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REVIEW

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Pathway to global elimination of hepatitis B: HBV cure is just the first step

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Abstract

Hepatitis B (HBV) is a major cause of global morbidity and mortality, and the leading cause of liver cancer worldwide. Significant advances have recently been made toward the development of a finite HBV treatment that achieves permanent loss of HBsAg and HBV DNA (so-called "HBV cure"), which could provide the means to eliminate HBV as a public health threat. However, the

Abbreviations: GHSS, Global Health Sector Strategy; POC, point-of-care.

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HBV cure is just one step toward achieving WHO HBV elimination targets by 2030, and much work must be done now to prepare for the successful implementation of the HBV cure. In this review, we describe the required steps to rapidly scale-up future HBV cure equitably. We present key actions required for successful HBV cure implementation, integrated within the World Health Organization (WHO) Global Health Sector Strategy (GHSS) 2022–2030 framework. Finally, we highlight what can be done now to progress toward the 2030 HBV elimination targets using available tools to ensure that we are preparing, but not waiting, for the cure.

INTRODUCTION

Worldwide, > 800,000 people die every year from chronic hepatitis B (HBV) infection–related liver failure and HCC.[1] In 2019, estimated 292 million people were living with HBV globally,[1] with the greatest burden of disease shouldered in South East Asia, sub-Saharan Africa, and the Western Pacific.[2,3] The high global burden of disease, availability of an effective vaccine, and safe and effective suppressive treatment prompted the World Health Organization (WHO) in 2016 to set aspirational HBV 2030 elimination targets within the WHO Global Health Sector Strategy (GHSS, 2016–2021).[4]

In response to this, HBV cure research has gained considerable momentum in recent years, with multiple classes of new HBV treatments now entering phase 2 and 3 trials.[5] However, the development of a safe, effective, and inexpensive HBV cure is only one step toward achieving 2030 WHO HBV mortality targets. Global rates of diagnosis, linkage to care, and treatment remain well below what is required to achieve the WHO 2030 targets and scale-up future HBV cure globally. In 2021, current global estimates of progress toward these targets were that only 10%–30% of individuals living with HBV were diagnosed, only 15%–30% of those requiring treatment were receiving treatment, and birth dose vaccination coverage was only 42%.[1,3] In sub-Saharan Africa, birth dose coverage is as low as 10%.[3] With such unacceptably low global rates of prevention, diagnosis, and linkage to care, it is clear that much work needs to be done now to ensure that we are in a strong position to rapidly upscale HBV cure when it becomes available.

Implementation of future HBV cure will be a challenge, hampered by the chronic nature of infection, high levels of endemicity in low- and middle-income countries, and the likely requirement for multiple agents from different drug classes possibly with parenteral routes of administration to achieve cure. This is further compounded by the current complexity of HBV guidelines, insufficient health resources, significant competing priorities, and the socio-economic impacts and stigma of HBV diagnosis.[2,6] Affordability of cure, HBV diagnostics, and models of care will be critical for rapid and equitable scale-up of future cure.

The 5 Strategic Directions set within the WHO GHSS 2022–2030 for HIV, viral hepatitis, and sexually transmitted infections provides a clear roadmap for the critical actions required now to strengthen the entire HBV cascade of care from early diagnosis, linkage to care, and treatment that should be harnessed for implementation of future HBV cure.[7] Countries should plan how they will integrate HBV cure costs into current health system budgets to minimize upfront costs. As we move toward HBV cure discovery, now is the time to work with affected communities to optimize the use of current HBV tools and health system synergies and undertake the preparatory groundwork required for the implementation of HBV cure.

In this review, we outline the necessary steps to ensure rapid implementation, scale-up, and achieve equitable access to future HBV cure. We integrate this into the suggested WHO GHSS 2022–2030 framework, highlighting key synergies and differences required for HBV cure integration. We also highlight what can be done to progress toward the 2030 HBV elimination targets using available tools and evidence while simultaneously preparing for future HBV cure.

HBV CURE: WHAT TO EXPECT AND CONSIDERATIONS FOR IMPLEMENTATION

HBV cure will likely take the form of a synergistic combination of drugs with different mechanisms of action to reduce high levels of HBV replication, restore HBV-specific immune function, and counter virological resistance.[5,8,9] The current main drug classes under investigation are outlined in Table 1 and include direct antivirals that target multiple aspects of the HBV lifecycle and immune-stimulating therapies. These agents target HBsAg production, reduce HBV DNA and RNA transcription, or directly stimulate the host immune response against HBV via innate or adaptive immune signaling pathways.[8,9] The definition of cure used in HBV

TABLE 1 Current therapeutics under investigation as potential HBV cure[5]

