

# Advancing the regulatory path on hepatitis B virus treatment and curative research: a stakeholders consultation

Jonathan Liu<sup>1,2</sup>, Pedro Goicochea<sup>1</sup>, Timothy Block<sup>3</sup>, Carol L Brosgart<sup>4</sup>, Eric F Donaldson<sup>9</sup>, Oliver Lenz<sup>5</sup>, Seng Gee Lim<sup>6</sup>, Ed G Marins<sup>7</sup>, Poonam Mishra<sup>9</sup>, Marion G Peters<sup>8</sup> and Veronica Miller<sup>1\*</sup>

<sup>1</sup> Forum for Collaborative Research, Washington DC, USA

<sup>2</sup> University of California, Berkeley School of Public Health, Division of Infectious Diseases and Vaccinology, California, USA

<sup>3</sup> Hepatitis B Foundation, Philadelphia, USA

<sup>4</sup> University of California, San Francisco, California, USA

<sup>5</sup> Janssen Research and Development, Beerse, Belgium

<sup>6</sup> National University of Singapore, Singapore

<sup>7</sup> Roche Molecular Systems, California, USA

<sup>8</sup> University of California San Francisco, California, USA

<sup>9</sup> US Food and Drug Administration, Silver Spring, Maryland USA

## Abstract

Hepatitis B infection remains a significant disease burden around the world, with an estimated two billion individuals infected and 350 million living with chronic hepatitis B. Current antivirals are efficacious, but require lifelong treatment for the majority of infected individuals. The field is galvanised to improve diagnostics and treatment with the goal to develop shorter, finite treatments leading to viral control after treatment discontinuation. Achievement of complete and functional cure is challenged by the complexity of the virus life cycle, the lack of adequate preclinical models, the cccDNA-mediated persistence of HBV in liver cells, the lack of validated biomarkers to predict viral control and cure, and the probable need for combination treatment involving antiviral- and immune-based strategies. Experts from diverse stakeholder groups participating in the HBV Forum (a project of the Forum for Collaborative Research) contributed their expertise and perspective to resolving issues and overcoming barriers in the regulatory path for novel HBV therapeutic strategies; addressing gaps in preclinical models, diagnostics, clinical trial design, biomarkers and endpoints, and public health efforts. Interviewees highlighted the need for open and collaborative ongoing dialogues among stakeholders in a neutral space as a critical process to move the field forwards. The Forum model facilitates dialogue and deliberation of this nature, with dedicated experts from all stakeholder groups participating. The promise of an HBV cure is exciting. Now is the time to work together toward that goal.

## Introduction

Hepatitis B virus (HBV) infection continues to be a prevalent epidemic in many parts of the world, with an estimated two billion people worldwide having been infected. HBV prevalence is estimated in 240 million people worldwide. More than 350 million have chronic, lifelong infections (CHB) and nearly 700,000 people die every year due to complications of CHB [1–5]. HBV infects the liver and is a major cause of acute and chronic hepatitis, cirrhosis, endstage liver disease, hepatocellular carcinoma (HCC), liver transplantation and death. Preventive vaccines and effective treatments are available; however, treatment is lifelong for the majority of chronically infected individuals. The HBV community is energised to capitalise on the momentum generated from the development of curative HCV regimens to explore new HBV therapeutic and curative strategies.

This paper is based on informed interviews with stakeholders of the HBV Forum, a project of the Forum for Collaborative Research [6,7] aimed to address the challenges and advance the regulatory science for HBV diagnostics and therapeutics.

## Methods

Between July 2015 and January 2016, JL and PG conducted interviews with experts representing different constituencies: academia and research, pharmaceutical and diagnostic companies, regulatory agencies and advocacy groups. Interviewees were purposely selected to provide a broad range of expert views on the major challenges faced in the search for innovative HBV therapeutic strategies.

Our semi-structured questionnaire included topics on preclinical models, diagnostic and treatment tools, definition of clinical endpoints (including HBV cure), biomarkers and clinical development of novel HBV drugs and diagnostics (including trial design and regulatory guidance). Questions addressed gaps in knowledge in HBV research, unmet medical needs, challenges in the regulatory pathway for new HBV therapies and the status of HBV-related public health efforts.

Participants were granted anonymity and are only identified by their stakeholder group. Interviewee quotations are denoted by the symbol (⚡ + group) as superscripts indicating to which group the quote belongs: AR: academic/researcher; PDC: pharma/diagnostic company; ADV: patient advocate; REG: regulator.

## Results

Expert input was obtained from 28 stakeholders. Table 1 describes the distribution of the interviews by group.

