Challenges in warranting access to prophylaxis and therapy for hepatitis B virus infection

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Abbreviations: ALT, alanine aminotransferase; AASLD, American Association for the Study of Liver Diseases ; CDC, Centers for Disease Control and Prevention; EASL, European Association for the Study of the Liver; HBcAg, hepatitis B core antigen; HBeAg, hepatitis B e antigen; HBIg, hepatitis B immunoglobulins; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; NA, nucleoside and nucleotide analogues; PWID, people who inject drugs; WHO, World Health Organization

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Abstract (max 250 words with 3-5 key words)

Despite an available vaccine and efficient treatment for hepatitis B virus (HBV) infections chronic HBV infection still remains a major global threat being one of the top 20 causes of human mortality.

One of the major challenges in controlling HBV infection is the high number of undiagnosed chronic carriers and the lack of access to prophylaxis and treatment in several parts of the world. We discuss relevant barriers that will need to be addressed thoroughly to reach global control of HBV infection and to finally make eradication possible. Most importantly vaccination will need to be scaled-up to lower the risk of vertical transmission and decrease the number of new infections and comprehensive screening programs with linkage to care will need to be installed to reach higher diagnosis and subsequent treatment levels. This, most likely, can only be reached if sustainable funding is available wherefore we emphasize the importance of making management of viral hepatitis a global health priority.

Keywords: Hepatitis B, screen-and-treat-programs, linkage to care, access to prophylaxis and treatment

Key point box

- Viral hepatitis and its consequences remain a global health burden and management of viral hepatitis should be made a global health priority.
- A major challenge is to warrant access to prophylaxis and treatment.
- Screening programs will allow priorization of vaccination and treatment especially in low-income countries.
- Specific strategies of care for special population groups, *e.g.* pregnant woman or patients undergoing immunosuppressive therapy, will help to further lower the burden in developed countries.
- Public awareness campaign will help to reach high-risk groups in high prevalence regions and will reduce stigmata in the general public but also in the health system in developed countries.

Main body (3000 – 3500 words)

Chronic hepatitis B virus (HBV) infections remain a major global health burden and are one of the top 20 causes of human mortality.[1] Together with HBV-related end stage liver disease HBV-related hepatocellular carcinoma (HCC) cause up to 1 million death per year and is responsible for up to 10% of cases of liver transplantation.[2] Worldwide more than 240 million people are chronically infected with HBV. Interestingly, there are tremendous regional variations and the prevalence of hepatitis B surface antigen (HBsAg) positive patients by country varies from low endemicity levels (<2%) to high levels (>8%).[3,4] The low prevalence in some countries emphasizes the potential of available anti-viral treatments and the vaccine, which exists since the 1980s. Importantly, implementation of universal infant HBV vaccination has been shown to reduce not only the incidence of HBV infections but also the incidence of HCC.[5,6] However, lack of accessibility of prophylaxis and also treatment options in low- and middle-income countries leads to the persisting high burden and sometimes actually increasing prevalence.[7] But even if it could be managed to increase the already good coverage and efficacy of vaccination to 100% by tomorrow, we still would face >50 years of caring for patients with already acquired HBV infection and subsequent consequences. Thus, better approaches in HBV treatment and management are urgently needed.

The course of HBV infections varies and ranges from an inactive carrier state to chronic hepatitis B potentially evolving cirrhosis and hepatocellular carcinoma (HCC),[8,9] whereas the persistence of viral replication and subsequent evolution to cirrhosis and HCC is directly linked to morbidity and mortality. Chronic hepatitis B patients may be hepatitis B e antigen (HBeAg)-positive or negative, whereas the prevalence of the latter form increases and represents in many countries the majority of cases.[10] Progression of chronic hepatitis B may be divided into the phases 'immune tolerant' or nowadays defined as "high replicative low inflammatory phase", 'immune reactive HBeAg-positive phase', 'low replicative inactive HBV carrier state', 'HBeAg-negative chronic hepatitis B' and 'HBsAg-negative phase', which are not necessarily being passed sequentially (for comprehensive review of the phases refer to European Association for the Study of the Liver (EASL) guidelines).[11] Not every patient who is HBsAg positive requires antiviral therapy (EASL / American