Drug class	Mechanism of action	Outcome	Example drugs in class	Drug trial
Antivirals				
Nucleos(t)ide analogs	Inhibit reverse transcriptase Liver-target prodrug	Reduce HBV DNA	ETV, TDF, TAF	Clinical use
Capsid assembly modulators (CAMs)	Interfere with capsid assembly	Reduce HBV DNA	JNJ-6379, JNJ-440, RO7049389, ABI-H0731	Phase I and II
Entry inhibitors	Blocks HBV entry receptor NTCP	Reduce HBsAg	Bulevirtide (Myrcludex)	Phase III
Translational inhibitors				
Small interfering RNA	mRNA degradation via RISC	Reduce HBsAg	JNJ-3989, VIR-2218	Phase II
Antisense oligonucleotides (ASOs)	mRNA degradation via RNaseH	Reduce HBsAg	GSK-3228836	Phase I and II
mRNA destabilizers	PPAD5/7 inhibition	Reduce HBsAg	EDP-721	Phase I
HBsAg secretion inhibitor (NAPs)	Decrease S antigen production, secretion, increase S degradation	Reduce HBsAg Anti-HBs seroconversion	NAPs: REP-2055/REP-2139 S-antigen traffic inhibit oligonucleic polymers: ALG-010133	Phase II and III Phase I
Immunomodulators				
Innate immune activators				
TLR7 agonists	Activation of TLR7 pathway plasmacytoid dendritic cells Induction of IFN-α, ISGs, NK cells	T-cell and NK cell activation	RO7020531	Phase I and II
TLR8 agonist	Activation of TLR8 pathway intrahepatic innate and adaptive immune responses	T-cell activation	Selgantolimod	Phase II
Adaptive immune activators				
Therapeutic vaccines	Expand HBV-specific T-cell responses	Anti-HBs seroconversion	BRII-179 (VBI-2601), VRON-0200, TG-1050	Phase I
Checkpoint inhibitors	Remove T-cell exhaustion by blocking PD-1/PD-L1 pathway	Reduce HBsAg Anti-HBs seroconversion	Nivolumab (anti-PD-1)	Phase II
Soluble bispecific TCRs	TCR-redirected CD8 cells	Anti-HBs seroconversion	IMC-I109V	Phase I
Fc engineered antibodies	Inhibition of viral entry, HBsAg clearance, increase Ag presentation to dendritic cells	Anti-HBs seroconversion	VIR-3434	Phase I and II
Direct cccDNA approaches				
Transcription inhibitors	Epigenetic modification	cccDNA reduction	FXR agonist, HBx inhibitors	Phase I
cccDNA elimination	Cleavage cccDNA by endonucleases	cccDNA reduction	CRISPR/Cas9, TALENS	Preclinical

Abbreviations: cccDNA, covalently closed circular DNA; FXR, farnesoid X receptor; HBx, hepatitis B x antigen; IFN-α, interferon α; ISG, interferon-stimulated gene; NAP, nucleic acid polymer; NK, natural killer; NTCP, sodium taurocholate co-transporting polypeptide; PD-1/PD-L1, programmed cell death protein 1/programmed death-ligand 1; RISC, RNA-induced silencing complex; TAF, tenofovir alafenamide; TCR, T-cell receptor; TLR8, toll-like receptor 8.

will, therefore, be determined by the mechanism of action of the drug regimen; this, in turn, will dictate how a curative outcome is measured and what diagnostics are required.[5]

DEFINITIONS OF HBV CURE

Functional cure in HBV is defined as achieving HBsAg loss, undetectable HBV DNA, and normalization of alanine aminotransferase levels, with or without concomitant anti-HBs seroconversion.[10,11] This is an uncommon natural event, occurring at ~1% per annum in people with untreated chronic HBV infection.[12] Current HBV curative research is largely focused on increasing rates of functional cure to levels approaching 30% or higher.[11] To achieve this, current drug classes under investigation reduce HBsAg titers with the aim of reducing immune exhaustion, inhibit HBV viral

replication (reducing HBV DNA and RNA levels), and aim to induce anti-HBs seroconversion.[5,9] Importantly, HBsAg loss represents remission of chronic HBV rather than cure due to the lifelong reservoir of persisting HBV genomic material within hepatocytes. Nevertheless, functional cure vastly diminishes the risk of developing liver disease and HCC.[13,14]

Complete cure additionally requires the eradication of all HBV genomic material from the hepatocyte nucleus, that is, removal of HBV covalently closed circular DNA (cccDNA) and integrated HBV DNA sequences from the host genome.[10] However, the removal of cccDNA and integrated HBV DNA has not been observed naturally, and pharmaceutical approaches that directly or indirectly target HBV cccDNA and integrated DNA are very early in development and likely to be costly and complex to deliver.

CONSIDERATIONS FOR FUTURE HBV CURE IMPLEMENTATION

One key consideration for HBV cure preparedness is the format that HBV cure may take and the related costs and health resources required for delivery. As seen with hepatitis C, the issue of cost and delivery has real-world implications for drug availability in low- and middle-income countries, where the greatest burden of HBV disease lies.[7] Currently, several early-phase drugs for HBV cure are delivered subcutaneously or intravenously,[5] which would present major barriers to universal delivery in most countries with intermediate to high HBV prevalence. Moreover, immunotherapies may require personalized approaches and/or frequent monitoring of treatment to prevent unwanted hepatic flares. However, these challenges and costs might be offset by the long half-life of these medications, facilitating intermittent dosing, sustained drug levels, and potentially greater patient adherence, a key determinant of the cost-effectiveness of treatment to achieve HBV elimination.[15]

Responses to cure may vary by virological and host factors, including the stage of HBV infection. It is vital that the cure for all genotypes and subpopulations is pursued to ensure equitable HBV elimination, including pediatric formulations. As with direct-acting antivirals (DAAs), it is likely that HBV cure development will be incremental, beginning with complicated regimens comprising multiple oral and parenteral medications that, over time, are refined into safer, simple "one-size-fits-all" treatment that will be effective in all HBsAg-positive patients. Furthermore, low- and middle-income countries with high burdens of hepatitis B should be included in hepatitis B clinical trials, ensuring the diversity of populations studied to optimize clinical outcomes. Though resourcing to deliver complex clinical trial protocols can be challenging in resource-limited settings, leveraging the expertise of experienced regional clinical trial centers and collaborating partners has proven effective in HIV, malaria, and tuberculosis trials, for example. Investment by global funders and pharmaceutical companies in regional clinical trial centers in low-resource settings, including training, staff resources, and infrastructure, will strengthen trial systems in low-resource settings and further support the broader health sector, facilitating implementation trials when HBV cure is ready to be delivered at scale.

