HEPATITIS B: SEARCHING FOR THE CURE

Clinical Trial Challenges and Solutions

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A high unmet need in hepatitis B treatment

Despite the widespread availability of highly effective vaccines, chronic hepatitis B infection remains a major global health issue, and there are >350 million people chronically infected with the virus.[1] The primary goal of current antiviral therapy is suppression of HBV replication and hepatic inflammation, thereby reducing morbidity and mortality by preventing progression to liver fibrosis, cirrhosis and hepatocellular carcinoma.[2]

Current HBV treatments either enhance host antiviral immune responses (interferon [IFN]-α) or inhibit HBV DNA replication (nucleos[t]ide analogs). Each of these treatments differ in their potency and rate of development of viral resistance.[3] Treatment with pegylated IFN-α (PEG-IFN) is not well tolerated, while nucleos(t)ide analog regimens, such as tenofovir and entecavir, are better tolerated; however, HBV surface antigen (HBsAg) seroconversion is not reliably achieved.[3,4] PEG-IFN can achieve higher rates of HBsAg seroconversion compared with nucleos(t)ide analog regimens, but these rates are still low.[3,4]

Even though HBV replication is often suppressed to undetectable levels with current treatments, discontinuation of antiviral therapy or immunotherapy often leads to reactivation of virus replication, as HBV persists in hepatocytes in the form of a covalently closed circular DNA (cccDNA).[1,5] Complete and prolonged suppression of the HBV polymerase should in theory lead to viral clearance as HBV replication and viremia are reduced, and cccDNA infected hepatocytes are eventually depleted. However, this has not been the case so far, and is the basis for the existing significant unmet need. A therapy leading to complete viral clearance is needed to relieve those infected with HBV from lifelong treatment that may be costly and/or limited by drug associated toxicity.

Recent hepatitis C treatment successes have resulted in an increase in research in hepatitis B hoping to achieve similar success and viral elimination. The increase in hepatitis B clinical trials over the past 15 years is shown in figure 1. This white paper provides an overview of hepatitis B treatments in development, and the opportunities, challenges and potential solutions that are important to consider when executing clinical trials for new treatments of chronic hepatitis B. Finally, this white paper summarizes the technological developments in HBV diagnostics that are currently underway at Covance.

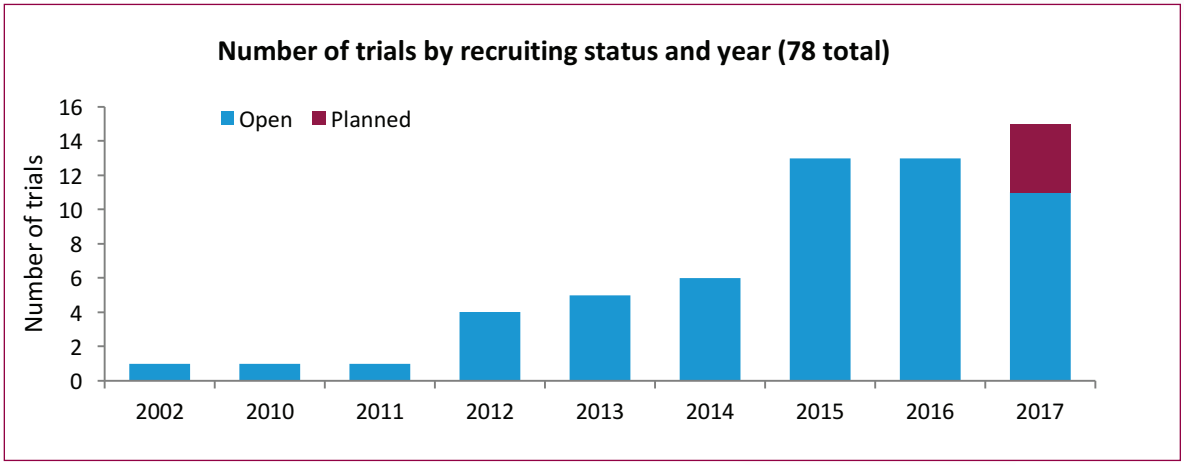

Figure 1. Number of trials (across all phases) per year. Source: Citeline (data accessed October 2017).

