516>.
102. Matthews GV, Bartholomeusz A, Locarnini S, et al. Characteristics of drug resistant HBV in an international collaborative study of HIV-HBV-infected individuals on extended lamivudine therapy. *AIDS*. 2006;20(6):863-870. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16549970>.
103. Sokal EM, Kelly DA, Mizerski J, et al. Long-term lamivudine therapy for children with HBeAg-positive chronic hepatitis B. *Hepatology*. 2006;43(2):225-232. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16440364>.
104. Matthews GV, Manzini P, Hu Z, et al. Impact of lamivudine on HIV and hepatitis B virus-related outcomes in HIV/hepatitis B virus individuals in a randomized clinical trial of antiretroviral therapy in southern Africa. *AIDS*. 2011;25(14):1727-1735. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21716078>.
105. Iacomi F, Vincenti D, Vairo F, et al. Effect of HIV co-infection on mutation patterns of HBV in patients with lamivudine-resistant chronic hepatitis B. *J Med Virol*. 2009;81(7):1151-1156. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19475624>.
106. Pal A, Sarkar N, Saha D, et al. High incidence of lamivudine-resistance-associated vaccine-escape HBV mutants among HIV-coinfected patients on prolonged antiretroviral therapy. *Antivir Ther*. 2015;20(5):545-554. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25654813>.
107. Rouet F, Chaix ML, Inwoley A, et al. Frequent occurrence of chronic hepatitis B virus infection among West African HIV type-1-infected children. *Clin Infect Dis*. 2008;46(3):361-366. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18171303>.
108. Jonas MM, Mizerski J, Badia IB, et al. Clinical trial of lamivudine in children with chronic hepatitis B. *N Engl J Med*. 2002;346(22):1706-1713. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12037150>.
109. Kim HN, Rodriguez CV, Van Rompaey S, et al. Factors associated with delayed hepatitis B viral suppression on tenofovir among patients coinfecting with HBV-HIV in the CNICS cohort. *J Acquir Immune Defic Syndr*. 2014;66(1):96-101. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24500175>.
110. Lee JH, Cho Y, Lee DH, et al. Prior exposure to lamivudine increases entecavir resistance risk in chronic hepatitis B patients without detectable lamivudine resistance. *Antimicrob Agents Chemother*. 2014;58(3):1730-1737. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24395227>.

111. Boyd A, Moh R, Gabillard D, et al. Low risk of lamivudine-resistant HBV and hepatic flares in treated HIV-HBV-coinfected patients from Cote d'Ivoire. *Antivir Ther.* 2015;20(6):643-654. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25852125>.
112. Kosi L, Reiberger T, Payer BA, et al. Five-year on-treatment efficacy of lamivudine-, tenofovir- and tenofovir + emtricitabine-based HAART in HBV-HIV-coinfected patients. *J Viral Hepat.* 2012;19(11):801-810. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23043387>.
113. Murray KF, Szenborn L, Wysocki J, et al. Randomized, placebo-controlled trial of tenofovir disoproxil fumarate in adolescents with chronic hepatitis B. *Hepatology.* 2012;56(6):2018-2026. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22544804>.
114. Choe JY, Ko JS, Choe BH, et al. Antiviral efficacy of tenofovir monotherapy in children with nucleos(t)ide-naïve chronic hepatitis B. *J Korean Med Sci.* 2018;33(2):e11. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29215820>.
115. National Institutes of Health. Study to evaluate the antiviral efficacy, safety and tolerability of tenofovir disoproxil fumarate versus placebo in pediatric participants with chronic hepatitis B infection. 2022. Available at: <https://clinicaltrials.gov/ct2/show/results/NCT01651403?term=01651403&rank=1>.
116. Aurpibul L, Lumbiganon P, Hansudewechakul R, et al. Response to tenofovir among lamivudine-experienced hepatitis B and HIV coinfected adolescents. *Pediatr Infect Dis J.* 2016. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/28005687>.
