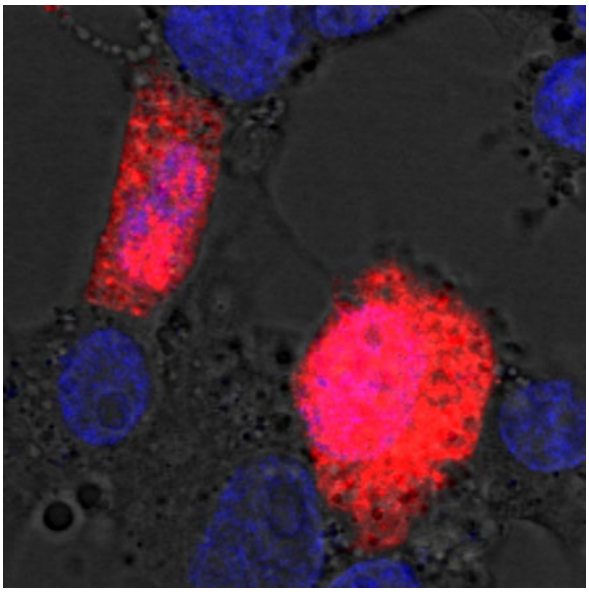

STRATEGIC PLAN FOR TRANS-NIH RESEARCH TO CURE HEPATITIS B

The NIH Hepatitis B Cure Strategic Plan Working Group

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National Institutes of Health

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Executive Summary

The United States National Institutes of Health (NIH) is committed to advancing efforts to end the hepatitis B epidemic. Hepatitis B is caused by a virus that attacks the liver and can cause both acute and chronic disease. According to the World Health Organization (WHO), approximately 257 million people worldwide are chronically infected with hepatitis B virus (HBV). In the United States (U.S.), between 850,000 and 2.2 million people have chronic hepatitis B. Worldwide, only about 10% of people with chronic hepatitis B are aware that they are infected. Life-threatening complications such as cirrhosis and liver cancer occur in 20%–30% of adults who are chronically infected. An ideal cure would not only eliminate HBV infection but also reduce the risk of liver failure and hepatocellular carcinoma (HCC).

The *Strategic Plan for Trans-NIH Research to Cure Hepatitis B* supports and aligns with NIH's ongoing efforts to intensify innovative hepatitis B research (Appendix 1), and with the U.S. National Viral Hepatitis Action Plan. The strategic plan proposes priorities to develop a hepatitis B cure and improved strategies for vaccination, screening, and follow-up to care (Box 1). The plan is structured around three research areas research areas that are vital to developing a cure, as outlined below.

Box 1. Trans-NIH Strategic Plan to Cure Hepatitis B

Vision: *To end the hepatitis B epidemic*

Mission: *To develop a hepatitis B cure and improved strategies for vaccination, screening, and follow-up to care*

- **Strategic Priority 1: Understand Hepatitis B Biology**—viral and host factors underlying HBV pathogenesis, immunity, reactivation, and transmission; impact of epidemiological factors, including coinfections with other hepatitis viruses, human immunodeficiency virus (HIV) and other microorganisms
- **Strategic Priority 2**: **Develop Tools and Resources**—biomarkers, cell culture and animal models, diagnostics, and clinical research capacity
- **Strategic Priority 3: Create Strategies to Cure and Prevent Hepatitis B**—strategies to block replication of HBV and eliminate HBV-infected cells; strategies to promote screening, vaccination, and follow-up to care; and guidelines for implementing a future cure regimen

NIH anticipates that this plan will serve as a foundation for future research investments that will provide the comprehensive research base needed to develop hepatitis B cure and prevention strategies. Implementing such strategies will depend on a concerted international effort by numerous public health stakeholders to end the hepatitis B epidemic.

Introduction

Although a highly effective preventive vaccine for hepatitis B has been available for more than 30 years, infection continues to spread. Each year, approximately 900,000 people die as a result of fulminant hepatitis (acute liver failure) and chronic HBV infection, mostly due to complications such as cirrhosis (scarring of the liver), liver failure, and hepatocellular carcinoma (HCC). Rates of HCC, which is caused mostly by chronic HBV infection, also are increasing worldwide. The annual number of deaths due to viral hepatitis is now higher than deaths due to HIV, tuberculosis, or malaria, underscoring the urgent need for better approaches to treat and cure those infected with HBV. In areas with high levels of infection, such as East Asia and Africa—where more than 6% of adults are infected—HBV infection is most often transmitted vertically from mother to child at birth or in early childhood by exposure to infected blood or other body fluids. Sexual contact, needle sharing, or other routes of exposure to infected blood or body fluids also can transmit the virus. Among infants infected during the first year of life, 80%–90% will develop chronic infection, while the rate lowers to 30%–50% for children infected between the ages of 1 and 5 years. Increasing the vaccination rate among infants and children is therefore a critical element in the effort to control the HBV epidemic. In contrast to children, about 95% of adults with acute HBV infection recover completely and do not become chronically infected (Figure 1).

