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REVIEW

Current advances in the elimination of hepatitis B in China by 2030

Shuye Zhang[1], Fusheng Wang[2], Zheng Zhang (✉)[3]

[1]*Shanghai Public Health Clinical Center and Institute of Biomedical Sciences, Fudan University, Shanghai 200032, China;* [2]*Department of Infectious Diseases, Beijing 302 Hospital, Beijing 100039, China;* [3]*Research Center for Clinical & Translational Medicine, Beijiing 302 Hospital, Beijing 100039, China*

Abstract **With its 78 million chronic carriers, hepatitis B virus (HBV) infection is still one of the leading public health challenges in China. Over the last two decades, China has made great progress on the prevention of HBV transmission through national vaccination programs. Zero transmission from mother to infant has been proposed as the current goal. Available anti-HBV therapy is efficacious in suppressing HBV replication; however, it fails to completely cure patients with chronic hepatitis B and even requires lifelong treatment. To reduce the costs and improve the efficacy, several trials have been recently conducted in China to optimize the current anti-HBV managements. Novel biomarkers were identified to predict treatment outcomes, and new promising treatment strategies were developed. Reports also indicate that coinfections of HBV with other hepatotropic viruses and human immunodeficiency virus are common in China and cause severe liver diseases, which should be recognized early and treated properly. Work is still needed to eliminate hepatitis B in China by 2030.**

Keywords HBV; CHB; biomarker; functional cure; coinfection

Introduction

Infection by the hepatitis B virus (HBV) can cause liver inflammation and injury, liver cirrhosis, or hepatocellular carcinoma (HCC). Despite the worldwide vaccination program, chronic hepatitis B (CHB) is still one of the biggest public health challenges, with an estimated 257 million people living with chronic HBV infection and more than 600 000 related deaths in 2015 [1]. In China, 78 million people are currently estimated to carry the hepatitis B surface antigen (HBsAg), and 28 million of them have active hepatitis and account for nearly one third of all the chronic infections in the world. Every year, approximately 300 000 Chinese die from HBV-related liver cirrhosis and HCC, accounting for 37%–50% of the mortality worldwide [2]. For this reason, China has largely expanded the funding support for HBV research, and many progresses have been made to better understand and control hepatitis B. We will summarize here the achievements in the prevention, diagnosis, and treatment of hepatitis B in China over the last decades.

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Correspondence: zhangzheng1975@aliyun.com

HBV vaccination campaign successfully reduces the HBV burden in China

Acquisition of HBV in perinatal or early childhood may play a major role in chronic infection, thus, the HBV vaccine should be administered within 24 h at birth. In China, the government has listed HBV vaccination as a priority public health measure [3]. HBV immunization was first introduced in China in 1987 and was recommended for routine vaccination of infants by the Ministry of Health in 1992. However, because of high costs for vaccine purchase and administration, infant vaccination occurred mainly in the wealthier eastern provinces until China launched the Expanded Program of Immunization (EPI) in 2002, when the cost of HBV vaccines was subsidized by the government, whereas administration fees of the vaccinations continued to be charged. Also in 2002, the Ministry of Health initiated a project with the Global Alliance for Vaccines and Immunization (GAVI) to ensure HBV vaccine availability in China's poorest provinces and

counties [4]. This 5-year China–GAVI project provided free HBV vaccines, targeting approximately 5.6 million children born each year in the poor middle-western area, covering approximately 36% of Chinese newborns. In 2005, the new vaccination policy in China abolished all charges and fees for all nationally recommended vaccines, including the hepatitis B vaccine.

For children with none, incomplete, or unknown HBV vaccination history, the Chinese government implemented the catch-up strategies. From 2002 to 2006, 16 provinces carried out the catch-up vaccination for children born from 2002 to 2005 and 8.2 million doses of the HBV vaccine were administered. In 2007, more than 7 million doses were administered to immunize children less than 15 years old in Jiangsu, Qinghai, Zhejiang, Tianjin, and Shandong provinces. From 2009 to 2011, all children less than 15 years of age who were never or incompletely immunized with the HBV vaccine were immunized by the catch-up HBV vaccinations [5].