### Improved models to study HBV

Although the toolbox of HBV cell culture and animal models has grown substantially over the last years, many aspects of HBV disease remain poorly understood. It is incumbent upon the field to characterise drug candidates as much as possible before entering clinical trials; a better understanding of the strengths and limitations of current tools is important to achieve this goal. Improved models will help to find and characterise better drugs.

Cell culture models are useful for examining the viral replication cycle and gaining preliminary information on new drug products, but they do have limitations (Table 2). Antiviral activity in cell culture supports a reasonable chance of clinical antiviral efficacy and allows detection of potential synergy. Improving access to resources, such as cell culture models, may give more parties the

\*Corresponding author: Veronica Miller, Forum for Collaborative Research, 1608 Rhode Island Ave NW, Washington, DC 20036, USA  
Email: veronicam@berkeley.edu

**Table 1.** Distribution of interviewees by stakeholder group

Stakeholder group	n
Academics/researchers	9
Patient advocates	3
Pharmaceutical/diagnostic companies representatives	10
Regulatory/policy organisation representatives	6
N	28

**Table 2.** Limitations of current cell models**Limitations of cell models**

- Human hepatocyte models require access to fresh human liver resections, which have varying quality of individual preparations [9]
- Do not provide an opportunity to observe an immune response [9]
- Mostly reside in academic-medical centers, due to their sophisticated nature, and often are not available to small commercial labs

opportunity to engage in research, reducing the financial burden that many companies face when establishing robust virology programmes thereby removing some barriers to drug development<sup>(βPDC)</sup>.

Animal models also have their limitations (see Table 3). An improved animal model recapitulating the entire HBV life cycle with similar immune responses to humans would enable researchers to make new discoveries to advance HBV therapeutic strategy

**Table 3.** Limitations of current animal models

Animal model	Limitation(s)
Chimpanzee	<ul style="list-style-type: none"> <li>• No longer available for experimental studies after being placed on the US Fish and Wildlife Services' Endangered Species list in 2015 [9]</li> <li>• (Considered to be the best model)</li> </ul>
Woodchuck	<ul style="list-style-type: none"> <li>• Expensive</li> <li>• Limited number of available animals</li> <li>• Different mechanisms of cancer development than in humans [47]</li> </ul>
Mouse	<ul style="list-style-type: none"> <li>• Not naturally susceptible to HBV infection, but can be humanised to study HBV infection.</li> <li>• Limited utility due to the absence of a complete functional immune system and human liver microenvironment</li> </ul>
Other animal models include the duck and the squirrel	

**Table 4.** Summary of the opinions on the approval of quantitative HBsAg assay in the US

Support for the approval of quantitative HBsAg assay	Opinions on why the quantitative HBsAg is not approved
<ul style="list-style-type: none"> <li>• Quantitative HBsAg is already being used to define clinical benefits and drug treatment effects in the different HBV drug trials being conducted<sup>(βAR)</sup></li> <li>• Provides the ability to monitor what is happening in a patient's body while on treatment in a dynamic fashion<sup>(βAR)</sup></li> <li>• Allows clinicians and researchers to better determine the phases of HBV infection<sup>(βPDC)</sup></li> <li>• Provides valuable information about the virus once HBV DNA levels drop below the diagnostic test's limit of detection and viral replication is inhibited by antiviral treatments<sup>(βPDC)</sup></li> <li>• Can help make decisions regarding whether to stop or continue therapy<sup>(βAR)</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Lack of sufficient good clinical utility data concerning the use of the assay in a clinical environment<sup>(βPDC)</sup></li> <li>• The assay does not take into consideration the complexity of the hepatitis B virus' life cycle and the natural history of HBV infection<sup>(βAR)</sup></li> <li>• Other HBV assays such as quantitative HBV DNA and qualitative HBsAg provide similarly useful information on a patient's progress on antiviral treatment as the quantitative HBsAg assay<sup>(βPDC)</sup></li> <li>• The assay is not required for defining cure, but does have prognostic value for complications, progression of disease, and response to treatment<sup>(βAR)</sup></li> <li>• Assay is not useful because few patients actually clear HBsAg at the end of treatment<sup>(βAR)</sup></li> </ul>

research<sup>(βAR)</sup>. An upgraded model would generate pharmacological data to support the microbiology package for new, potentially curative treatments<sup>(βPDC)</sup>.