The development of diagnostics that enable rapid, accurate measures of HBV cure and potentially on-treatment response will also be required, which, ideally, can be delivered in a low-cost, easy-to-use point-of-care (POC) test format. Further research will be required to determine what are the optimal biomarkers of HBV cure and when, how, and in whom these should be measured.[16] While existing measures of functional HBV cure, such as HBsAg and anti-HBs antibody tests, are available as POC tests,[17,18] current diagnostics for HBV DNA level, HBsAg titer, and HBV RNA are expensive, difficult to access, or simply unavailable in most countries where HBV is prevalent.[2,19] "Near POC" nucleic acid amplification test systems, such as GenXpert, provide the capacity to measure HBV DNA in venepuncture samples,[17] with work underway to validate fingerstick HBV DNA measurement (personal communication). Such nucleic acid amplification test platforms could potentially measure HBV RNA. Novel POC immunoassay-based approaches to other potential biomarkers of HBV cure and/or treatment response, such as HBsAg, HBeAg, or HBcAg titers, also need exploration (though it is worth noting that the development of HBcAg assays for clinical use has been challenging). Dried blood spot collection facilitates centralized laboratory testing of HBV DNA and HBsAg titers and is a feasible solution for low-resource and remote settings.[20] Novel and affordable diagnostics development, including self-testing as has been developed for HIV and COVID-19, should occur in parallel with drug development to ensure that we are best placed to rapidly upscale cure.

A final consideration of HBV cure implementation is that, unlike hepatitis C, HBV confers a lifelong risk of HCC development even in the absence of cirrhosis. Though functional cure markedly reduces HCC risk,[21] HCC can still develop in people without cirrhosis due to residual cccDNA and integrated HBV DNA at an annual rate of between 0.3% and 0.6%,[13,14] particularly if HBsAg loss is achieved over the age of 50 years.[14,21] In addition, the risk of reactivation with immune suppression remains in the setting of functional cure due to cccDNA persistence in the hepatocyte nucleus.[21] Therefore, countries will need to determine whether long-term surveillance for HCC after a future HBV cure is cost-effective within their population context, particularly within populations with an older age structure, who carry a greater residual risk of HCC postcure.

WHO TO TREAT WITH HBV CURE

Availability of HBV cure would require a careful re-evaluation of which populations should be treated to achieve HBV elimination goals. Universal, ethical access to HBV cure should be the ultimate goal to minimize complications, prevent transmission, reduce stigma, and achieve health equity for people living with HBV. However, the effectiveness, adverse event profile, cost, and resource requirements of cure delivery must be balanced against the morbidity, mortality, and quality of life benefits of the cure. People with HBV who have a high risk of disease progression, such as those with cirrhosis, a family history of HCC, or with hepatitis D or HIV coinfection,[21] will require rapid access to HBV cure to achieve HBV mortality reduction targets. Current agents being trialed have differing response profiles by HBeAg status, degree of fibrosis, genotype, and host genetics, which may require complex, tailored responses to optimize cure delivery. Coinfection with hepatitis C, hepatitis D, and/or HIV may further impact cure implementation through potential drug interactions and on-treatment monitoring requirements.

Modeling has shown that the availability of an HBV cure will not only expedite global elimination but will also reduce the global costs, morbidity, and mortality of HBV.[15] Provisional estimates of price thresholds for a functional cure to be considered cost-effective in 3 national (Australia, China, and the USA) showed that even a 30% efficacious HBV cure would be potentially highly cost-effective for the treatment of all people with HBV with and without cirrhosis.[22] This modeling did not account for the form that HBV cure would take, required resourcing, optimal population selection or the impact of COVID-19 setbacks on HBV elimination progress. Further modeling is required to determine key target populations to treat within current national, regional, and international contexts based on a variety of plausible characteristics of a cure. As was the case for hepatitis C cure, it is likely that a simplified, universal access approach to HBV cure will overcome barriers presented by costly monitoring and complex guidelines, with the additional benefits of reducing onward transmission and maximizing quality-adjusted life years.[23,24]

Codesigned research to determine the optimal age to treat chronic HBV is a special requirement for the implementation of HBV cure.[25] Currently, children and young adults with HBV are not actively treated in the absence of clinically significant liver damage, despite very high levels of viremia and associated very high risk of transmission.[21,25] This treatment paradigm is being challenged by recent data demonstrating liver inflammation in children who are in the chronic HBeAg-positive infection or immune-tolerant phase of infection.[26–28] In addition, major disruptions to health service infrastructure, such as conflicts, natural disasters, and the COVID-19 pandemic, have fractured infant vaccination programs and maternal-child services, rendering infants at risk of acquiring HBV.[7,19,29] Availability of cure may have a significant positive impact on stigma and discrimination for young people, HBV transmission, and future liver cancer risk; over their lifespan, accrued benefits in DALYs averted and productivity are likely to drive cost-effectiveness of treatment. Determining the safety and efficacy of HBV cure for children, adolescents, and pregnant and breastfeeding women through their inclusion in clinical trials will be of great importance to ensure that no populations are left behind in achieving elimination targets.

TRANSLATING LESSONS LEARNED FROM IMPLEMENTATION OF OTHER DISEASE PROGRAMS TO HBV

The discovery of hepatitis C cure with DAAs revolutionized the fundamental paradigm of hepatitis C care.[30] Significant work was undertaken to determine the most cost-effective usage and delivery of DAAs to achieve WHO 2030 hepatitis C elimination targets worldwide, including adoption of novel models of community-based care, simplified guidelines, restructuring of health systems, and redevelopment of health policy,[19] though much of this work occurred in parallel with DAA implementation, rather than in advance. Seven years on from the availability of DAAs, rates of hepatitis C diagnosis and treatment uptake remain below the required levels to achieve the 2030 targets[31]; however, progress is substantially better in countries where cure preparation began before DAA availability.[31,32] In many countries, implementation of DAAs within existing health structures was done retrospectively, leading to inefficiencies, delays, and now challenges in maintaining adequate rates of diagnosis and treatment to achieve WHO hepatitis C elimination targets.[19,33,34] Preparing for the HBV cure now will reduce these challenges.

