Hepatitis B Virus Infection and the Progress toward its Elimination

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Hepatitis B virus (HBV) infection is a major global health problem and may cause acute, fulminant, chronic hepatitis, liver cirrhosis, or hepatocellular carcinoma (HCC).[1,2] In May 2016, the World Health Assembly adopted the first Global Health Sector Strategy on Viral Hepatitis, 2016-2021. The strategy has a vision of eliminating viral hepatitis as a public health problem. The global targets are set to reduce new viral hepatitis infections by 90% and reduce deaths attributable to viral hepatitis by 65% by 2030 (http://www.who.int/mediacentre/factsheets/fs204/en/). Because mother-to-infant transmission (MTIT) is an important route of HBV transmission, the strategy of eliminating HBV infection should start from the fetal and infancy period.

Among the strategies to eliminate HBV infection, HBV vaccination is the most cost-effective way to prevent new HBV infection and its complications. Despite the availability of effective HBV vaccines for 3 decades, it is estimated that still more than 240 million persons worldwide are chronically infected with HBV.[3] To reach the goal of HBV elimination, we must understand current challenges and set strategies to overcome these difficulties.

HBV transmission usually occurs through exchange of body fluids and blood contact. Routes of acquiring HBV infection vary geographically and are related to the incidence of infection. In endemic areas, MTIT is the principal mode of acquisition of HBV.[4] Mothers seropositive for hepatitis B e antigen (HBeAg) are at high risk for perinatal transmission of HBV.[5] In the prevaccination era, approximately 90% of infants born to mothers seropositive for HBeAg became chronically infected. This contrasts with low endemicity regions such as the US and Europe where HBV infection is predominantly acquired through horizontal transmission via sexual contact with individuals with chronic HBV infection, or by percutaneous exposure. Even in the regions of low endemicity, children of immigrants from endemic areas have a risk of MTIT and chronic infections. The rate of HBV chronicity is related to the age at primary infection: >90% in infants, 23%-30% in preschool children, 5%-7% in older children, and <3% in immunocompetent adults.[6,7]

ALT	Alanine aminotransferase
Anti-HBc	Antibody to hepatitis B core antigen
CHB	Chronic hepatitis B
ETV	Entecavir
HBeAg	Hepatitis B e antigen
HBIG	Hepatitis B immune globulin
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
IFN	Interferon
LAM	Lamivudine
LdT	Telbivudine
MTIT	Mother-to-infant transmission
NA	Nucleoside analogue
PegIFN	Peginterferon
TDF	Tenofovir disoproxil fumarate
WHO	World Health Organization

Natural History of Chronic HBV Infection

Chronic HBV infection (defined as persistence of hepatitis B surface antigen [HBsAg] for more than 6 months) acquired perinatally or in early childhood consists of 3 phases: immune tolerant phase (high virus replicative phase with normal alanine aminotransferase [ALT] level), immune-active phase (inflammatory phase or immune clearance phase), and inactive carrier phase (low or nonreplicative phase). Some cases can progress to reactivated phases (HBeAg-negative chronic hepatitis).

In neonates born to HBeAg-positive carrier mothers, maternal HBeAg can traverse the placenta, and in utero exposure to HBeAg may elicit specific unresponsiveness of T lymphocytes to HBeAg and to hepatitis B core antigen [HBcAg] (because HBeAg and HBcAg are highly cross-reactive at the T-cell level), resulting in ineffective recognition and cytotoxic lysis of HBcAg-expressing hepatocytes by T-cells.[8,9] Maternal-derived HBeAg also alters macrophage function in offspring to drive viral persistence after vertical transmission.[10] These findings may explain why 90% of the infants of HBeAg-positive carrier mothers became chronic carriers in the prevaccination era.