Association for the Study of Liver Diseases (AASLD) guidelines).[11,12] However, it is important that those who fulfill the criteria for treatment indication have access to treatment. The most recent recommendations for an optimal management are given in the above-mentioned guidelines. Currently available therapies for the management of chronic hepatitis B include alpha interferons and nucleoside and nucleotide analogues (NA). Treatment with interferon alpha is a finite treatment option and achieves more often immune control of HBV infection compared with NA but side effects and subcutaneous injections are a barrier for this therapy.[11] NA are potent inhibitors of replication and after five to six years of treatment in almost all patients HBV DNA levels are below the limit of detection. Also, effective NA treatment is associated with fibrosis regression and reduction of HCC.[13] However, the ultimate goal, HBsAg clearance which is the surrogate for clinical cure is a rare event and thus demanding life-long treatment in most patients.[14] Importantly, NA therapy is safe also after long-term application, thus, side effects do not hinder a wide usage.[15] However, the drugs are not widely accessible and used in low- or middle-income countries hindering a timely intervention that is crucial to prevent the onset of advanced liver disease or reactivation and reduce the risk of mother to child transmission. Even in high-income countries, *e.g.* the US, many patients who are eligible for antiviral treatment do not receive therapy due to several barriers in the health care system.[16]

To globally control or even eliminate HBV infection several public health interventions will be needed. With the global vaccination campaign, especially for infants, a large decrease in new infections is already reached. However, 63 million new cases of chronic infections are predicted between 2015 and 2030 without scaling-up the vaccination coverage.[17] In addition, ambitious population-wide testing will be needed to allow treatment of carriers and prevention measures for their contacts or people at risk.[18] Currently, worldwide only an estimated 10% of chronically infected people are diagnosed and in fact only 1% adequately treated (Figure 1). In Europe, there are no common guidelines for HBV screening but some national guidelines, *e.g.* in Germany, included recommendations for diagnosis of risk groups.[19] Also, the Centers for Disease Control and Prevention (CDC) published screening recommendations that include *e.g.* individuals born in high prevalence areas, those infected with

hepatitis C (HCV) or Human Immunodeficiency Virus (HIV), pregnant woman or candidates for blood / tissue / organ donation.[20] Nevertheless, even though the general content of the available national policies are similar, there are also differences.[21] Thus, an international consensus reflected in a guideline will foster wide implementation of appropriate HBV screening.

In the following paragraphs we will discuss important steps for improving access to vaccination and treatment, focusing on high-prevalence regions in low- to middle-income countries with the main challenge of cost constraints and low-prevalence regions in middle- to high-income countries with also not easy to overcome challenges as low screening rates, missing public awareness, social stigma and discrimination and more recent problems due to the refugee crisis in Europe. Finally, we also elaborate on special cases of HBV management, namely in pregnant woman and their infants and in patients undergoing immunosuppressive therapy.

Access to vaccination and treatment in high-prevalence regions

As mentioned above liver cancer is a leading cause of cancer death and high-prevalent regions, mostly developing countries, are even disproportionally affected.[4] Facing an increase in the incidence of HCC mostly due to chronic viral hepatitis infections, warranted access to vaccination and treatment in those regions is of utmost importance. However, in low- and middle-income countries costs and allocation of resources remain a major challenge. Recently, WHO has released a guideline for the prevention, care and treatment of chronic HBV infections targeting especially low- and middle-income countries, *e.g.* alternative diagnostic tests, which are more readily available and associated with lower costs, are considered in the guideline due to their feasibility of use in those countries.[22] This guideline may assist in developing national policies and country-specific guidelines to scale-up hepatitis B prevention, care and treatment.

The first step improving access to therapy is to scale-up screening. Identification of high replicative asymptomatic people with HBV infection and implementing prevention measures is likely to reduce the disease burden. For example, it would be crucial to identify HBsAg positive mothers and ideally know about the viral load or at least HBeAg, which is a major determinant of perinatal HBV transmission, the main source of HBV infections in high prevalence regions. In countries with limited

resources, this could lead to an at least prioritized implementation of World Health Organization's (WHO) prevention recommendations for all infants to receive at least the first dose of hepatitis B vaccine within 24 hours of birth.[23] Ideally, infants also receive passive immunization with hepatitis B immunoglobulins (HBIg) and mothers with high viral load receive antiviral therapy to prevent vertical transmission as discussed below (EASL guidelines).[11] Unfortunately, this is hampered by many factors as available infrastructure, associated high costs for diagnostics and subsequent treatment or poor public awareness. However, a recent study in a sub-Saharan African setting showed that large-scale screen-and-treat programs for HBV infections are feasible with an acceptability rate of 60-80% and a linkage to care of 40-80%.[24] A parallel study assessed the cost-effectiveness and reported cost of about $511 per quality-adjusted life-year and $645 per life-year saved.[25] Even though this seems not to be much it is comparable with the annual income per capita in the region surveyed. And as the local governments do not support health-care costs through insurance systems most people won't be able to afford the costs. Thus, without having public awareness for chronic hepatitis B and considering it as health priority to make community financial support available such screen-and-treat-programs are unlikely to be successful.