There is much that can be learned from the process of global upscaling of DAAs for hepatitis C that is translatable to HBV cure. Key components of the hepatitis C response that proved highly effective for cure implementation are strong community engagement and stigma reduction, including the use of peer-led education and testing; adoption of POC test-led, community-based models of care; removing barriers to cure prescribing by primary care health workers; simplified guidelines with minimal on-treatment monitoring; targeted approaches to key risk populations; and universal access to treatment to reduce both mortality and transmission.[24,30,35] From a financing perspective, the development of national investment cases, cost-effectiveness, and disease impact modeling have been vital to catalyze investment and political engagement, private-public sector partnerships, and generic licensing for affordable DAA access.[32] Financial support of hepatitis councils and the not-for-profit sector representing the needs of high-

risk populations were also vital for community education and driving demand for DAAs.[30]

However, major challenges were also identified in upscaling DAAs globally that are also likely to impact the roll-out of HBV cure. These include persisting stigma and discrimination impacting patient willingness to be tested; socioeconomic deprivation and geographical isolation preventing access to health services; a punitive regulatory framework that impacts who can access DAAs and where they can be treated; siloed approaches to health systems and funding; and cross-sectoral competing priorities and competing health demands, such as the COVID-19 pandemic.[34,36,37] The final phase of hepatitis C elimination, where access to care is required for highly marginalized populations who face the greatest barriers to care, remains incredibly challenging and requires far greater resources for a smaller proportion of outcomes.[34] Given the low uptake rates of HBV testing and treatment despite longstanding availability, elimination efforts in many countries will require activities to engage marginalized populations in care.[34] While there are synergies in approaches to increase community engagement between HBV, hepatitis C, and HIV, an HBV-specific approach will be required, which focuses on communities such as migrants and refugees from intermediate- to high-prevalence settings.

While the COVID-19 pandemic has derailed progress toward HBV elimination, it has provided significant opportunities to leverage pandemic health systems to deliver HBV elimination activities, including future HBV cure. Targetted culturally appropriate education campaigns to improve knowledge and awareness of COVID-19 and reduce related stigma proved critical to increased COVID-19 vaccination, testing, and treatment uptake; this approach should be leveraged for hepatitis B programs. Public familiarity with and acceptability of POC tests paves the way for increased access to HBV testing, including self-testing. Surveillance systems have been considerably strengthened in most countries to meet the demands of the COVID-19 pandemic and provide a scaffold for HBV testing and surveillance.[6] Telehealth models of care and task-shifting to community and nurse-led models of care have proven effective and acceptable. Lessons learned from global and regional approaches to pooled procurement of vaccines, testing kits, and treatments should be harnessed to improve access and coverage of affordable hepatitis B testing and treatment in low-resource settings.

IMPLEMENTATION OF HBV CURE: WHAT IS REQUIRED

Preparation for the HBV cure needs to begin now, rather than waiting for cure discovery. Modeling has already shown that HBV elimination is achievable with currently available tools for prevention, diagnosis, and treatment[15,38]; however, the current global uptake of these tools is inadequate to achieve elimination targets.[1] Improved prevention, awareness, testing uptake, and linkage to current treatments will all reduce deaths and prevent new infections while we await the availability of HBV cure.[15]

The current WHO GHSS 2022–2030 for HIV, viral hepatitis, and sexually transmitted infections provides a strong framework for achieving HBV elimination and upscaling HBV cure, recognizing the need to integrate elimination activities across disease programs and leverage health system strengthening across sectors to be truly cost-effective.[7] Key components of this framework are outlined in Figure 1. A global investment framework for HBV was also published that aligns with the GHSS to empower governments and policymakers to invest in HBV elimination activities with the greatest economic returns,[6] specific to their setting and level of investment (Supplemental Figure S1, http://links.lww.com/HEP/H816). These activities will strongly support the rapid upscale of cure when available.

The following section outlines the key steps required for cure preparedness to achieve HBV elimination, nested within the 5 Strategic Directions of the latest GHSS 2022–2030 elimination framework.[7] A summary of key activities is outlined in Panel A and Figure 2.

Panel A: Key activities required to prepare for hepatitis B cure implementation

1. Reduce the numbers of people needing cure: Invest in hepatitis B prevention by increasing birth dose coverage.
2. Activate the affected community: Build community engagement and demand for ethical hepatitis B elimination and cure.
3. Find those living with Hepatitis B: Invest in accessible diagnostics and surveillance.
4. Broaden access to care: Simplify guidelines and invest in community models of care.
5. Fund implementation: Increase investment in hepatitis B elimination activities, including curative research.
6. Don't wait for cure: optimise use of current effective tools and networks to improve the hepatitis B care cascade and achieve hepatitis B elimination targets by 2030.

STRATEGIC DIRECTION 1: DELIVER HIGH-QUALITY, EVIDENCE-BASED, PEOPLE-CENTERED SERVICES

Invest in HBV primary prevention including increasing birth dose coverage

Mother-to-child transmission, along with early childhood infection, is the most common route of transmission worldwide and carries the greatest risk of HCC,[21,39]