Most HBsAg-positive children initially are in tolerant phase, remain HBeAg-positive and usually have high HBV DNA level, normal or mildly elevated ALT level, and minimal liver histologic changes.[11] Although recent studies challenge the concepts of immune tolerance, it is noted that the immune tolerant phase does not mean a complete absence of all HBV-specific T cells but is better defined as "the deletion or silencing of a sufficient number of T cell clones to preclude significant liver injury and subsequently clearance or modulation of the infection."[12,13]

The transition from immune tolerant phase to immune active phase usually occurs during the second to fourth decades of life, but may occur at any age. During this phase, most patients remain asymptomatic or have mild, nonspecific symptoms

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but with persistent or intermittent elevation of ALT levels ranging from below 100 IU/L to more than 1000 IU/L reflecting liver damage resulting from virus-host interaction.[14] A longer duration of this phase may associate with progression to cirrhosis and HCC.[15] Spontaneous HBeAg to antibody to hepatitis B e antigen seroconversion is not a rare event. The annual HBeAg clearance rate was <2% in children under 3 years of age, and ~5% in children above 3 years of age.[16] Patients with genotype C infection undergo HBeAg seroconversion at an older age than those with genotype A, B, D, and E.[17] The annual rates of HBeAg seroconversion is higher in Caucasians infected through horizontal routes than in Asian children infected through perinatal transmission.[16,18]

After HBeAg seroconversion, patients enter into low or nonreplicative phase characterized by gradual normalization of ALT levels, mild or nonspecific liver histology, and low or undetectable serum HBV DNA by polymerase chain reaction. Spontaneous HBsAg clearance occurs in a few cases, with an annual clearance rate of 0.58%.[19] Children with an initial low HBsAg serum level (<1000 IU/mL) or children who were born to noncarrier mothers were more likely to develop HBsAg clearance.[19] The majority of patients who clear HBsAg have undetectable HBV DNA in the serum.

Some patients may progress to a reactivation phase (HBeAg-negative immune active phase), during which serum HBV DNA and ALT levels become elevated. In a group of patients followed long term and mainly infected in the perinatal period, the annual incidence of HBeAg-negative hepatitis was 0.37% among spontaneous HBeAg seroconverters to antibody positivity.[20] HBeAg seroconversion before 18 years of age predicts a low risk of HBeAg-negative hepatitis in later life.[20] The reactivations can occur at any time, either spontaneously or as a result of immune suppression. It is important that antiviral therapy should be given to prevent reactivation in infants and children with disease related immunosuppression or chemotherapy.

Although HBeAg seroconversion generally is considered a favorable event and an important endpoint in antiviral therapies, subsequent development of cirrhosis or HCC is occasionally noted. Early HBeAg seroconversion may not necessarily indicate a good prognosis because severe and permanent liver damage can develop in some patients during the process of HBeAg seroconversion. During a long-term follow-up study, 3.4% of Italian HBsAg carriers with raised ALT levels progressed to liver cirrhosis[21]; 2 of 10 Taiwanese children who had HBeAg seroconversion before 3 years of age developed HCC at 10-15 years of age.[22]

Prevention of HBV Infection by Passive and Active Immunization

Immunization of neonates born to HBsAg-positive carrier mothers is the most important step toward the elimination of chronic HBV infection and its complications.[23] In 1992, the World Health Organization (WHO) recommended that HBV vaccine should be integrated into national immunization programs by 1997.[24] Hepatitis B vaccine and hepatitis B immune globulin (HBIG) are available for the prevention of HBV infection. The most important strategy has been the universal immunization in infancy to prevent both perinatal and horizontal transmission of HBV.

There are 3 main strategies in current programs for universal hepatitis B immunization in infancy: (1) testing pregnant women for both maternal HBsAg and HBeAg and administering HBIG to newborns of HBeAg-positive mothers (such as in Taiwan)[25]; (2) testing pregnant women for HBsAg and administering HBIG to newborns (>2000 g) of HBsAg-positive mothers within 24 hours of birth as well as universal immunization of all newborns (as in the US)[26]; and (3) immunizing every neonate without antenatal screening of the mothers or administration of HBIG (as in Thailand).[27] Selection among strategies should be based on local epidemiologic conditions and availability of medical resources.

