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LETTER TO THE EDITOR

Hepatitis B virus-induced cirrhosis: Mechanisms, global variations, and treatment advances

Jun-Ya Cheng, Guan-Yue Shan, Hui Wan, Yi-Ying Liu, Yu-Xin Zhang, Wen-Na Shi, Hai-Jun Li

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Abstract

We focus on hepatitis B virus (HBV)-induced cirrhosis, global differences, and the evolution of antiviral treatment strategies. Chronic HBV (CHB) infection affects more than 250 million people globally, leading to cirrhosis and hepatocellular carcinoma. The aim of this article was to synthesize the current understanding of the pathophysiological mechanisms and clinical consequences of HBV-induced cirrhosis, and explore differences in disease progression between geographic regions. Disease progression varies across regions due to differences in HBV subtypes, transmission routes, and immune responses. The challenge of late diagnosis and treatment, particularly in resource-limited areas, highlights the urgency and importance of CHB service expansion. Modern nucleos(t)ide analogues, such as tenofovir and entecavir, have emerged as the main therapeutic regimens to improve clinical outcomes in patients by suppressing viral replication and attenuating liver fibrosis. However, drug resistance challenges highlight the need for ongoing research and personalized treatment strategies. This article highlights the mechanisms and impact of cirrhosis progression in the context of CHB infection, aiming to reduce the incidence of cirrhosis and its serious consequences, thereby improving the long-term health of CHB patients worldwide, especially in Africa.

Key Words: Chronic hepatitis B virus; Hepatitis B virus-induced cirrhosis; Nucleos(t)ide analogues

Core Tip: Understanding the global variation in hepatitis B virus-induced cirrhosis highlights the complex interplay between viral factors, host genetics, and environmental influences. Cirrhosis due to chronic hepatitis B virus (CHB) infection results from a cascade of fibrosis processes driven by persistent viral replication and immune-mediated hepatocyte injury. Over time, evolving antiviral treatment strategies have transformed from interferon-based therapies to nucleos(t)ide analogs, such as tenofovir, which effectively inhibit viral replication and attenuate liver injury. Future research should focus on elucidating new therapeutic targets to improve treatment efficacy and reduce the global burden of cirrhosis associated with CHB infection.

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TO THE EDITOR

We comment on the article by Ismael *et al*[1] published in the recent issue. Chronic hepatitis B virus (CHB) infection remains a significant global health challenge, impacting over 250 million individuals worldwide and contributing substantially to the burden of liver disease, including liver cirrhosis and hepatocellular carcinoma (HCC)[2-4]. Cirrhosis advances in up to one-fifth of those with CHB, resulting in hepatic decompensation in 20% of these cases and HCC in 15%[5,6].

The pathophysiological mechanisms underlying hepatitis B virus (HBV)-induced cirrhosis are complex and vary across different geographic regions and patient populations[7]. This article integrates current knowledge on these mechanisms and consequences of HBV-induced cirrhosis, emphasizing regional and population differences in disease dynamics. It also explores the pivotal role of liver fibrosis in driving disease progression and highlights the clinical implications of cirrhosis progression and current antiviral treatment strategies. From traditional interferon (IFN) therapy to contemporary nucleos(t)ide analogues (NAs), significant progression have been made in improving patient outcomes by suppressing viral replication and mitigating liver fibrosis. However, challenges such as drug resistance persist in certain patient subgroups, there is a need to continue to explore novel treatment modalities and personalized therapeutic approaches[8]. This article aims to inform clinical practice and guide the development of innovative strategies to mitigate HBV-induced liver cirrhosis progression and its devastating consequences.