These HBV immunization strategies were highly successful and have resulted in significantly reduced HBsAg prevalence among young children and prevented approximately 16–20 million HBV carriers. A nationwide HBV seroepidemiological survey conducted in 1992 showed that the HBsAg carrier rate in the whole population was 9.75%, which, by contrast, has declined to 7.18% among those aged 1–60 years in 2006 [6,7]. Of note, because the coverage of the three doses of hepatitis B vaccine in infancy reached more than 95%, it has substantially reduced HBV transmission in newborns, as reflected by the reduction in HBV prevalence to less than 1% among aged < 15 years and a prevalence of HBsAg to 0.32% among those aged < 5 years [8]. Thus, China has been transferred from a country with high endemicity to one with intermediate or low endemicity.

The neonatal HBV vaccination significantly reduced the risk of primary liver cancer and other liver diseases in young adults in rural China. In a retrospective analysis on a population-based, cluster randomized, controlled trial between 1985 and 1990 in Qidong County, China, the authors included 38 366 newborns who had completed the HBV vaccination series and were randomly assigned to the vaccination group and 34 441 newborns who received neither a vaccine nor a placebo and were randomly assigned to the control group. Based on the intention-to-treat analysis, the incidence rate of primary liver cancer and the mortality rates of severe end-stage liver diseases and infant fulminant hepatitis were significantly lower in the vaccination group than those in the control group with efficacies of 84%, 70%, and 69%, respectively [9]. The findings indicate that HBV vaccine functions as the first-line intervention to prevent liver cancer and end-stage liver disease. However, the global coverage with the initial birth dose vaccination is still low at 39% in 2015 [1]. China needs to maintain the high birth coverage rate of HBV vaccine so as to further decrease HBV-associated liver diseases in the future.

Zero transmission through strengthening the prevention of mother-to-infant transmission (MTIT)

Regarded as the most common HBV transmission route in China, MTIT during the perinatal period usually leads to chronic HBV infection. Standard passive–active immunoprophylaxis with hepatitis B immunoglobulin (HBIG) and hepatitis B vaccine in neonates is highly effective in preventing MTIT, although it is not completely protective [10]. The percentage of prophylactic failure could reach 5%–10% for pregnancies with high levels of HBV load [11]. With around 15 million births occurring annually, approximately 50 000 newborns acquire HBV infection yearly in China, especially those from the hepatitis B e-antigen-positive ($HBeAg^+$) mothers. An increasing body evidence suggests that antiviral treatments may significantly reduce the risk of MTIT among mothers with an HBV DNA level of > 6 $\log_{10}$ copies/mL [12]. Pan *et al.* evaluated the regimen of tenofovir disoproxil fumarate (TDF) treatment among pregnant HBV mothers and found that MTIT was significantly lower in the TDF group than that of the control group, both in the intention-to-treat analysis (with transmission of virus to 5% of the infants [5 of 97] versus 18% [18 of 100]) and the per-protocol analysis (with transmission of virus to 0% versus 7% [6 of 88]). The safety profiles were similar in the TDF group and the control group [13]. Approximately 6% of fertile women have chronic HBV infections in China, thus the antiviral therapy of using TDF with HBIG for HBV-infected mothers will efficiently reduce the risk of MTIT to nearly zero infection rate.

Based on these findings, the Chinese Foundation for Hepatitis Prevention and Control launched the Hepatitis B Shield Project in 2015, which aims to set up a network to break down the barriers among hepatologists, general practitioners, gynecologists, and HBV-infected mothers. A mobile app as an educational tool is first on trial in ten key centers; afterwards, it will be introduced to other hospitals across the country. Next, the clinical trial will compare the HBV MTIT rate between mothers who are using the Shield app and those who are not. These actions will bring China closer to the HBV-free generation in the near future [14].

Current antiviral treatment in patients with CHB is being improved

The long-term outcome of HBV infection varies from minimal hepatic inflammation to extensive fibrosis,

cirrhosis, and HCC. In China, CHB is the leading cause of cirrhosis and HCC, leading to high morbidity and mortality, posing heavy burden to the society and patients. Sustained suppression of serum HBV DNA by antiviral treatments improves the quality of life, prevents liver disease progression, and reduces mortality. However, the generally low income in China has been a major barrier for urgent treatment. The data of the China Registry of Hepatitis B shows that only 2.8 million (10%) of patients with CHB are currently receiving the needed treatment. In addition, drugs with low antiviral potency or low genetic barrier, including lamivudine (LAM), adefovir (ADV), and telbivudine (LDT), and other drugs with uncertain antiviral efficacy, are widely used in China [15]. The use of these drugs increases the rate of resistance or poor response. In addition, more than 90% of the treated patients with CHB are receiving nucleos(t)ide analog (NA) therapy, whereas the majority of NA-treated patients are unable to achieve HBsAg loss and may require lifelong therapy. Although pegylated interferon (Peg-IFN) represents a valuable, finite option for NA-treated patients [16], new strategies for reducing virus resistance and optimizing HBsAg loss are also required.

