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Review Article

Hepatitis B virus as a risk factor for hepatocellular carcinoma: There is still much work to do

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ABSTRACT

Hepatitis B virus (HBV) infection is a significant health problem that can result in progression to liver cirrhosis, decompensation, and the development of hepatocellular carcinoma (HCC). On a country level, the prevalence of chronic HBV infection varies between 0.1% and 35.0%, depending on the locality and the population being investigated. One-third of all liver cancer fatalities worldwide are attributable to HBV. The adoption of standard birth-dose immunization exerted the most significant impact on the decline of HBV prevalence. HCC incidence ranges from 0.01% to 1.40% in noncirrhotic patients and from 0.9% to 5.4% annually, in the settings of liver cirrhosis. Although antiviral therapy significantly reduces the risk of developing HBV-related HCC, studies have demonstrated that the risk persists, and that HCC screening is still essential. This review discusses the complex relationship between HBV infection and HCC, recent epidemiological data, different aspects of clinical disease characteristics, and the impact of antiviral therapy in this context.

1. Introduction

Hepatitis B virus (HBV) infection is a serious global health issue and a significant cause of morbidity and mortality associated with complications such as liver decompensation, cirrhosis, and hepatocellular carcinoma (HCC).[1] One-third of all liver cancer fatalities worldwide are due to HBV infection.[2,3] Furthermore, 820,000 people die from liver cirrhosis and HCC each year due to the more than 1.5 million avoidable new infections that still occur annually and the estimated 296 million individuals with chronic HBV infection.[4] HCC accounts for more than 80%–90% of all cases of primary liver cancer and is the third most common cause of cancer-related deaths worldwide.[5] Nevertheless, the occurrence of HCC associated with viral liver disease is declining in affluent nations although simultaneously being offset by an increasing frequency of non-alcoholic fatty liver disease (NAFLD).[2] This review discusses the evolving epidemiology of HBV infection and HCC, the underlying oncogenic mechanism of HBV infection, and the impact of vaccination and antiviral interventions on the global landscape of HBV infection and HCC progression.

2. HBV structure and replicative cycle

HBV, which belongs to the Hepadnaviridae family, is a double-stranded DNA virus with an outer envelope. It comprises 10 distinct genotypes, denoted from A to J.[6] The Asia-Pacific area shows a significant prevalence of genotypes B and C, whereas genotypes A and D are widely distributed in Africa, Europe, and North America.[7] A remarkable disparity exists in the risk of developing HCC across various genotypes of HBV.[7] The genome of HBV has four distinct genes, namely P, preC/C, S, and X, which are responsible for encoding five primary proteins: polymerase (encoded by gene P), hepatitis B core antigen (HBcAg) (encoded by gene C), hepatitis B envelope antigen (HBeAg) (a product of preC), hepatitis B surface antigen (HBsAg) (encoded by gene S), and a replication cofactor X (encoded by gene X).[8] The protein known as HBx, generated from the X gene, plays a critical role in the development of HBV infection and the transcription of the virus. Fig. 1 demonstrates the replication cycle of HBV and the manner by which it integrates into the host genome. The nucleocapsid, which carries either the relaxed

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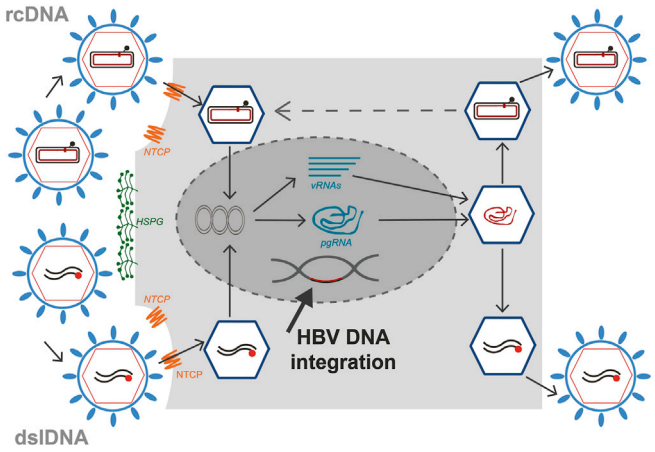