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Therapies in development for hepatitis B

HBV therapies currently in development can be divided into two broad categories: direct-acting antivirals and host-targeting antivirals. Regardless of their mechanism, these novel therapeutic agents aim to improve upon current treatments by minimizing side effect profiles, reducing the course of treatment and increasing the rate of viral clearance leading to a functional cure.[6]

Direct-acting antivirals target specific steps in the viral replication process, and include polymerase inhibitors and disruptors of cccDNA. Host-targeting antivirals are divided into immunomodulators, such as toll-like receptor agonists and therapeutic vaccines, and those that target host function, such as epigenetic modifiers.[6]

It is likely that a combination of approaches holds the key to a cure for hepatitis B. For example, suppressing viral replication with potent direct-acting agents while enhancing the host immune system with agents that promote the elimination of cells that harbour cccDNA, such as programmed death (PD)-1/PD-L1 ligand pathway inhibitors.

The need for a cure creates both opportunities and challenges

The number of active hepatitis B trials is estimated at almost 80, and their geographic location with respect to trial sites is displayed in Figure 2.

As interest in hepatitis B drug development increases, so does the competition for trial sites and patients. Strategies should be considered early in clinical development to ensure an adequate number of sites are committed to the trial. Historically, this competition has focused on the Asia-Pacific (APAC) region, which is populated by a large number of hepatitis B patients.

Conducting an HBV trial in regions with the highest chronic hepatitis B prevalence can influence the success of a trial and reduce its cost. As such, we have a wealth of experience in hepatitis B trials in the APAC region, and access to many sites in key countries (such as South Korea, China, Taiwan, Hong Kong and New Zealand).

The growing migration of individuals from the APAC region to Europe and North America has expanded the HBV clinical trial delivery opportunities outside the APAC region. It is important to draw from Covance experience and expertise in all regions when designing and executing hepatitis B trials, including North American and European countries such as the U.S., Canada, Italy, Bulgaria, the U.K. and the Netherlands. We understand that lasting and productive relationships with major clinical research centers and key opinion leaders are built on a foundation of long-term collaboration and successful trial execution. The latter of these can be achieved through expediting study progress utilizing our rapid start-up processes and adaptive trial designs.