In the recent issue of the *World Journal of Hepatology*, Ismael *et al*[1] published the interesting paper: This cohort study enrolled 193 HIV-negative adults with CHB at Hiwot Fana Specialized University Hospital in Harar, Eastern Ethiopia, from June 2016 to December 2019. Most participants were male (68.4%) with a median age of 30 years. At enrollment, 31.1% already had cirrhosis, of whom 58.3% had decompensated cirrhosis, indicating advanced disease at diagnosis. This highlights late presentation and underscores the urgent need for accessible HBV services in the region. Factors associated with cirrhosis included khat use, HBeAg positivity, and high viral load (> 2000 IU/mL). Khat, a widely used stimulant in Eastern Ethiopia, is linked to hepatotoxic effects, exacerbating CHB progression to cirrhosis. HBeAg positivity and high viral load are established risk factors for severe disease progression, consistent with global findings. Regarding treatment, 66 patients (34.2%) met criteria for antiviral therapy (AVT) initiation, with 30.6% starting tenofovir disoproxil fumarate (TDF). After 24 months of TDF treatment, significant improvements were observed in liver fibrosis markers (median APRI score decline from 1.54 to 1.10; $P = 0.002$) and high viral suppression rates (80.9% at 12 months, reaching 100% at 24 months), indicating TDF's efficacy in suppressing viral replication and improving liver function. However, challenges were noted. Initial mortality among treated patients was high (20.3% within 6 months), primarily due to complications of decompensated cirrhosis like upper gastrointestinal bleeding and spontaneous bacterial peritonitis. This underscores advanced disease at treatment initiation and the critical need for earlier diagnosis and intervention. In conclusion, this study underscores the urgent need to scale up HBV prevention, diagnosis, and treatment services in Eastern Ethiopia. The high prevalence of cirrhosis at diagnosis and mortality among those with decompensated cirrhosis highlight the severe consequences of delayed care access. Efforts should prioritize early detection through expanded screening, enhancing access to affordable antivirals, and providing comprehensive care to alleviate the CHB burden in resource-limited settings.

GLOBAL DIFFERENCES IN HBV-INDUCED CIRRHOSIS

HBV-induced liver cirrhosis exhibits varying pathophysiological mechanisms and developmental trends across different regions[3]. In Asia, different HBV genotypes such as B and C prevail, impacting viral replication rates, immune evasion capabilities, and the extent of hepatocellular damage, thus influencing the progression and severity of cirrhosis[9]. Liver disease complicated by co-infection with hepatitis C virus and infectious diseases such as hepatitis E or tuberculosis is common in this region and accelerates the development of cirrhosis[10]. High prevalence rates of HBV in childhood or adolescence, notably in Southeast Asia and mainland China, predispose individuals to chronic infection, creating a conducive environment for cirrhosis progression[9].

Meanwhile, in Africa, HBV infection usually occurs in childhood and is usually transmitted vertically, while adult infections are mainly transmitted horizontally through sexual contact or blood exposure[11]. The biological impact of these transmission patterns on viral dynamics within the host may differ, influencing disease course and progression rates. Additionally, regions with high HIV-HBV co-infection rates in Africa experience exacerbated liver pathology due to HIV's cooperative interaction effects on hepatocellular injury[12-14]. Limited healthcare resources in some African regions result in a lack of timely access to effective AVT and cirrhosis management, thereby increasing the risk of disease progression and cirrhosis progression[15]. In the study by Ismael *et al*[1], in Eastern Ethiopia, the determinants of cirrhosis in patients with CHB infection include khat consumption, HBeAg positivity, and high hepatitis B viral load. Khat use was independently associated with liver cirrhosis, likely exacerbating CHB-related liver damage. HBeAg-positive patients and those with a viral load exceeding 2000 IU/mL were at significantly greater risk of developing cirrhosis. The study also emphasized that male patients and individuals from certain regions, such as Oromia, were more likely to have cirrhosis, highlighting the impact of both viral and socio-demographic factors.

In Western countries, immigrant populations from HBV-endemic areas may carry chronic HBV infections[16]. Factors such as incorporation alcohol abuse or obesity further complicate disease progression in some western patients, cooperative interacting with HBV infection to accelerate liver fibrosis[17,18]. Outbreaks still occur even in high-income countries, such as the United States, where the epidemic of opioid use coupled with low vaccination rates among adults have been associated with an increase in incidence of acute HBV infection[19,20].