Fig. 1. Replication cycle of hepatitis B virus (HBV). The replication cycle of HBV and the manner by which it integrates into the host genome are shown. Abbreviations: dslDNA, double-stranded linear DNA; HSPG, heparan sulfate proteoglycan; NTCP, sodium taurocholate cotransporting polypeptide; pgRNA, pregenomic RNA; rcDNA, relaxed circular DNA; vRNAs, viral RNAs.

circular DNA (rcDNA) (in the top half) or the double-stranded linear DNA (dslDNA) (in the bottom half), of the HBV genome is transported into the cytoplasm through the sodium taurocholate cotransporting polypeptide (NTCP). Within the nucleus, both variants possess the ability to transform into covalently closed circular DNA (cccDNA), which acts as the template for transcribing all viral RNAs (vRNAs), including pregenomic RNA (pgRNA). pgRNA acts as the template for reverse transcription, which occurs inside the nucleocapsid and results in the formation of rcDNA or dslDNA. The nucleocapsids can subsequently be enclosed within a protective envelope and released as viral particles. The intranuclear dslDNA of HBV has the ability to incorporate itself into the genetic material of the host cell at the location where breaks occur in dslDNA. Recent findings indicate that the reimport of dslDNA-containing nucleocapsids exerts a minimal impact, whereas the input HBV DNA is the primary factor contributing to HBV DNA integration in *in vitro* models.[8–10]

3. Global epidemiology of HBV infection

Despite the World Health Organization (WHO)'s objectives to eradicate viral hepatitis as a public health threat by 2030, there has been a persistent increase in mortality caused by viral hepatitis in the past decade.[11] This is in contrast to the declining rates observed for other comparable diseases such as tuberculosis and human immunodeficiency virus (HIV) infection. Africa represents approximately 17% of the global population.[12] However, a disproportionate percentage ranging from 20% to 30% of people affected with HBV infection is concentrated in sub-Saharan Africa.[13] Chronic HBV infection exhibits variability between geographic regions and people, with national prevalence rates spanning from 0.1% to 35.0%.[14,15] The occurrence of HBV infection, as indicated by the presence of HBsAg, is categorized into four degrees of endemicity: low (<2.0%), lower intermediate (2.0%–4.9%), higher intermediate (5.0%–7.9%), and high (≥8.0%).[15] In general, there exists a remarkable disparity in prevalence rates, with men showing a much greater frequency.[16] Approximately 60% of the global population resides in regions with a high incidence of chronic HBV infection.[17] Regions with a high endemicity of HBV infection encompass several geographical areas, including Asia, sub-Saharan Africa, the Pacific, portions of the Amazon Basin, sections of the Middle East, the Central Asian Republics, India, and some Central and Eastern Europe countries.[15,18]

Intermediate-endemic regions of HBV infection that may be found in Eastern and Southern Europe, the Middle East, South America, and Japan. Within these specific communities, the prevalence of HBV infection ranges from approximately 10% to 60%, whereas 2%–7% of individuals become chronic carriers of the virus. This epidemiological trend included both childhood and adult infection,[17,19] and these figures correspond to a comparable proportion of the global population observed in regions with high prevalence rates (slightly >40%).[19] Western and Northern European nations, North America, Central America, and the Caribbean have a low incidence of chronic HBV infection, with rates <2%. The acquisition of HBV infection typically occurs during adulthood in these regions.[20]

Remarkably, areas characterized by significant HBV infection rates also exhibit elevated incidence rates of HCC. Moreover, HCC is among the top three leading etiologies of cancer-related mortality in Asia, sub-Saharan Africa, and the Pacific.[14,21] The incidence of this phenomenon has exhibited a global increase due to the combined factors of population growth and aging.[22]

According to estimates by the WHO in 2019, more than 296 million individuals, accounting for approximately 3.8% of the global population, were living with chronic HBV infection.[23,24] The establishment of standard HBV immunization in infancy has resulted in a remarkable decrease in the prevalence of chronic HBV infection among children aged ≤5 years.[24] The estimated frequency of chronic HBV infection among children aged ≤5 years is 1.3%.[25] The global rate of HBV–HIV coinfection among patients infected with HIV is 7.4%.[26] The estimated global prevalence of HBsAg positivity among individuals who inject drugs is 8.4%. This prevalence is particularly high in East Asia, Southeast Asia, and Eastern Europe, where the most substantial numbers of HBsAg-positive individuals who inject drugs are found.[27]