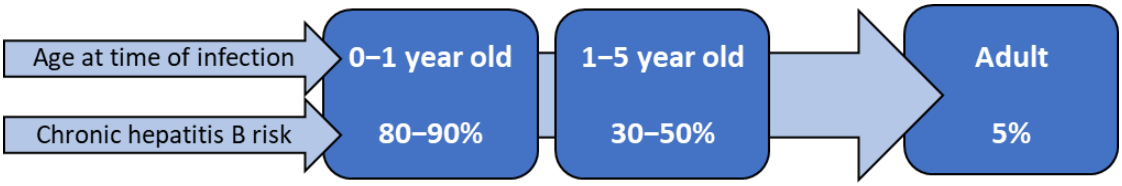

Figure 1: Age at time of HBV infection correlates with risk of developing chronic hepatitis B. Among infants 0–1 year old at time of HBV infection, 80-90% typically develop chronic hepatitis B. This rate drops to 30–50% in children 1–5 years old at time of infection, 80-90% typically develop chronic hepatitis B. This rate drops to 30–50% in children 1–5 years old at time of infection, and 5% for individuals infected as adults.

Current treatment regimens help control HBV infection, but treatment is required for many years or for life. In addition, high treatment costs, the need to continuously monitor the disease, and adherence to the regimen are significant burdens. Furthermore, the risk of developing cirrhosis and liver cancer is still elevated among treated patients compared with uninfected individuals. Recent advances in hepatitis B research, starting with the 2012 discovery that the sodium taurocholate co-transporting polypeptide (NTCP) receptor is necessary for viral entry into cells, have generated optimism that a cure for hepatitis B may be possible.

The Trans-NIH Hepatitis B Cure Working Group (WG), led by the National Institute of Allergy and Infectious Diseases (NIAID), was established to codify the role of NIH in supporting research to facilitate the development of a hepatitis B cure. The WG consisted of scientific and policy experts from NIAID, the National Institute of Diabetes and Digestive and Kidney Diseases

(NIDDK), National Cancer Institute (NCI), National Institute of Minority Health and Health Disparities (NIMHD), and NIH Office of the Director (OD) (members listed in Appendix 2). To seek broad public input, the WG issued a Request for Information (RFI) and received 34 responses from academia, advocacy organizations, industry, government, clinical trial networks, and not-for-profit organizations, as summarized in Appendix 3.

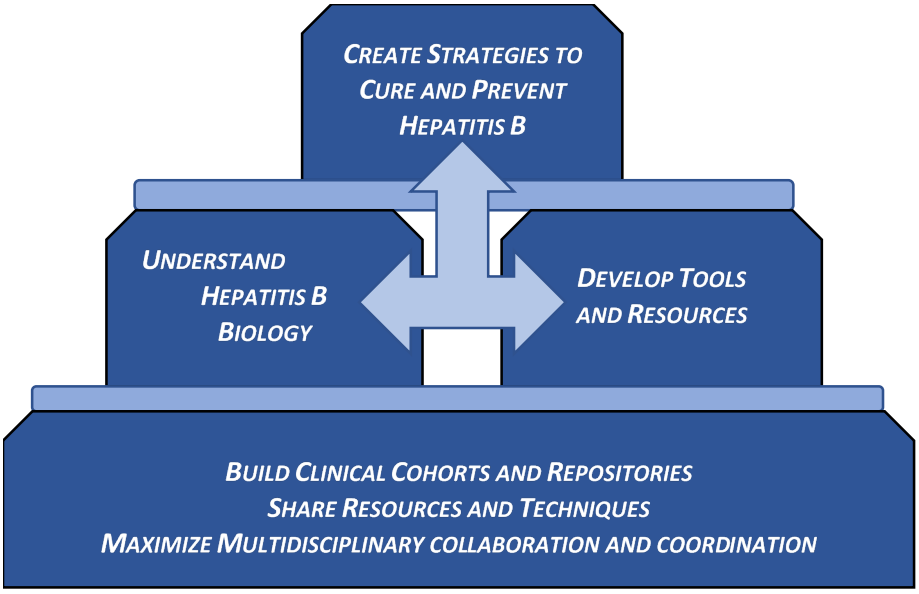

Figure 2: Trans-NIH Strategic Plan to Cure Hepatitis B proposes to maximize the use of resources by leveraging clinical cohorts and biorepositories, sharing resources, and drawing on multidisciplinary biomedical collaborations. The plan's strategic priorities are: 1. Understand hepatitis B biology, 2. Develop tools and resources to advance HBV research, and 3. Create strategies to cure and prevent hepatitis B.