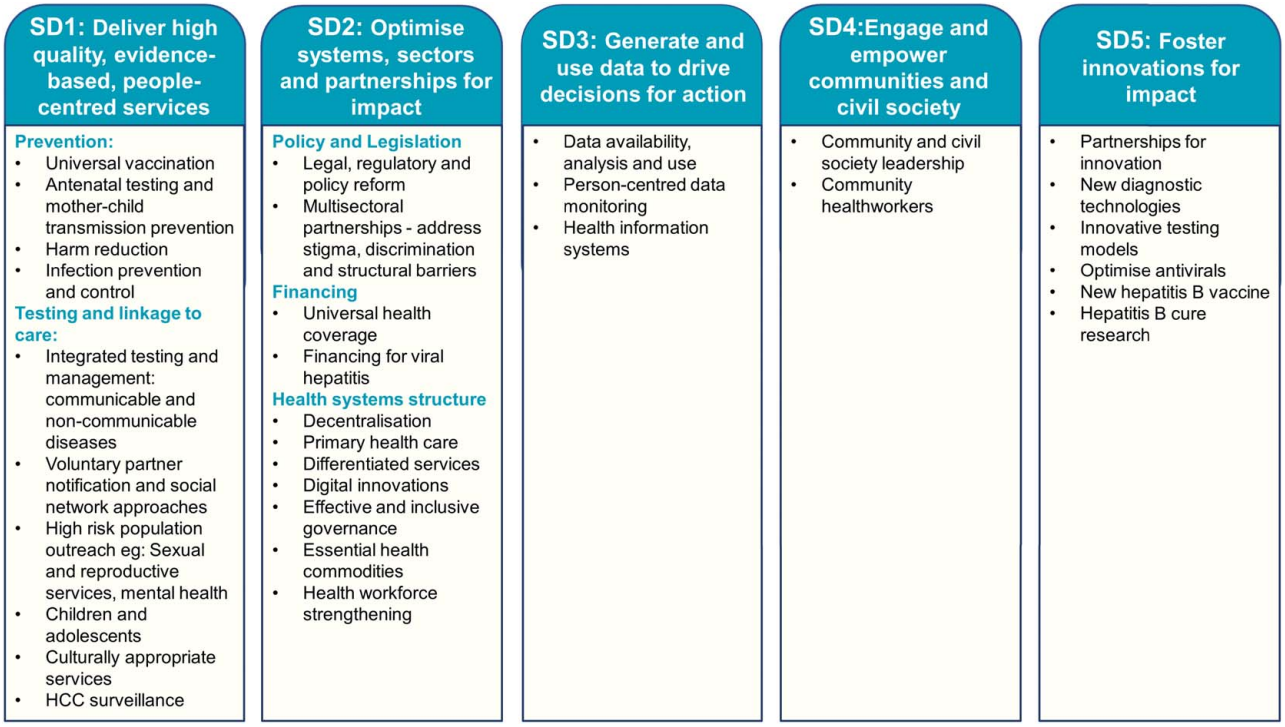

FIGURE 1 SDs framework for hepatitis B elimination.[7] Abbreviation: SD, Strategic Direction.

with body fluid and blood exposure being additional routes of transmission in adulthood.[21] Universal vaccination of infants, including a birth dose within 24 (ideally 12) hours of birth, is the cornerstone of chronic HBV prevention. Modeling demonstrates that increasing birth dose coverage is essential to achieve HBV elimination targets.[15,40–42] While the HBV birth dose has been included for catalytic financing in Gavi's most recent Vaccine Investment Strategy (VIS),[43] overcoming barriers associated with timely delivery in low-resource settings (including logistics, cold chain, lack of skilled healthworker access, and home births outside of health facilities) remains critical for reaching the WHO target of 90% coverage by 2030.[40,42] Increasing the proportion of births in health facilities and using skilled birth attendants outside of health facilities are important strategies to increase the delivery of the birth dose.[40] In addition, this can leverage antenatal care services and related funding streams to minimize upfront costs.[44–46] The effectiveness of this approach has been demonstrated in several countries within the WPRO region, such as China, Mongolia, and many of the Pacific Islands and Territories.[2,47] Use of vaccines within a controlled temperature chain[41] and delivery via single-use, autodisable inject devices are cost-effective measures to increase access to timely birth dose for infants born outside of healthcare facilities.[40] These strategies are now supported by the Strategic Advisory Group of Experts on Immunization.[48] Disruptions to current infant vaccination programs due to COVID-19 must be addressed through catch-up programs to achieve WHO HBV incidence targets by 2030.[29]

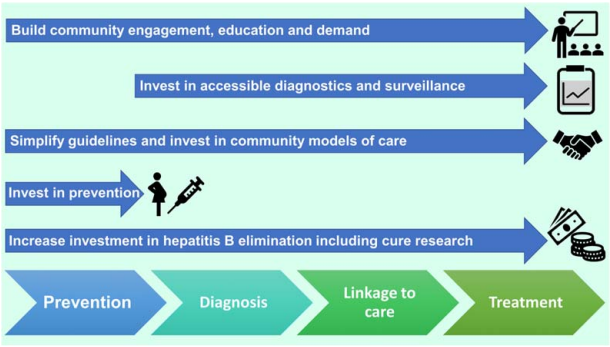

FIGURE 2 Summary of key actions to achieve hepatitis B elimination and impact on the hepatitis B cascade of care.

Routine antenatal screening of pregnant mothers with HBsAg testing is used to determine whether additional HBV prevention tools are required, including hepatitis B immune globulin given to infants born to HBsAg-positive mothers and tenofovir given to mothers who are HBeAg-positive or who have a high viral load during mid-late pregnancy.[49] Routine antenatal screening presents an important opportunity for women with HBV infection to be diagnosed and linked to care, as well as for partners, family members, and household contacts to be tested and vaccinated.[50,51] However, even in high-resource settings, antenatal diagnosis of HBV often does not lead to effective linkage to care of women with HBV.[51] Additional strategies to reduce mother-to-child transmission of HBV include

incorporating tenofovir into the Essential Medicines list for HBeAg-positive pregnant women and those with high a viral load.[52] This reduces the transmission risk to <1%[49] and is supported by WHO as a cost-effective strategy for achieving the WHO elimination target of <0.1% prevalence among children by 2030.[15,44,53,54] Preliminary data from the TA PROHM study demonstrating that tenofovir with full schedule HBV vaccination alone may be similarly effective to hepatitis B immune globulin plus tenofovir and full schedule HBV vaccination for prevention of mother-to-child HBV transmission are encouraging[55] though further studies are needed before widespread adoption of this strategy. Tenofovir alafenamide has a higher safety profile than tenofovir disoproxil fumarate (including in pregnancy), would be preferable to tenofovir to reduce adverse event monitoring requirements and costs,[56] however, remains unaffordable in most countries, and is not yet included in WHO guidelines.