To improve the antiviral effect of drugs with low genetic barrier, the "roadmap concept" was proposed in 2007, which suggested that patients with suboptimal response after 24 weeks of initial treatment switch to a potent agent or add a second agent without cross-resistance. The Efficacy Optimization of Response to Telbivudine (EFFORT) study prospectively evaluated the efficacy and safety of the roadmap strategy by adding ADV to LDT for suboptimal responders [17]. Results showed that, in comparison with the control group, more patients in the optimized group achieved HBV DNA $<$ 300 copies/mL (76.7% versus 61.2%) and less genotypic resistance (2.7% versus. 25.8%) at week 104. For suboptimal responders, LDT plus ADV showed additional antiviral potency, with 71.1% achieving virological response and only 0.5% developing resistance at week 104, compared with 46.6% achieving virological response and 37.8% developing resistance in the LDT monotherapy group. Thus, the roadmap strategy will benefit the patients by adding ADV with additive antiviral potency and low resistance to suboptimal responders.

Other studies focused on HBsAg loss by using various combinations or switching regimens of NAs and Peg-IFN for patients with CHB. In the "Optimising HBeAg Seroconversion in HBeAg-positive CHB Patients with Combination and Sequential Treatment of PegIFN alfa-2a and ETV" (OSST) study by Dr. Ning, $HBeAg^+$ patients with CHB received long-term ETV treatment (up to 3 years) and then switched to a 48-week Peg-IFN treatment. These patients achieved significantly higher rates of HBeAg seroconversion than those who continued ETV monotherapy (14.9% versus 6.1%). The authors found an increase of HBsAg loss rates from 8.5% to 9.7% one year after the treatment endpoint, whereas none of the patients on ETV monotherapy achieved HBsAg loss [18,19]. Furthermore, prolonging the duration of Peg-IFN treatment increased the response rates in patients who switched from long-term NA therapy. The "New Switch" study showed that, in comparison with patients who received Peg-IFN for the standard duration of 48 weeks, those who extended Peg-IFN treatment to 96 weeks achieved higher rates of HBsAg loss (16.3% versus 21.3%) and HBsAg seroconversion (14.4% versus 16.0%) [20]. These data showed that the switch strategy, on some extent, increased HBeAg and HBsAg seroconversion, although the efficacy was limited.

For the Peg-IFN add-on strategy, the "Augmenting Response to Entecavir with Peginterferon a-2a for the Treatment of HBeAg-positive Chronic Hepatitis B" (ARES) trial showed that adding on 24-week Peg-IFN to ETV in $HBeAg^+$ patients significantly improved off-treatment response and achieved greater decline in HBsAg levels compared with using ETV treatment alone [21]. The "Lowering Viral Load with Nucleos(T)Ide Analogues Prior to Peginterferon Alfa-2b Treatment to Increase Sustained Response in HBeAg-positive Chronic Hepatitis B" (PEGON) study showed that patients who received 48-week add-on Peg-IFN achieved higher rates of HBeAg seroconversion than those who continued NAs monotherapy (21.0% versus 8.0%) [22]. Add-on strategies for $HBeAg^-$ patients have also been investigated in recent large multicenter trials. In the "Randomized Study to Assess the Loss of HbsAg After a 48-week Treatment Period with Pegylated Interferon Alpha 2a in Patients with Chronic Hepatitis B" (PEGAN) study, HBsAg loss and seroconversion rates with add-on Peg-IFN were 8% and 7% at the end of treatment, but only 3% and 1%, respectively, in those who remained on NA monotherapy [23]. Interestingly, a recent trial in China evaluated the Peg-IFN as a therapeutic option for inactive HBsAg carriers. Peg-IFN and Peg-IFN combined with ADV were used for treating subjects with HBV DNA of $<$ 2000 IU/mL, with therapy duration no more than 96 weeks. Results showed that the HBsAg clearance rate and seroconversion rate in the treatment group were 29.8% and 20.2% at week 48 and increased to 44.7% and 38.3% at week 96. However, the HBsAg clearance rate in the control group was 2.4% at weeks 48 and 96, and none achieved HBsAg seroconversion [24]. Therefore, Peg-IFN treatment offers the opportunity for $HBeAg^-$ patients to achieve decreased levels of HBV DNA and HBsAg and for inactive HBsAg carriers to achieve increased HBsAg loss.