Impact of Universal Infant Immunization on HBV-Related Liver Disease Burden

The effectiveness of a given vaccination program can be monitored by surveillance of acute hepatitis B in the vaccinated population.[28] After universal HBV immunization, the incidence of acute hepatitis B has been shown to decline dramatically.[29,30]

The prevalence of chronic HBV infection in children has been markedly reduced in areas where universal HBV vaccination has been successfully introduced. In the past 3 decades, the HBsAg carrier rate in Taiwan decreased from approximately 10% before the vaccination program (1984) to 0.5% in vaccinated subjects (2014), and the total infection rate, as reflected by antibody to hepatitis B core antigen (anti-HBc) seropositivity, declined from 27.9% in unvaccinated subjects <15 years of age in 1984 to 3.1% in vaccinated subjects <16 years of age (or 4.5% in vaccinated subjects <30 years) in 2014.[31,32] In the reports from many countries such as the Gambia, universal vaccination programs have been equally successful.[33] Universal vaccination is more effective than selective immunization for high-risk groups.

The mortality rate of fulminant hepatitis in infants born between 1974 and 1984 was 5.36 per 100 000 in Taiwan and was reduced to 1.71 per 100 000 between 1985 and 1998.[34] Although HBV was rarely the cause of fulminant hepatitis in immunized children, it still remained as a major cause of fulminant hepatitis in infancy. These infants were most likely perinatally infected from their HBeAg-negative carrier mothers despite vaccination.[35]

Children with HCC in Taiwan are nearly 100% HBsAg-positive: 86% are HBeAg-negative, and 94% are born to HBsAg-positive carrier mothers.[36] Integration of the HBV genome into the host genome has been demonstrated in HCC tissues in children.[37] The launch of the infant hepatitis B vaccination program in July 1984 in Taiwan has led to the dramatic reduction of HCC incidence in children. The annual incidence of HCC in children aged 6-14 years was reduced from 0.52 to

0.54 per 100 000 children born before 1984 to 0.13-0.20 per 100 000 children born after 1984.[38] This cancer preventive effect of the HBV vaccination has been extended to young adults 20-26 years old.[39] The risk of developing HCC for the vaccinated cohort was significantly associated with incomplete HBV vaccination, prenatal maternal HBsAg, or HBeAg seropositivity.[40] This was the first example that human cancer can be prevented by vaccination. Failure to prevent HCC results mostly from unsuccessful control of HBV infection by highly infectious mothers.[39,40]

In a recent population-based study in Taiwan, the estimated frequency of occult HBV infection per 10 000 HBsAg-negative subjects declined from 160.7 in the unvaccinated cohort to 11.5 in the vaccinated cohort.[41]

Current Challenges to the Elimination of HBV Infection

Suboptimal Global Rates of Newborn HBV Vaccination

Low rates of vaccine coverage in the developing world are due to inadequate resources. It is important to find ways to reduce the cost of HBV vaccines and to increase funding for HBV vaccination of children living in low-income countries endemic for HBV infection. Opposition to HBV vaccination may result from anxiety regarding adverse reaction of vaccination and inadequate recognition of occurrence and consequences of chronic infection even in countries with adequate resources, and can be reduced by better communication and clarification for these events.[42]

Failure of Immuno-Prophylaxis

Breakthrough infection of HBV is defined as "having HBV infection (evidenced by anti-HBc seropositivity) despite receiving three or more doses of HBV vaccine." In 1 survey, 10 (87%) of 12 HBsAg-positive, immunized children with known family history had HBsAg-positive mothers, suggesting that MTIT accounts for the majority of cases with failure of immunoprophylaxis alone.[32] These failures are the causes for 30% residual incidence of HCC in Taiwan.[40]

There are several causes of breakthrough HBV infection during MTIT including intrauterine infection, high maternal viral load, delayed or incomplete vaccination, nonresponsiveness to HBV vaccine, and vaccine-escape mutations.

