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Evidence-Based Strategies for Micro-elimination of Chronic Hepatitis B Virus Infection

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Abstract

Purpose of Review Hepatitis B (HBV) remains a health threat around the world. Hepatitis C is closer to meeting the World Health Organization's 2030 elimination goal compared to HBV. To achieve a successful micro-elimination and macro-elimination, there are certain objectives that need to be met.

Recent Findings HBV infects more than 262 million people worldwide and is associated with significant morbidity and increased mortality. There have been previous HBV and hepatitis C virus micro-elimination trials with varying success. Micro-elimination programs should be designed to move services forward with a plethora of avenues for monitoring, testing, and treatment.

Summary Ultimately, successful and maintained micro-elimination is needed to achieve macro-elimination of HBV. Here, we propose 5 core tenets of micro-elimination that can be expanded to macro-elimination; these 5-line guidelines provide for 5 pillars of HBV management that support a path to a successful global elimination of HBV.

Keywords HBV · CHB · HBV elimination · HBV prevention

Introduction

Hepatitis B (HBV) is a viral infection that is a major cause of acute and chronic liver disease. HBV is cleared spontaneously in more than 95% of adults who have acute infection [1]. But HBV can also progress to a chronic disease state, which affects 262 million people worldwide. In the USA, there are around 2.4 million people who are infected with chronic HBV, with 60,000 new cases annually [1, 2]. The Indian sub-continent, sub-Saharan Africa, and Central Asia are most affected due to limited access to health care.

In 2016, the World Health Organization (WHO) called for the elimination of HBV and hepatitis C (HCV) as public health problems by 2030, as defined by a 90% reduction in incidence and a 65% decrease in mortality compared to 2015 levels [3]. Unfortunately, as of March 2023, no countries are on track to achieve WHO elimination targets for HBV by 2030, which is in stark contrast to HCV, for which 9 countries are on track to achieve WHO elimination targets [4]. To combat this infection, we will review HBV micro-elimination goals and propose 5 pillars and a 5-line guideline to reduce HBV disease worldwide.

Micro-elimination

HBV carries some innate qualities making it more difficult to eliminate, such as the absence of a "true" cure for the disease, as well as the disease having the greatest mortality and morbidity in low- and middle-income countries where resources are limited [5]. However, inefficiencies in current approaches to eliminating HBV have also been documented. Several countries have enacted macro-elimination approaches to prevent and treat HBV, some even prior to the WHO announcement in 2016 [6–13]. Although

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countries that have employed nationwide efforts have experienced reductions in HBV incidence and prevalence in younger populations, several common limitations to their strategies have been cited: insufficient government funding for programs, vaccines, and/or treatments; lack of coordination between government policy, programs, and/or community members; and inadequate scale of coverage. These barriers to better eliminate HBV have consequently spurred the emergence of other ideas for HBV elimination, namely, micro-elimination. In addition, complex guidelines are a barrier to treatment access.

Micro-elimination involves identifying individual groups for which treatment and prevention measures can be implemented efficiently and pragmatically. These individual groups can be specified by geography (e.g., a specific city), setting (e.g., a prison), comorbidity (e.g., HIV, dialysis), age range (e.g., women of childbearing age, children), demographic (e.g., intravenous drug users, migrants, health care workers, those with lower education), or any other common factors that can allow for a targeted effort. By focusing on a distinct population, important components contributing to elimination such as linkage to care, treatment, prevention, and surveillance can all be specifically tailored to the needs of that distinct population, resulting in more effective results compared with a generalized effort.

However, micro-elimination is not successful without clear goals and an alliance of agreed criteria. This means a more narrowly defined strategy, which is less complicated and less expensive to organize. Although the concept of micro-elimination has been used in the past, it was formally defined and popularized when the European Association for the Study of the Liver (EASL) proposed it as a practical solution for HCV [14, 15]. Since the concept of micro-elimination has been used extensively and successfully in numerous studies to help curb HCV [16].

