REVIEW ARTICLE

How to improve access to therapy in hepatitis B patients

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Abstract
Despite the availability of a preventive vaccine and active antiviral treatments that stop disease progression and reduce the risk of hepatocellular carcinoma, hepatitis B is still a major public health problem. Only an estimated 10% of the 257 million people living with HBV have been diagnosed and as few as 1% are being adequately treated. Barriers to diagnosis and treatment include: (i) limited awareness and lack of knowledge about HBV infection and HBV-related diseases; (ii) under-diagnosis with insufficient screening and referral to care; (iii) limited treatment due to drug availability, costs, reimbursement policies and the need for long-term or life-long therapy. These barriers and the actions needed to improve access to treatment are strongly influenced by the prevalence of infection and affect middle-high vs low-middle income countries differently, where most HBV carriers are found. In high-prevalence regions and low-to-middle-income countries, the main challenges are availability and cost while in low-prevalence regions and middle-to-high-income countries low screening rates, public awareness, social stigma and discrimination play an important role. Overcoming these challenges on a global scale is a complex clinical and public health challenge and multilateral commitment from pharmaceutical companies, governments, funders and the research community is lacking. The new WHO 2016 Global Health Sector Strategy on viral hepatitis targets testing and treatment, suggesting that important but strong actions are needed from advocacy groups, scientific societies and funding agencies to foster awareness and access to cure.

KEYWORDS
access to treatment, chronic HBV infection, disease awareness, HBV screening, vaccine availability

1 | THE GLOBAL BURDEN OF HBV INFECTION AND THE HBV CASCADE

More than 50 years after the discovery of the Australia antigen linked to hepatitis B virus (HBV) infection and despite the availability of a preventive vaccine and antiviral treatments that stop disease progression and reduce risk of liver cancer, hepatitis B still remains a major public health problem worldwide, similar in scale to the human immunodeficiency virus (HIV), malaria and tuberculosis. According to the last WHO Global Hepatitis Report published in 2017, the prevalence of HBV infection in the general population is 3.5%, with about 257 million persons living with HBV chronic infection, making it the most...
common chronic viral infection.\textsuperscript{2,3} HBV mortality (887 000 deaths/year\textsuperscript{4}) is now twice that of malaria (429 000 deaths/year\textsuperscript{5}) and HBV (hepatitis B, HBV-related cirrhosis and HBV-related liver cancer) represents the seventh highest cause of mortality worldwide.\textsuperscript{6} HBV is responsible for >50% of the hepatocellular carcinomas (HCCs) worldwide,\textsuperscript{7,8} and up to 10% liver transplants.\textsuperscript{8}

The major burden of morbidity and mortality from HBV is found in low/middle income countries in tropical and subtropical countries.\textsuperscript{9} Including chronic HBV among neglected tropical diseases (NTDs), according to WHO definitions, was recently suggested to strengthen a unified global approach for the elimination of HBV using the NTD management paradigm.\textsuperscript{10} The prevalence of HBV varies greatly in the different geographical regions with the highest prevalence in sub-Saharan Africa (>8%), the western Pacific (>5% overall and >8% in China, South Korea, Philippines, and Vietnam), the Balkans, the Pacific Islands and the Amazon basin of South America.\textsuperscript{11-16} The prevalence of chronic HBV infection is low in most European countries (France, Hungary, Italy, The Netherlands, Portugal, Spain, and the UK) (0.5%-0.7%) but this increases to 1%-5% in Turkey, Romania and Serbia and to >5% in Albania and Moldavia, with a clear Eastern to Western gradient.\textsuperscript{15,16} In the United States, the prevalence of HBV infection is approximately 0.3% but this varies widely depending on geographic origin and ethnicity with Asian-Americans and African-Americans having the highest prevalence (up to 15%) while Latinos having a prevalence similar to the general US population.\textsuperscript{17-19} Overall, approximately three-quarters of individuals with chronic HBV are found in the Asia-Pacific region. There are between 7 and 12 million individuals with chronic HBV infection in Latin America and the Caribbean,\textsuperscript{14} approximately 14 million in Europe\textsuperscript{16} and 2.2 million in the United States.\textsuperscript{17} Despite vaccination and other public health efforts, the overall prevalence of chronic HBV infection in developed countries has remained constant during the last decade with up to 70%-95% of the new cases of chronic HBV infection attributed to immigration from regions with moderate to high HBV endemicity.\textsuperscript{16,19}