Besides the importance of screening and linkage to care, ensuring safety of blood and blood products is crucial. WHO notes that the safety of blood products is positively correlated with the economic status of the country resulting in a higher risk of iatrogenic transmission of HBV for patients in low-income countries. This calls for better and also in resource-poor settings affordable assays to lowering the risk of transmitting infection from donors. In addition, preventing in-hospital infection of both healthcare workers and patients is important. Here, securing the vaccination of all healthcare workers, the installation of all necessary preventive measures and an increment in awareness are critical.

Access to vaccination and treatment in intermediate to low prevalence regions using the example of Europe

In Europe, health-care strategies as well as cost and reimbursement issues vary among countries as the policies are being determined at national level. Resulting differences in the management of chronic HBV infections may be reflected in country-

specific monitoring patterns or hospitalization rates.[26] Looking at the prevalence, Europe can generally being considered as low to intermediate. However, there are regional differences and the prevalence increases eastwards and in many southern European countries the burden of HBV-related chronic liver diseases increases as the unvaccinated population comes to age.[3] In addition, recent economic constraints influences public health spending and thereby impact sustainable invest in HBV management.[27] Thus, the public health potential of HBV management is still not fully accomplished and to achieve a relevant reduction in HBV-related liver disease in Europe, specific national programs that take into account the country-specific health-care policy will need to be installed.

While such programs and considerations will affect the more general population some specific population or patient groups at particular risk of chronic HBV infection will not being reached. These specifically vulnerable population groups include undocumented migrants, asylum seekers or refugees, people without health insurance, people who inject drugs (PWID) or abuse alcohol and persons in detention centers or jails. Not even that the prevalence in those population groups is higher than in the general reference population, also limited access to treatment was reported.[28,29] Facing the current challenge in Europe with high numbers of refugees entering, it is essential to assess the prevalence also in those population groups and to adapt the control strategies accordingly. For example, in Germany the prevalence of HBsAg in refugees is much higher with around 2-3% compared to the German population with 0.3%, but the treatment of chronic diseases are only covered by social welfare if there is a life threat.[29] Here it is important to note that infections do not respect borders or population groups and transmission of HBV is not restricted within the immigrant population but will spread horizontally, creating new HBV transmission dynamics throughout Europe. Thus, factual lack of vaccination uniformity, as until recently, several European countries with lower HBV prevalence rates (*e.g.* UK, Denmark, Norway, Sweden) have not implemented routine HBV vaccination, together with high levels of immigration within Europe may lead to the spread of HBV from country to country.

Besides the described threat by the current refugee crisis and the existing barriers for preventive measures, the access to treatment for the general population is also

demanding. Barriers that limit access to treatment in many Western or European countries are the lack of awareness and understanding combined with the social stigma and discrimination. But also declining resources and thus fiscal constraints hamper an adequately HBV management. Thus, due to the misperception in the primary care setting that elevated alanine aminotransferase (ALT) levels are mainly associated with alcohol abuse and screening for viral hepatitis is not performed frequently.[30] On the other hand, primary care physicians may not screen for viral hepatitis if liver enzymes are not elevated. However, a big proportion of patients with chronic HBV infection have normal ALT levels.[31] Due to these circumstances the majority of patients with chronic HBV infection are undiagnosed. A recent screening study from Germany in more than 20,000 patients who attended primary care physicians showed an HBsAg prevalence of 0.52% but 85% of infections were unknown before.[31] Consequently, it will be important to increase awareness about risk scenarios in the primary care setting. However, prejudices about above-mentioned vulnerable groups (PWID, prisoners, immigrants) are immense barriers requiring specific education to increase participation in screening and early diagnosis programs.

Finally, also the step from diagnosis to care is suboptimal and many patients, even though diagnosed and eligible for treatment, are not treated according to the available guidelines.[30] The main barrier here is the lack of evidence-based knowledge of HBV hindering an informed management of patients.[27] Thus, an increase in knowledge and awareness – both on patient and physician side – is essentially needed to reach higher redirection rates to the specialists, subsequent higher implementation of antiviral treatments and thus, better care of the patients.