4. HBV infection and risk of HCC development

The global public health problem arises from the increasing prevalence and fatality rates of HCC caused by HBV infection. According to available estimates, more than half of HCC cases globally are related to chronic HBV infection.[28] After the global deployment of HBV vaccination, there has been a remarkable reduction in the general prevalence of HBV infection. Nevertheless, it is important to acknowledge that certain regions still experience a significant burden of HBV infection.[29] According to Perz *et al.*,[29] HBV is responsible for an annual incidence of 749,000 new cases of HCC and 692,000 fatalities attributed to HCC. The annual occurrence of HCC is anticipated to be <1% for those infected with HBV who do not have cirrhosis. However, for those with cirrhosis, the predicted incidence of HCC is between 2% and 3%.[30]

The burden of HCC attributable to HBV varies due to global and geographical differences in HBV occurrence. Asia-Pacific and sub-Saharan Africa have been identified as having the maximum prevalence of HCC on a global scale, as reported by a study.[30] The United States has a significantly reduced risk of HCC development associated with HBV infection, with an incidence of <20%. In contrast, Europe shows regional variations, with Western and Northern regions demonstrating a low risk of 18%, whereas Eastern and Southern regions show a higher risk of 51%.[30]

The incidence of HCC in individuals infected with HBV is affected by several variables, including those related to the virus itself, the host, as well as dietary and lifestyle factors.[31] In cases of HCC associated with HBV infection, approximately one-third of patients do not exhibit cirrhosis, in contrast to other causes of liver disease, where cirrhosis is present in the majority (80%) of cases.[32] Advanced age and male gender are well recognized as established variables associated with an increased risk of HCC development.[33]

Increasing data suggest that HCC associated with HBV infection exhibits gender differences and could be classified as a hormone-responsive malignancy. Androgen and estrogen, which are sex hormones, have been found to exert distinct effects on the progression of HBV infection and the development of HBV-related HCC. Sex hormones can regulate the transactivation of HBx by binding to their specific cellular receptors and affecting the corresponding signaling pathways. This can result in the chronic release of inflammatory cytokines in the hepatocellular microenvironment and contribute to epigenetic and genetic alterations in hepatocytes. All these functions are potentially associated with hepatic carcinogenesis. An in-depth examination of the molecular mechanisms that cause the difference in HBV-related HCC between genders should provide a fresh viewpoint for understanding its development and discovering more efficient approaches to avoid and cure this disease.[34] Furthermore, it has been observed that infections with additional liver-specific viruses, such as chronic hepatitis C virus (HCV) and HIV infections, in individuals with chronic HBV infection might elevate the risk of HCC development.[31] Similarly, individuals coinfected with both HBV and HDV have a threefold greater probability of developing cirrhosis and a 3.2-fold higher risk of rapidly advancing to HCC than those only infected with HBV.[35] Moreover, Chen *et al*.[36] provided evidence supporting a positive correlation between the amount of HBV DNA and the probability of developing HCC. A significant correlation was also found between the levels of HBsAg and the incidence of HCC in individuals with lower levels of HBV DNA.[37] HBV DNA levels were higher in HCC tissue samples than in adjacent and remote nontumor tissues samples. Meanwhile, HBV pgRNA and total RNA expressions were lower in HCC tissue samples. Further evidence for HBV replication in HCC tissue samples was provided by sequencing the HBV S, reverse transcriptase, and X genes, which demonstrated that HBV sequences and genotypes differed between HCC tissue and matched adjacent and remote nontumor tissues samples. The detection of pgRNA and OCT4 in distal nontumor tissues correlated with the recurrence of HCC in surgically resected HCC samples, indicating an existing HBV replication in HCC with a weak transcriptomic signature.[38] Regarding HBV genotypes, it has been observed that genotype C correlates with an elevated susceptibility to HCC.[39] It has also been indicated that genotype B is associated with an increased susceptibility to HCC in pediatric and non-cirrhotic patient populations.[40] Platelet counts, levels of alanine aminotransferase (ALT) HBV DNA, and the presence of HBeAg are additional risk variables that are associated with HCC development.[41] Precise evaluation of HCC risk and implementing consistent screening methods are vital in patients with chronic hepatitis B (CHB) to achieve early detection and improve the disease outcome. Several risk prediction models for HCC have been developed for patients with CHB, providing clinicians an effective diagnostic tool. However, because of the variations in the fundamental attributes of each model during the process of obtaining and validating the population, the applicable population and predictive accuracy still varies, rendering it challenging to develop a universal solution.[42] Various risk scores have been proposed to evaluate the probability of developing HCC in patients with CHB, such as the guide with age, gender, HBV DNA, core promoter mutations, and cirrhosis-HCC (GAG-HCC) score, Chinese University-HCC (CU-HCC) score, platelet, age, and gender-hepatitis B (PAGE-B) score, modified PAGE-B (mPAGE-B) score, and age-male-albumin-bilirubin-platelet (aMAP) score. These scores consider factors such as age, gender, HBV DNA, core promoter mutations, cirrhosis and HCC, albumin and bilirubin levels, and platelet data.[41–43] The literature includes some studies that have attempted comparing various available risk scores for predicting HCC risk in patients with CHB. A systematic review and meta-analysis were performed followed by external validation in an independent multicenter cohort with 986 patients with CHB who received entecavir treatment.[44] The study identified 14 models with 123,885 patients (5452 HCC cases), with the risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B), CU-HCC, GAG-HCC, PAGE-B, and mPAGE-B models being widely externally validated. Discrimination was generally acceptable for all the tested models for 10-year prediction. In the external validation cohort, the real-world effectiveness from the Asia-Pacific Rim Liver Consortium for HBV (REAL-B) showed the highest discrimination for 3- and 5-year prediction. The REAL-B model also well calibrated in the external validation cohort.[44]