The rates of intrauterine infection was estimated to be <5% in infants of high-risk mothers. In a 10-year follow-up study in Taiwan, 2.4% of infants of high-risk mothers were persistently seropositive for HBsAg from the first day of life, despite the combined use of HBIG and HBV vaccine.[43] Transplacental leakage of maternal blood, induced by uterine contraction and disruption of placental barriers during pregnancy, is the most likely causes of intrauterine infection.[44]

Mutations of the HBV surface gene located in or around the "a" determinant of HBsAg, first found in infants born to carrier mothers following immunoprophylaxis, can result in breakthrough infections in immunized individuals.[45,46] Based on the detection of HBsAg mutants in HBV DNA-positive children seropositive for HBsAg or anti-HBc, a long-term survey during a universal immunization program in Taiwan has shown that "a" determinant mutants were associated with 20%-30% immunoprophylaxis failures, whereas in prevaccination era the prevalence of these mutants was only 8%.[46,47] Late onset of G145R mutant infection in immunized infants was primarily due to vaccine nonresponder, suggesting mutant virus escape from HBIG rather than from vaccine-induced antibody.[48]

Despite passive-active immunoprophylaxis, approximately 10% of infants born to HBeAg-positive mothers still become infected with HBV.[49] Transmission from highly viremic mothers still remains a major challenge in eradicating HBV-related diseases even with immunoprophylaxis.[50] Maternal viral load has been determined to be the most important risk factor for MTIT. Under adequate neonatal immunoprophylaxis, MTIT seldom occurred if maternal viral load was <6 $\log_{10}$ copies (5.3 $\log_{10}$ IU/mL). The rate of MTIT increased stepwise if maternal viral load was ranging from 6 to 9 $\log_{10}$ copies/mL.[51-54] Estimated rates of chronic infection in infants at maternal HBV DNA levels of 6, 7, 8, and 9 $\log_{10}$ IU/mL were 2.5%, 5.7%, 12.4%, and 24.7%, respectively.[51]

As stated by World Health Assembly, only 97 (50%) of the 194 member states introduced the hepatitis birth dose of HBV vaccine by 2016. Even in countries with adequate resources, poor adherence to completion of vaccine schedule for variable reasons and the fact that many infants are born at home and are unlikely to receive the birth dose of vaccine still remain challenges for complete elimination of HBV infection.[55]

Issues of Long-Term Immunity and Protection from Infection Following Vaccination

Humoral immunity in individuals immunized with HBV vaccines may begin to wane during the second decade, with studies reporting that approximately 50% of children show anti-HBs <10 IU/L 15-20 years after neonatal immunization, and 2%-10% of the vaccinated population also had lost their HBV vaccine-induced booster response.[56,57] This raised concerns about the potential risk of breakthrough infection. However, the finding of no increase in HBsAg-positive individuals at different ages in the same cohorts fully covered by universal immunization suggests that there is no increased risk of chronic HBV infection with age.[58]

Long-term longitudinal studies of HBV vaccine efficacy have been conducted in Alaska, Taiwan, Thailand, China, and Gambia. A follow-up study of Alaska Natives showed that protection could last for 22 years, and no new acute or chronic HBV infections were identified.[59] Another study in Thailand showed the transient presence of HBsAg or transient and/or long-term presence of anti-HBc of the immunized population during the follow-up period, but no new case of chronic HBV infection.[60] In immunized subjects, anamnestic anti-HBs responses can occur rapidly and eliminate acute HBV infection, even if the anti-HBs titer is below a protective level.[61] Thus, a booster vaccination is currently not recommended in immunocompetent children and adolescents, but should be

considered for those with high risk of infection and immunocompromised status (if anti-HBs <10 mIU/mL), and for liver transplant recipients (keeping anti-HBs >200 mIU/mL before transplantation).

Strategies to Achieve Global Elimination of HBV Infection

Hepatitis B immunization has been most effective in preventing HBV infection and the sequelae of chronic HBV infection. The following additional strategies are considered important to achieve the WHO goal of global elimination of HBV.

Screening to Identify Unrecognized People with Chronic HBV Infection

Screening HBsAg/HBeAg among pregnant women is the first step in the interruption of MTIT. Women with positive HBsAg can be followed regularly to screen for, and prevent HCC. Universal screening of pregnant women for HBV appears to be more effective than selective approaches focusing on high-risk groups.[50]

In the postvaccination era, it is very important to survey and identify HBsAg-positive children born to HBsAg carrier mothers resulting from failure following neonatal management. High-risk infants should be tested for HBV serologic markers (HBsAg and anti-HBs) at age 9-18 months. Booster HBV vaccine should be administered to infants seronegative for anti-HBs.[62] For HBsAg-positive children, periodic follow-up for surveillance and management of hepatic inflammation and HCC are required as early as possible.