A project focusing on the native population of Alaska remains the earliest and most successful micro-elimination project for HBV [17]. The annual incidence of acute symptomatic HBV declined by over 90% in just 3 years, and a follow-up 25 years later demonstrated complete elimination of acute symptomatic HBV and hepatocellular carcinoma (HCC) in children [18]. This project encapsulated important elements of micro-elimination, including a specific focus group of need, a clearly outlined plan, collaboration between multiple stakeholders, and adequate follow-up demonstrating efficacy.

Here, we propose 5 core tenets for micro-elimination in HBV:

1. Following a 5-line guideline (Table 1) to identify those who are eligible for vaccination or treatment for chronic HBV infection
2. Identifying a specific focus group with limited access to care and/or decreased awareness of HBV prevalence in their community.
3. Preparing a dedicated plan tailored to the focus group that addresses 5 pillars of elimination: vaccination, stigma and awareness, screening and diagnosis, treatment, and forward-looking considerations.
4. Ensuring close collaboration of multiple stakeholders (government officials, health care providers, and individuals within the community including civil service organizations).
5. Providing adequate patient follow-up to monitor for efficacy, areas of improvement, and complications.

Five-Line Guideline for HBV in Adults

A recent *Morbidity and Mortality Weekly Report* (MMWR) advised testing all adults who are 18 years or older with a triple panel (HBsAg, anti-HBc, and anti-HBs) at least once in their lifetime [19••]. A study by the Infectious Disease Society of America found that screening all with HBsAg at least once is more cost-saving compared to the current American Association for the Study of Liver Diseases (AASLD) treatment recommendation alone [20•]. This would prevent an additional 23,000 deaths from liver disease and liver cancer

Table 1 The 5-line guidelines for HBV in adults[a]

Test all adults with HBV triple panel (HBsAg, anti-HBc antibody, and anti-HBs antibody)
Vaccinate all adults who are triple panel negative
If HBsAg-positive, follow-up with qDNA and anti-HDV
Treatment: treat all HBV-DNA-positive patients including those with cirrhosis (treat until HBsAg loss +12-month consolidation)
Stage liver disease and determine need for surveillance for HCC and treatment of concomitant liver disease (i.e., MAFLD, NASH, AALD, HDV, HCV)

Abbreviations: *anti-HDV* total antibody to hepatitis D virus, *HBsAg* hepatitis B surface antigen, *anti-HBs* total antibody to hepatitis B surface antigen, *anti-HBc* total antibody to hepatitis B core antigen, *HCV* hepatitis C virus, *HCC* hepatocellular carcinoma, *HDV* hepatitis D virus, *MAFLD* metabolic- (dysfunction) associated fatty liver disease, *MASH* metabolic-associated steatohepatitis, *qDNA* quantitative HBV-DNA

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with an estimated savings of $596,000,000 [20•]. Therefore, universal screening of adults is cost-effective, while reducing transmission risk and identifying those at risk of HBV reactivation and those who will benefit from treatment or HBV vaccination [19••].

The current HBV treatment guidelines by EASL, AASLD, and the Asian Pacific Association for the Study of the Liver (APASL) are complex and impractical to implement [21, 22]. Simplified treatment guidelines are needed. A start would be a simplified treatment plan by Dieterich et al., which recommended treatment for those without cirrhosis with HBV-DNA ≥ 2000 IU/mL who are 30 years or older or younger than 30 years with alanine transaminase (ALT) greater than the upper limit of normal [22]. However, we need a more simplified approach (Table 1). A recent study in North America found that lower percentages of African American (AA) or Blacks met the AASLD treatment criteria when compared to Asians and Caucasians [23•]. Therefore, the treatment initiation rates were higher among Asians and Caucasians compared to AA or Blacks [23•]. It seems that Africa-born AA or Black participants had lower prevalence of HBeAg and genotype A2, compared to US-born participants [23•], which may be why they did not meet the treatment criteria [23•].