**Better diagnostic tools**

The detection of serum hepatitis B surface antigen (HBsAg) and antibodies to hepatitis B core antigens (anti-HBc) typically serve for diagnosing HBV infection. Other tests include hepatitis B envelope antigen (HBeAg), HBV DNA, HBcAg and HBV core-related antigen (HBcrAg) [8,9]. The presence of HBsAg antibodies (anti-HBs) signifies either recovery from HBV infection or immunisation. Anti-HBc provides evidence of current or past infection and can indicate ongoing HBV infection in the apparent absence of HBsAg (occult HBV infection) [10]. The US Food and Drug Administration (FDA) -approved and US Clinical Laboratory Improvements Amendments (CLIA) -compliant diagnostic tools to measure these markers are all similarly sensitive across the different manufacturers and usually perform adequately in a diagnostic setting<sup>(βAR,βPDC)</sup>. However, these tools will need improvement to be quantitative; distinguish serotypes and genotypes; better characterise the natural history and phases of chronic HBV infection in patients on treatment; better detect any possible new markers for new therapies; and be more able to serve the needs of researchers developing curative strategies<sup>(βAR)</sup>.

Quantitative HBsAg diagnostic assays, available for clinical use in many countries but restricted to research purposes in the US, could play an important role in therapeutic research [11]. Whether FDA approval would provide significant advantages is being debated<sup>(βREG)</sup> (Table 4); it would require interested parties to collaborate across clinical trials and dedicate resources to generate the required data.

### Limitations of current treatment options

Approved therapeutic options include standard or pegylated interferon-alpha and five oral nucleos(t)ide analogs (NUCs). The most recent, tenofovir alafenamide (TAF), was approved by the FDA in late 2016 [12].

Interferon and pegylated-interferon, parenteral agents prescribed for a finite duration, are associated with substantial toxicity. Only 3–7% of patients achieve HBsAg seroconversion following a 48-week pegylated-interferon-alpha based regimen [13–15]. Given the safety and tolerability issues and the low HBsAg clearance rates, an interferon-based regimen is an unlikely cornerstone of HBV cure research<sup>(BAR)</sup>.

On the other hand, NUCs suppress viral replication efficiently, are well tolerated, have minimal side effects, and drug resistance has not been of major concern<sup>(BAR)</sup>. However, lifetime therapy is needed in the majority of patients. Only 1% of NUC-treated patients per year achieve HBsAg loss during treatment [16,17]. HBV persistence, even in the face of long-term suppression of viral replication, is driven by the stable covalently closed circular viral DNA (cccDNA) in hepatocyte nuclei, the major source of all viral-specified gene products and a requirement for the formation of infectious viral particles. cccDNA is not inhibited by current NUCs, thus allowing HBV to persist in the liver despite documented viral suppression in plasma [18].

The risk of developing HCC remains in NUC-treated patients with virological control (albeit substantially reduced). HCC risk in CHB patients with maintained virological response remained higher than in those who presented as inactive carriers [19–21], indicating that viral control may not confer the same benefit as host immune control of HBV [22].

The robustness of current licensed drugs to control HBV replication, with little additional benefit observed in combination therapy trials, and low HBsAg clearance rates, have provided little incentive for developing novel therapeutic approaches [23] to overcome the disadvantages of lifelong therapy – inconvenience, drug-related complications and potential drug resistance. Patients may not understand the need to take a daily pill to manage their disease without curing it, all the while feeling ‘well’<sup>(BPA)</sup>. The significant burden of disease in early adulthood [24] (childbearing years) and reluctance to take medication during pregnancy is another potential reason for non-compliance<sup>(BAR, BPA)</sup>. Inconsistent adherence could contribute to drug resistance or flares in underlying disease, especially in patients with advanced fibrosis or cirrhosis. Evidence on the long-term toxicity of NUC therapies is lacking but some anticipate the emergence of safety signals as more people are treated<sup>(BAR, BREG)</sup>.

Cost, both domestic and global, is another barrier for consistent access to treatments<sup>(BPA, BREG)</sup>. A curative therapy with similar or better safety profile, finite in duration and more effective at achieving HBsAg clearance and maintenance of viral suppression off therapy, would ameliorate these concerns.

### The benefit–risk profile for new treatments

A favorable benefit–risk profile is the cornerstone of both regulatory approval and the clinical use of a new regimen(s). Benefit–risk is not static, rather, it is dependent on the severity of disease and the efficacy, safety and tolerability profiles of available treatment options. Exposing patients to potentially risky interventions for a disease, for which safe and effective treatment is available, requires careful consideration and ethical review. Input from diverse patient communities is crucial. Attitudes towards (and acceptance of) risk may change: younger people might be more

receptive to trying new, possibly riskier, therapies with the potential for cure<sup>(BAR)</sup>. Older patients, aware of their disease status and HCC risk and accustomed to taking daily pills, may prefer to remain on existing treatments<sup>(BAR)</sup>.