Finally, the response-guided therapy can be used to optimize Peg-IFN treatment in China. The "Response-guided peginterferon therapy in patients with HBeAg-

positive chronic hepatitis B" (EXCEL) study was conducted recently to test the strategy. In this study, 264 $HBeAg^+$ patients with CHB were enrolled to receive Peg-IFN treatment for 24 weeks. Early responders (defined as HBsAg $<$ 1500 IU/mL and HBV DNA $< 10^5$ copies/mL at week 24) received Peg-IFN for another 24 weeks. Non-early responders were randomized to receive Peg-IFN for another 24 weeks, prolonged treatment of Peg-IFN for another 72 weeks, or the addition of ADV. Mean decline in quantitative HBsAg from baseline to 24 weeks after the treatment was higher in early responders than that in non-early responders. However, no significant difference was observed among groups of non-early responders in any other efficacy endpoints. Results demonstrated that the early responders to Peg-IFN had a high rate of HBsAg loss, whereas the prolonged duration or addition of ADV may have no additional efficacy for non-early responders [25].

In summary, Chinese hepatologists are exerting great effort into improving the efficacy of antiviral therapy based on current antiviral drugs. Some of the new findings have been adopted by the Asian-Pacific clinical practice guidelines on the management of hepatitis B and the 2015 updated guidelines for CHB management [26].

Novel treatment strategies and biomarkers are promising

Novel therapeutic strategies to treat CHB

The current therapy is not effective in clearing viral reservoir (intrahepatic covalently closed circular DNA, cccDNA), thus curative HBV interventions will likely combine antiviral drugs with an immunotherapeutic approach to enable the restoration of a functional adaptive immune response [27]. A promising immunotherapeutic approach with broad applicability would be a therapeutic vaccination [28]. An antigen–antibody (HBsAg–HBIG) complex therapeutic vaccine candidate with alum as adjuvant was invented and tested in China. It showed promising results in a double-blind, placebo-controlled, phase IIb clinical trial in China [29]. However, results of the phase III clinical trial that included 450 patients failed to show any efficacy, possibly due to immune fatigue [30]. Thus, the strong tolerance to HBsAg possibly limits the therapeutic effect of the conventional HBsAg vaccination in patients with CHB. Recently, a preclinical study indicated that patients with CHB presented reduced immune tolerance to the preS1 domain of the HBV large surface antigen. The study suggested that targeting the weak tolerance of preS1 region induced robust immune responses in the HBV carrier mice and even reduced the tolerant status of HBsAg, opening a therapeutic window for the host to respond to the HBsAg vaccine. This study suggests that preS1 can function as a therapeutic vaccination for the control of CHB and needs future concept-in-proof evidence before clinical trial [31].

In addition, finding a potential vaccine adjuvant is important to enhance the efficacy of current therapeutic vaccine in clinics for patients with CHB. Granulocyte–macrophage colony-stimulating factor (GM-CSF) is known to be a potential vaccine adjuvant despite contradictory results from animal and human studies. A study used GM-CSF as a novel adjuvant for HBV therapeutic vaccine and found that GM-CSF in combination with the recombinant HBV vaccine could induce strong immune responses in HBV-transgenic mice and subsequently break the immune tolerance of HBsAg. These data indicated that GM-CSF may possibly become a novel immunotherapy for patients with CHB. Currently, a randomized controlled trial is undergoing tests to assess the clinical efficacy and safety of GM-CSF as an HBV therapeutic vaccine adjuvant [32].

Aside from therapeutic vaccines, antibody-mediated immunotherapy has gained attention. A novel monoclonal antibody (mAb), E6F6, has exhibited the most striking therapeutic effects in several HBV-persistent mice. Single-dose administration of E6F6 profoundly suppressed the levels of HBsAg and HBV DNA for several weeks and facilitated the restoration of anti-HBV T cell response in HBV carrier mice. These results indicated that E6F6-like mAbs may be a novel immunotherapeutic agent against chronic HBV infection [33,34]. These data provide some clues and guidance to facilitate the development of therapeutic antibodies against persistent HBV infection.