A study from China investigated the effect of expanding chronic HBV therapy to those with elevated ALT levels versus HBsAg-positive individuals [24••]. The study found that treating HBsAg-positive, regardless of ALT levels, with 80% coverage allowed them to achieve WHO's 2030 goal [24••]. This approach had the highest reduction in HBV-related complications and the highest quality-adjusted life-years compared to ALT level-based treatments [24••]. Additionally, this approach was more cost-effective in the long run by 2025 [24••].

There is a risk for HBV spread even with the clearance of HBsAg, because there can still exist low levels of HBV-DNA in the bloodstream in a subset of patients [25]. Patients with occult hepatitis B infection (OBI) still have a risk of HBV spread [26, 27] and have a reactivation risk during chemotherapy, HCV therapy, or immunosuppressive therapy [28]. A recent study found that the baseline HBV-DNA plus HBV RNA was more positively correlated with cccDNA than quantitative HBsAg. This is because HBsAg is also produced by HBV-DNA integrated into the host genome [29]. Importantly, the persistence and disease sequalae of chronic HBV infection are due to cccDNA [30]. For example, there is still a risk for HCC and cirrhosis development in patients with detectible HBV-DNA or intrahepatic cccDNA [31].

Additionally, about 20% of patients with chronic hepatitis B (CHB) experience extrahepatic manifestations [32]. The most common renal manifestations include glomerulopathies, such as membranous nephropathy and membranoproliferative glomerulonephritis (MPGN) [33]. However, there are also systemic, cardiovascular, musculoskeletal, autoimmune, and dermatological manifestations as well as associations with other cancers [33–35]. These extrahepatic syndromes have been linked to increased serum HBsAg levels and immune complexes that result from it [33–36].

The current treatment recommendations are complicated; for example, AASLD, EASL, and APASL all have different criteria to stop therapy in CHB [37–39]. Nevertheless, all societies agree that patients with CHB and those with compensated cirrhosis can discontinue antiviral therapy if HBsAg loss persists for at least 1 year [36–39]. We recommend treating everyone who is HBV-DNA-positive, until they are HBsAg-negative and HBV-DNA-negative for at least 12 months (Table 1).

Five Pillars for HBV Elimination

1st Pillar: HBV Screening, Diagnosis, Virology, and Surveillance

Previously, recommendations of risk-based testing for HBV have failed, as it did for HCV and HIV. To eliminate HBV, the Centers for Disease Control and Prevention (CDC) updated their recommendations for the first time since 2008 to expand testing for all adults with a triple panel of HBsAg, anti-HBs, and total anti-HBc least once in their lifetime [19••]. Expanding screening was partly influenced by findings that 67% of HBV carriers were unaware of their infection and the cost-effectiveness of universal screening [19••]. The US Department of Health and Human Services found that from 2013 to 2016, only 32% of chronic HBV carriers were aware of their infection contributing to the underdiagnosis of cirrhosis and HCC [40]. Increased screening efforts for HCV across communities in the USA, including the Northshore University Health System, resulted in successfully screening 64.3% of the eligible population born between 1945 and 1965 [41].

Acute HBV infection, similar to chronic HBV infection, has the diagnostic presence of hepatitis B surface antigen (HBsAg) [42]. In chronic HBV, viral replication will persist throughout the rest of their life resulting in a persistently positive HBsAg [42]. A key component to differentiate the 2 is that only in acute HBV will there be a presence of IgM hepatitis core antibody (anti-HBc) [42]. In some instances, where HBsAg is rapidly cleared by the body, only IgM anti-HBc will be positive in acute HBV infection [42]. The presence of anti-HBs alone remains the standard to detect immunity against the virus. OBI is a condition where viral DNA is present in the liver [43]. Most patients are found to have HBV-DNA levels around 20,000 to 90,000 copies/mL, but much lower titers of HBV-DNA levels can also be observed [44–46]. In this state of chronic HBV, the

covalently closed circular DNA (cccDNA) is replicating at a lower rate; thus, the HBV-DNA presence for diagnosis is inconsistent on serum serologies. Other serology markers for OBI are shown in Table 2 [43].