### Defining cure

HBV cure is being discussed at different levels, depending on the degree of viral control and/or eradication, such as complete cure (eradication of cccDNA) and functional cure (HBsAg clearance and cessation of liver disease) [25,26]. The former is more challenging and many experts believe not achievable with currently available drugs<sup>(BAR)</sup>, which do not target intracellular cccDNA. Reductions in cccDNA are likely to correlate with turnover of infected hepatocytes. The latter, controlling virus while off treatment without eliminating cccDNA, may be more realistic but immune suppression later in life may reactivate HBV<sup>(BAR)</sup>. A functional cure, with long-term clinical benefits similar to that achieved in natural infection of adults who suppress HBV DNA, lose HBsAg and acquire HBsAb [27], may well be achieved on the way to discovering a complete cure.

The above definitions are suitable for setting goals and generating commitment from sponsors and funders, but for drug development and regulatory purposes, ‘cure’ needs to be operationalised in the context of registrational clinical trials, that is, it needs to be measurable in a reliable and consistent manner within a reasonable time frame. This requires identification of biomarkers (and changes in biomarker levels) that predict sustained control of viral replication [11] and correlate with the clinical outcome of cure [28].

### Biomarkers and endpoints

Biomarker validation and acceptance for drug development is resource intensive, ideally suited to collaboration across diagnostics, pharmaceutical, academic and regulatory sectors. HBV DNA, HBsAg, HBeAg and HBcAg or their respective antibodies have been primarily used as biomarkers for viral detection, with HBV DNA suppression considered an important endpoint<sup>(BREG)</sup> [9], although, low fluctuating levels have been reported in some patients [13]. Improving the sensitivity of the current HBV DNA assays to measure low levels of HBV DNA could be important for determining when to discontinue treatment<sup>(BPOC)</sup>. HBsAg sero-clearance is associated with a better clinical prognosis and a reduced risk of HCC [29], thus, HBsAg clearance (achieved in a minority of patients, see above) could be the basis for treatment discontinuation. The benefit of HBsAg reduction without sero-clearance remains uncertain. Development of HBsAb in the following months, if not years, after HBsAg loss, is not a 100% surrogate marker of cure<sup>(BAR)</sup>.

Assessment of HBeAg sero-clearance in eAg-positive patients, an important step towards functional cure, is not sufficient on its own. The role of quantitative HBeAg assessments as a marker for subsequent HBeAg loss or even functional cure remains to be assessed [9,30].

Other potential new biomarkers include HBV RNA and HBcrAg. HBV RNA levels strongly correlate with HBV DNA levels in untreated patients. Furthermore, a decline in serum HBV RNA levels while on NUC therapy was reported to be a strong predictor of subsequent HBsAg seroconversion [31]. Early studies have shown serum HBcrAg levels correlate with serum HBV DNA, intrahepatic HBV DNA and cccDNA levels, and disease activity [31]. HBcrAg levels have also been strongly associated with the development of HCC and proposed as a marker of HBV reinfection after liver transplantation [31]. A biomarker that predicts which patients will develop cirrhosis or HCC would be valuable<sup>(BAR, BREG)</sup>.

Additional biomarkers will need to be included in trials investigating immune-based interventions.

Intracellular and intrahepatic cccDNA elimination would ensure no relapse of infection after treatment completion. As such, it is an attractive target; however, accessing it remains a problem<sup>(BAR,PREG)</sup>. There is no standardised assay readily available to measure it<sup>(BAR)</sup>, and discriminating between cccDNA and other forms of HBV DNA is technically challenging. Liver biopsy, the only option to measure cccDNA levels, is limited by sampling error, its invasive nature, associated hazards, and patients' reluctance to undergo multiple biopsies<sup>(PREG)</sup>. However, liver biopsies are routinely performed for non-alcoholic steatohepatitis (NASH) studies, thus may potentially be used for small proof-of-concept studies to demonstrate the kinetics of cccDNA decline. Discovering a plasma marker that predicts cccDNA levels as well as other non-invasive methods to monitor cccDNA is an area for future development. Once cccDNA can be measured less invasively, larger studies to determine the amount of cccDNA loss necessary to predict cure become relevant<sup>(PREG)</sup>.