In sum, regional and demographic differences in HBV-induced cirrhosis arise from different infection dynamics, prevalence of complications, and differences in healthcare services. Individualized treatment strategies and a comprehensive management approach are essential to mitigate the progression of cirrhosis and improve clinical outcomes in diverse patient populations.

THE MECHANISMS AND CONSEQUENCES OF LIVER CIRRHOSIS IN CHB INFECTION

The pathophysiological process of CHB infection involves several key steps. The natural course of CHB infection is dynamic, reflecting a balance between host immune surveillance and viral replication[2]. Initially, the virus enters the host through blood or body fluids. Upon entry, HBV primarily infects hepatocytes by interacting with its surface antigen (HBsAg) and hepatocytes receptor such as NTCP[21-23]. Inside hepatocytes, HBV DNA is released and transported to the nucleus where it can integrate into the host DNA or form covalently closed circular DNA (cccDNA)[24]. These processes lead to viral replication, producing HBV RNA and proteins. Viral particles assemble and are released into the bloodstream, infecting new hepatocytes or being excreted *via* bile[25]. The release of viral particles has a direct toxic effect on hepatocytes, thereby promoting necrosis and apoptosis. Prolonged viral replication increases the burden on hepatocytes and triggers liver inflammation and fibrosis[26]. HBV infection triggers host immune responses including both cellular and humoral immunity, involving infiltration of inflammatory cells like $CD4^+$ T cells and $CD8^+$ T cells, and the release of inflammatory mediators such as IFNs and tumor necrosis factor[27-31]. Cytokine release and activated immune cells (*e.g.* Kupffer cells and macrophages) resulting from chronic inflammation produce fibrosis-mediating substances that exacerbate structural changes in the liver[32-34]. Overall, CHB involves a complex interaction between viral replication, immune responses, and liver damage, ultimately impacting liver function and potentially leading to severe liver disease. The mechanism is shown in Figure 1.

CHB infection can lead to liver cirrhosis through a complex interplay of liver fibrosis and functional decline[30]. Upon HBV infection, persistent inflammation and hepatocellular injury trigger a cascade of events promoting the deposition of extracellular matrix proteins, primarily collagen, within the liver parenchyma[35]. This process, known as liver fibrosis, represents the initial response to chronic liver injury and serves as a precursor to cirrhosis[36]. The progression from liver fibrosis to cirrhosis is characterized by the gradual replacement of normal liver tissue with fibrous scar tissue, disrupting the liver's structure and impairing essential functions such as metabolic regulation, detoxification, and protein synthesis [37]. At the same time, ongoing hepatocellular damage and inflammation perpetuate fibrogenesis, further exacerbating liver fibrosis and contributing to the irreversible alteration of liver architecture[38]. Clinically, the degree of liver fibrosis critically determines disease prognosis and guides clinical management decisions[37]. Advanced fibrosis stages, particularly bridging fibrosis and cirrhosis, are associated with increased risks of complications including portal hypertension, ascites, hepatic encephalopathy, and HCC[39-42]. Therefore, it is critical to early detection and accurate staging of liver fibrosis to prevent irreversible liver damage.

Understanding the basic mechanisms of liver fibrosis and functional decline in CHB infection is essential for developing targeted therapies aimed at blocking or reversing fibrogenesis, thereby reducing the incidence of cirrhosis and its associated complications. Current research endeavors are focused on elucidating the molecular mechanisms underlying the progression of liver fibrosis in individuals with CHB infection, including a spectrum of studies aimed at identifying specific targets and pathways. Numerous studies have identified novel targets, including TRAF2, STING, and HIF1α, among others[43-45]. These efforts to identify new therapeutic targets may improve clinical outcomes and enhance the quality of life for patients with CHB infection.