Current HBV golden standard testing is carried out by enzyme immunoassay (EIA) with an analytical sensitivity of 0.05 IU/mL for most commercial tests [48]. Rapid diagnostic tests (RDT), also known as point-of-care tests, are widely being studied to make HBV testing more available. They minimize turnaround time, require less blood, are easier to interpret, and can detect HBV sooner [49]. Determine™ HBsAg 2 is the most popular RDT and has shown a sensitivity of 90.8% and specificity of 99.1%; however it drops to 56–100% sensitivity in populations infected with HIV [50]. Though RDTs are less accurate than current gold standard testing, they present a promising alternative for low-resource settings burdened with underdiagnosis of HBV. Like the success of Egypt, who is achieving WHO's targets, countries need to consider rolling out free RDTs due to their ease of interpretation and availability to increase access to testing [51]. Increased accessibility to testing is imperative to achieve micro-elimination of HBV.

The AASLD 2018 guidelines recommends chronic HBV carriers without cirrhosis to have surveillance for HCC with an ultrasound +/− alpha-fetoprotein (AFP) every 6 months [52]. Sadly, less than 40% of patients undergo annual HCC surveillance [53]. Improved HBV surveillance is a key component in preventing progression of disease and mortality. As new policies and guidelines are unveiled, consistent surveillance is an important tool to monitor micro-elimination efforts in the context of incidence, progress, and mortality benefit [51].

2nd Pillar: Vaccination

Because there is no true cure for HBV, prevention of the disease by vaccination is a core component for micro-elimination. Currently, the WHO recommends HBV vaccination in all children worldwide, including a monovalent "birth dose" vaccine within 24 h of birth, as well as vaccination of high-risk groups [54]. Additionally, WHO guidelines recommend that infants of HBsAg-positive mothers should receive both the hepatitis B vaccine and hepatitis B immunoglobulin (HBIG) within 12 h after birth, followed by the next 2 doses of the vaccine at 1 and 6 months old.

As of May 2022, over 80 countries were on track to achieve a target HBsAg prevalence of ≤ 0.1% in children ≤ 5 years old [55]. However, while promising, this progress must be taken with a grain of salt, as socioeconomic factors severely skew the data. Although most high-income countries such as the USA have already achieved a HBsAg prevalence of ≤ 0.1% in children ≤ 5 years, lower-income countries still carry a prevalence of up to 8.0% [56]. Unfortunately, many lower-income countries are unable to incorporate a birth dose vaccine or HBIG into their universal vaccination protocols due to cost and logistics, thus having inadequate coverage for their vaccination programs [57]. For reference, even though the majority of member WHO countries have implemented universal childhood vaccination programs, just over half adopted a policy to provide a birth dose vaccine [58]. For many resource-limited countries, pentavalent or even hexavalent vaccines are supplied free of charge by GAVI (the Vaccine Alliance). These combination vaccines cover additional diseases but can only be administered 6 weeks after birth and do not include a birth dose vaccine (Table 3).

Fortunately, regions lacking the birth dose vaccine represent a critical focus group that can be targeted by micro-elimination studies. A micro-elimination effort in the capital of Vietnam demonstrated a gap in existing vaccination programs [59]. Pham et al noted that Vietnam had implemented a universal childhood vaccination program since 2003 but found in their study that less than < 20% of the adult population was vaccinated despite 37.7% of adults being susceptible to HBV infection. As such, vaccinating triple-negative patients who are susceptible to HBV infection is an important consideration for future micro-elimination projects. The importance of screening triple-negative patients was highlighted when the USA recently revised their guidelines to recommend screening all adults ≥ 18 years old with HBsAg,

Table 2 HBV serology markers [47]

HBV status	HBsAg	HBcAg	Anti-HBs	Anti-HBc (IgM)	Anti-HBc (IgG)	HBeAg	Anti-Hbe	HBV-DNA
Acute infection	+	+	−	+	+	+	-	+
OBI	−	+/−	+/−	+/−	−	+/−	+/−	+/−
Vaccine immunity	−	−	+	−	−	−	−	−
Immune-controlled	−	−	+	−	+	−	+/−	(−) or + (very rare)
Chronic infection	+	+	−	−	+	+/−	+/−	+