Improvements in blood safety and screening, injection safety, harm reduction policies, and provision of needle and syringe programs, including the use of safety-engineered devices for injections, are also key WHO targets that generally prevent blood-borne virus transmission, including HBV.[7,57]

Expand access to affordable diagnostics and decentralized testing programs

Access to affordable and accessible diagnostics is critical to HBV elimination yet remains challenging due to inequitable distribution of laboratory resources, skilled technicians, and cost. In many countries, HBV tests that are essential to guide treatment are unavailable or prohibitively expensive, with disease evaluation and monitoring costing more than treatment.[17,19,58] While drug costs have decreased over time, there has not been a commensurate fall in the cost of diagnostics; WHO Essential Diagnostics Listing, national production licenses, pooled procurement, industry partnerships [eg, Foundation for Innovative Diagnostics (FIND)], and supportive legislation are necessary to make diagnostics more affordable for low-resource settings.[19] This should extend to new diagnostics that may be required to measure treatment responses to or eligibility for HBV cure. Diagnostics manufacturers should develop tests for commercialization and submit these rapidly to WHO for prequalification to align with the availability and scale-up of HBV cure. Consideration of waste burden associated with diagnostics (eg, nonrecyclable test cartridges) should also be made, along with rationalization of testing frequency.

In many endemic countries, laboratory capacity must be increased, laboratory systems must be strengthened, and measures must be taken to integrate testing platforms for multidisease approaches. Integration of HBV testing into existing disease programs can be leveraged to overcome access barriers and increase coverage. In some settings, one-time universal HBV testing of the general population has been shown to be cost-effective and can be offered through decentralized community-based testing programs,[59,60] particularly for adults born before the introduction of universal infant HBV vaccination. Dried blood spot measurement, used in other disease programs, such as HIV, has been validated for HBsAg and HBV DNA measurement, and overcomes cold chain requirements to expand access to centralized laboratory testing in low-resource and remote settings.[18,20] WHO prequalified HBsAg PoC rapid diagnostic tests are already available and have been shown in multiple settings to be cost-effective alternatives to improve HBV diagnosis access.[61,62] GenXpert machines already in use for other disease programs, such as HIV, malaria, tuberculosis, and hepatitis C, should be harnessed to upscale HBV diagnosis and treatment evaluation.[6] Noninvasive blood test–based algorithms, such as aspartate aminotransferase to platelet ratio index and fibrosis-4 index, should be used to assess liver fibrosis.[63] Alternative diagnostics that circumvent PCR requirements and lend themselves to POC test formats, such as loop-mediated isothermal amplification assay–based HBV DNA quantification[64] and HBV core–related antigen titer,[65] should be validated, in addition to novel diagnostics to evaluate liver damage.[66] Improved access to hepatitis delta testing, including POC test formats, is also important, particularly in countries in which the HDV is endemic, although treatment options are currently limited and costly.

Strengthen nonspecialist, integrated community–based models of care

Decentralized, primary care, and community-based models of hepatitis care offer greater service coverage and lower access barriers for people living with HBV,[6,67] particularly communities in rural settings or those who may experience stigma and discrimination in traditional models of healthcare.[6] Both linkage and retention in care are vital to prevent poor outcomes from HBV.[19] There are insufficient specialists in most countries to manage and treat all people with HBV, and the majority can be safely managed in primary care settings by trained health workers.[2] Greater efficiency gains are achieved through task-shifting and redistribution of existing health workers, supported by hub-and-spoke models of care, for example, within HIV programs in sub-Saharan Africa.[61,68,69] It is notable that the Global Fund has now agreed to fund HBV care delivered through HIV programs. However, task-shifting is only possible with simplified hepatitis B diagnostic and management algorithms.

HBV testing and management should be integrated into diverse existing primary care models that are optimized to reach specific high-risk populations, such as refugee and migrant health networks, First Nations people administered health services, mental health services, sexual health clinics, prisons, and community services for people who inject drugs. To be successful, culturally safe education and primary healthworker training, first language educational resources, capacity building, and the use of peer workers within a multidisciplinary team are essential components.[70] Currently, people with chronic HBV require lifelong care, therefore integration of HBV care into chronic disease management programs with routine monitoring, such as HIV and diabetes capitalizes on strong mechanisms to retain people in care longitudinally.[71] This approach reduces upfront costs by enabling HBV management to be incorporated into existing disease programs, such as tuberculosis or type 2 diabetes.[72,73] HBV is experienced and understood within generational and community contexts[74,75]; therefore, models of care that leverage family and community approaches to HBV testing, linkage, and retention in care are needed. Appropriate integration of hepatitis B care within child and adolescent health services should be prioritized. However, when HBV cure becomes available, HBV management should pivot into both acute and chronic disease management services to rapidly upscale access to cure, as has been done with hepatitis C cure delivered through needle-syringe programs,[76] for example. HBV testing should be performed in accordance with WHO "5 Cs" guiding principles for testing that enshrines human rights and should be offered within models of care that benefits the health and well-being of people with HBV through linkage to high-quality, evidence-based care, and treatment.[75,77,78]

Consideration must be given to postcure monitoring in HBV, which differs from hepatitis C. Unlike cure in people with hepatitis C without cirrhosis, functional cure in HBV reduces but does not eliminate the risk of HCC, particularly when this occurs after 50 years of age.[79–81] In most intermediate to high-prevalence countries with high coverage of universal infant vaccination, the population living with HBV is older and, therefore, at greater risk of HCC, necessitating consideration of the cost-effectiveness of HCC surveillance for those who achieve HBV cure. In many low-resource countries with high HBV prevalence, particularly within sub-Saharan Africa, HCC surveillance programs are very limited and most present with incurable advanced-stage HCC.[82,83] Moreover, treatment options in low-resource settings are extremely limited.[83] Investment in longitudinal disease monitoring postcure for a proportion of patients is required, taking into consideration the local availability of effective HCC management programs. Biomarker-based algorithms for the prediction of HCC risk in treated and untreated patients based on routine blood tests and demographics, such as PAGE-B, REACH B, and REAL B scores,[81,84] may prove useful to guide postcure monitoring for HCC. The development of assays to assess cccDNA and HBV DNA integration in the host genome in the context of cure research may, in the future, facilitate a tailored approach to HCC risk profile stratification. Regardless, research to explore this critical issue must be undertaken as curative therapies become available to determine the long-term risk of HCC once cure is achieved within different populations and the cost-effectiveness of ongoing HCC surveillance post-HBV cure, particularly for those treated early in the course of infection.