EVOLUTION OF ANTIVIRAL TREATMENT STRATEGIES FOR CHB

Over time, significant advances have been made in the treatment of CHB infection aimed at attenuating or reversing the progression of cirrhosis. The current therapeutic objective for CHB is the sustained loss of HBsAg 24 weeks after the end

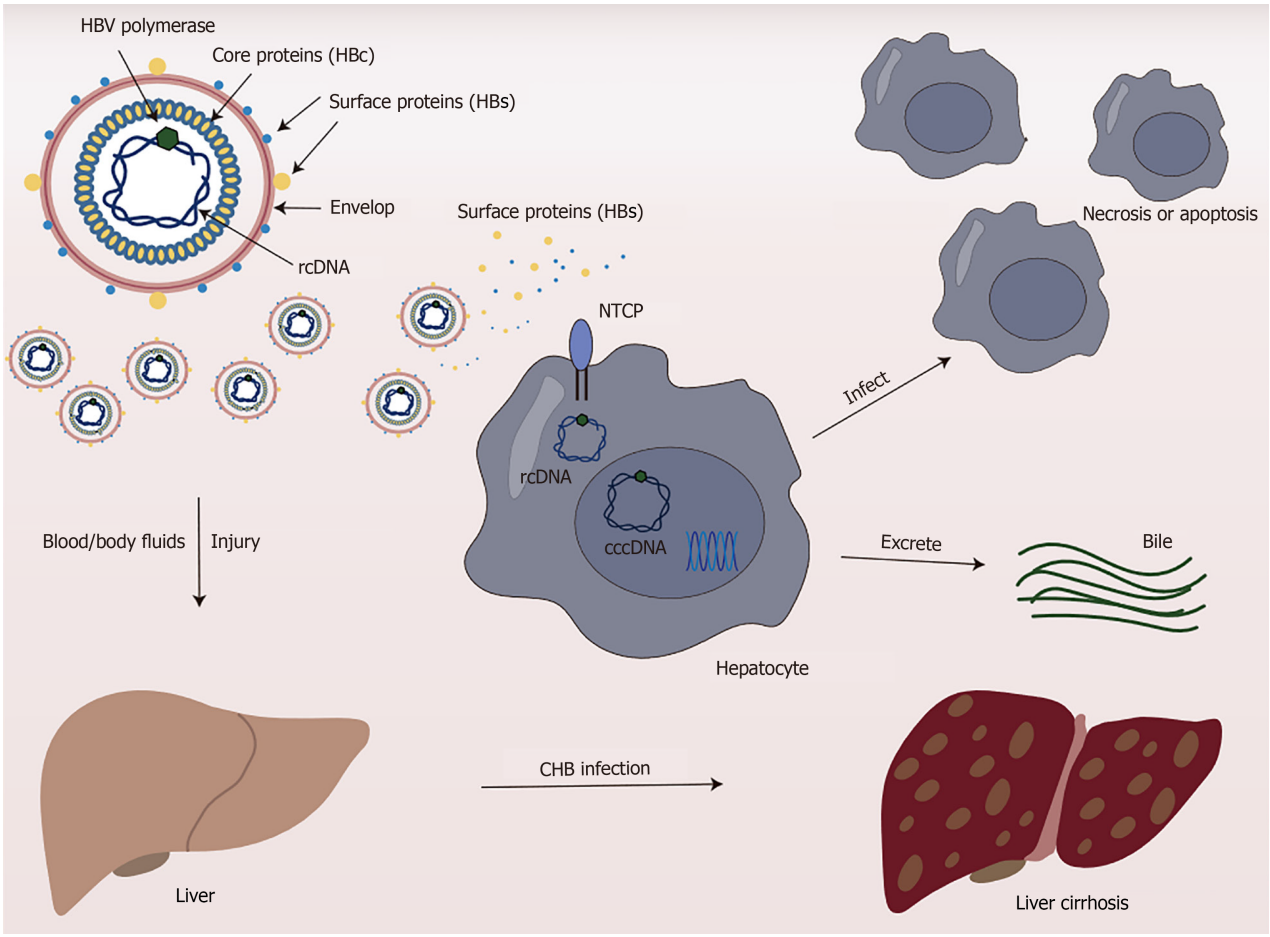

Figure 1 Hepatitis B virus is transmitted through blood or body fluids, which leads to infection of hepatocytes in the liver. The virus particle is composed of an outer envelope containing surface proteins (HBs) and an inner nucleocapsid containing core proteins (HBc) and relaxed circular DNA (rcDNA). Upon entry into hepatocytes *via* the sodium taurocholate cotransporting polypeptide receptor, the viral rcDNA is transported to the nucleus where it is converted into covalently closed circular DNA (cccDNA). This cccDNA serves as a template for viral transcription and replication, leading to the production of new viral particles. Some of the infected hepatocytes experience necrosis or apoptosis as a result of viral replication, while others excrete viral particles by bile. Chronic hepatitis B infection can cause persistent liver damage, eventually leading to liver cirrhosis and significant loss of liver function. NTCP: Sodium taurocholate cotransporting polypeptide receptor; rcDNA: Relaxed circular DNA; CHB: Chronic hepatitis B; HBV: Hepatitis B virus.

of therapy, a goal that remains elusive under existing treatment strategies[46]. NAs-based therapies effectively inhibit HBV reverse transcription but do not directly target cccDNA, whereas IFN therapies induce immune clearance only in a minority of individuals[27]. NAs are generally well tolerated but require long-term treatment, often for the lifetime of the patient. Compared with NAs, pegylated IFN (pegIFN) treatment for about 1 year has a slightly higher functional cure rate but is less well tolerated. Even though NAs therapy is effective in suppressing viral replication and reducing disease progression, the risk of cirrhosis and even HCC has not been eliminated, and the search for new treatment strategies is urgent[47].