5. The triumphant story of HBV immunization

Plasma-derived vaccinations, the initial HBV vaccines, have been in commercial use since 1982.[45] Although concerns surrounding the transmission of bloodborne diseases, such as HIV, and the safety of these vaccinations have been demonstrated to be baseless, public apprehensions regarding their safety have continued to exist. These suspicions hindered their acceptability across several communities.[46] Additional obstacles included exorbitant vaccine expenses and the absence of worldwide vaccine regulations.[47] The first genetically engineered HBV vaccine using recombinant HBsAg appeared in 1986.[48] Genetically engineered HBV vaccines effectively stimulate a serological response of >95% in healthy newborns, children, and young adults.[49] Initially, the primary focus of HBV control policies was the vaccination of high-risk groups.[50] However, it was challenging to approach populations at higher risk who frequently acquire the infection before receiving the vaccine.[51] Under the WHO, the Global Advisory Group of the Expanded Program on Vaccination advised in 1991 that the HBV vaccine should be included in national vaccination programs in all countries by 1997,[52] and the World Health Assembly in 1992 approved the 1991 suggestion.[53] Over time, the usage of HBV vaccination has increased, and it has been expanded to provide the highest level of protection.[54] Furthermore, the WHO currently advises that all infants be vaccinated against HBV infection at birth (universal vaccination), as perinatal and early postnatal transmission are the primary sources of HBV transmission. The WHO also recommends catch-up vaccination for children and adolescents who did not receive HBV vaccine at the time of their birth.[55] Countries that have implemented the vaccination suggestion had a significant decrease in carrier rates and consequences associated with HBV infection, such as HCC. The prevalence of chronic HBV infection in children aged <5 years has significantly decreased over time because of the vaccination policies, decreasing from 4.7% during the period before the vaccination was available to <1.0% in 2019.[56] The introduction of standard birth-dose immunization has resulted in a marked reduction in the disease prevalence in the Western Pacific Region, which decreased from 8.30% in the pre-vaccination era to 0.93% between 2002 and 2015.[57] Relying primarily on vaccination, the WHO established ambitious goals for eliminating HBV infection, as a public health goal by 2030.[58]