Advances in the three priority areas are expected to be interdependent and complementary. Several themes, outlined below, cut across the strategic plan to maximize the use of resources and accomplish the plan's objectives (Figure 2):

- **Building on existing human cohorts and biorepositories (Appendix 4)** will enable a better understanding of the basic clinical presentation of hepatitis B, the development of better biomarkers and diagnostics, and the evaluation of putative cure strategies
- **Sharing resources (Appendix 4) and standardizing techniques** will accelerate basic research into the complexities of HBV disease processes and preclinical testing of promising candidates

- **Broad, multidisciplinary biomedical collaboration and coordination** is vital to advancing HBV research, as is training the next generation of hepatitis B scientists to capitalize on emerging scientific opportunities

Reflecting discussions at numerous HBV cure workshops, the WG defined hepatitis B cure as a sustained loss of hepatitis B virus surface antigen (HBsAg), preferably with antibodies against HBsAg, and undetectable HBV DNA in serum after completion of a finite course of treatment (Box 2). The WG utilized this definition as it reflects a feasible and clinically relevant goal. An absolute cure would imply the elimination of all HBV DNA from the body, an endpoint that may not be necessary clinically and cannot be assessed using current technology. The WG included prevention in the plan because prevention is a crucial factor in eliminating transmission of HBV and is inextricably linked to curing hepatitis B. To effectively address the global public health challenges posed by HBV, a curative treatment will need to go hand in hand with better approaches for screening, follow-up to care, and vaccination coverage.

Box 2. Hepatitis B Cure Definition

The Trans-NIH Hepatitis B Cure Working Group defines hepatitis B cure as a sustained loss of hepatitis B virus surface antigen (HBsAg), preferably with antibodies against HBsAg, and undetectable HBV DNA in serum after completion of a finite course of treatment.

Strategic Priority 1: Hepatitis B Biology

The clinical manifestations of chronic hepatitis B vary greatly and can transition between different phases (immune-tolerant, immune-active, and inactive). These phases can be differentiated using markers of viral replication (hepatitis B e antigen [HBeAg], hepatitis B s antigen [HBsAg], and HBV DNA), and markers of liver disease such as alanine aminotransferase (ALT) levels.

Developing a cure for HBV will require an increased understanding of the complex molecular and immune mechanisms underlying infection and disease. Studies that elucidate the viral lifecycle and host responses to infection can identify potential targets for intervention in HBV infection and disease.

NIH will leverage existing research activities, resources, and human cohorts—such as the NIDDK Hepatitis B Research Network (HBRN) and its repository—to achieve the scientific objectives outlined below, while building the new tools and resources needed for further advances. New resources, especially cell culture and animal models, and emerging technologies—such as comprehensive systems biology analyses of patient data, laser capture microdissection, digital droplet polymerase chain reaction (PCR), and deep sequencing—will help researchers explore the mechanisms of viral pathogenesis, including HBV reactivation following chemotherapy or immunosuppressive therapy.

Box 3. Strategic Priority 1—Hepatitis B Biology	
1.1	*Identify viral factors that control infection and disease*
1.2	*Understand immune and other host factors of HBV infection*
1.3	*Characterize clinical pathology and factors that affect disease progression and control in various subpopulations and age groups*

During HBV replication, covalently closed circular DNA (cccDNA) is generated as a key replication intermediate in the host cell nucleus and serves as a template for all viral RNAs. Silencing cccDNA is therefore considered essential for a cure and developing assays to quantify cccDNA and assess its transcriptional activity will be important. Understanding the function of various viral proteins and host factors will be necessary for improving the assays, models, and other resources needed to move toward a cure. The discovery of the NTCP receptor for HBV entry has led to the development of NTCP transgenic animals and cell lines that are susceptible to HBV infection. Further fundamental discoveries will enable the identification of essential biomarkers and the development of new techniques and assays.

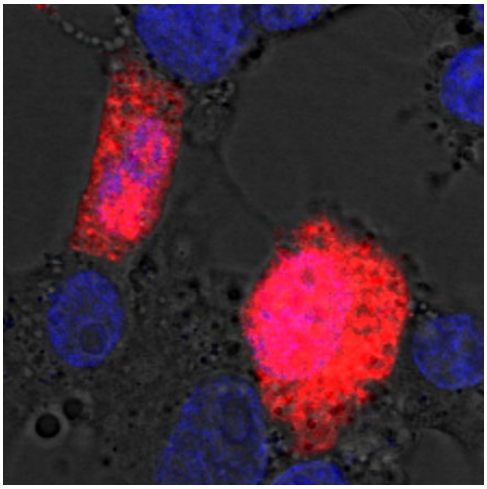

Figure 3: Hepatitis B core antigen (HBcAg, red) in the nucleus and cytoplasm of human liver cancer cells (HepG2) transfected with HBV. Cell nuclei are labelled in blue (easily visible in non-transfected cells). Credit: NIAID

The clinical outcomes of HBV infection are affected by many factors, including age, sex and gender, ethnic or geographical origin, host and viral genotype, immunosuppression, comorbidities (especially other forms of liver disease), and coinfection with hepatitis D virus (HDV), hepatitis C virus (HCV), HIV, or other microorganisms. Thus, large and diverse clinical studies will be needed to provide insights into the complexity and diversity of host-pathogen interactions. Results from these investigations will help inform the breadth of assays and studies needed to develop and evaluate diagnostic tools and curative therapies for use in various care settings and populations.