It is important to note that the overall prevalence of chronic HBV infection may be greater than the results of sero-epidemiological studies. Not only is overt (HBsAg positive) HBV infection under-diagnosed\textsuperscript{2} but so-called “ occult HBV infection” (defined as persistence of free and/or integrated forms of HBV-DNA in the liver in the absence of HBsAg in serum\textsuperscript{20}) which is associated with an increased risk of the development of HCC,\textsuperscript{21-23} can be overlooked due to HBsAg negativity in serum. To date only an estimated 10% of patients with chronic infection have been diagnosed worldwide.\textsuperscript{2} The absence of robust data on the number of diagnosed HBV patients who have been referred for care, begun and continued treatment and with suppressed viremia, make it difficult to estimate the proportion of patients with chronic hepatitis B (CHB) who are adequately treated worldwide, but the figure could be <1% (Figure 1). It is important to note that without treatment, as many as 25% of patients with chronic HBV infection are at risk of developing cirrhosis, decompensated cirrhosis, liver failure and hepatocarcinoma during their lifetime.\textsuperscript{24}

### Key points

- Viral hepatitis and its consequences (HBV-related cirrhosis and HBV-related liver cancer) remain a global health burden.
- HBV is under-diagnosed and only 1% of HBV carriers are adequately treated.
- Cost of diagnosis and treatment are the main challenges in high-prevalence regions and low-to middle-income countries.
- In low-prevalence regions and middle-to high-income countries, low screening rates, public awareness, social stigma and discrimination play an important role.
- The implementation of the WHO global strategy (for the elimination of HBV as a public health threat by 2030) requires a multilateral commitment from pharmaceutical companies, governments, funding agencies and the research community and proportionate financial support.

### 2 CONTROLLING HBV INFECTION

After decades of relative neglect, the global elimination of HBV infection has recently become a priority in international health agendas, due to a general consensus among doctors, researchers, health agencies and governments that available antiviral therapies and vaccines should be sufficient to eliminate HBV if they are adequately implemented. In 2016, the World Health Organization assembly approved a global strategy (Global Health Sector Strategy—GHSS) to eliminate viral hepatitis as a public health threat by 2030.\textsuperscript{25} Based on the 2015 baselines, countries and regions need to reduce new infections (incidence) by 90% and deaths (mortality) by 65%. Increased efforts to eliminate HBV are also supported by the Sustainable Development Goals (SDGs) initiative.\textsuperscript{26} Because of the estimated global burden of >250 million chronic carriers,\textsuperscript{2} most of whom are unaware of their infection, the WHO strategy is an ambitious goal and an enormous challenge.\textsuperscript{2} According to the WHO GHSS, HBV elimination requires a synergy of the following measures: (i) immunization against hepatitis B; (ii) prevention of mother-to-child transmission of HBV; (iii) blood and injection safety; (iv) prevention of transmission in persons who inject drugs (PWID) through comprehensive harm reduction strategies and services; (v) and increased testing and treatment.

Universal infant HBV vaccination has been shown to reduce not only the incidence of HBV infections but also the incidence of HCC.\textsuperscript{27,28} Other preventive measures (ie blood safety, health-care injection safety, harm reduction for PWID) further reduce the transmission of HBV.\textsuperscript{2} However, even if the coverage and efficacy of vaccination could be immediately increased to 100%, the need to care for patients with acquired HBV infection and its consequences would remain. The Global Burden of Disease (GBD) project estimates that cirrhosis and HCC account for most viral hepatitis morbidity and
While the lack of available vaccines and prophylaxis can partly explain the high HBV disease burden in many low-middle-income countries, better approaches to treatment and management of infection in both low-middle income and high income countries are also needed.

### 3 | BARRIERS TO HBV TREATMENT

The main factors that limit the access to treatment of chronic HBV include:

1. limited awareness and lack of knowledge about HBV infection and HBV-related disease,
2. under-diagnosis with inadequate screening and referral to care
3. limited treatment due to drug availability, costs, reimbursement policies and long-term or life-long therapy
4. social stigma and discrimination

The impact of these different barriers and the actions needed to improve access to treatment differ in low-middle and middle-high income countries and are strongly influenced by the prevalence of infection and comorbidities. In high-prevalence regions and low-to middle-income countries the main challenges are availability and cost, while in low-prevalence regions and middle-to high-income countries low screening rates, public awareness, social stigma and discrimination play an important role.

