

The hepatitis B epidemic and the urgent need for cure preparedness

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More than 250 million people worldwide are chronically infected with the hepatitis B virus (HBV). In this Comment, members of the International Coalition to Eliminate HBV appraise the current policy environment and the need for appropriate cure research and preparedness to complement the WHO global elimination strategy, the HBV vaccine and the well-tolerated but poorly accessed therapy.

In 2016, the estimated global prevalence of the hepatitis B virus (HBV) surface antigen (HBsAg) was 3.9% (95% uncertainty interval (UI) 3.4–4.6), corresponding to 292 million (95% UI 251–341) infections¹. With the adoption of the WHO Global Health Sector Strategy on Viral Hepatitis in 2016, countries were galvanized to eliminate HBV as a public health threat². However, an estimated 90% of people living with chronic hepatitis B (CHB) remain undiagnosed, and only 5% of those eligible receive treatment¹. These are the ‘missing millions’ to be found, according to the 2018 World Hepatitis Day theme.

Although HBV infection early in life typically remains asymptomatic, CHB confers substantial risk for hepatocellular carcinoma³, even in the absence of advanced liver disease⁴. CHB is associated with up to 40% mortality within 10–25 years⁵ and the WHO estimated 880,000 HBV-related deaths in 2015 (REF.⁴). Although a safe and effective vaccine has been available for >30 years, **only 46% of all infants receive timely birth-dose vaccination** — and only 3% in low-income countries². Antiviral treatments for HBV, which can reverse liver fibrosis and reduce liver cancer rates, have been available for >20 years but reach only a minority of those eligible⁴.

Addressing the HBV epidemic to meet WHO elimination targets² requires that the scientific community and policymakers, along with other stakeholders such as affected communities, progress from a ‘control paradigm’ to a ‘cure paradigm’ for CHB.

Policy advances

International policy responses to address HBV elimination in the past few years have been encouraging, and although the Sustainable Development Goals’ (SDGs) call on the global community to “...combat hepatitis”⁶ is neither specific nor ambitious, a 2017 analysis of resource needs for achieving the SDGs in low-income and middle-income countries specifically mentions

reducing HBV incidence through investments to expand vaccine coverage⁷. Notably, the WHO viral hepatitis strategy sets HBV targets that are more ambitious than those for hepatitis C virus (HCV), including prevention of mother-to-child transmission, extensive vaccination coverage and greater treatment uptake (Supplementary Table 1). The currently required long-term HBV treatment raises issues of medication adherence and requires considerable investment for ongoing monitoring, adding to the challenges of achieving the elimination targets.

A true global elimination strategy should ‘eliminate’ (that is, cure) the virus in those who are chronically infected. However, the cure aspect is often overlooked. Even if vaccine coverage were radically expanded to prevent all new infections from this point on, it is difficult to imagine HBV elimination without offering a cure for existing infection. New discoveries and technological advances⁸ give reason for optimism within the scientific community about the possibility of an HBV cure. Achieving this therapeutic breakthrough will require new research investments, increased scientific collaboration, policy commitment and community engagement. Next, the challenge will be to deliver with equity^{2,6} these new technological advances to the populations most affected by CHB, as they reside in areas that lack universal health coverage and require strengthening of health systems⁶. With these considerations in mind, it will become important to set up intellectual property systems for current and future HBV treatment combinations and ensure that these are included in the Unitaid mandate, which identifies new funding mechanisms and partnerships for other health issues.

Cure preparedness

Considering the questionable sustainability of rolling out indefinite antiviral treatment and monitoring for people living with CHB, investments in cure could

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markedly lower both the disease burden and costs of care⁹. Firstly, however, access to existing treatments must be scaled up urgently to save as many lives as possible while cure research is ongoing. This process will also link people living with CHB to care and help ensure they are 'in care' when cure becomes possible, which will be a profound enabler of early uptake. The WHO target to increase the number of people treated with current therapies for CHB from ~1.5 million to 5 million by 2020, with 80% of treatment eligible patients being treated by 2030 (REF²), will go a long way to meeting this need.

A global strategy encompassing a public health approach that links people to care is critical to disrupt the current situation of underdiagnosis and low treatment access⁸. Obtaining high-quality epidemiological data relying on robust surveillance systems is key. Healthy and holistic policy formulation requires data exploring the life-altering benefits of cure over and above medical benefits. These data should include the effect of cure at every socioeconomic level and its potential to reduce the marginalization of people living with CHB. Importantly, preparedness requires scientific understanding and communication to communities about to what extent a 'cure' can be achieved (partial, functional or complete; for definitions see Supplementary Table 2). Not least, preparedness will require product registration and pharmacovigilance at regional levels for adequate follow-up of adverse events and long-term clinical outcomes in different patient groups. The growing interest of the Medicines Patent Pool in the HBV field is encouraging and hopefully this will translate into earlier, more equitable access to an HBV cure globally.

Curing is more than having a cure

Previous ethical analyses of HBV cure research suggest the need to remain cognizant of the risks of intervention and communicating these risks and benefits, outcome measures, monitoring and modelling, selection of study populations, language, informed consent and fairness¹⁰. Given the complexity associated with HBV cure, the social, political and economic ethical implications of

cure must be at the forefront of policy discussions as well as the expectations of what cure means.

The concepts associated with cure must be consciously and deliberately used by key stakeholders. The differing biomedical outcomes associated with different cure endpoints might be understood by the scientific community but there is potential for misconceptions in the broader community, including people living with CHB. Discrepancies in how different stakeholders make use of the concept of cure, with subsequent effects for consent, fairness, access and engagement around potential cure, must be recognized.

Conclusion

With a large proportion of people living with CHB unaware of their status, the critical question is how cure availability will benefit these individuals. It is an ethical imperative that we rapidly scale-up diagnosis and treatment of these 'missing millions' and build the universal health systems to engage them to provide equitable access to cure therapies once they become available. Lessons from access to and distribution of HIV and HCV treatments highlight the necessity of collaborative partnerships on a global scale, as well as the need to involve both public and private sectors. To achieve the WHO targets to eliminate HBV as a public health threat by 2030, we should aim for cure and not stop once we discover it — because then the greater challenge, delivering HBV cure to all who need it, will begin.

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Competing interests

The authors declare no competing interests.

Supplementary information

Supplementary information is available for this paper at <https://doi.org/10.1038/s41575-018-0041-6>.

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