6. HBV oncogenic mechanism in HCC development

The replication process of HBV involves the utilization of reverse transcription. However, it is worth mentioning that integration is not a crucial aspect of its lifecycle because it does not produce replication-competent virus.[59] During the reverse transcription of pgRNA, approximately 90% of the time, a partially double-stranded reverse-complementary DNA (rcDNA) is generated. In the remaining 10% of situations, a dslDNA is generated.[60] The presence of HBV dslDNA in virions has been observed, and it can undergo repair processes to generate cccDNA.[61] The integration of dslDNA is

a phenomenon that has been observed to occur in approximately 1 of every 10, 000, 000 infected hepatocytes. Populations with a greater proportion of dslDNA integration include children as young as 5 months old and patients diagnosed with acute HBV, CHB, and HCC.[62]

Tu *et al*.[60] comprehensively explained the processes behind HCC development driven by HBV integration. These mechanisms include chromosomal instability resulting from the integration of HBV DNA, the induction of mutation in proto-oncogenes and tumor suppressor genes by insertion, and the production of mutant HBV proteins. Integration typically occurs in proximity to vulnerable locations, such as intergenic regions, CpG islands, simple repeats, repetitive regions, and telomeres. This leads to the second mechanism, the induction of HCC.[63] To validate this, recent studies using next-generation sequencing have observed that HCC often exhibits a higher frequency of integration events and a high rate of incorporation in coding or promoter regions compared with the incorporation sites of HBV in nontumor tissues that are matched to the tumors.[60]

In addition, the HBx protein, which has a molecular weight of 17 kDa and does not directly interact with the genome, has several functions in both the lifecycle of HBV and development of HCC.[64] The HBx protein exhibits localization in multiple cellular compartments, including the cytoplasm, nucleus, and mitochondria. Within these compartments, it exerts its impact on various cellular processes such as signal transduction, transcriptional regulation, and mitochondrial functionality. Consequently, the HBx protein induces the transactivation of both viral and cellular genes, contributing to HCC development through four primary mechanisms. These mechanisms comprise the integration of *HBx* into the genome of hepatocytes, which promotes genetic instability. The HBx protein also induces oxidative stress by interacting with mitochondrial and other cellular proteins. Moreover, it activates signaling pathways that promote cell survival while simultaneously inactivating tumor-suppressor proteins. Finally, the HBx protein induces epigenetic modifications, including histone acetylation, DNA methylation, and alterations in microRNA expression.[65] Consequently, HBx possesses the capacity to regulate several proto-oncogenic signaling pathways implicated in inflammation and proliferation, including the mitogen-activated protein kinase (MAPK)/Ras/Raf/c-Jun, JAK/STAT, protein kinase C, Src, survivin, and phosphoinositide 3-kinase (PI3K) cascades.[66] HBx may also facilitate the activation of the Wnt/β-catenin pathway, a significant oncogenic pathway, either through the binding of antigen-presenting cell protein or the inactivation of glycogen synthase kinase-3 (GSK-3). Consequently, there occur an accumulation of catenin and upregulation of the transcription of proangiogenic/metastatic proteins.[67] HBx can interact with p53 inside the cytoplasm, impeding the translocation of p53 to the nucleus. Therefore, this results in the suppression of the functionality of p53, leading to genomic instability and disruption of tumor suppressors.[68]

7. HCC screening in patients at risk

Multiple cohort studies have demonstrated a significant correlation between HCC surveillance and enhanced 3-year survival rates (odds ratio, 1.09; 95% confidence interval (CI), 1.67–2.17).[69] The most reliable evidence concerning the importance of HCC screening is derived from a substantial randomized controlled trial, which demonstrated that screening individuals with chronic HBV infection resulted in improved early detection of tumors (stage I: 60.5% *vs*. 0%), increased rates of curative interventions (resection: 46.5% *vs*. 7.5%), and improved overall survival (37%; hazard ratio 0.63; 95% CI, 0.41–0.98) compared with those who were not screened.[70] The development of >90% of HCC cases in the Western world occurs within the context of cirrhosis, which represents the advanced stage of any chronic liver damage.[71] Individuals diagnosed with cirrhosis have an annual probability of HCC development ranging from 2% to 4%.[71] Due to the significant level of risk involved, there is an agreement among guidelines established by large international scientific societies that HCC surveillance is advised for cirrhotic patients, irrespective of the underlying cause of liver disease.[72–75] Screening for HCC is often restricted to individuals with compensated cirrhosis, i.e., those classified as Child-Pugh class A or B. Moreover, patients with Child-Pugh class C cirrhosis who are candidates for liver transplantation must be screened.[73]