### 3.1 | Lack of knowledge and awareness

Several factors may contribute to the lack of interest and investment in HBV education, research, advocacy and clinical care. HBV has been overshadowed by higher profile infections such as HIV, malaria and tuberculosis. There has been a certain complacency among doctors, research policy makers and health institutions that existing resources and approaches would result in the elimination and control of HBV infection and disease progression, undermining awareness. This silent infection may not be diagnosed until the disease has progressed, contributing to the large pool of undiagnosed infection and ongoing transmission. Globally, knowledge and education is poor among patients, the public, and healthcare workers and the global burden of infection is underestimated. HBV infection and HBV-host interactions are complex resulting in a complicated and wide spectrum of HBV-related diseases. Several factors may contribute to the lack of interest and investment in HBV education, research, advocacy and clinical care. HBV has been overshadowed by higher profile infections such as HIV, malaria and tuberculosis. There has been a certain complacency among doctors, research policy makers and health institutions that existing resources and approaches would result in the elimination and control of HBV infection and disease progression, undermining awareness. This silent infection may not be diagnosed until the disease has progressed, contributing to the large pool of undiagnosed infection and ongoing transmission. Globally, knowledge and education is poor among patients, the public, and healthcare workers and the global burden of infection is underestimated. HBV infection and HBV-host interactions are complex resulting in a complicated and wide spectrum of HBV-related diseases.

Moreover, the higher disease burden is in low/middle-income countries, where investment is not a priority and poverty contributes to lack of patient and public involvement. The quality of available regional/country based data on epidemiology and risk factors is often poor. Infrastructures to collect robust data and provide education, prevention, diagnosis, and treatment are lacking. Evaluations on the feasibility of proposed interventions are often overlooked. The impact of stigma is underestimated. Finally, the extremely limited number of major funding agencies dedicated to HBV has also played a role and this disease has remained out of the scope of agencies such as the Melissa and Bill Gates Foundation and the Global Fund. Several simple actions can be taken to overcome this lack of knowledge and awareness (Table 1).
3.2 Under-diagnosis with limited screening and referral to care

Screening of HBV infection is the cornerstone to identify patients requiring treatment to prevent and/or delay progression of HBV-related liver disease and further transmission. HBV screening based on HBsAg detection in serum by enzyme immunoassays (EIA), chemiluminescence immunoassays, electro-chemi-luminescence assays, is not optimal because most individuals with chronic HBV infection are asymptomatic until they develop cirrhosis or HCC. Primary care-based screening will mostly identify previously unknown infections, even in a low-prevalence/high-income countries such as Germany.8

In low-income settings, HBsAg testing is expensive and the infrastructures, storage facilities, human resources and expert technical staff are limited.2,25,29 To overcome these limitations, HBV testing could be integrated into pre-existing platforms for the diagnosis of HIV or sexually transmitted diseases.29 Low-cost, point-of-care (POC) Rapid Diagnostic Tests (RDTs) for the detection of HBsAg can provide results within a few minutes.29 RDTs do not require laboratories, can be performed with serum, plasma or whole blood collection on fingersticks and can be performed near to the patient, at POCs, or even by self-testing.29 The International Consortium for Blood Safety (ICBS) has evaluated 51 HBsAg EIA assays and 19 POC HBsAg RDTs.30 Although EIA assays are generally more sensitive than RDTs, the performance of EIA assays also varies greatly with up to 10-fold differences in the detection of HBsAg for different HBV genotypes.31 Multiplex, multidiase anti-HIV/anti-HCV, anti-HIV/syphilis/anti-HCV, anti-HIV/syphilis/ HBsAg and anti-HIV/anti-HCV/HBsAg RDTs are under development.31 These multiplex RDTs have numerous advantages such as lower specimen volumes, improved client flow, results for multiple pathogens at the same time, fewer patient visits and reduced transport costs. Self-testing, with individual specimen collections, test executions and interpretation of results is used for HIV in many settings and has increased the volume testing in patients who cannot be reached by other means. Although results of hepatitis B self-testing are still very limited, it is a potentially important approach to expand access to testing in the future.