IFN, characterized by its immunomodulatory and direct antiviral effects, was historically a foundation of HBV therapy, but limited by prolonged treatment and a large number of adverse effects[48]. A new study evaluated the impact of adding pegIFN-alpha to pre-existing nucleoside (acid) analog therapy in patients with CHB. This study innovatively found that pegIFN-alpha treatment significantly increased T-cell function and decreased HBsAg levels in CHB patients with low baseline HBcrAg levels, providing a new biomarker for personalized therapy[8].

The clinical outcomes for patients with CHB have significantly improved since the introduction of NAs[49]. Lamivudine, the first widely used NA, initially showed efficacy, but resistance developed with prolonged use[50]. Entecavir and tenofovir, modern NAs, represent current first-line therapies due to their potent antiviral activity and low resistance profile. They inhibit HBV replication through distinct mechanisms, thereby improving liver function and reducing the incidence of liver cirrhosis[51,52]. Adefovir, another NA, competitively inhibits HBV reverse transcriptase, effectively lowering serum HBV DNA levels and ameliorating liver inflammation and fibrosis progression over extended treatment periods[53]. However, prolonged use of adefovir may lead to mast cell degranulation and promotes interstitial fibrosis [54]. Tenofovir, in contrast to adefovir, requires intracellular conversion to its active form (tenofovir diphosphate) to inhibit HBV DNA polymerase. Tenofovir is widely recognized as a primary treatment for CHB infection due to its steady efficacy in quickly reducing serum HBV DNA levels, enhancing liver function, and markedly decreasing the risk of liver cirrhosis[55]. However, TDF may have adverse effects on the kidneys and bones in long-term treatment[56]. Tenofovir alafenamide (TAF), a novel NAs prodrug designed to deliver the active drug to hepatocytes more efficiently, has a better