### Drug trial design

Consensus is needed among drug developers and regulatory agencies on primary endpoints demonstrating drug efficacy relevant for HBV cure<sup>(PREG,PREG)</sup> as well as selecting the appropriate patient population for the intervention being studied<sup>(BAR,PREG)</sup>. Consistency, or lack thereof, across the different regulatory agencies around the world can be a challenge. Drug developers support some level of harmonisation of the requirements for drug approval<sup>(PREG)</sup>, although, with continually increasing knowledge and technology, relevant stakeholders will need to discuss and agree upon what is required to demonstrate success for therapies with novel mechanisms of action including therapies such as RNAi therapy or CRISPR/Cas9 technology. An alignment on the regulatory requirement for different novel therapies will be important: proceeding on a case-by-case, agent-by-agent, programme-by-programme, or agency-by-agency basis is not efficient. Finally, a clearer understanding of the endpoints needed in the post-market setting will also be helpful for drug sponsors<sup>(PREG)</sup>.

CHB often takes 20–40 years from time of infection to disease presentation. Will remnants of an HBV 'functional cure' potentially cause disease reactivation 10–30 years later? The follow-up needed to assess the long-term success of an intervention is logistically challenging and resource intensive thus raising a cost barrier. Drug developers need to be convinced that the return on their investment will offset the costs accumulated by taking a drug from discovery through the approval process and post-marketing commitments<sup>(BAR)</sup>. These issues, not unique to HBV treatments, need to be clarified as much as possible to facilitate development of new drugs and diagnostics.

### Strategies from other disease areas

Many of the researchers we interviewed for this paper entered the HBV field after working with HIV and HCV. Their experience of developing drugs against new targets and creating innovative methodologies could contribute to progress in the HBV field while avoiding recognisable obstacles in the regulatory approval pathway<sup>(BAR)</sup>. As seen in HIV and HCV treatment, combination therapy using drugs with different mechanisms of action is the most likely pathway to an HBV cure. Clarity on the rules governing the combined use of licensed and unlicensed agents from regulatory agencies across the world will be helpful in trial design<sup>(BAR,PREG)</sup>. Historical controls, as used in HCV, could be an option along with more traditional trial designs<sup>(BAR)</sup>. Validated

reference assays are essential so that results between different commercially available tests can be better understood. These tests often have different analytical performance characteristics that might impact the endpoint outcomes. Pharmaceutical companies conducting trials must collaborate with diagnostic companies to make sure that the endpoints being used are consistent with the way the assay is used to report the results during the trial<sup>(PREG)</sup>, as has been the case with HBV and HCV [32–34].

The cost of HCV cure has made its accessibility a controversial issue. Earlier attention to drug pricing through coalitions following the HIV and HCV model might be one approach to navigate potential access issues in HBV<sup>(PREG)</sup>. On a broader level, the cure for HCV empowers HBV advocacy. The reality of a cure for a potentially fatal chronic condition such as HCV is a powerful message to share with legislators, policy influencers and the overall public in moving HBV cure forwards<sup>(BAR,PREG)</sup>.

## Discussion

Experts contributing to the discussion on the current state of the science on HBV provided different perspectives on gaps that need to be addressed including: improved models to study HBV, development of better assays and treatment options, a common and operational definition of cure, and an agreement on biomarkers and endpoints between researchers, clinicians and regulators.

Many HBV clinical diagnostic tools were created for blood-bank donor screening before being applied to the research setting [10]. Measuring the presence or amount of virus for the purpose of therapeutic research differs from the safety requirements of screening blood donations. The existing assays should be examined to determine if they are quantitative and specific enough to serve the best needs of the researchers as treatments, and the goals of treatments, are evolving<sup>(BAR,PREG)</sup>.

Agreement on the markers and endpoints that HBV assays measure is important. While evaluating existing biomarkers, the field needs to remain flexible towards new options as science and technology evolve. Whether the treatment targets are aimed at achieving a complete or functional cure will determine the specific endpoints of trials. Endpoints should be well vetted with evolving consensus among pharmaceutical sponsors, diagnostic companies, the regulatory agencies and the academic and clinical communities<sup>(PREG,PREG)</sup>.

HBV differs significantly from HCV and HIV. The integration of the cccDNA minichromosome into the host genome leads to a completely distinct host–virus relationship compared to HCV, an RNA virus. Thus, the HCV cure definition: sustained viral response (SVR) 12 weeks after the completion of therapy, is likely to not apply [35]. The HBV expert community will need to be clear on the intricacies of the HBV life cycle to better manage expectations for what is deemed successful for HBV 'curative' treatments, which might differ from other viral diseases<sup>(BAR)</sup>.

The search for a curative intervention for HBV needs to be viewed in context of what is currently available for HBV treatment, prevention and management. Tenofovir DF, lamivudine and entecavir are available as generics at low cost in most countries and tenofovir DF/emtricitabine is expected to be available in its generic form by the end of 2017. In contrast to HIV, no international system of donor funding has been established to allow universal access to HBV treatment.