Although current HBV guidelines do not recommend universal screening in the general population, there is a consensus that screening should be performed in individuals at increased risk of infection. General practitioners may screen for hepatitis B in patients with elevated ALTs, thus excluding HBV carriers with normal ALTs who represent more than half of these cases.22 HBV screening should target populations with high risk sexual behaviour (multiple sexual partners, lack of condom use or men having sex with men—MHSMM), undocumented migrants, asylum seekers and refugees, institutionalized persons, persons in detention centres or jails, frequent transfusion recipients, persons who inject drugs (PWID) or abuse alcohol and those with tattoos and body piercings.12,16,17,32 Other populations to be screened include individuals undergoing immunosuppressive treatments or receiving biological therapies for autoimmune conditions and chemotherapy for cancer.34

Once HBV infection is detected, HBV-DNA and ALT must be measured and liver function and the stage of liver disease should be assessed with invasive or noninvasive tests to guide treatment decisions.13,16,17

HBV-DNA testing and non-invasive tests for fibrosis (NITs) are generally not available in low-income settings and reimbursement policies vary across middle/high income countries.25 Dry Blood Spots (DBSs) for HBV viral load testing are a good alternative to plasma
because of the stability at room temperature, easy handling, storage and transport even in rural areas. Sensitivity is lower than standard plasma assays but sufficient to detect patients with high viral load who require treatment and to monitor antiviral treatment response. DBSs are the only available, viable option for HBV-DNA testing in resource-limited settings. A number of innovative platforms and technologies for HBV-DNA quantification have been developed to be used in POCs and resources-limited regions including microchip PCR-based HBV-DNA amplification devices, an isothermal amplification (LAMP) technology that avoids fluorescence reagents and a Nanoplasmonic Electrical field-enhanced Resonating Device (NE2RD). All these assays must be validated for broader dynamic ranges and in different HBV genotypes.

Besides serological testing, assessment of the stage of liver disease must be determined. Liver biopsy is considered to be the gold standard to determine the degree of fibrosis using systems such as the METAVIR or Ishak scores. Liver biopsy is invasive and costly, inconvenient and associated with a small, yet measurable, risk of complications such as significant bleeding (1.1%-1.6%) and sampling errors. Non-invasive tests of fibrosis (NITs) include simple/indirect serum markers, direct/patented serum markers and imaging modalities. NITs based on blood or serum parameters such as aspartate transaminase (AST)-to-platelet ratio index (APRI) and the fibrosis index based on the four factors (FIB-4) have the advantage of using a few, inexpensive laboratory tests and are recommended by WHO guidelines to detect significant fibrosis in resource-limited settings. Recently, the gamma-glutamyl transpeptidase (GGT) to platelet ratio (GPR) and the APRG (ALP/PLT/RDW-SD/globulin) score have been shown to be more accurate than traditional APRI/FIB-4 scores to estimate liver fibrosis in patients with CHB. Direct serum tests, such as the Fibrotest, are patented, must be performed in laboratories that meet certain quality standards, are more expensive and less accessible. Transient elastography (FibroScan) is a non-invasive, highly reproducible, technique for staging liver fibrosis, however, it is operator-dependent. High necro-inflammatory activity, cholestasis, high total bilirubin and obesity are potential confounding factors. This technique is limited by the high cost of equipment, the need for preventive and corrective maintenance and the lack of extensively validated cut-off values for specific stages of fibrosis. A portable transient elastography (Fibroscan) device has become available and allowing disease staging to be performed at the patient’s side. However, cost may again be an important limitation.

Measures that can be implemented or supported to improve HBV screening and patient referral to care are listed in Table 1.

### 3.3 Limited access to treatment

Several factors limit access to treatment in chronic HBV patients: (i) the complexity of the virus-host interplay resulting in multiple entities/phases of disease with different management and treatment strategies; (ii) the available treatments require long-term to lifelong treatment. They result in HBsAg loss only in a minority of cases. This is a significant end-point making it possible to stop therapy. In these cases, it is associated with clinical benefit; (iii) the cost and availability of treatment especially in low-middle income countries, and the different reimbursement policies in middle-high income countries (Table 1).