Notably, a recent pilot study using fecal microbiota transplantation seemed to prompt HBeAg seroconversion in $HBeAg^+$ patients with CHB under long-term antiviral therapy, revealing an unexpected role of intestinal microbes in antiviral immunity [35]. The changes in intestinal microbiota seem to play an important role in the induction and promotion of HBV-induced chronic liver disease progression [36], thus fecal microbiota transplantation may be a useful therapy for HBV-related diseases in the future [37]. However, available data in this field remain limited and relevant scientific work has only just commenced.

The HBV core proteins are involved in capsid assembly, pregenomic RNA packaging, and cccDNA maintenance [38]. Six different chemical classes of inhibitors targeting the HBV capsid have been developed [39], and two chemotypes of nucleocapsid assembly inhibitors—an isothiafludine compound NZ-4 [40] and a pyridazinone compound 3711 [41]—were first discovered by Chinese researchers. Mechanistically, the core inhibitors will disrupt the viral nucleocapsids by either prevention of assembly or induction of misassembly [42]. The assembly of chimeric capsids from wild-type and drug-resistant core proteins could also be inhibited by core inhibitors. Hence, HBV core protein is a dominant antiviral target that may

suppress the selection of drug-resistant viruses during core protein-targeting antiviral therapy [39]. Several inhibitors have been shown to inhibit HBV replication in mouse models and are currently under active preclinical and clinical development [43–47].

Intrahepatic cccDNA is the key to a functional cure of CHB. To specifically target HBV cccDNA, several Chinese groups have explored the cutting-edge genome editing technologies, including transcription activator-like effector nucleases [48] and the clustered regularly interspaced short palindromic repeats (CRISPR)/CAS9 [49,50], as novel therapeutic approaches, which resulted in HBV inhibition and cccDNA mutation *in vitro* and *in vivo*. Recently, a multiplexed gRNA-guided CRISPR system [51,52] and a combined approach using CRISPR and RNAi [53] against HBV were invented. These approaches showed more synergistic antiviral effects than the single gRNA designs, making cccDNA repair more difficult and favoring its elimination. Thus, significant progress had been made, and gene editing therapeutics for CHB cure is likely to be tested in clinical trials soon.

HBV RNA as a surrogate marker of cccDNA

The elimination of cccDNA marks the complete cure of CHB. However, in clinical practice even the "functional cure" of CHB, which is the serum HBsAg loss, is far from satisfactory [54]. Due to the high frequency of HBV DNA integration, serum HBsAg does not necessarily correlate with intrahepatic cccDNA, obscuring the usefulness of HBsAg as a biomarker, and better biomarkers for safely discontinuing the antiviral treatments is urgently required. Recently, a study identified that the HBV pregenomic RNA (pgRNA) is present in patients' serum, encapsidated, and enveloped in virus-like particles [55]. Because the 3.5 kb serum pgRNA can only be produced from cccDNA, the dynamic decline of serum HBV RNA could reflect the status of intrahepatic cccDNA during NA therapy. Indeed, in comparison with HBV DNA, serum HBV RNA shows superiority in monitoring the sustained viral response or even in monitoring the exhaustion of the intrahepatic cccDNA pool. Therefore, it is reasonable to postulate that sustained loss of serum HBV RNA implicates the elimination or transcriptional silence of cccDNA, a status that could be defined as "parafunctional cure" [56]. In contrast to the HBsAg loss in "functional cure," "parafunctional cure" could be serum HBsAg positive. Thus, a considerable number of patients with CHB could be expected to stop NA therapy safely based on their serum HBV RNA levels.