Objective 1.1 Identify viral factors that control infection and disease

The mechanisms involved in HBV replication are obvious therapeutic targets. Indeed, current treatments include nucleos(t)ide analogues, which block viral replication, and interferon, which both boosts the host immune response and prevents viral replication. However, discontinuing treatment usually leads to a rebound of viral replication. A better understanding of each step of the HBV lifecycle and the role of various viral factors in the progression of disease will lead to new classes of antivirals and new treatment strategies to cure chronic hepatitis B. The general function of many essential viral proteins (including HBx, HBsAg, HBcAg, and HBeAg) are known, but their multiple interactions in HBV replication, immune suppression, and pathogenesis

remain to be elucidated. The biogenesis, homeostasis, decay, and transcriptional regulation of cccDNA, are all potential targets for therapeutic intervention.

Continued investigations of the mechanisms of the HBx protein in viral replication, its regulatory function in the transcription of cccDNA, and its role in HBV pathogenesis may lead to the development of antiviral agents that target HBx and block cccDNA transcription. Defining these mechanisms at the molecular level across the different HBV and host genotypes will lay the foundation for targeting cccDNA, either directly or indirectly, to cure patients chronically infected with HBV.

Studies of HBV DNA integrated within host chromosomes, which is known to cause host genetic perturbations, may help explain the multistep process of HCC development. New technology-intensive studies using genome-wide association studies (GWAS), RNA sequencing, and single-cell sequencing may advance important mechanistic insights.

Objective 1.2 Understand immune and other host factors of HBV infection

The fact that acute HBV infection resolves in 95% of adults indicates that the immune response can clear the infection and prevent it from becoming chronic. Furthermore, up to 10% of patients with chronic HBV spontaneously become functionally cured, exhibiting a sustained loss of HBsAg and antibodies against HBsAg. Research to understand the nature of such effective host immune responses will be crucial for replicating them therapeutically. Successful therapies will likely comprise two strategies: one that directly inhibits viral activity and a second that prevents viral spread to uninfected cells.

HBV is regarded as a “stealth” virus because infection does not appear to induce innate immune responses. However, agonists of innate immunity have been shown to activate interferon expression and may represent novel approaches to anti-HBV therapy. Interpretations of the role of innate immunity in HBV infection are unresolved and controversial. Adaptive immunity is crucial in control of HBV infection. Extensive analyses of T-cell and B-cell responses, T-cell exhaustion in HBV persistence, and T-cell recovery—both spontaneously and with existing treatments—are needed to understand immune control of the virus. These studies will have to consider the impact of coinfections with either HCV, HDV, or HIV on HBV-specific immunity, as well as various stages of liver disease.

Objective 1.3 Characterize clinical pathology and factors that affect disease progression and control in various subpopulations and age groups

Factors that affect disease progression reflect variability in biological mechanisms of disease and also are likely to impact response to a cure. Age at the time of infection is the most significant factor in a person’s risk of developing chronic HBV infection, with children at highest risk of chronic infection. A cure that is effective in children will have the most impact and will require the identification of age-related differences in the immune response to HBV.

GWAS in people with chronic hepatitis C have linked single-nucleotide polymorphisms with spontaneous and treatment-induced clearance of hepatitis C virus infection. This association also appears to be dependent on race, HCV genotype, and viral load. Several GWAS have suggested linkages between gene variants and HBV persistence and HBV-related HCC. Further research is needed to identify relevant genes and elucidate mechanisms of HBV disease progression.

HBV genotype is another factor affecting disease progression. Patients with cirrhosis are usually considered at higher risk of developing HCC, but certain HBV genotypes, such as African A1 and Alaskan F1b, are strongly associated with HCC without underlying cirrhosis. Additional studies are needed to examine the role of HBV genotype in disease progression, including the development of cirrhosis and HCC, and in the response to therapy.

Coinfections may affect the clinical outcome and effectiveness of a cure. Coinfection with HCV or HIV leads to more severe liver disease and higher mortality. Furthermore, treating HCV infection in patients coinfected with HBV can potentially cause HBV to flare and the reverse may also be true. HDV is an incomplete, unique RNA virus that requires HBV to provide HBsAg for virion assembly, release, and transmission. HDV coinfection significantly exacerbates both acute and chronic liver disease. Several social, behavioral, and dietary factors also should be considered, particularly as they relate to important comorbidities and coinfections. Alcohol use and other dietary factors can compound HBV-induced liver disease in the presence of comorbidities such as cirrhosis and fatty liver disease. Other behaviors, such as intravenous drug use, can lead to coinfection with either HIV, HDV, or HCV.