Patients with chronic HBV infection are classified into four main categories based on their serological profile and liver disease activity: (i) HBeAg positive chronic infection (previously referred to as “immunotolerant patients”); (ii) HBeAg positive chronic hepatitis and (iii) HBeAg negative chronic hepatitis (previously collectively referred to as “immunoactive patients”); (iv) HBeAg negative chronic infection (previously referred to as “inactive carriers”). Although these clinical categories do not encompass the complex and dynamic interplay between the virus and the host responses, they are used to guide clinical and therapeutic decisions. Definitions of an HBV cure have recently been proposed: (i) complete sterilizing cure with undetectable HBsAg in serum and eradication of HBV DNA including intrahepatic cccDNA and integrated HBV DNA; (ii) functional cure with sustained, undetectable HBsAg and HBV DNA in serum with/without seroconversion to anti-HBs after completion of finite treatment, accompanied by resolution of liver damage and a decreased risk of HCC over time, but with persistent residual levels of cccDNA.

Not all HBsAg positive patients require treatment according to European, American and Asia-Pacific guidelines for the management and treatment of HBV. Even in developed countries, many patients who are eligible for antiviral treatment do not receive therapy due to gaps in the healthcare system. A meta-analysis of 13 studies (6 US, 7 non-US) including 31,342 individuals found that only 41% of treatment-eligible individuals actually received antiviral therapy. In a regional study of patients diagnosed with chronic HBV infection in Italy, 84% of treatment-eligible patients did not undergo therapy. Available treatment options for CHB include pegylated interferon alpha2a (PegIFN) and nucleos(t)ide analogues (NAs). PEG-IFN is a finite treatment that leads to HBsAg loss more often than NAs but is associated with side effects and the need for subcutaneous injections. NAs are potent inhibitors of HBV replication that lead to HBV viremia negativization in virtually all treated patients. Effective NA treatment is associated with the regression of fibrosis and no disease progression and a reduction in the risk of HCC after 5-6 years of treatment. Recent developments and the availability of innovative in vitro and in vivo preclinical models as well as sensitive molecular techniques have created new avenues to define new therapeutic targets. Several novel antivirals and immuno-modulatory compounds that silence cccDNA and/or reduce the size of the cccDNA pool for a functional cure with finite treatment duration have reached preclinical and/or early clinical evaluation.

Management of chronic HBV infection differs among countries as shown by both regional and national HBV guidelines. The availability and reimbursement of drugs by national healthcare systems and insurance vary based on policies that are mainly determined on a national level and affect treatment outcomes. Patents on Tenofovir (TDF) and Entecavir (ETV) have now expired and lower cost generics are available worldwide. Tenofovir alafenamide (TAF), a new form that
leads to high concentrations of intracellular tenofovir diphosphate and lower renal and bone toxicity than TDF, recently became available in Europe and the USA, and will remain on patent for another 10 years. Specific national programs must be developed to take into account country-specific healthcare policies. The availability of finite treatment will be important to enlarge access to treatment in middle-high income countries, as long as these options are not too expensive.

In low-middle income countries, the cost and availability of existing drugs, as well as the lack of infrastructures and limited medical personnel represent the major barriers to treatment. The feasibility of screen-and-treat programs were assessed in Gambia with an acceptability rate of 60%-80%, a link to care of 40%-80%57 and a cost of $645 per life-year saved.48 Despite the low cost of this comprehensive approach, large scale implementation is impossible for local governments in Gambia as well as in most low-income countries. Increased public awareness and establishing HBV as a health priority are needed to obtain a commitment from governments, communities and international funding agencies to increase access to the treatment and cure of HBV in Africa and other low-middle income regions.

3.4 | Funding limitations and need for the allocation of resources

HBV has attracted far fewer resources for clinical management and research than other chronic infectious diseases such as HIV, HCV or malaria.10 A recent report in the UK shows that HBV receives 0.7% of total expenditures compared to 3.0% for HCV, 13.9% for malaria and 17.5% for HIV.49 As mentioned, mortality from HBV is now higher than that of malaria while the latter receives nearly five times more funding. Hepatitis delta virus (HDV) which co-infects 20 million HBV carriers and results in more aggressive liver disease, receives nearly no resources.

4 | CONCLUSIONS

To meet the current challenges in patients with HBV, access to diagnosis and treatment is required on a global scale. This complex clinical and public health issue currently lacks the necessary multilateral commitment from pharmaceutical companies, governments, commissioners, funding agencies and the research community. The new WHO 2016 Global Health Sector Strategy on viral hepatitis targets testing and treatment and provides an important framework for this effort. Strong actions from advocacy groups, scientific societies and funding agencies should foster awareness and access to cure. Global initiatives by scientists for an HBV cure, such as the ICE-HBV group58 will play an important role.

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CONFLICTS OF INTEREST

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