Quantitative anti-HBV core antibody and HBcrAg as novel markers

HBV infection induces strong immune responses to hepatitis B core antigen (HBcAg). Anti-HBc IgM is transiently elevated following acute HBV infection or acute flares in patients with CHB, whereas anti-HBc IgG persists after the first exposure to HBV. Recently, a novel assay for the quantification of total anti-HBc antibodies (qAnti-HBc) has been developed in China and was suggested to correlate with the host immune responses against HBV. qAnti-HBc levels were found to be positively correlated with ALT in HBV-infected patients [57–59]. More importantly, the qAnti-HBc levels can distinguish different clinical phases of HBV infection. Among HBsAg carriers, those in an inflammatory state have significantly higher qAnti-HBc levels than those in immune tolerance and inactive carrier phases. In addition, qAnti-HBc can predict the response of antiviral therapy with Peg-IFN and NAs. Baseline qAnti-HBc levels could predict HBeAg seroconversion in $HBeAg^+$ patients with CHB [60]. Patients with higher baseline qAnti-HBc levels exhibited a higher rate of HBeAg seroconversion than patients with lower qAnti-HBc levels, and the qAnti-HBc levels steadily declined in the treatment responders. Collectively, total qAnti-HBc level is a novel serological marker for HBV-induced liver disease and is complementary to current quantitative viral markers, including HBsAg and HBV DNA levels. Its potential role in predicting antiviral treatment response deserves further investigation.

Hepatitis B core-related antigen (HBcrAg) consists of three proteins synthesized from the precore/core gene: HBcAg, HBeAg, and a small core-related protein (p22cr). HBcAg, HBeAg, and p22cr share a 149-long amino-acid sequence that is detected using HBcrAg assays [61]. HBcrAg is a marker for viral replication and the amount of intrahepatic cccDNA on some extent in both $HBeAg^+$ and $HBeAg^-$ patients [62,63]. Increasing studies suggest that HBcrAg levels help to predict treatment responses [64–66], safe cessation of NA therapy [67], risk for disease progress [68,69], and HBV reactivation during immunosuppressive therapy [70]. Currently, the specific assay only measuring HBcAg is still under development and not available yet. Whether HBcAg as HBV marker will be more precise than HBcrAg is still unknown. Certainly, the clinical utility of HBcrAg and HBcAg as predictors needs further investigation.

Coinfections of HBV and other hepatotropic viruses should not be neglected

In general, there are five hepatotropic viruses that are responsible for most cases of viral hepatitis, including hepatitis A virus (HAV), HBV, hepatitis C virus (HCV), hepatitis D virus (HDV), and hepatitis E virus (HEV). In China, due to the epidemic status, the coinfection with HCV, HDV, and HEV may be cofactors of liver diseases

caused by chronic HBV infection.

The epidemic caused by HCV affects all regions, with major differences between and within countries. Direct-acting antiviral agents (DAAs), a huge success in modern medicine, have been demonstrated to cure most patients with chronic hepatitis C (CHC). However, HBV reactivation occurs in patients with CHC with HBV coinfections treated with DAAs [71]. The severity of hepatitis could range from HBV reactivation without hepatitis to fulminant hepatic failure, requiring liver transplantation. Recently, a study reported the HBV reactivation among patients receiving DAAs for HCV infections in areas endemic for HBV in China. Cases with HBV reactivation were identified, and HBsAg presence was a strong risk factor for developing reactivation during treatment [72]. Thus, more attention should be drawn to HBV reactivation, and evaluating HBV status is important before initiating DAAs therapy in HBV-endemic areas. The underlying mechanisms of HBV reactivation during DAAs therapy for CHC remain speculative. New insights have been obtained from cell culture studies, where HBV and HCV were shown to replicate in the same hepatocytes without evidence of interference, suggesting that HCV suppresses HBV replication via an indirect immune mechanism [73,74].

HDV is a satellite viroid that depends on HBV for its production [75] and infects only those persons who already have HBV infection. In HBV/HDV-coinfected patients, HDV virions are produced in coinfected liver cells, along with HBV particles. The HDV RNA can replicate to high levels in the hepatocyte nucleus, leading to the production of HDV ribonucleoproteins that can egress in the presence of HBV envelope proteins to produce HDV virions. The latter can subsequently infect human hepatocytes. The chronic HBV/HDV coinfection significantly worsens the course of the liver disease as compared to the HBV monoinfection, and the anti-HBV NA therapy fails to suppress the HDV activity [76]. Only IFN-based treatments can be used, and the response is suboptimal. The distribution of HDV infection varies around the world. In China, data regarding the HBV/HDV coinfections are scarce. Several recent studies in Guangdong and Hunan provinces showed an approximately 5% prevalence of HDV among patients with CHB and injection drug users [77,78]. The HDV prevalence was considered to be very low in China, but this figure could be largely underestimated possibly due to the low sensitivity of the detection method. In this aspect, a novel quantitative microarray antibody capture assay has been developed and identified an extremely high HDV prevalence among the HBV-infected Mongolians [79]. Interestingly, the high prevalence of HDV among Chinese Mongolian patients with CHB was also identified in our unpublished data. Therefore, future studies may screen the Chinese population with HBV infection using the method.