Clinical pathology studies will need to focus on persons in and from HBV-endemic countries, particularly in the Asia-Pacific and Africa regions, to examine biological, environmental, social, or cultural factors that might affect the response to the virus and disease progression in these groups. Environmental exposures to mold-derived aflatoxin, smoking, or the parasitic disease schistosomiasis may affect the progression of hepatitis B induced liver disease. Factors that may protect certain populations also need to be examined.

These studies and subsequent interventional trials can be facilitated by building on advances made through existing clinical research networks, such as HBRN and its repository, and global networks, such as the International Epidemiological Databases to Evaluate AIDS (IeDEA), the HIV/AIDS Clinical Trials Networks and the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) (see Appendix 4).

Strategic Priority 2: Tools and Resources

Box 4. Strategic Priority 2—Tools and Resources	
2.1	*Standardize and share reagents, procedures, and assays*
2.2	*Improve cell culture and cell-free systems to support fundamental research and product development*
2.3	*Improve and create new animal models that reflect the progression of human liver disease*
2.4	*Establish biomarkers for disease progression and response to therapy*
2.5	*Develop diagnostics and tools for monitoring disease and evaluating therapeutics*
2.6	*Expand clinical research capacity*

Achieving the research objectives outlined in Strategic Priority 1 and advancing our understanding of hepatitis B biology will require standardized tools and resources including reagents, laboratory methods, animal models, and assays. Use of biorepositories and online platforms will allow investigators to share resources, tools, data, and samples for basic research, product testing, and clinical evaluation. Improved cell culture systems to support fundamental research and product development, and new animal models that better reflect human HBV infection and related diseases, also are necessary. Biomarkers for various stages of disease and improved diagnostic, monitoring, and assessment tools will advance fundamental and clinical HBV research. Finally, increased clinical research capacity will be required both to learn more about the disease in humans and to test cure strategies.

Objective 2.1 Standardize and share reagents, procedures, and assays

HBV research is conducted globally in an array of academic, government, and industry settings. Harmonizing procedures for producing and purifying infectious HBV nucleic acid species and proteins to be used in preclinical research will enable researchers to integrate scientific findings on drug candidates and vaccines from diverse locations. This includes establishing standard recombinant plasmids for inducible and constitutive bacterial and eukaryotic expression of HBV proteins and developing hybridomas for monoclonal antibodies to HBV proteins. Standardizing protocols for immunoassays, such as methods that quantify cytokine-secreting cells, intracellular cytokine staining, and T-lymphocyte proliferation and cytotoxicity assays, also will be important. Together, these steps will facilitate the exchange of standardized samples and data between investigators and expand the hepatitis B knowledge base.

To promote this objective, NIH will support the development of standardized reagents, protocols, and assays. NIH is facilitating the sharing of key resources through biorepositories such as BEI, a repository developed by NIAID (https://www.beiresources.org/). NIH will leverage existing clinical/epidemiological cohorts, biorepositories, and reagent resources (Appendix 4) to advance hepatitis B cure research.

Objective 2.2 Improve cell culture and cell-free systems to support fundamental research and product development

Although cell culture systems for HBV are improving, continued investigations on improved systems are critical to support research toward a hepatitis B cure. Current studies primarily rely on transfection of human hepatoma cell lines, such as HepG2 2.2.1, with expression plasmids containing HBV genomic DNA. The recent identification of the NTCP receptor has enabled infection of a variety of cultured cells engineered to express NTCP, such as HepG2-NTCP and Huh7-NTCP. However, these cells are not easily infected, possibly reflecting the need for other, unidentified, receptor components. Virus secretion and spread within these cultures also remain low. New cell culture or co-culture models that are easily infected and support cell-to-cell spread of the virus are needed to elucidate the mechanisms of infection, viral persistence, and clearance—whether spontaneous, drug-mediated, or immune-mediated. Such models also will be required to screen antiviral drugs and evaluate combination therapy approaches that target multiple steps in the replication cycle (e.g., inhibitors of viral entry, translation, and assembly).

Advanced resources such as cell lines derived from human embryonic stem cells collected within existing guidelines or induced pluripotent stem cells will aid the development of robust, specific, and reliable cccDNA reporter cell culture systems that would be particularly useful for developing antiviral therapies. The development of organoids that may physiologically reflect normal liver biology would also be useful for advancing fundamental knowledge of HBV biology and developing and screening potential new therapies.

New cell-free test systems for high-throughput screening of potential antiviral agents will be necessary to spur progress in developing hepatitis B cure therapies. Potential agents include oligopeptide libraries of factors likely to produce promising cure strategies, such as known T-helper and cytotoxic T-cell epitopes. Automated screening of biomolecules can also be used to examine virus-specific targets affecting transcription, translation, viral packaging, export, and infection.

Objective 2.3 Improve and create new animal models that reflect the progression of human liver disease

Developing animal models that recapitulate human disease is crucial for both basic and preclinical studies. Preclinical studies will require a clear understanding of which aspects of the disease each model accurately reflects. A model to study mother-to-child transmission, a major cause of chronic HBV infection, would be valuable.