HBV vaccines, which are safe and 94–98% effective, are excellent prevention tools and their use should be increased [36]. Vaccination of neonates and HBV-negative adults has subsequently reduced the risk of liver cancer and other liver diseases in young adults in rural China [24]. HBV can be transmitted perinatally and efforts



to identify infected mothers and vaccinate their children should continue. Implementation of vaccine programmes is a matter of cost, availability and infrastructure around the world, requiring collaboration between governments, communities, and public health agencies to ensure that all who need the HBV vaccine receive it<sup>(6AR)</sup>. Vaccination has been largely directed towards infants and children. Most uninfected adults in the US have not been immunised and among those who have been immunised, coverage with at least three doses of the hepatitis B vaccine was only 32.6% for adults aged 19–49 years [37].

Screening for chronic HBV infection is not part of routine primary care. HBV surveillance is underfunded, underdeveloped and poorly integrated, thus, the number of HBV infected individuals in the US and worldwide is unclear [38]. Recent studies estimate that up to 2.2 million people are living with CHB in the US [39,40] and that between 40% and 70% of HBV cases may come from foreign-born individuals who emigrated from areas of high HBV prevalence [38]. These individuals may be reluctant to engage in hepatitis surveillance and disclose their health status. Although a national surveillance system for chronic viral hepatitis in the US is lacking, hepatitis surveillance is slowly improving. Several states are being used as proxies to gauge national incidence, but more funding and resources are needed at the global, national, state and local level<sup>(6PA)</sup>. The urgency is demonstrated by recent HBV outbreaks: HBV and HCV outbreaks in Indiana, Kentucky, Tennessee and West Virginia among injecting drug users; or within nursing homes, assisted living centres, board and care facilities, dialysis clinics and dental clinics [41,42]. Those with chronic infection need linkage to care and treatment; the uninfected need vaccination to prevent infection.

Globally, recent sero-epidemiological studies are similarly inadequate in quality and quantity, particularly in regions of high HBV endemicity such as sub-Saharan Africa and Asia/Pacific. The studies that do exist often focus on specific regions or populations or have relied on older, outdated, publications [43]. In addition, HBV stigma as an ‘immigrant disease’<sup>(6PA)</sup> masks its importance, contributing to its lower priority in public health policy circles and playing a role in the reluctance for people to seek treatment. Efforts to increase disease education and eliminate stigma should continue. Furthermore, obtaining accurate epidemiological data is important to justify the allocation of public health resources and treatment interventions.

Curing HBV will address the unmet treatment and cure needs of people co-infected with HDV, a virus acquired sexually, perinatally or through blood, but only in the presence of concomitant HBV infection [44,45]. A cure for HBV will only reach its full potential if it is accessible to those who need it. Currently available treatments and vaccines are not implemented to their full potential. Gaps in epidemiological, screening, referral and treatment programmes will need to be addressed.

Limitations of this study include convenience sampling from a group of collaborators related in one way or another with the Forum’s work in the field of liver diseases. Many stakeholders are Western-centric in their representation. Only a few interviewed participants represented Asia or other parts of the world where HBV is highly endemic.

## Conclusion

Many difficulties exist along the path to developing and approving a HBV cure, but optimism remains. Several new investigational agents, all targeting different aspects of the HBV life cycle, are in early stages of development [26]. Many interviewees for this paper mentioned the need for open and collaborative ongoing dialogues among stakeholders in a neutral space as a critical

process to move the field forwards<sup>(6REG,6PA,6AR,6PDC)</sup>. The Forum has facilitated conversations of this nature, in the fields of HCV, HIV and NASH [6,7], and is entering the field of HBV with the same spirit, with the formation of the HBV Forum. ‘Cross-talk’ is already occurring, as demonstrated by the initiatives being held by various groups such as the Hepatitis B Foundation, L’Agence nationale de recherches sur le sida et les hépatites virales (ANRS), the European Association for the Study of the Liver (EASL), the American Association for the Study of Liver Diseases (AASLD), the International Coalition for the Elimination of HBV [46] and others. The promise of an HBV cure is exciting. Now is the time to work together towards that goal.

## Acknowledgements

The authors thank Dr Gertrude Buehring for her guidance on the first version of this manuscript, which was the first author’s thesis for his Public Health Master’s Degree at the University of California, Berkeley; and the stakeholders who participated in the interviews for their time and honesty.

## Disclaimer

This article reflects the views of the authors and should not be construed to represent FDA’s views or policies.