Infection with HEV is reported worldwide, but it is most common in East and South Asia. A vaccine to prevent HEV infection has been developed and is licensed in China, but it is not yet available in most other countries [80]. In China, HEV is endemic with a prior HEV infection rate of 20%–40% (anti-HEV IgG positivity) of the total population and an additional 1% of new infections annually [81]. Due to the high prevalence of both HBV and HEV, coinfections by the two viruses are not rare in China. Nearly 20%–40% of all symptomatic HEV infections were determined to be indeed coinfections [82]. The underlying CHB could predispose the coinfected patients to more severe symptoms than HEV monoinfections. HEV infection may also aggravate the clinical outcome of HBV infection, especially under conditions of liver cirrhosis. Notably, HEV superinfections were reported as the second most prevalent precipitating factor in triggering acute-on-chronic liver failures in patients with CHB in China [83]. Our recent study revealed that underlying CHB-related cirrhosis poses a great risk for adverse outcomes in patients with superimposed hepatitis E [84]. An $HBeAg^-$ status and intermediate HBV DNA levels were shown to be associated with severe diseases in noncirrhotic superinfected patients with CHB. Based on these new findings, we proposed that prophylactic HEV vaccination and potent anti-HBV therapy in high-risk patients with CHB should be strengthened to largely reduce the morbidity and mortality from superimposed hepatitis E.

Several recent surveys have shown that HBV coinfection accounts approximately 10% of all human immunodeficiency virus (HIV)-infected population in China, varying between 8.7% and 16.2% depending on different regions [85–89]. Probably due to direct infection of liver cells by HIV, increased microbial translation from the gut, and immune hyperactivation and exhaustion, HBV–HIV infection is a risk factor for severe liver diseases than monoinfection [90]. Even with effective suppression of both HBV and HIV by TDF-based treatment, liver fibrosis still occurs in a subset of HBV–HIV-coinfected patients, leading to higher morbidity and mortality than in monoinfected patients. Regarding the anti-HBV treatment, drug resistance under TDF therapy is very low; moreover, LAM-based cART is also efficacious for HBV treatment through 48 weeks in HIV–HBV coinfections when baseline HBV DNA is less than 20 000 IU/mL [91]. Interestingly, inflammation by acute HIV- or AIDS-associated immune reconstitution disease may benefit from the HBsAg loss [92]. In the future, new treatment should be explored to reduce liver fibrosis, and specific consideration of HIV–HBV-coinfected patients will be required when assessing the role of new antivirals for both HBV and HIV.

Table 1 Recent advances in the clinical research of CHB in China

Category	Projects	Major findings
Prevention of transmission	HBV vaccine, EPI	Reduced HBV prevalence among age <15 years to less than 1%
	Antiviral treatment in preventing MTIT	Safe and greatly reduced MTIT to nearly 0
Treatment	EFFORT	Evaluated the efficacy and safety of the roadmap strategy and reduced HBV resistance
	EXCEL	Demonstrated the response-guided therapy
	OSST or New Switch	Increases sAg loss and seroconversion
	Peg-IFN add-on (ARES, PEGON)	Increases eAg and sAg loss and seroconversion
	Peg-IFN treatment for inactive sAg carriers	Increases sAg loss and seroconversion
New treatment	HBsAg–HBIG therapeutic vaccine phase III trial	No benefits
	preS1 therapeutic vaccine preclinical model	Broke sAg tolerance and increased immune response to sAg
	GM-CSF adjuvant	Increased immune responses to sAg in model
	E6F6 antibody	Restored immune response to sAg in model
	Fecal microbiota transplantation	Promoted eAg seroconversion in patients
	Core inhibitors	Inhibited nucleocapsid assembly
	CRISPR/Cas9	Mutated or eliminated cccDNA
Predictor markers	pgRNA	Represented cccDNA, predicted off-treatment of NA timing
	Anti-core Ab	Differentiated immune status, predicted eAg seroconversion
	HBcrAg	Marker for cccDNA, predicted treatment outcome and HBV reactivation
New problems	HCV coinfection	DAA treatment induced HBV reactivation
	HDV coinfection	Worsened liver disease and NA failure
	HEV coinfection	Aggravated clinical outcome of HBV infection
	HIV coinfection	Severe liver diseases and drug–drug interactions
Elimination of HBV	Government	More investment and reduce drug cost
	Scientist	Find a new functional cure therapy
	Clinicians	Pay more attention on coinfections with other hepatotropic viruses

Functional cure of CHB and elimination of HBV by 2030?