Other high-risk groups also should be screened for HBV infection, including household contacts of individuals with HBV infection, adolescents and young adults who have risk behaviors, and children and their parental immigrants from endemic areas.

Combined Use of Antiviral Agents and Immunoprophylaxis to Minimize MTIT of HBV

Antiviral therapy can decrease viral load in highly viremic pregnant women with chronic HBV infection and, hence, can reduce the risk of HBV transmission to their infants under current immunoprophylaxis. The only antiviral agents studied in pregnant women are lamivudine (LAM), telbivudine (LdT), and tenofovir disoproxil fumarate (TDF).[63]

A prospective, well-controlled trial of TDF in Taiwan recruiting pregnant women with HBV DNA >7 $\log_{10}$ IU/mL, showed a reduction of HBsAg positivity of infants at 6 months of age from 10.7% to 1.5% ($P = .0481$), with OR of 0.10 ($P = .0434$) in the tenofovir-treated group.[64]

An open-label, randomized, controlled trial of TDF in pregnant women with HBV DNA >200 000 IU/mL in China also showed a reduction of HBsAg positivity from 18% to 5% ($P = .007$) in the intention-to-treat analysis, and a reduction from 7% to 0% ($P = .01$) in the per-protocol analysis.[65]

A multicenter, double-blind, randomized clinical trial conducted in pregnant women in Thailand has shown that the rates of HBsAg-positivity of infants at 6 months of age was 0% (95% CI 0-2) in the TDF group compared with 2% (95% CI 0-6) in the placebo group ($P = .12$). The authors concluded that in the setting in which the rate of HBV transmission was low with the administration of HBIG and HBV vaccine in infants born to HBeAg-positive mothers, the additional maternal use of tenofovir did not significantly reduce the rate of MTIT.[66]

A meta-analysis, including 26 studies that enrolled 3622 pregnant women, revealed that antiviral therapy (LAM, LdT, and TDF) lowered HBV DNA levels and reduced the rates of MTIT, with no increased risk of adverse maternal or fetal outcomes. The use of these antiviral agents in women who are HBeAg-positive and have HBV DNA >200 000 IU/mL in the third trimester to prevent MTIT is recommended by authors.[67]

The 2015 WHO Hepatitis Guidelines for Management of Chronic HBV Infection did not recommend antiviral treatment for pregnant women.[68] However, the 2015 updated Asian Pacific Association for The Study of the Liver clinical practice guidelines did recommend short-term nucleoside analogues (NAs) starting from 28 to 32 weeks of gestation using either TDF or LdT for pregnant women with HBV DNA >6-7 $\log_{10}$ IU/mL.[69] The 2016 American Association for The Study of Liver Diseases guidelines recommend antiviral treatment for pregnant women seropositive for HBsAg with an HBV DNA level >200 000 IU/mL.[70] The 2017 European Association for The Study of the Liver clinical practice guidelines recommend that antiviral prophylaxis with TDF should start at week 24-28 of gestation in pregnant women with HBV DNA levels >200 000 IU/mL or HBsAg levels >4 $\log_{10}$ IU/mL.[71,72] The 2018 American Association for The Study of Liver Diseases guidelines stated that antiviral therapy was started at 28-32 weeks of gestation and discontinued at birth to 3 months postpartum in most of the studies.[63] Based on limited data, the cut point level of HBV DNA >200 000 IU/mL for antiviral therapy is considered to be a conservative recommendation.[63] Breast feeding is not contraindicated, although the unknown risk of low-level exposure to the infant should be discussed with mothers.[63]

Taken together, TDF use during late pregnancy in mothers with high viral load appears to be safe and may reduce, but not prevent all cases of MTIT. Before it becomes the standard care to prevent MTIT of HBV, such a short-term TDF therapy for pregnant mothers should be considered only in highly viremic mothers after discussing the potential risk for the infant (**Figure**).