## References

1. Basnayake SK, Easterbrook PJ. Wide variation in estimates of global prevalence and burden of chronic hepatitis B and C infection cited in published literature. *J Viral Hepat* 2016; **23**: 545–559.
2. Centers for Disease Control. Hepatitis B. In: Hamborsky J, Kroger A, Wolfe S (eds.) *Epidemiology and Prevention of Vaccine-Preventable Diseases*. 13th ed. Washington, DC: Public Health Foundation, 2015; 149–174.
3. WHO. Hepatitis B. Fact sheet No. 204. 2016. Available at: [www.who.int/mediacentre/factsheets/fs204/en/](http://www.who.int/mediacentre/factsheets/fs204/en/) (accessed December 2016).
4. MacLachlan JH, Locarnini S, Cowie BC. Estimating the global prevalence of hepatitis B. *Lancet* 2015; **386**: 1515–1517.
5. Schweitzer A, Horn J, Mikolajczyk RT *et al*. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. *Lancet* 2015.
6. Miller V. The forum for collaborative HIV research: a model for an integrated and inclusive approach to clinical research and drug development. *Clin Pharmacol Ther* 2009; **86**: 332–335.
7. Hutchison C, Kwong A, Ray S *et al*. Accelerating drug development through collaboration: the Hepatitis C Drug Development Advisory Group. *Clin Pharmacol Ther* 2014; **96**: 162–165.
8. Maasoumy B, Wiegand SB, Jaroszewicz J *et al*. Hepatitis B core-related antigen (HBcrAg) levels in the natural history of hepatitis B virus infection in a large European cohort predominantly infected with genotypes A and D. *Clin Microbiol Infect* 2015; **21**: 606.e601–610.
9. Krajden M, McNabb G, Petric M. The laboratory diagnosis of hepatitis B virus. *Can J Infect Dis Med Microbiol* 2005; **16**: 65–72.
10. Gerlich WH. Medical virology of hepatitis B: how it began and where we are now. *Viral J* 2013; **10**: 239.
11. Tuailon E, Mondain AM, Nagot N *et al*. Comparison of serum HBsAg quantitation by four immunoassays, and relationships of HBsAg level with HBV replication and HBV genotypes. *PLoS One* 2012; **7**: e32143.
12. FDA. FDA approved drug products: VEMLIDY (tenofovir alafenamide). 2016. Available at: [www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&AppNo=208464](http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&AppNo=208464) (accessed December 2016).
13. Marcellin P, Ahn SH, Chuang WL *et al*. Predictors of response to tenofovir disoproxil fumarate plus peginterferon alfa-2a combination therapy for chronic hepatitis B. *Aliment Pharmacol Ther* 2016.
14. Janssen HL, van Zonneveld M, Senturk H *et al*. Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomised trial. *Lancet* 2005; **365**: 123–129.
15. Lau GK, Piratvisuth T, Luo KX *et al*. Peginterferon Alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. *N Engl J Med* 2005; **352**: 2682–2695.
16. Lai CL, Gane E, Liaw YF *et al*. Telbivudine versus lamivudine in patients with chronic hepatitis B. *N Engl J Med* 2007; **357**: 2576–2588.
17. Chang TT, Gish RG, de Man R *et al*. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. *N Engl J Med* 2006; **354**: 1001–1010.
18. Riviere L, Ducroux A, Buendia MA. The oncogenic role of hepatitis B virus. *Recent Results Cancer Res* 2014; **193**: 59–74.
19. Cho JY, Paik YH, Sohn W *et al*. Patients with chronic hepatitis B treated with oral antiviral therapy retain a higher risk for HCC compared with patients with inactive stage disease. *Gut* 2014; **63**: 1943–1950.