Abbreviations: *anti-HBc (IgG)* hepatitis B core antibody immunoglobulin G, *anti-HBc (IgM)* hepatitis B core antibody immunoglobulin M, *anti-Hbe* hepatitis B envelope antibody, *anti-HBs* hepatitis B surface antibody, *HbcAg* hepatitis B core antigen, *HbeAg* hepatitis B envelope antigen, *HBsAg* hepatitis B surface antigen, *HBV-DNA* hepatitis B virus DNA, *OBI* occult hepatitis B infection

Table 3 Currently available hepatitis B vaccines

Name	Manufacturer	Number of doses	Timing of doses	Ages covered	Combination	Notes
Recombivax HB	Merck	3	0, 1, and 6 months	All ages	No	
Engerix-B	Merck	3	0, 1, and 6 months	All ages	No	Can be given on an accelerated schedule
PreHevbrio	VBI	3	0, 1, and 6 months	≥18 years old	No	Only 3-antigen vaccine
Twinrix	GSK	3	0, 1, and 6 months	≥18 years old	Yes—HepA	Can be given on an accelerated schedule
Pediarix	GSK	3	6, 14, and 24 weeks	6 weeks–6 years	Yes—DTAP, IPV	Patients need separate monovalent HBV vaccine within 24 h at birth
Vaxelis	MCM	3	6, 14, and 24 weeks	6 weeks–4 years	Yes—DTAP, Hib, IPV	Patients need separate monovalent HBV vaccine within 24 h at birth
Heplisav-B	Dynavax	2	1 month apart	≥18 years old	No	Only 2-dose vaccine
Pentavalent/hexavalent[1]	Multiple	3	6, 10, and 14 weeks	Up to 1 year old	Yes	Patients need separate monovalent HBV vaccine within 24 h at birth

DTAP diphtheria, tetanus, and whooping cough; *Hib Haemophilus influenzae* type b, *HepA* hepatitis A, *IPV* inactivated poliovirus

[1]There are several pentavalent and hexavalent combination vaccines available worldwide, including but not limited to Pentabio, Eupenta, and Hexaxim. A full list of vaccines prequalified by the WHO can be found at https://extranet.who.int/pqweb/vaccines/list-prequalified-vaccines

anti-HBs, and anti-HBc [19]. Recently, a novel 2-dose vaccine (Heplisav-B) with doses spread apart by only 1 month was introduced to facilitate efforts to "catch up" susceptible adults who are triple-negative. Beyond the improved convenience of less doses, Heplisav-B is also notable for superior efficacy compared to traditional 3-dose vaccines (Table 3) [60].

In summary, vaccination as a prevention for HBV is a powerful tool for a disease that otherwise lacks truly curative therapies. When possible, we recommend that all micro-elimination efforts should emphasize not only universal childhood vaccination but ensure also the coverage of a monovalent birth dose vaccine as well as HBIG. Additionally, all adults should be screened with HBsAg, anti-HBs, and anti-HBc, and triple-negative patients should be linked with appropriate care. The HBV vaccine is safe and effective, and vaccinating all susceptible individuals can reduce overall transmission.

3rd Pillar: Reducing Stigma and Improving Quality of Life

Stigma is the social process by which perception results in unwarranted adverse judgment about a person or group through the means of exclusion and/or rejection [61]. There are 3 categories of stigma: social, internalized, and institutional [62]. Social stigma of HBV is largely due to the assumption that those who live with the disease endorse a risky lifestyle that involves illicit injection drug use or unprotected sex [63]. The implications are vast and can result in delays in seeking care for those suspected of being at risk of having the virus. From the perspective of micro-elimination of the virus at the global level, this substantiates the problem due to many unaware people living with the disease who are potentially transmitting the virus onward [62].