Effective Treatment to Eradicate the Virus from Chronically Infected Persons

To eliminate all of the infectious sources, an effective treatment regimen is required to eradicate the virus from all infected individuals. Current treatment regimens are unable to eradicate the virus because of their inability to eliminate covalently closed circular DNA in the liver. The current goal of therapy is to terminate viral replication, reduce the intensity and duration of chronic inflammatory activity, and, hence, the risk of progression to cirrhosis and HCC.[73]

Most children with chronic HBV infection are in the immune-tolerant phase; in this phase, current treatment

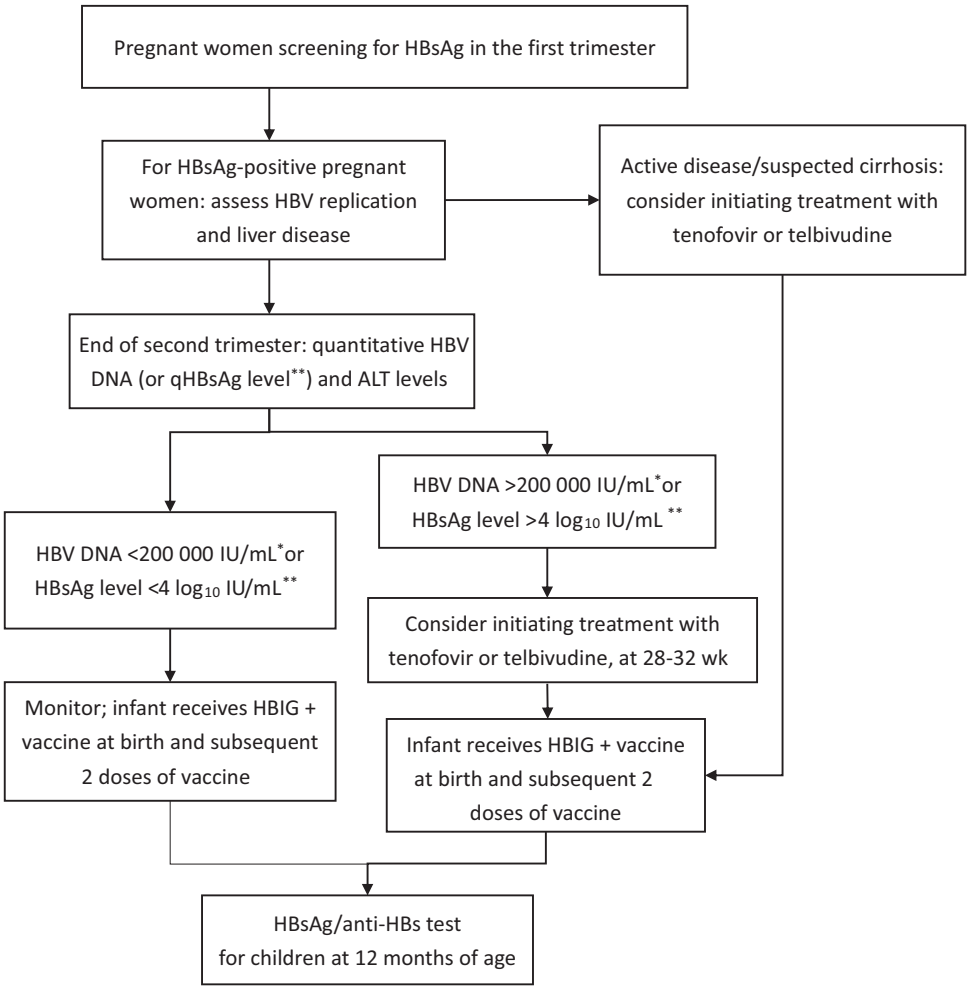

Figure. Management in pregnant women and their children for preventing MTIT of HBV.[63,67,70-72]
*The concensus cut-off level of maternal HBV DNA level for initiation of therapy during pregnancy is still unclear. HBV DNA >200 000 IU/mL can be considered for therapy in pregnant women and is most widely acceptable.[63,67,70,71]
**Quantitative HBsAg level >4 $\log_{10}$ IU/mL is a potential alternative method for screening high infective mothers.[71,72]