117. Matthews GV, Avihingsanon A, Lewin SR, et al. A randomized trial of combination hepatitis B therapy in HIV/HBV coinfected antiretroviral naïve individuals in Thailand. *Hepatology.* 2008;48(4):1062-1069. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18697216>.
118. Schmutz G, Nelson M, Lutz T, et al. Combination of tenofovir and lamivudine versus tenofovir after lamivudine failure for therapy of hepatitis B in HIV-coinfection. *AIDS.* 2006;20(15):1951-1954. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16988516>.
119. Chu M, Cho SM, Choe BH, Cho MH, Kwon S, Lee WK. Virologic responses to add-on adefovir dipivoxil treatment versus entecavir monotherapy in children with lamivudine-resistant chronic hepatitis B. *J Pediatr Gastroenterol Nutr.* 2012;55(6):648-652. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22688509>.
120. Jonas MM, Chang MH, Sokal E, et al. Randomized, controlled trial of entecavir versus placebo in children with hepatitis B envelope antigen-positive chronic hepatitis B. *Hepatology.* 2016;63(2):377-387. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26223345>.
121. Huang YS, Chang SY, Sheng WH, et al. Virological response to tenofovir disoproxil fumarate in HIV-positive patients with lamivudine-resistant hepatitis B virus coinfection in an area hyperendemic for hepatitis B virus infection. *PLoS One.* 2016;11(12):e0169228. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/28033344>.

122. Gallant J, Brunetta J, Crofoot G, et al. Brief report: efficacy and safety of switching to a single-tablet regimen of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide in HIV-1/hepatitis B-coinfected adults. *J Acquir Immune Defic Syndr*. 2016;73(3):294-298. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27171740>.
123. McGlynn KA, Petrick JL, London WT. Global epidemiology of hepatocellular carcinoma: an emphasis on demographic and regional variability. *Clin Liver Dis*. 2015;19(2):223-238. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25921660>.
124. Raffetti E, Fattovich G, Donato F. Incidence of hepatocellular carcinoma in untreated subjects with chronic hepatitis B: a systematic review and meta-analysis. *Liver Int*. 2016;36(9):1239-1251. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27062182>.
125. Korean Association for the Study of the L. KASL clinical practice guidelines: management of chronic hepatitis B. *Clin Mol Hepatol*. 2016;22(1):18-75. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27044762>.
126. Hearn B, Chasan R, Bichoupan K, et al. Low adherence of HIV providers to practice guidelines for hepatocellular carcinoma screening in HIV/hepatitis B coinfection. *Clin Infect Dis*. 2015;61(11):1742-1748. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26240206>.
127. Gelu-Simeon M, Sobesky R, Haim-Boukobza S, et al. Do the epidemiology, physiological mechanisms and characteristics of hepatocellular carcinoma in HIV-infected patients justify specific screening policies? *AIDS*. 2014;28(10):1379-1391. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24785953>.
128. McMahon BJ, Bulkow L, Harpster A, et al. Screening for hepatocellular carcinoma in Alaska natives infected with chronic hepatitis B: a 16-year population-based study. *Hepatology*. 2000;32(4 Pt 1):842-846. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11003632>.
129. Gounder PP, Bulkow LR, Meltzer MI, et al. Cost-effectiveness analysis of hepatocellular carcinoma screening by combinations of ultrasound and alpha-fetoprotein among Alaska Native people, 1983–2012. *Int J Circumpolar Health*. 2016;75:31115. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27197711>.
130. Zhang XF, Liu XM, Wei T, et al. Clinical characteristics and outcome of hepatocellular carcinoma in children and adolescents. *Pediatr Surg Int*. 2013;29(8):763-770. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23794023>.
131. De Monte A, Courjon J, Anty R, et al. Direct-acting antiviral treatment in adults infected with hepatitis C virus: reactivation of hepatitis B virus coinfection as a further challenge. *J Clin Virol*. 2016;78:27-30. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26967675>.