Smith-Palmer et al. published a robust systematic literature review in 2020 on stigma in patients with chronic HBV using a total of 23 articles, 17 of which were quantitative and 6 qualitative [62]. Stigma was best characterized in China whereas studies in the North America, Europe, and Africa were lacking, which is in line with China having the highest prevalence of HBV in the world. They found that in China, a large proportion of stigma was attributed to fear. This was perpetuated by a law (i.e., institutional stigma) that allowed employers and colleges to screen applicants for HBV and deny them based on their result. The antidiscrimination law was not banned until 2010; however, that has not prohibited employers from working around the law to ask their applicants to take a voluntary test [62]. Institutional stigma resulted in Smith-Palmer et al.'s finding that up to 20% of chronic HBV carriers believed they would be denied health care [62]. This highlights the importance of efforts to reduce stigma in the context of micro-elimination.

Stigma contributes to lower health-related quality of life (HRQoL) and mental health in chronic HBV carriers [63]. Patients who are newly diagnosed with HBV should undergo training in coping strategies. Therapy and on-line support groups are methods that provide a platform to share their experiences and create a supportive network [64]. Similarly, Li et al.'s study also found that HBV-related stigma

adversely affected HRQoL in many facets of life, especially in the early stages of the disease where fear of acceptance was the greatest [65]. This emphasizes the importance of providing education, therapy, and support for patients at the time of diagnosis.

Additionally, stigma can also lead to disengagement and decreased treatment compliance thereby leading to increased mortality [64]. Similar to how efforts have been made through posters and television to reduce stigma associated with HIV, effective ways of spreading awareness and educating the public on HBV should also be undertaken [66]. Raising awareness is an important aspect of stigma and micro-elimination projects. Two separate community-based outreach programs in the USA demonstrated how establishing strong ties within a community contributed to increased success of HBV screening, diagnosis, and surveillance [67, 68]. It is imperative to implement public health strategies that are aimed at reducing the burden of stigma to meet goals for micro-elimination of HBV.

4th Pillar: Reducing Infectivity with Enhanced Treatment Recommendations

Surprisingly, about two-thirds of those with chronic HBV are not aware of their infection [69], and unfortunately, HBV is 50–100 times more infectious than HIV [70]. HBV can survive outside the body for at least 7 days, and during this time, it can still cause infection [71]. In addition, those with HBV-DNA positivity are more infectious than those who are HBV-DNA-negative due to the high viral load. HBV is so infectious that 9% of newborns born to a mother with chronic HBV infection, who received appropriate passive-active immunoprophylaxis, will still acquire HBV infection [72]. This risk is truer for those who are born to mothers with a viral load higher than 8 $\log_{10}$ copies/mL (7.3 $\log_{10}$ IU/mL) [73]. Sadly, newborns have a 90% chance of developing a chronic infection after being infected with HBV [72].

Unfortunately, at-risk mothers in resource-limited settings may be unable to access adequate health care facilities. Indeed, the prevalence of home births is higher in these settings due to both socioeconomic and cultural factors, and these mothers and their newborns often lack access to immunoglobulin treatment or vaccinations at home and have delays to access a proper health care facility with vaccine capabilities [57]. Prophylactic treatment of pregnant mothers with antiviral treatment during gestation has previously been proposed as an alternative solution in eliminating mother-to-child-transmission in underserved populations [74]. In remote regions along the border of Thailand and Myanmar, Bierhoff et al. demonstrated promise in prophylactic daily antiviral therapy started early in gestation as a substitute for mothers who are unable to access immunoglobulin or vaccines with a facility birth [75]. This indication for prophylactic tenofovir use was also used in Thompson et al [76].

The risk of HBV infection after blood exposure can still occur with low levels of HBV-DNA. There have been reported infections with viral copies as low as 2–5 copies/mL. However, no infection has been reported for HBV-DNA level around 200 copies/mL [77]. Some have suggested that a minimum infection dose may be as low as 16 copies/mL [78]. This further solidifies the need to treat everyone who is HBV-DNA-positive.