strategies do not result in higher rate of HBeAg seroconversion compared with no treatment.[74] Children in the immune-tolerant phase with normal ALT levels are not recommended to be treated unless liver cirrhosis is present or the patient will be undergoing immunosuppressive therapy.[68,74] Only children in the immune-active phase with an ALT level above 1.3 times the upper limit of normal on at least 2 occasions for 6 months or longer are considered for treatment.[70] Because spontaneous HBeAg seroconversion is not infrequent, watchful waiting remains an option for children with immune-active chronic hepatitis B (CHB), especially those with ALT >10 times of the upper limit of normal.

In children and adolescents who meet treatment criteria, currently Food and Drug Administration-approved drugs, including interferon (IFN)-α, LAM, entecavir (ETV), and peginterferon (PegIFN) alfa-2a, can be used in children; adefovir, LdT, and TDF can be used in adolescents (**Table**). IFN-α, the first licensed antiviral in the US, has both immunoregulatory and antiviral activity against HBV. Conventional IFN-α therapy remains an effective treatment for children with chronic hepatitis B, with virologic response in 20%-50% of treated children compared with 8%-17% in the control group.[68,75] HBsAg seroreversion to negative occurred in 10% of treated children compared with 1% in the control group.[75] Long-term studies have shown that untreated patients eventually experienced a rate of HBeAg seroconversion not significantly different from that of IFN-α treated children, indicating that IFN-α might simply accelerate spontaneous clearance.[76,77]

A phase III clinical trial using a 48-week course of PegIFN alfa-2a treatment was conducted in children aged 3-18 years with CHB. The treatment strategy was associated with significant increase in the rates of HBeAg seroconversion (25.7% vs 6%, $P = .0043$) and HBsAg clearance (8.9% vs 0%, $P = .03$) at 24 weeks post-treatment in comparison with the control group.[78] PegIFN alfa-2a treatment of children in the immune-active phase of CHB was efficacious and well tolerated and was associated with higher incidence of HBsAg clearance than in

Table. Drugs currently Food and Drug Administration-approved for treatment of chronic hepatitis B in children and adolescents in the US

Medications	Age groups	Dose and duration	Advantages	Disadvantages
INF-α	≥12 mo	6 MU/m^2 3 times a wk for 24 wk	- No drug resistance - Short duration	- Intramuscular delivery - High side effect profile - Contraindicated in decompensated cirrhosis, transplantation, pregnancy, psychiatric illnesses, thyroid diseases and autoimmune diseases.
PegINF-α-2a	3 to <18 y	180 mcg/1.73 m^2/wk (maximum 180 mcg) for 48 wk	- No drug resistance - Once a wk administration - Short duration	- The same as Interferon-α
LAM	≥2 y	3 mg/kg/d, once daily (maximum 100 mg) for ≥1 y*	- Oral delivery - Minimal side effects	- Drug resistance high, 20% in the first y and subsequent increase of 20% per y
Adefovir	≥12 y	10 mg, once daily, for ≥1 y*	- Oral delivery - Minimal side effects - Partially effective against lamivudine resistant HBV	- Lower potency than lamivudine - Drug resistance high, 2% in 2 y - Dose-dependent nephrotoxicity - Not approved for children <12 y - Reduced bone mineral density.
ETV	≥2 y	0.015 mg/kg (maximum 0.5 mg), once daily for ≥1 y*	- Oral delivery - Few side effects - High potency - Low drug resistance	- Less effective against lamivudine-resistant HBV - Not approved for children <2 y - Drug resistance 1.0% at 5 y
LdT	≥16 y	600 mg, once daily for ≥1 y*	- Oral delivery - Minimal side effects - High potency	- Drug resistance high, 25% at 2 y - Telbivudine-induced myopathy and neuropathy
TDF	≥12 y	300 mg, once daily for ≥1 y*	- Oral delivery - Minimal side effects - High potency - No drug resistance	- Not approved for children <12 y - Mild renal toxicity and reduced bone mineral density.