renal and bone safety profile and a high barrier to resistance compared to TDF[57,58]. Its relatively low resistance profile and stability make it suitable for long-term therapeutic management. In a recent randomized controlled trial reported by Yuen *et al*[47], JNJ-73763989 (JNJ-3989), a small interfering RNA, was demonstrated to target all HBV RNAs, thereby reducing HBV protein production. JNJ-56136379 (JNJ-6379, also known as bersacapavir) acts as a capsid assembly modulator to inhibit HBV replication. These findings indicated that JNJ-73763989 induced dose-dependent achievement of NA cessation criteria in some patients; however, very few achieved HBsAg seroclearance. Nevertheless, a significant reduction in HBsAg levels was observed in the majority of patients receiving JNJ-73763989 treatment. A Phase II REEF-2 trial[59] assessed JNJ-3989 and JNJ-6379 plus NAs for treating CHB. The trial found no functional cure but showed less HBV DNA and ALT increase after stopping treatment in the combination group *vs* NA alone. Moreover, the combination group had more sustained HBsAg reductions post-treatment. These above results suggest that combination therapy may potentially enhance liver conditions, bolster immune control responses, and thereby improve the efficacy of immune-modulating treatments. Although a functional cure was not achieved, the data provide valuable insights for future treatment strategies.

According to the latest treatment guidelines issued by the World Trade Organisation[60], the above commonly used drugs are summarized in Table 1.

In conclusion, the transition from IFN-based therapies to modern NAs like tenofovir represents significant advancements in managing CHB. These developments strive to enhance clinical outcomes and quality of life for individuals with CHB infection. Continued research efforts are pivotal for refining therapeutic approaches and addressing remaining challenges in HBV treatment.

FUTURE RESEARCH DIRECTIONS AND CLINICAL APPLICATIONS

Treatment strategies in different regions must be formulated according to variations in CHB infection. Factors such as genotype variations, transmission patterns, healthcare resources, and public health policies must be considered to ensure treatment plans align with the specific needs and conditions of the region. In resource-limited regions, treatment often relies on cost-effective approaches and preventive measures, whereas in resource-rich areas, personalized and long-term management strategies are more prevalent.

The latest clinical research by Chan *et al*[61] on CHB treatment highlights long-term use of TAF, which shows high rates of viral suppression and improved safety profiles, particularly for renal and bone health. Over five years, TAF demonstrated similar efficacy to TDF but with fewer adverse effects on kidney function and bone mineral density, making it a preferred option for long-term treatment of CHB. These findings enhance the need for safer, long-term treatment strategies to manage the global CHB burden effectively.

Future research in CHB aims to enhance treatment outcomes and prognosis of HBV-related cirrhosis patients. This includes developing novel therapeutic strategies, personalized medicine approaches, and innovative methods to mitigate cirrhosis complications. The exploration of new treatments holds promise for revolutionizing CHB-related liver cirrhosis management. Gene therapy, which utilizes technologies such as CRISPR-Cas9 to target HBV DNA destruction, represents a cutting-edge approach for achieving sustained viral suppression and potentially inducing a functional cure[62]. In addition, advances in RNA interference and antisense oligonucleotide therapeutics provide new mechanisms for inhibiting viral replication and preventing disease progression[63]. Immunotherapy is gaining attention for enhancing host immune reactions to HBV, managing liver inflammation, and reducing fibrosis[64]. Efforts are focused on developing vaccines that elicit lasting immune reactions against HBV antigens, with the objective of clearing the virus or curbing its replication over the long term[65]. Furthermore, immune checkpoint inhibitors, which are extensively used in oncology, are being investigated for their potential to rescue impaired T cell responses specific to chronic HBV infections[66].

Current research is actively revealing the disease's underlying mechanisms and discovering new treatment targets. Implementing these emerging therapies in clinical settings has the potential to rebuild treatment options and enhance patient outcomes. An integrated strategy encompassing prevention, timely intervention, and comprehensive disease management is essential for reducing cirrhosis morbidity and mortality in CHB patients, thereby improving long-term patient health.