Previous treatment recommendations are complicated and is based on ALT and HBV-DNA levels [79]. These complicated guidelines have resulted in less than 20% of chronic HBV infections being treated [71]. Here, we recommend treating all who are HBV-DNA-positive (Table 1). This is because there is a very small difference between those who are HBV-DNA-positive and HBsAg-positive. Although, the HBsAg seroclearance is rare with current treatments (1–10%) [80], it will reduce the infectivity of those with chronic HBV infection. By screening all adults for HBV and treating all who are HBV-DNA positive, we are more likely to identify and treat those who are infectious. Reducing the infectivity of those with chronic HBV and thus reducing the risk of HBV spread are an important step towards HBV elimination.

5th Pillar: Current Therapies for HBsAg Clearance

The current treatment options for HBV are either interferons (INFs) or nucleos(t)ide analogues (NAs): lamivudine, telbivudine, adefovir, entecavir (ETV), tenofovir disoproxil fumarate (TDF), tenofovir alafenamide fumarate (TAF), and clevudine. NAs are generally better tolerated than the INFs. Within the NAs, TAF is better tolerated than TDF due to its more stable structure and effective delivery to the liver (Table 4) [79, 81, 82].

There are different definitions of HBV "cure": complete and sterilizing cure, functional cure, and partial cure (Table 5) [84]. The current goal is to achieve functional cure as it is associated with better clinical outcomes, and it is more feasible with current available treatment. Unfortunately, there is only about 1–10% chance of HBsAg seroclearance (HBsAg loss) [80] and functional cure is extremely rare (< 1% of patients per year) [79, 85] with the current therapies. However, even with low rates of functional cure, there still is a clinical benefit of antiviral therapy and lowering HBsAg and HBV-DNA levels. The clinical benefits are reducing risk for liver cirrhosis, HCC, extrahepatic manifestations, liver transplant, and mortality [80, 86, 87] and improving QoL [88]. Therefore, we recommend treating all who are HBV-DNA-positive until HBsAg loss in efforts towards HBV elimination and improved QoL.

Table 4 Summary of current HBV therapies and their advantages and limitations [79, 81–83]

	Advantages	Limitations
Conventional INF and pegINF		Poor efficacy and tolerability Avoided in decompensated liver failure
Entecavir	No bone or renal toxicity risk	Higher risk of resistance Avoid in women of childbearing age or in children Risk of severe lactic acidosis in those with MELD > 20 No renal or bone toxicity
TDF	Stronger antiviral effect than adefovir Strong against LAM-resistant HBV	Increased renal and bone toxicity
TAF	Less renal and bone toxicity Better ALT suppression	Not recommended for CrCl < 15 mL/min or those receiving dialysis

Abbreviations: *ALT* alanine aminotransferase, *CrCl* creatinine clearance, *HBV* hepatitis B virus, *INF* interferon, *LAM* lamivudine, *MELD* model for end-stage liver disease, *pegINF* pegylated interferon, *TAF* tenofovir alafenamide fumarate, *TDF* tenofovir disoproxil fumarate

Table 5 Types of HBV cure [84]

Types of HBV cure	Definition
Complete loss of cccDNA	Undetectable HBsAg with or without seroconversion (anti-HBsAg antibody) Eradication of HBV-DNA: intrahepatic cccDNA and integrated HBV-DNA
Sterilizing cure	Loss of integrated virus
Functional cure	Undetectable HBsAg with or without seroconversion (anti-HBsAg antibody) Undetectable HBV-DNA
Partial Cure	Detectable HBsAg but persistently undetectable HBV-DNA

Abbreviations: *cccDNA* covalently closed circular DNA, *HBsAg* hepatitis B surface antigen

Future for HBV Elimination

To eliminate HBV, there needs to be improved access to care and uptake of HBV therapy regionally and nationally around the world. There are many challenges to accessing clinical services and obtaining treatment in both the developed and developing world [4]. The shortage of liver specialists in low- and middle-income countries and the placement of specialists at tertiary centers in high-income countries limit access to patients [89]. There are not enough hepatologists and infectious disease physicians to treat all with HBV. To combat this, local primary care physicians, nurse practitioners, pharmacists, and physician assistants should be trained to treat HBV. Previously, training local medical practitioners has shown to improve HIV and HCV diagnosis and treatment [90, 91], and this should extend to HBV as well. A recent study predicted the effects of improved antiviral treatment coverage for the population with higher incidence of HBV infection [92]. Using a mathematical model, Taye et al. found that improved antiviral coverage of 20% resulted in reduced HBV-related mortality and chronic HBV cases. To improve our chances of HBV elimination, there needs to be improved access to care as well as an increase in the number of patients with chronic HBV receiving antiviral treatments.