Chimpanzees, the only nonhuman primate that can be infected with HBV, have previously been an important experimental model. Due to bioethical considerations, the use of chimpanzees for NIH-sponsored research is no longer permitted. *In vivo* studies currently rely on tupaia, woodchuck, duck, and mouse models. The tupaia, commonly known as a tree shrew, is the only

non-primate that can be infected with HBV, however viral replication in these animals is low and transient. This model was used to identify NTCP as a receptor for HBV. The woodchuck model is often used for preclinical studies but is a surrogate model that relies on infection with the woodchuck hepatitis virus (WHV), which is similar to HBV.

Infection of mice with HBV is complicated and necessitates either an alternate delivery method, such as microinjection or the use of an HBV-carrying vector; modification of the mice by transgenic expression of the virus; or transplantation of human liver cells into immunodeficient mice to enable long-term replication and establishment of cccDNA.

The limitations of these small animal models underscore the need for developing a viable nonhuman primate model and an immunocompetent mouse model to address complex questions in HBV research. Fortunately, several new models of chronic HBV infection are being developed. Notably, the transgenic expression of the HBV entry receptor NTCP in mice and rhesus macaques enables HBV infection and replication in immunocompetent animals, although it does not yet lead to viral persistence or cause disease. Preliminary results suggest that alternate models, such as spider monkeys, can develop long-term HBV infection. NIH will support studies to determine how well the dynamics of host-pathogen interactions, viral pathology, and responses to vaccines and therapeutics seen in animal models are replicated in humans.

Objective 2.4 Establish biomarkers for disease progression and response to therapy

There is a need for biomarkers to detect early HBV infection, stages of liver injury (including HCC), viral replication, and response to therapy. Potential biomarkers include pre-genomic RNA (pgRNA) and quantitative HBsAg. HBV cccDNA, a key indicator of HBV replication, is restricted to the nucleus of infected hepatocytes and difficult to measure. Surrogate serum markers of cccDNA and HBV replication within liver cells are needed. Recent reports suggest that the HBC core-related antigen (HBcrAg) is a reliable indicator of cccDNA transcription and may be superior to other markers. HBcrAg may also be useful in predicting outcomes of chronic hepatitis B disease.

Using state-of-the art technologies to systematically collect and analyze clinical, immunologic, and virologic data from people with chronic HBV will be vital to understanding complex host-pathogen interactions and their relationship to clinical outcomes. Analysis of these data can in turn help identify biomarkers that reflect disease progression and predict the response to treatment in various populations. Such biomarkers will form the basis of improved assays not only to further fundamental knowledge of HBV and identify vulnerabilities that can be exploited for a cure, but also to evaluate the efficacy of potential cure approaches. These biomarkers will need to be validated in different racial and ethnic populations to ensure their wide applicability.

Objective 2.5 Develop diagnostics and tools for monitoring disease and evaluating therapeutics

Diagnostics and monitoring tools for clinical research, which build on biomarkers identified as part of Objective 2.4, will need to be developed in parallel with candidate therapies. Developing low-cost point-of-care diagnostics suitable for use in resource-limited settings and in low- and middle-income countries where chronic HBV infection is prevalent is a priority.

NIH will support the development of improved assessments of treatment efficacy, such as minimally invasive approaches to measure disease progression. This could involve enhancing clinical techniques that build on existing biopsy methods to obtain liver tissue for examination and advancing noninvasive *in vivo* imaging methods such as transient elastography, a specialized form of ultrasound. NIH also will support the development of improved methods to assess liver synthetic function and hemodynamics (portal hypertension). Expanding assessment approaches will be key to developing and evaluating promising HBV countermeasures.

In addition, improved diagnostics will be needed to enable early detection and treatment of HCC in the context of HBV infection. Existing antiviral drugs reduce but do not eliminate the risk of developing HCC. As some risk of developing HCC remains even after HBV infection has been eliminated, periodic post-treatment monitoring of individuals will be important. Such monitoring will be especially important for people with cirrhosis and those who were infected with HBV genotypes known to be associated with HCC in the absence of cirrhosis.

Objective 2.6 Expand clinical research capacity

Clinical research studies will be essential in the early stages of discovery research and at later stages to test putative cure regimens and new diagnostics across populations at high risk of HBV, including children and underserved populations. Clinical studies that aim to increase fundamental knowledge and inform the development of an HBV cure will require multidisciplinary collaborations. These studies will draw on expertise from diverse disciplines, including virology, immunology, systems biology, data science, genetics, and epidemiology.

Building clinical research capacity includes multiple components, from identifying clinical research sites and recruiting relevant diverse populations to training staff and deploying new tools at clinical sites. NIH will build on its existing investments in clinical research infrastructure and resources (Appendix 4) in the United States and in locations where HBV is endemic. In addition, leveraging NIH resources in settings where both HBV and HIV are endemic will facilitate the development of an HBV cure as well as treatment approaches for people coinfected with HIV.