In the context of patients with hepatic or nonhepatic disorders resulting in a life expectancy of ≤1 year, it is generally believed that screening does not have a significant value.[72,73] However, geographic diversity exists in the several risk factors associated with cirrhosis.[71] Although HBV infection is responsible for almost 70% of HCC cases in Africa and East Asia, most cases in the Western world and Japan are attributed to HCV infection.[71] Studies have documented the increasing role of NAFLD, with its relation to metabolic dysfunction, in HCC development.[76,77] Furthermore, it is worth mentioning that alcohol use is a prevalent nonviral cause of cirrhosis, as demonstrated by a previous study.[78] According to a meta-analysis, using a high volume of alcoholic beverages (defined as three or more drinks per day) was associated with a 16% higher probability of developing liver cancer than abstaining from alcohol.[78] According to Asia-Pacific recommendations, it is also suggested to evaluate individuals with less prevalent causes of cirrhosis, including primary biliary cholangitis, hemochromatosis, and autoimmune hepatitis.[74]

Chronic HBV infection is well acknowledged as a significant risk factor for HCC and is responsible for most HCC cases worldwide.[71] The cost-effectiveness of HCC surveillance has been demonstrated in patients with HBV infection without cirrhosis, but only when the annual incidence rate is >0.2%.[73] HCC screening is often limited to specific subpopulations of individuals without cirrhosis and who are infected with HBV.[72–75] Despite the significant reduction in HCC risk in patients with chronic HBV infection who receive antiviral therapy, current research findings have indicated the presence of persistent risk and the ongoing need for HCC screening.[79]

8. Evolving antiviral therapy for chronic HBV infection

The management of patients with chronic HBV infection has witnessed significant growth in recent decades, characterized by the emergence of a more comprehensive array of treatment modalities and the accessibility of several antiviral medications.[80,81] It has been demonstrated that the administration of nucleoside/nucleotide analog (NUC) treatment reduces the occurrence of HCC and deaths related to HCC in patients with chronic HBV infection by inhibiting viral replication.[82] The primary objective of antiviral treatment is to decrease the occurrence of HCC development successfully.[83] For untreated patients with chronic HBV infection, the estimated HCC incidence rates per 100 patient-years were 0.03–0.17 in inactive carriers, 0.07–0.42 in asymptomatic carriers, 0.12–0.49 in patients with chronic hepatitis, and 2.03–3.37 in patients with cirrhosis. For patients undergoing antiviral therapy, the risks of HCC development are 40%–60% lower than those for untreated patients.[82] Patients treated with residual detectable HBV DNA or intrahepatic cccDNA still have a risk of HCC development. However, the current antiviral treatment remains unsatisfactory, prompting the development of novel techniques and/or medications. Lamivudine (LAM), adefovir dipivoxil (ADV), and telbivudine (LdT) have become almost obsolete because of the high drug resistance. In contrast, entecavir (ETV), tenofovir disoproxil

fumarate (TDF), tenofovir alafenamide (TAF), and pegylated interferon (PEG-IFN) are currently considered the preferred initial treatment options in anti-HBV therapy.[80,84]