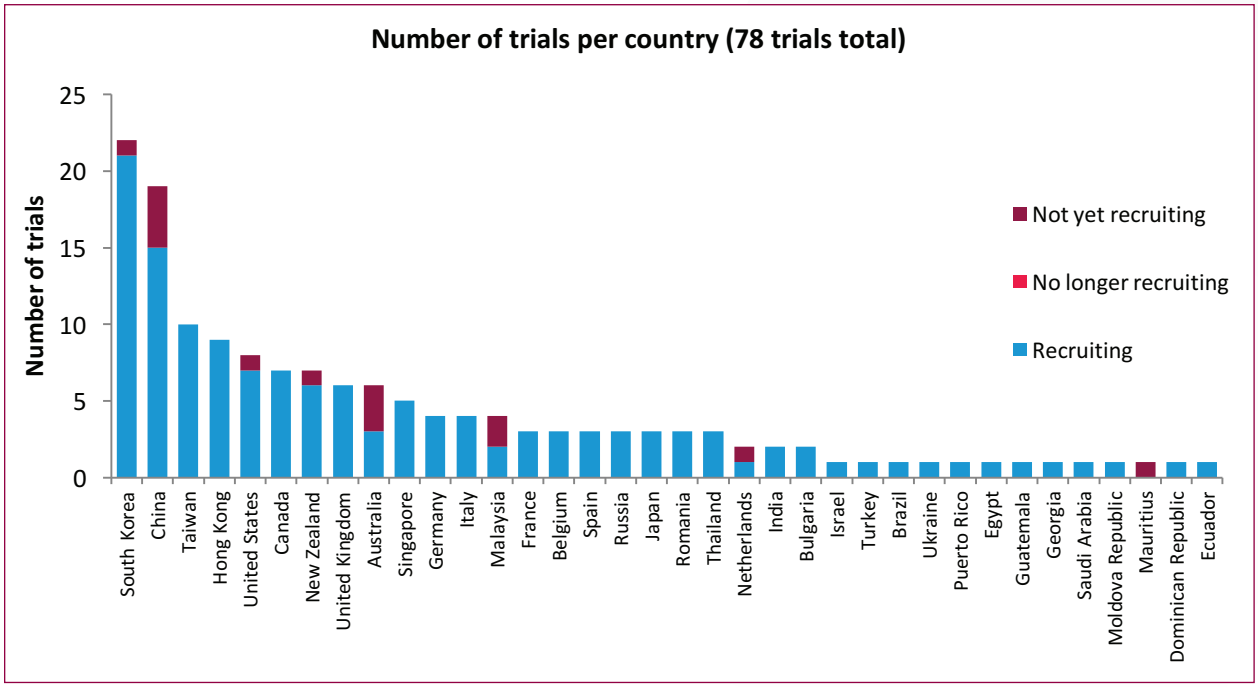

Figure 2. Number of trials (across all phases) per country. Please note that many clinical trials encompass several sites across different countries, and therefore trials may be represented more than once. Source: Citeline (data accessed October 2017).

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Overcoming hepatitis B clinical trial challenges

Covance has identified several significant challenges that frequently impede hepatitis B trials. Our vast experience in these trials has enabled the development of solutions to overcome each of these barriers (summarized below).

Challenge	Solution(s)
Defining eligibility criteria	
▸ Ensure a large pool of qualified patients by appropriately defining the ranges of viral DNA and level of HBsAg expression for patient inclusion, in addition to other factors such as the presence or absence of comorbidities and other viral infections	▸ Covance protocol database combined with LabCorp patient data in the U.S. allow pressure testing of trial protocols before finalizing entry criteria to maximize the number of qualified and available patients
Locating qualified patients and selecting optimal trial sites	
▸ Studies may require treatment-naive patients, treatment-experienced patients (with or without prior treatment failures) and patients that test positive (at a desired cut-off level) or negative for HBV DNA and hepatitis B e-antigen (HBeAg)	▸ Leverage LabCorp and World Health Organization data, and use our proprietary informatics software (Xcellerate® Trial Design) to locate desired patient populations and make evidence-based decisions on trial site location (Figure 2)
Patient enrollment	
▸ Frequent clinic visits and blood tests and the uncertainty of patient benefit in early-phase trials presents a greater challenge to patient recruitment compared with late-phase trials ▸ Lack of strong relationships with investigators (particularly in the APAC region) can impact recruitment ▸ Willingness to participate in trials varies between countries due to differences in standard of care	▸ Gain insights into patient preferences using voice of patient surveys, and incorporate into trial design to ensure patient-centric trials ▸ Leverage Covance's longstanding physician relationships worldwide for patient referral ▸ Locate high-performing investigators using Xcellerate® Trial Design, and the Covance network of known and experienced investigators
Patient retention	
▸ Duration of late-phase trials is often long (follow-up can be up to 48 weeks), resulting in high rates of loss to follow-up	▸ Nurture physician and investigator relationships with patients ▸ Communicate long-term trial benefit to the patient (e.g. compassionate use program after trial completion) ▸ Retention strategies such as SMS appointment reminders and mobile health video technology
Accurate measures of treatment efficacy	
▸ Assays capable of accurately measuring viral decay kinetics and resistance are not widely available	▸ Leverage established partnership with Monogram Biosciences, Inc., a globally recognized leader in viral diagnostic development and antiviral drug resistance testing ▸ Covance and LabCorp offer a comprehensive HBV and hepatitis assay portfolio and are actively developing new and more sensitive analytical methods

Table 1. A non-exhaustive list of hepatitis B clinical trial challenges and Covance solutions.