To accomplish this ambitious research agenda, it will be critical to recruit and train investigators in the field of HBV research for both clinical and basic research. A recent analysis of the NIAID hepatitis B portfolio revealed that few researchers focus exclusively on HBV. However, many investigators do include HBV in studies of HIV, liver cancer, or other aspects of liver function.

Pursuing the research opportunities described in this plan should enable an increased focus on HBV research and an expansion of the cadre of HBV researchers across NIH.

Strategic Priority 3: Hepatitis B Cure and Prevention Strategies

Developing strategies for the cure of chronic HBV infection will include interventions to reduce related morbidity and mortality and will build on insights gained on the biology of HBV and protective immune mechanisms in acute infection, as outlined above. The model systems, assays, biomarkers, and other resources developed as outlined in Strategic Priorities 1 and 2 will be critical for testing potential new therapies and advancing the most promising approaches into clinical studies. Realizing these goals will require collaborations between academic and industry partners.

In addition to curing hepatitis B, improving prevention strategies is essential to ending the hepatitis B epidemic. Implementation of the WHO guidelines to vaccinate all children and high-risk adults would make significant progress towards eliminating transmission of HBV.

Objective 3.1 Create cure strategies that suppress viral replication and/or stimulate the immune response

As outlined in Strategic Priority 1, multiple approaches will be required for blocking viral entry into uninfected hepatocytes, preventing viral replication, and silencing or eradicating cccDNA. Drugs to target each of the viral proteins are in various stages of development, and some are already being evaluated in clinical trials. NIH will stimulate research aimed at developing these approaches, including advancing small molecule drugs that target essential HBV proteins and crucial strategies that degrade or suppress transcription of cccDNA. Current approaches to degrade cccDNA (e.g., by CRISPR/Cas9) are challenging in terms of translation to the clinic.

Box 5. Strategic Priority 3— Development of Hepatitis B Cure and Prevention Strategies	
1.1	*Create cure strategies that suppress viral replication and/or stimulate the immune response*
1.2	*Evaluate curative approaches in various subpopulations*
1.3	*Develop effective strategies to screen and vaccinate high-risk and underserved populations and ensure follow-up to care and adherence to treatment*

NIH also will promote the development and testing of new and existing approaches to facilitate an effective host immune response to the virus, as in individuals who naturally resolve an acute or chronic HBV infection. Immunotherapies aimed at curing HBV could eliminate infected cells, prevent virus spread from persistently infected cells, and block mechanisms used by the virus to evade the host immune response. These agents may include those that modulate adaptive immunity, such as immune checkpoint inhibitors (e.g., anti-PD1/PD-L1 antibodies) and chimeric antigen receptor (CAR) T cells, which are already being used to treat a wide range of cancers, as well as agents that modulate innate immunity.

Combination therapies that can suppress viral replication and stimulate the immune response to prevent viral spread are likely to be the most effective approaches to cure hepatitis B. New therapies will need to be explored as potential combinations and developed together.

Objective 3.2 Evaluate curative approaches considering subpopulations and comorbidities

Factors such as sex, gender, race, and ethnic background will need to be considered when evaluating potentially curative therapies and the long-term clinical residual risk of liver disease progression and HCC. The risk of progression from cirrhosis to HCC is considerably higher in men than in women, and higher in Hispanic men in the southern Texas border area compared to other areas in the United States.

Development and evaluation of potential HBV cures should focus particularly on pediatric populations, which are at highest risk for chronic HBV infection and its long-term sequalae. Other important subpopulations include chronically infected women of childbearing age, who risk transmitting the virus to their infants during childbirth or in early childhood; and injection drug users and men who have sex with men, two groups at higher risk of HBV infection. These vulnerable populations should be prioritized when considering the testing of potential cures.

Any potential cure will need to be evaluated in HBV-infected individuals with other complicating medical conditions or coinfections to ensure effectiveness in these populations, especially considering that the therapy itself may result in cytotoxicity and liver inflammation. Therapies are also needed specifically for patients whose immune systems are suppressed because of cancer treatment, treatment with biologic therapies, or immunodeficiency disorders, since immunosuppression sharply increases the risk of HBV reactivation.

Dietary, behavioral, and social variables also will affect the clinical impact of a cure. Heavy alcohol consumption is an independent risk factor for cirrhosis and HCC; the risk of developing alcohol-associated HCC is increased in the context of chronic HBV infection. Individuals with alcohol use disorders as well as injection drug users, who are at increased risk of HBV infection, may be particularly difficult to reach with potentially curative therapies. Finally, obesity, type 2 diabetes, and other factors can contribute to non-alcoholic steatohepatitis (NASH), a form of fatty liver disease that may lead to cirrhosis and HCC. The risk of developing HBV-related cirrhosis and HCC thus may be increased in people with NASH-related liver damage. These considerations will affect the public health impact of a cure and inform the development of guidelines for its implementation.