The covalently closed circular DNA (cccDNA) serves as a stable reservoir for HBV infection. A major limitation in achieving complete or sterilizing cure is that current available therapies do not eradicate the cccDNA in hepatocytes and integrated HBV-DNA. There is a constant replenishment by incoming virions and recycling of cccDNA within the hepatocytes [84]. NAs and INFs block reverse transcription within the hepatocytes but have only a small effect on cccDNA production [84]. Additionally, current treatments have very little effect on the HBsAg production and do not modify the immune response [93, 94]. This is the reason why present treatment is more of a suppressive therapy with the expectation of long-term treatment. Fortunately, there are many new therapies in the pipeline that can improve rates of functional cure, HBsAg loss, and HBV-DNA negativity (Table 6). These new antivirals, immunomodulators, and vaccines target different aspects of the HBV life cycle. These can be found in PubMed and on the Drug Watch of the Hepatitis B Foundation website. With these new emerging therapies, we may be able to

Table 6 Emerging therapies [81, 85, 95–103]

Mechanism	Drugs
Blocking entry	Bulevirtide
	AB-543
Blocking protein synthesis (siRNA, LNA, ASO)	ARC520
	RG6004/RO7062931
	GSK3389404
	Bepirovirsen
	VIR-2218
	AB-729
Inactivating cccDNA (CRISPR/Cas9)	EBT107
Blocking core synthesis (CpAMs)	NVR3-778
	Vebicorvir (ABI-H0731)
	AB-836
Blocking release and formation of virions (HBsAg)	REP-2139
	BJT-574
Directly inhibit HBsAg with monoclonal antibody	Lenvervimab
	VIR-3434
Mediate T-cell response	GS-4774
	LT-V11
TRL7 agonist	Vesatolimod (GS-9620)
	RG7854
TRL8 agonist	GS-9688
	CB06
	SBT8230
PD-1 inhibitors	Nivolumab
	GS 4224
	RG6084
Vaccines	HepTcell
	HerberNasvac
	AIC 649
	TherVacB

Abbreviations: *ASO* antisense oligonucleotide, *ccDNA* closed covalent circular DNA, *CpAMs* capsid assembly modulators, *HBsAg* hepatitis B surface antigen, *HBV* hepatitis B virus, *LNA* locked nucleic acid, *PD-1* programmed death-1, *siRNA* small interfering RNAs

effectively target multiple mechanisms for which cccDNA is recycled and replenished. Therefore, we may be able to achieve a finite course of HBV therapy and possible HBV cure using a multi-drug approach.

Conclusion

Currently, we are not projected to meet the WHO's goal to eliminate HBV as a health threat by 2030. To assist in achieving this goal, we propose guidelines for future elimination of HBV. To achieve macro-elimination, we first need to be successful at micro-elimination. We presented 5 core tenets of micro-elimination to help guide future elimination programs. Secondly, we brought forth A 5-line guideline to simplify the approach and treatment of HBV in adults. This will increase identification and treatment for those with chronic HBV while identifying those who are eligible for vaccine. Thirdly, we outlined 5 pillars of HBV to emphasize important aspects of HBV prevention, illness, and treatment. With these 5 core tenets of micro-elimination, the 5-line guideline, and 5 pillars of HBV, we hope for a successful and maintained micro-elimination and ultimately macro-elimination of HBV.

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Data Availability The authors confirm that the data supporting the findings of this paper are available within the article.

Compliance with Ethical Standards

Conflict of Interest No potential competing interest was reported by the authors. There are no financial or non-financial interests that are directly or indirectly related to the work submitted for publication by all authors.

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- • Of importance
- •• Of major importance

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