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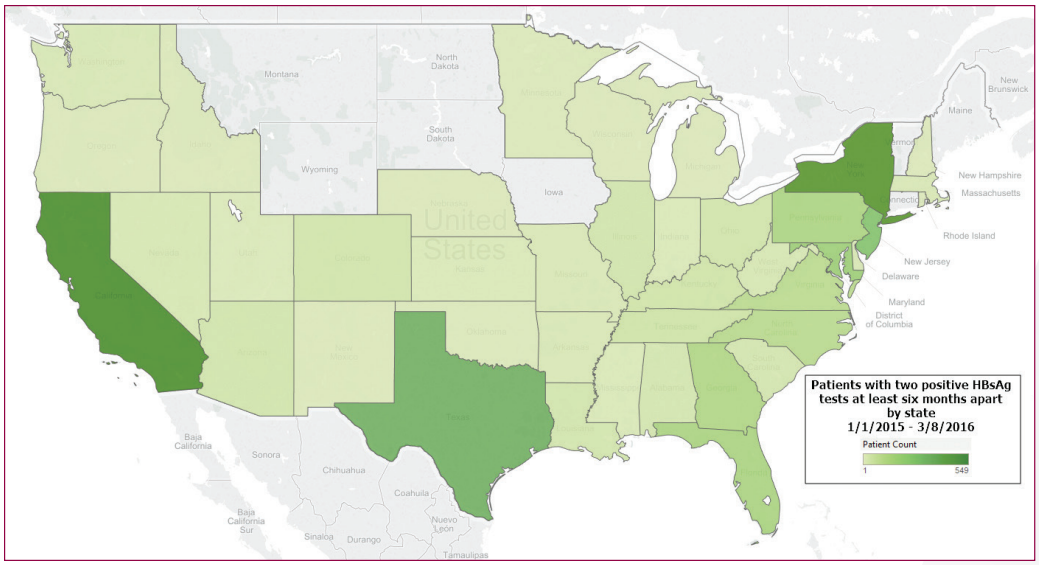

Figure 2. Data from LabCorp can be leveraged for identification of hepatitis B patients in the U.S. (Can view patient populations by HBV DNA levels on a state-, city- or zip code-level)

Covance and the future of hepatitis B treatment

Together with LabCorp and Monogram Biosciences, Inc., Covance is actively developing a number of viral diagnostics technologies that are advancing the discovery, development and clinical evaluation of potential cures for hepatitis B. Ongoing development efforts include:

- Sequencing assays that can interrogate full-length HBV genomic DNA and pre-genomic RNA, which may reveal and validate new therapeutic targets, provide a more complete understanding of resistance mechanisms and accurately assign HBV genotype across the entire genome
- PCR assays that are capable of measuring HBV pre-genomic RNA production in the setting of complete suppression of HBV replication
- Sensitive quantitative HBsAg measurements to evaluate the kinetics of viral suppression and clearance more accurately than current qualitative methods
- A cell-based infectivity assay that measures the susceptibility of patient-derived HBV isolates to conventional and novel antiviral agents, and is more cost-effective and less labor intensive than current methods

Covance is committed to helping clients succeed in hepatitis B drug development. We have the operational, laboratory and scientific expertise to help companies with established pipelines or those with emerging assets, and our global footprint provides the flexibility to rapidly adapt to the changing hepatitis B landscape.

References

1. Tseng, T. C. & Kao, J. H. (2017). Elimination of hepatitis B: Is it a mission possible? *BMC Medicine, 15*(1), 53. DOI: 10.1186/s12916-017-0820-x.

2. Rajbhandari, R. & Chung, R. T. (2016). Treatment of hepatitis B: A concise review. *Clinical and Translational Gastroenterology,* 7(9), e190. DOI: 10.1038/ctg.2016.46.

3. Chang, J. *et al.* (2014). Therapeutic strategies for a functional cure of chronic hepatitis B virus infection. *Acta Pharmceutica Sinica B, 4*(4), 248-257.

4. Woo, A. S. J. *et al.* (2017). Alpha-interferon treatment in hepatitis B. *Annals of Translational Medicine, 5*(7), 159. DOI: 10.21037/atm.2017.03.69.

5. Liang, T.J. *et al.* (2015). Present and future therapies of hepatitis B: From discovery to cure. *Hepatology, 62*(6), 1893-1908.

6. Block, T. M. *et al.* (2015). Chronic hepatitis B: A wave of new therapies on the horizon. *Antiviral Research, 121,* 69-81.

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