CONCLUSION

Although CHB drug development is advancing rapidly, treatment strategies vary based on local healthcare resources, disease prevalence, and economic conditions in different regions. CHB treatment in low-income countries, particularly in Africa, faces many challenges.

In the African region, including Ethiopia, limited medical resources and restricted access to newer drugs are primary barriers to effective CHB treatment. A study by Minier *et al*[66] conducted in Africa, including Ethiopia, demonstrated that clinical diagnostics such as aminotransferases (aspartate aminotransferase, alanine aminotransferase) and platelet counts are typically available at the district hospital level, while HBeAg and on-site HBV DNA (Xpert) testing are only accessible at regional or provincial hospitals. This highlights that diagnostic tools required to assess eligibility for AVT are frequently unavailable in peripheral health facilities across the African region. The latest clinical studies by Delphin *et al*[67] show that HBV clinical trials in the World Health Organisation (WHO) African Region are severely deficient, although the region accounts for 70% of new infections globally. Less than 1% of global HBV clinical trials are conducted in this region, and a lack of investment in prevention, diagnosis, and treatment infrastructure has contributed to substantial

Table 1 Commonly used antiviral drugs for chronic hepatitis B virus patients

Drug	Sort	Advantages	Disadvantages	Development stage
Interferon-alpha	Interferon	Immunomodulatory and direct antiviral effects; A foundation of HBV therapy	Limited by prolonged treatment and significant adverse effects	Second-line therapy
Pegylated interferon-alpha	Interferon	Enhances T-cell function and reduces HBsAg levels with longer half-life; Better efficacy than regular interferon.	Side effects and tolerance differences; Longer treatment time	Second-line therapy
Lamivudine	Nucleoside analog	Initial efficacy; Easy availability	Cost-effective; High rate of resistance with prolonged use	Not recommended
Entecavir	Nucleoside analog	Potent antiviral activity; Low resistance profile	Risk of resistance with long-term use; Higher cost	First-line therapy
Adefovir	Nucleoside analog	Competitively inhibits HBV reverse transcriptase; effective in lowering HBV DNA levels	Risk of interstitial fibrosis with prolonged use	Not recommended
Tenofovir (TDF)	Nucleoside analog	Steady efficacy; Quick reduction in HBV DNA levels; Widely recognized as primary treatment	Long-term use associated with renal and bone adverse effects	First-line therapy
Tenofovir alafenamide	Nucleotide analog prodrug	Improved renal and bone safety profile; High barrier to resistance	Relatively recent introduction; Higher cost compared to TDF	First-line therapy
JNJ-73763989 (JNJ-3989)	Small Interfering RNA	Target all HBV RNAs; Reduce HBV protein production	Rarely led to HBsAg seroclearance	Phase II

HBV: Hepatitis B virus.

health inequities. These findings highlight the urgent need for increased clinical research, funding, and tailored intervention strategies to address the HBV burden in Africa, as well as to meet global HBV elimination targets.

In this study by Ismael *et al*[1], TDF treatment was shown to be highly effective in achieving viral suppression and improving liver fibrosis markers. However, CHB treatment strategies in low-income countries must consider drug availability and cost-effectiveness. For instance, entecavir and tenofovir are two effective HBV treatments recommended by the WHO, but their patent status, licensing, cost, and availability on the global market may limit their use in these regions.

To improve the coverage and effectiveness of CHB treatment, WHO and other international organizations are providing technical support and resources to facilitate diagnosis and treatment. WHO has provided technical guidance and other support to help African countries meet the 2030 goal of eliminating viral hepatitis as a public health threat. Additionally, successful approaches in hepatitis C treatment, such as early local approval of generic drugs, can be valuable for improving treatment accessibility in low-income countries.

Overall, increased international cooperation and resource investment are essential for improving drug access and affordability, strengthening healthcare infrastructures, and raising public awareness about CHB prevention and treatment.

FOOTNOTES

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