Simplify guidelines

Simplifying current guidelines by expanding treatment eligibility is an important step toward HBV elimination.[82] National hepatitis policies and guidelines should define testing strategies for general and high-risk populations in accordance with the epidemiology of HBV in that country. In addition, current HBV treatment guidelines are complex, requiring the interpretation of multiple test results longitudinally to determine treatment eligibility and regular disease monitoring to ensure that the treatment is started at the right time to prevent liver cirrhosis and reduce the risk of HCC.[21,85] This strategy is a major barrier to HBV management in primary care settings.[86,87] Moreover, the costs and inaccessibility of diagnostics required to determine treatment eligibility, such as transient elastography and HBV DNA PCR, hamper decentralized models of care.[19] Simplification of current HBV guidelines to a screen-and-treat approach would reduce the high costs of specialist management and diagnostics,[88] offsetting the higher initial costs of HBV cure. This would facilitate POC test-led, community models of HBV screening, and treatment that have proved highly cost-effective for increasing access to hepatitis C cure when delivered across a diverse range of settings, particularly among marginalized populations.[76] It is likely that the impact of HBV cure when given early in the course of infection will significantly reduce HCC risk; therefore, ongoing HCC surveillance costs might be mitigated if the annual risk of HCC postcure falls below the cost-effectiveness threshold to support ongoing HCC surveillance.

The prospect of an HBV cure provides an opportunity to substantially rethink current HBV guidelines now, rather than in the future when a cure is available. Current nucleos(t)ide analog therapy removes the risk of hepatic decompensation in cirrhosis and reduces HCC risk by 50%–80% and liver-related mortality by 60%–80%.[89] However, even when current treatment guidelines are followed, HCC can still occur in a proportion of individuals who are not eligible for treatment[90] and in those who do go onto timely nucleos(t)ide therapy.[80,90,91] International

HBV guidelines[21,85] have been slowly expanding treatment criteria in recent years in light of emerging evidence of increased liver damage and adverse outcomes among those not currently eligible for treatment.[90] Interestingly, in the last 2–3 years, several publications have demonstrated the cost-effectiveness and mortality impact of expanding treatment to people in the so-called immune-tolerant (HBeAg-positive infection) phase of infection across a range of settings.[92–96] For example, Kim et al[97] used a Markov model to show that, in the context of South Korea, treating all individuals with HBV with either entecavir or tenofovir in the immune-tolerant phase was a cost-effective strategy for HCC prevention from a health service payer perspective (ICER US$16,516 per quality-adjusted life year gained), where annual HCC incidence was >0.4%–0.5%.[97] Cost-effectiveness was even greater when a societal perspective accounting for lost productivity costs was assumed. Similar modeling outcomes have been shown across other national settings, including the USA[96] and Saudi Arabia.[94]

A treat-all strategy is already the mainstay of therapy for people with HBV-HIV coinfection, where it is often started in the immune-tolerant phase, including in childhood.[79] Importantly, among coinfected people who commenced tenofovir before the age of 46 years, annual HCC incidence is very low, well below the current annual incidence threshold where HCC surveillance is considered cost-effective.[79] This suggests that significant HCC surveillance costs may be averted by early treatment of HBV in childhood or early adulthood. Further work with affected communities is required to better understand the risks and benefits of this approach and develop care pathways that facilitate informed patient choice.

STRATEGIC DIRECTION 2: OPTIMIZE SYSTEMS, SECTORS, AND PARTNERSHIPS FOR IMPACT

Increase investment in HBV elimination activities, including research

Financers of healthcare will require detailed cost-effectiveness analyses of any future HBV cure to justify the investment. Mechanisms to increase sustainable funding of international and national viral hepatitis elimination activities are outlined elsewhere.[6,23,30] Integration of HBV cure and related elimination activities into national "health benefits packages" as part of Universal Health Care (UHC) embedded within Sustainable Development Goal models is important, such as was done with hepatitis C cure in Egypt and Pakistan.[98,99] The WHO's Making Fair Choices for Universal Health Coverage report recommends prioritizing health interventions based on 3 criteria: cost-effectiveness, priority to the worst off, and financial risk protection. These 3 factors were chosen to maximize the health of populations and avoid catastrophic out-of-pocket health spending to reduce poverty while enshrining health equity. These same criteria form the backbone of the Disease Control Priorities Project (DCP) for the Essential Universal Health Coverage model for countries to determine what is included in their Universal Health Care packages.[100] Therefore, national cost-effectiveness models should be developed as early as feasible for future cures across a diverse range of settings and disease burdens to prepare governments and key stakeholders for investment through UHC and pharmaceutical price negotiations.[100,101] Duration of treatment will be one consideration but unlikely to be a major driver of the drug cost.