ETV, an analog of cyclopentyl guanosine, exerts strong inhibitory effects on HBV polymerase. A previous study showed that ETV achieves a significant mean decrease of 6.9 log in blood HBV DNA levels.[85] That study, including several centers, demonstrated a remarkable decrease in probability for cirrhotic complications, HCC, and death among individuals with HBV-related cirrhosis after a 4-year treatment with ETV.[85] TDF is a pharmacological compound that functions as an acyclic adenine nucleotide analog, demonstrating efficacy against both HBV and HIV. A phase III randomized study indicated that TDF 300 mg daily is more effective than ADV 10 mg daily in suppressing HBV DNA in both HBeAg-positive and HBeAg-negative individuals.[86] The administration of TDF therapy over 7 years resulted in the attainment of undetectable HBV DNA levels in 99.3% of patients. Furthermore, 80% of patients had normalized ALT levels, whereas 54.5% of patients had HBeAg loss. HBsAg loss was also observed in 11.8% of patients who had previously experienced HBeAg loss.[87] Kim *et al.*[88] demonstrated a decrease in the occurrence of HCC in patients without cirrhosis who received long-term treatment with TDF, as demonstrated by the REACH-B risk calculator. Recently, a low-molecular-weight oral prodrug of tenofovir, known as TAF, has received approval for managing chronic HBV infection. This approval arises from the need to substitute long-term TDF therapy due to concerns regarding renal damage and reduced bone mineral density.[89] A pharmacokinetic study demonstrated that a 25 mg dosage of TAF exhibited a systemic tenofovir concentration that was >90% lower than that by a 300 mg dose of TDF administration. In addition, the intracellular concentration of TAF was greater.[89] The efficacy of TAF and TDF treatment in HBeAg-positive and HBeAg-negative patients was compared in a randomized, double-blind trial, which demonstrated comparable rates of reaching HBV DNA levels of <29 IU/mL at week 48.[90] Regarding the evaluation of renal safety by measuring the estimated glomerular filtration rate (eGFR), it was found that patients who received TAF experienced a comparatively lesser decline in renal function than those who received TDF therapy.[90] Examination of the reduction in bone mineral density at the hip and spine showed that patients who received TAF therapy had considerably lesser reductions than those who received TDF therapy, irrespective of the HBeAg status.[90,91]

However, there is a lack of clarity regarding the comparative efficacy of TDF and ETV treatments in preventing HCC development in patients with chronic HBV infection.[92–94] A recent study demonstrated that patients who received TDF treatment had a reduced incidence of HCC compared with that in patients who received ETV treatment, specifically among individuals with decompensated cirrhosis.[95] In addition, two recent retrospective studies have demonstrated that the administration of TDF was substantially associated with a reduced probability of late HCC recurrence compared with the administration of ETV.[96,97]

There are more recent data on the effect of besifovir dipivoxil maleate (BSV), a new NUC, on the occurrence of HCC in patients with chronic HBV infection. A Korean study evaluated the reduced risk of HCC occurrence in 188 patients with chronic HBV infection who received BSV treatment for up to 8 years. The investigators prospectively evaluated HCC incidence compared with risk from prediction models derived from the REACH-B model and GAG-HCC model, respectively. The standardized incidence ratio was 0.128 ($P = 0.039$) at 7 years in patients with noncirrhotic chronic HBV infection and 0.371 ($P = 0.047$) at 7.5 years in cirrhotic patients, suggesting a significantly reduced HCC incidence in both groups.[98]

9. Challenges facing the current antiviral therapies

9.1. IFN-based therapy

Despite being endorsed as a primary treatment option in all therapeutic recommendations, its administration through subcutaneous injection, low tolerability, and remarkable adverse effect profile have imposed limitations. Moreover, it is important to note that this treatment is not recommended for patients with hepatic decompensation, immunosuppressed conditions, serious concomitant disorders, or who are pregnant.[99] Therefore, it can be observed that PEG-IFN is administered to a minority of real-world patients, i.e., <5%. This treatment option is generally favored by young patients with immediate plans for parenthood and individuals who decline long-term NUC therapy.[99]

9.2. NUC therapy

Considering that NUCs can significantly suppress HBV DNA levels, it must be noted that they do not exert a direct impact on cccDNA that is observed in hepatocytes infected with HBV. Consequently, the ongoing and indefinite administration of long-term NUC treatment is often required to sustain a virological response.[80,84] According to mathematical modeling research, it has been projected that three to four decades of uninterrupted NUC treatment would be required to attain a functional cure.[100] Nonetheless, a number of issues and limitations concerning the use of life-long NUC treatment have been identified.[101] A comprehensive cohort study conducted on a global and multicenter scale, with a substantial number of 4769 patients and focusing on the long-term effects of ETV/TDF therapy, reported a 10-year HBsAg loss rate of 2.1%, indicating a relatively low occurrence. The study also reported an annual incidence of only 0.22%, further emphasizing the infrequency of this outcome.[102] The cost and drug-resistance concerns originate from previous studies that have indicated the potential emergence of resistance mutants in low genetic barrier NUC therapies, such as LAM and ADV.[80] Furthermore, individuals from countries or areas with limited resources, such as Asia, may have financial constraints that prevent them from bearing the costs associated with long-term NUC treatment.[103]