20. Rapti I, Hadziyannis S. Risk for hepatocellular carcinoma in the course of chronic hepatitis B virus infection and the protective effect of therapy with nucleos(t)ide analogues. *World J Hepatol* 2015; **7**: 1064–1073.
21. Papatheodoridis GV, Chan HL, Hansen BE *et al*. Risk of hepatocellular carcinoma in chronic hepatitis B: assessment and modification with current antiviral therapy. *J Hepatol* 2015; **62**: 956–967.
22. Locarnini S, Hatzakis A, Chen DS, Lok A. Strategies to control hepatitis B: public policy, epidemiology, vaccine and drugs. *J Hepatol* 2015; **62**: S76–86.
23. Lok A. Does antiviral therapy for hepatitis B and C prevent hepatocellular carcinoma? *J Gastroenterol Hepatol* 2011; **26**: 211.
24. Qu C, Chen T, Fan C *et al*. Efficacy of neonatal HBV vaccination on liver cancer and other liver diseases over 30-year follow-up of the Qidong hepatitis B intervention study: a cluster randomized controlled trial. *PLoS Med* 2014; **11**: e1001774.
25. Zeisel MB, Lucifora J, Mason WS *et al*. Towards an HBV cure: state-of-the-art and unresolved questions – report of the ANRS workshop on HBV cure. *Gut* 2015; **64**: 1314–1326.
26. Block TM, Rawat S, Brosgart CL. Chronic hepatitis B: a wave of new therapies on the horizon. *Antiviral Res* 2015; **121**: 69–81.
27. Gish RG, Given BD, Lai CL *et al*. Chronic hepatitis B: virology, natural history, current management and a glimpse at future opportunities. *Antiviral Res* 2015; **121**: 47–58.
28. Block TM, Gish R, Guo H *et al*. Chronic hepatitis B: what should be the goal for new therapies? *Antiviral Res* 2013; **98**: 27–34.
29. McMahon BJ. Natural history of chronic hepatitis B. *Clin Liver Dis* 2010; **14**: 381–396.
30. Funk ML, Rosenberg DM, Lok AS. World-wide epidemiology of HBeAg-negative chronic hepatitis B and associated precore and core promoter variants. *J Viral Hepat* 2002; **9**: 52–61.
31. Fourati S, Pawlotsky JM. Recent advances in understanding and diagnosing hepatitis B virus infection. *F1000Res* 2016; **5**.
32. Lontok E, Mani N, Harrington PR, Miller V. Closing in on the target: sustained virologic response in hepatitis C virus genotype 1 infection response-guided therapy. *Clin Infect Dis* 2013; **56**: 1466–1470.
33. Allice T, Cerutti F, Pittaluga F *et al*. COBAS AmpliPrep-COBAS TaqMan hepatitis B virus (HBV) test: a novel automated real-time PCR assay for quantification of HBV DNA in plasma. *J Clin Microbiol* 2007; **45**: 828–834.
34. Westland CE, Yang H, Delaney WE *et al*. Week 48 resistance surveillance in two phase 3 clinical studies of adefovir dipivoxil for chronic hepatitis B. *Hepatology* 2003; **38**: 96–103.
35. Hoofnagle JH, Sherker AH. Therapy for hepatitis C – the costs of success. *N Engl J Med* 2014; **370**: 1552–1553.
36. Chen DS. Hepatitis B vaccination: the key towards elimination and eradication of hepatitis B. *J Hepatol* 2009; **50**: 805–816.
37. Williams WW, Lu PJ, O'Halloran A *et al*. Vaccination coverage among adults, excluding influenza vaccination – United States, 2013. *MMWR Morb Mortal Wkly Rep* 2015; **64**: 95–102.
38. Colvin HM, Mitchell AE, (eds), Committee on the Prevention and Control of Viral Hepatitis Infections; Institute of Medicine. *Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C*. Washington DC, USA: National Academies Press, 2010.
39. Cohen C, Holmberg SD, McMahon BJ *et al*. Is chronic hepatitis B being undertreated in the United States? *J Viral Hepat* 2011; **18**: 377–383.
40. Kowdley KV, Wang CC, Welch S *et al*. Prevalence of chronic hepatitis B among foreign-born persons living in the United States by country of origin. *Hepatology* 2012; **56**: 422–433.
41. Centers for Disease Control. Healthcare-associated hepatitis B and C outbreaks reported to the Centers for Disease Control and Prevention (CDC) 2008–2015. 2016. Available at: [www.cdc.gov/hepatitis/outbreaks/healthcarehepoutbreaktable.htm](http://www.cdc.gov/hepatitis/outbreaks/healthcarehepoutbreaktable.htm) (accessed December 2016).
42. Harris AM, Iqbal K, Schillie S *et al*. Increases in acute hepatitis B virus infections – Kentucky, Tennessee, and West Virginia, 2006–2013. *MMWR Morb Mortal Wkly Rep* 2016; **65**: 47–50.
43. Schweitzer A, Horn J, Mikolajczyk RT *et al*. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. *Lancet (London, England)* 2015; **386**: 1546–1555.
44. Noureddin M, Gish R. Hepatitis delta: epidemiology, diagnosis and management 36 years after discovery. *Curr Gastroenterol Rep* 2014; **16**: 365.
45. Flores R, Ruiz-Ruiz S, Serra P. Viroids and hepatitis delta virus. *Semin Liver Dis* 2012; **32**: 201–210.
46. Revill P, Testoni B, Locarnini S, Zoulim F. Global strategies are required to cure and eliminate HBV infection. *Nat Rev Gastroenterol Hepatol* 2016; **13**: 239–248.
47. Harrington M. State of the (research) chimp. *Lab Animal* 2012; **41**: 1.