Access to treatment in special populations: pregnant woman

HBV infection during pregnancy requires special management for an optimal outcome for both, the mother and the fetus. This is particularly important, as it is known that in high prevalence regions most people acquire infection as infants through vertical transmission, which actually is the route with the highest rate of chronicity. To prevent vertical transmission, the infants should be vaccinated within the first 24 hours after birth and ideally receive additional HBIg.[20,32] However, HBIg may not be available everywhere and although the vaccine has a good global

coverage > 80% it is sometimes ineffective in infants born from mothers with very high viral loads. It has been shown that vaccine failure and no access to HBIg are the main problems preventing eradication of HCC.[33]

In addition to active and passive vaccination vertical transmission might be reduced by consequently lowering the viral load of pregnant women. Antiviral therapy with NA treatment of mothers with HBV DNA >200,000 IU/mL could significantly reduce chance of transmission when combined with immunoglobulin prophylaxis and vaccination.[34,35] Thus, the optimal scenario would be a screening of the mother in the first trimester and subsequent treatment starting at gestation weeks 28-32 if HBV DNA is higher than 200,000 IU/mL. However, in low-income countries screening of pregnant woman and thus also the subsequent treatment of newborns is rare.[36] Here, a better understanding of the HBV epidemiology will help to prioritized implementation of prevention measures as discussed above. However, even in high-income countries, access to treatment is challenging. For example, in Germany mothers are screened in gestation week 32. This is far too late to transfer an HBsAg positive mother to the specialist who decides if antiviral treatment is recommended.

Access to treatment in special populations: patients undergoing immunosuppressive therapy

Patients positive for HBsAg irrespective of HBV DNA replication undergoing immunosuppressive therapy are at high risk for HBV reactivation and subsequent liver failure and death.[11] Importantly, prevention of HBV reactivation with prophylactic antiviral therapy is highly effective. Thus, current guidelines recommend screening all persons undergoing immunosuppressive treatment to identify patients being at elevated risk for HBV reactivation.[37] Persons who are negative for HBsAg but positive for hepatitis B core antigen (HBcAg) still have a up to 10% risk for HBV reactivation if treated with the CD20 antibody rituximab.[38] Thus, for this group of patients we would expect the highest rate of screening. However, the rates of screening among rituximab-treated patients as well as underutilization of antiviral prophylaxis are low, even among gastroenterologists.[39-41] Thus, efforts to improve the screening and treatment rates are urgently needed as the mortality due to HBV reactivation is a preventable outcome.

Conclusion

Despite the fact that chronic HBV can be prevented and controlled, there are still many people worldwide newly infected and suffering or even dying from the infection. In this review, we discuss measures to improve access to care (summarized in Table 1 and

Table 2). However, to address the mentioned barriers sustainable funding is crucial, wherefore management of viral hepatitis should become a global health priority. Given that, the suggested measures are likely to help further approaching the ultimate aim to globally eradicate HBV.

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Tables

Table 1 Measures to improve access to care for HBV patients in low- to middle-income countries with high prevalence

Challenge	Measure to improve access to care
Lack of knowledge and awareness	Education of the public
	Improve communication especially to reach high risk groups
Safety of blood	Implement policies on safety of blood and blood products
	Support development of easy-to-use and low-cost assays
Limited screening and linkage to care	Foster implementation of national policies on HBV screening
	Diagnostic assays which are more readily available at lower costs
	Point of care screening
Lack of vaccination	Scaling-up vaccination coverage
	HBeAg testing in mothers to prioritize active (and ideally also passive) immunization of the newborn
	Prioritized vaccination of high risk groups and healthcare workers
Limited treatment	Lower cost constraints by developing insurance systems supported by local governments
	Increase accessibility of drugs by innovative cost models

Table 2 Measures to improve access to care for HBV patients in middle- to high-income countries with access to prophylaxis and treatment

Challenge	Measure to improve access to care
Lack of knowledge and awareness	Support studies to increase evidence-based knowledge to create an appreciation of the impact of the disease
	Increase awareness among physicians who treat with immunosuppressive drugs to improve screening and prevent reactivation
Limited screening and linkage to care	International policy on appropriate HBV screening
	Screening of risk groups (according to guidelines) incl. vulnerable populations to increase treatment uptake
	Screening of pregnant woman before gestation week 32 to guarantee antiviral therapy if HBV DNA > 200,000 IU/mL
	Screening of immigrants from high prevalence regions
Lack of vaccination	Implementation of universal infant vaccination in all countries
	Consequent vaccination of risk groups to avoid horizontal transmission
Limited treatment	Increase awareness among patients
	Better training of physicians to optimally treat based on the available guidelines
	Simplify and ensure reimbursements for treatment
Social stigma and discrimination	Increase knowledge in the general population and among physicians

Figure legends

Figure 1 Diagnosis and Treatment of Hepatitis B. Worldwide about 2000 million people are infected with HBV and more than 240 million of them suffer from a chronic infection. Currently, only an estimated 10% of those are actually diagnosed and only 1% finally treated.