10. Summary and future perspectives

HBV infection is a significant health issue that can result in the development of HCC. HBV prevalence varies depending on the region and the studied population. Although antiviral therapy significantly reduces the risk of developing HBV-related HCC, studies have demonstrated that the risk persists, and that HCC screening is still essential. HBV vaccination should be expanded worldwide, especially in highly prevalent and poor areas, by different health care facilities. Pregnant women must be tested in their early antenatal visits for health care education on HBV infection. This should include the knowledge about HBV nature, the transmission mode, and the importance of full vaccination. Existing antiviral treatments exert strong inhibitory effects on HBV replication and may improve liver histopathology. Nonetheless, they seldom succeed in eliminating chronic HBV infection. Therefore, there is an urgent need for novel antiviral medications. Further research is still necessary to understand the HBV oncogenic mechanism to develop better antiviral therapies. An optimal HCC screening system should be adequately established for patients with chronic HBV infection with and without liver cirrhosis. Fig. 2 illustrates the strategies that we can go through for preventing HBV-related HCC.

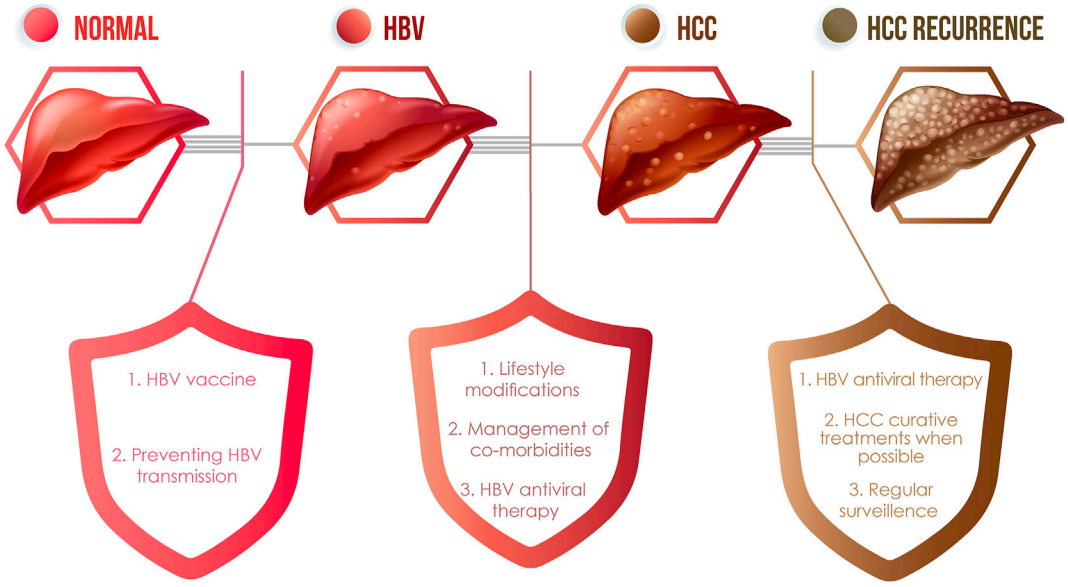

Fig. 2. Strategies for preventing HBV-related HCC. HBV vaccination, lifestyle modification, and HBV antiviral therapy can help prevent HCC development in patients with HBV infection. Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

Authors' contributions

Mohamed El-Kassas and Walaa Abdelhamed contributed to this manuscript with the conception and design of the work and literature review. Walaa Abdelhamed wrote the first draft of the manuscript. Mohamed El-Kassas provided critical revision and editing. Both authors revised and approved the final version of the manuscript.

Declaration of competing interest

The authors declare that there is no conflicts of interest.

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