In summary, China has made great progress in the clinical studies of hepatitis B over the last two decades (Table 1). Elimination of HBV by 2030 was proposed by WHO as the next goal for HBV management. With the largest HBV-infected population in the world, the Chinese government, scientists, and hepatologists are working together to realize this dream—the functional cure of CHB and elimination of HBV, which still remains as two unmet critical issues. As the first step, both ETV and TDF with stronger antiviral effect and much lower drug resistance have been listed as the priority of antiviral drugs in the updated 2015 guideline for management of patients with CHB in China, similar to the WHO recommendation. In addition, scientists are actively seeking novel therapies for the functional cure of chronic HBV infection (Fig. 1). In the cure status, patients should have a sustained viral suppression, HBeAg and HBsAg seroconversion after the cessation of antiviral treatment, and a persistent immunologic control of HBV infection despite the presence of residual cccDNA within the liver. Moreover, HBV coinfections with HCV, HDV, HEV, and HIV need more attention because they will cause severe liver diseases. Further innovation is also needed to optimize vaccines and other prevention interventions, diagnostics, prognostics, and models of service delivery, focusing on improving efficacy, quality, safety, and access and efficiently documenting and achieving public health impact.

In 2017, the leading professional organizations in liver disease—the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver, the Asian Pacific Association for the Study of the Liver, and the Latin American Association for the Study of the Liver—have published the "Joint Society Statement for the Elimination of Viral Hepatitis," which urges governments, health care organizations, and nongovernmental organizations to implement the action plans to eliminate viral hepatitis. We believe that committed research funding will ensure continuous progresses in the mechanistic discovery, drug development, and clinical research. Combinatory therapy with novel antiviral that targets HBV antigens and cccDNA and the induction of HBV-specific immunity will eventually lead to the functional cure of CHB, whereas a functional cure, ultimately, would complete the set of tools available for final elimination.

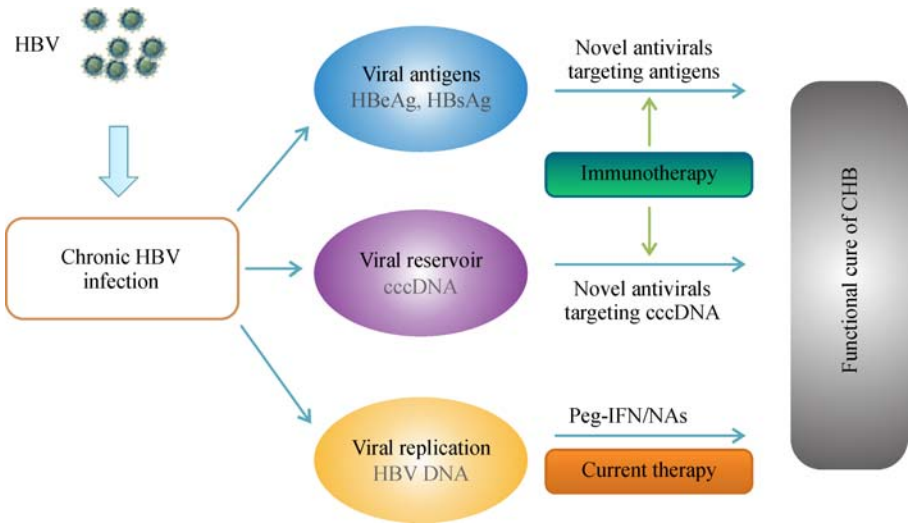

Fig. 1 Functional cure of chronic HBV infection, the challenges, and opportunities. Current therapy is effective in inhibiting viral replication but fails in the control of either HBV antigens or cccDNA. For the functional cure of CHB, novel antivirals or HBV-specific immunotherapy targeting the suppression of both HBsAg and cccDNA are required, which are the key challenges but also mean opportunities.

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Compliance with ethics guidelines

Shuye Zhang, Fusheng Wang, and Zheng Zhang declare that they have no conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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