TDF, Tenofovir disoproxil fumarate.
*Continue until 12 months after HBeAg seroconversion.

adults. This adds an important treatment option for children with HBeAg positive CHB.

NAs are effective inhibitors of HBV replication but have similarly low rates of HBeAg seroconversion as does IFN-α and seldom result in the clearance of HBsAg.[68,71] If an NA is used, treatment may last 2 or more years and it should be continued for at least 12 months (consolidation) after HBeAg seroconversion. Close monitoring for at least 12 months after discontinuing treatment is recommended.

LAM has fewer side effects but a high risk of selecting resistant mutants.[79] Compared with other NAs, adefovir is a less preferred drug because of its limited efficacy.[80] ETV is a good option for the treatment for children with compensated liver disease who prefer oral agents rather than injections of interferon. ETV was reported to be superior to adefovir in virologic response and is associated with a low rate of resistance (0.6% at year 1 and 2.6% at year 2).[81]

TDF is associated with viral suppression and rare development of drug resistance, and has been US Food and Drug Administration-approved for adolescents ≤12 years of age.[82] Tenofovir alafenamide fumarate, which is an orally bioavailable prodrug of tenofovir, has similar pharmacology to TDF with higher delivery to hepatocytes but lower plasma and kidney exposure.[83,84]

Most previous guidelines recommended against the use of antiviral therapy in HBeAg-positive children with persistently normal ALT. However, a pilot study has reported that LAM pretreatment followed by a combination of LAM and IFN-α can induce complete viral control in immune-tolerant children perinatally infected with HBV.[85] Another recent study using a sequential combination of IFN-α and LAM therapy in children with chronic HBV infection and immune-tolerant characteristics also showed beneficial effects.[86]

Therapeutic vaccines have been developed recently to stimulate or boost the host immune response to restore immunologic control, suppress HBV replication and eliminate infection.[87,88] Experiments using innovative strategies to overcome T cell tolerance or by blocking immune checkpoint inhibitory receptors to restore HBV-specific T cell function have been evaluated, with limited success.[89-91] Other potential new strategies, including inhibition of virus entry, small molecules that modulate covalently closed circular DNA transcription, RNA interference technologies, inhibitors of nucleocapsid assembly, and combination of inhibitors of negative regulators with therapeutic vaccines, are also under active development in attempts to reach the goal of functional cure of HBV.[92]

Conclusions

To reach the goal of eliminating HBV infection, attention must start in the fetal and neonatal period. For infants born to HBeAg-positive mothers, timely administration of HBIG and birth dose vaccine (within 12 hours after birth) is currently

the most important and effective method for preventing MTIT. However, MTIT of HBV in utero or during the perinatal period remains the major cause of immunoprophylaxis failure in the postvaccination era. To mitigate the occurrence of approximately 1000 cases of perinatally transmitted HBV infection that still occur annually in the US (mainly because of miscommunication of maternal status), a birth dose within 24 hours is recommended for all infants >2000 g whose mother is HBsAg negative.[26,93] High maternal viral load is the most important risk factor of MTIT. Administration of NA therapy may decrease the viral load in highly viremic pregnant women with chronic HBV infection and reduce the risk of MTIT under current immunoprophylaxis. Because viral eradication from the host is not feasible at this time, the current goal of therapy in children with chronic HBV infection is to achieve HBeAg seroconversion with complete suppression of viral replication and reduction of the intensity and duration of chronic inflammatory activity in the liver and, hence, the risk of progression to cirrhosis and HCC. IFN-α and NAs can be considered for use in children with immune-active CHB as recommended by most recent guidelines. However, most children with chronic HBV infection remain in the immune-tolerant phase with poor response to current antiviral therapy and are at risk for significant clinical complications in later life. New therapeutic approaches targeting the virus as well as the host are in development, with the goal of functional cure of HBV. With these efforts, the tools are at hand to achieve, in the foreseeable future, the complete elimination of HBV starting in the fetal and neonatal period. ■

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