Affordability of future HBV cures is a major concern, particularly for high-prevalence, low-resource settings, as are inconsistencies in mechanisms for the registration of new medicines and the inherent barriers presented by complex regulatory approval systems. Despite patents for entecavir and tenofovir expiring, there is considerable variation in drug costs across countries and between regions.[102,103] Licensing future HBV cures, including pediatric formulations, on the Medicines Patent Pool is one way to facilitate low-cost HBV cures before new patents expire.[6] Generic production and competitive price-sharing arrangements between governments and pharmaceutical companies also facilitate low-cost cure availability, as has occurred for hepatitis C.[6] Pooled procurement for regional groups of smaller nations, or countries with fragmented demand and low-volume orders, is an alternative strategy,[6] as used in the Pacific Islands and Territories.[47] Domestic funding is the mainstay of national HBV elimination financing at present as most global donors, such as The Global Fund and the Bill and Melinda Gates Foundation, do not support large-scale HBV elimination activities.[6] Sustainable funding of HBV elimination programs can be supported through inclusion in national essential packages for UHC and national insurance schemes.[6]

Scaling up HBV cure delivery will require increased health workforce education, strengthening, and support, including task-shifting within existing health services.[6] Digital technologies, such as telehealth combined with hub-spoke ECHO models of care,[7] can also increase access to HBV services to deliver the cure. The use of digital models of care became more widespread during the COVID-19 pandemic[6,104]; these models of care can be utilized to increase coverage of HBV care, particularly through providing specialist support and oversight for new prescribers of HBV cure as they gain confidence. Legislation and policy that facilitate universal access to HBV cure and prescribing by trained nonspecialist health workers in primary care settings will be imperative to rapidly expand access to HBV cure, as has been shown with hepatitis C cure in countries such as Australia, India, and Rwanda.[6,32] Other nondiscriminatory legislations,

such as nonpunitive testing of migrants through visa application processes, should also be adopted.[105]

STRATEGIC DIRECTION 3: GENERATE AND USE DATA TO DRIVE DECISIONS FOR ACTION

Invest in high-quality, person-centered data capture, and surveillance systems

The inverse face of the diagnostics coin is surveillance: diagnostics reporting systems that are embedded in models of care streamline case identification and outcome measurement by national surveillance systems, thus enabling data-driven timely decision-making.[7] Without high-quality surveillance data to inform burden estimation, the real costs and impact of HBV are unknown, and HBV will not be prioritized for inclusion in SDG packages.[106] Passive national disease surveillance and active sentinel site surveillance systems work synergistically to provide holistic views of progress toward 2030 targets.[6] The WHO Viral Hepatitis Continuum of Care Monitoring and Evaluation Framework provides guidance for surveillance systems investment,[107] while electronic medical record and data collection systems, such as Open MRS (OpenMRS Inc.) supported by WHO, enable local data collection to monitor HBV elimination programs.[108] Guidance on the measurement of impact and validation of WHO HBV elimination targets is provided in the 2021 "Interim guidance and framework for country validation of hepatitis elimination"[109] and can be adapted to the implementation of HBV cure when available.

STRATEGIC DIRECTION 4: ENGAGE AND EMPOWER COMMUNITIES AND CIVIL SOCIETY

Build community engagement and demand for HBV elimination and cure

Strong community engagement is essential to reduce stigma from HBV,[110] drive demand for HBV testing and treatment, and, thereby, garner support among governments, policymakers, and investors to catalyze action. Current low levels of HBV awareness and health literacy, coupled with stigma and discrimination experienced by people living with HBV, have hampered diagnosis and treatment uptake globally.[2,75,98] Misunderstandings about how hepatitis B is transmitted affect the personal and professional lives of people living with hepatitis B, leading to discriminatory policies that impact employment, education, and socioeconomic opportunities in addition to healthcare access.[75,110]

Investment in a strong civil society workforce facilitates advocacy, awareness, and health literacy promotion at both the general population and community levels, including children and adolescents, with knowledge of traditional health belief frameworks. Empowered community organizations and affected populations enable codesign of effective health service interventions; they also provide partnerships to tackle and measure progress toward stigma and discrimination targets, which are critical steps in an effective HBV elimination response. Community organizations have also driven the development of national HBV strategies in many WHO states.[111]

Fearless and sustained community activism, supported by research and modeling to highlight individual country benefits and global benefits, delivered widespread availability of pharmaceuticals for HIV.[112] Such advocacy has also been successful in leading to a rapid decrease in the costs of hepatitis C treatment globally.[30] Though lessons learned from these campaigns are very relevant to the design of future HBV cure campaigns, it is imperative to recognize that structural, socioeconomic, and political barriers mean populations living with HBV may not be in a similar position to advocate as strongly for equitable access to HBV cure.[75]

STRATEGIC DIRECTION 5: FOSTER INNOVATIONS FOR IMPACT

Invest to innovate: use public-private partnerships to support high-quality research

International private and public partnerships, agencies, and donors must come together to support research to optimize the delivery of HBV cure and achieve HBV elimination.[18] Despite the high burden of disease globally, no large-scale international fund exists to support HBV elimination and research, particularly in low-resource settings. The Hepatitis Fund remains the only specific international fund for hepatitis B elimination activities. Initiatives providing financial and technical support for diagnostics development from industry partners and not-for-profits, such as the Foundation for Innovative Diagnostics (FIND), PATH, and the Global Innovation Fund, should be utilized for HBV.[6] This could be done in partnership with existing organizations dedicated to HBV cure, including the HBV Foundation and the International Coalition to Eliminate (ICE) HBV.[113] Even when the HBV cure becomes a reality, critically important gaps in HBV knowledge will remain, which require ongoing investments in research. The ICE-HBV has successfully catalyzed research collaborations and funding[114]; further global initiatives are urgently required to build on this momentum.

CONCLUSIONS

The path toward HBV elimination is becoming clearer, illuminated by promising HBV cure research. However, the cure is only one part of the solution to achieve HBV elimination globally. The groundwork for a cure must begin now with the optimization of current tools to improve the HBV cascade of care and facilitate rapid upscale of cure when it becomes available. However, we must also continue to work toward HBV elimination with the safe, effective, and affordable vaccine and treatments that we already have to achieve HBV mortality targets by 2030. We must proactively prepare, but not wait, for the HBV cure.

CONFLICTS OF INTEREST

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