NIH will continue to support the development of improved clinical trial designs with the appropriate clinical endpoints, including validated surrogate markers to assess efficacy. These studies could be implemented by leveraging the clinical research networks used in Strategic Priority 1 and existing NIH-sponsored networks such as the HIV clinical trial networks.

Objective 3.3 Develop effective strategies to screen and vaccinate high-risk and underserved populations and ensure follow-up to care and adherence to treatment

Innovative, effective strategies to screen and vaccinate populations at high risk for HBV infection, including underserved populations, must be devised and implemented. Improved access to the existing and highly effective HBV vaccine, particularly for infants and other individuals at high risk for infection, will be critical to eliminating hepatitis B. Improved screening, vaccination of uninfected individuals, and treatment of HBV-infected individuals will reduce the number of HBV infections and the complications and deaths due to long-term sequelae of chronic HBV infection.

Current WHO guidelines recommend the vaccination of all children starting at birth. Current HBV vaccines are nearly 100% effective after three doses in most populations, especially children. A newly approved HBV vaccine has higher response rates with just two doses in adults who are usually poor responders, such as those with complicating comorbidities or coinfections (e.g. obesity, HIV, renal failure, transplantation). The efficacy of this new vaccine still needs to be assessed and recommendations made for its use.

Current guidelines for HBV treatment and prevention are not being implemented in underserved areas in the United States. Improved approaches are needed to promote primary and secondary prevention strategies to vaccinate and screen individuals from HBV endemic areas and treat infected individuals. New strategies that are more effective at decreasing infection could be considered, such as promoting HBV vaccination for school age children, and screening of all adults upon college enrollment. Systematically screening patients for HBV infection prior to cancer chemotherapy or immunosuppressive treatment would decrease the risk of HBV reactivation. Interventions will need to be designed to better implement HBV cure guidelines and to facilitate clinical follow-up and adherence to treatment in high-risk populations. Public health strategies to promote follow-up to care and adherence to treatment for individuals who test positive for HBV and are eligible for treatment—and thereby reduce viral transmission—must also be part of the global effort to control the hepatitis B epidemic. These strategies will need to address the stigma of chronic HBV infection in some populations, which poses challenges for achieving effective screening and follow-up to care. Lifelong or long-term adherence to treatment to control HBV infection is challenging, especially in resource-limited settings, where both the cost and availability of existing antiviral therapies are current barriers to care. Improved approaches to monitor long-term complications, and the development of a cure, will help alleviate these challenges.

Once effective cure regimens have been developed, a coordinated international effort will be required to develop guidelines and strategies for implementing a cure, at both the U.S. and global levels. These guidelines may need to reflect the role of HBV genetic variability over time and under the pressure of therapy.

Conclusion

NIH will continue to advance research to find a cure for hepatitis B using available mechanisms and resources to address this critical health threat. Addressing gaps in HBV research and developing needed resources and tools will facilitate the development of strategies to cure and prevent hepatitis B.

The *Strategic Plan for Trans-NIH Research to Cure Hepatitis B* aligns with the HHS National Viral Hepatitis Action Plan and builds on recommendations from the U.S. National Academies of Science, Engineering and Medicine; the Hepatitis B Foundation Roadmap for a Cure; the International Coalition to Eliminate HBV; the American Association for the Study of Liver Diseases; the European Association for the Study of Liver; the American Liver Foundation; the ACTG Hepatitis Transformative Sciences Group; the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT); the Alaska Native Tribal Health Consortium Liver Disease and Hepatitis Program; and other groups. It furthermore supports the World Health Organization goal to eliminate hepatitis B by 2030 by strengthening the research foundation that will inform new approaches to prevent, diagnose, treat, and cure this disease.

A dedicated strategy will require coordination of hepatitis B research across NIH Institutes, Centers, and Offices and build on the existing portfolio of resources and investments in biomedical research to strengthen the NIH hepatitis B research program. These efforts will reinvigorate hepatitis B research and will focus on expanding understanding of hepatitis B biology, developing tools and resources to advance HBV research, and creating strategies to cure and prevent hepatitis B.

Appendix 1. HBV Funding Opportunity Announcements (FOAs)

This list indicates opportunities in the Summer of 2019. For a comprehensive, up-to-date list, please consult the NIH Guide to Grants and Contracts.

FOA Number	Title
PA-19-097	Research to Advance HBV Cure: HIV/HBV Co-Infection and HBV Mono-infection (R01 Clinical Trial Not Allowed)
PA-18-677	Epidemiologic Research on Emerging Risk Factors and Liver Cancer Susceptibility (R01 - Clinical Trial Not Allowed)
PA-18-678	Epidemiologic Research on Emerging Risk Factors and Liver Cancer Susceptibility (R21 - Clinical Trial Not Allowed)
NOT-HD-19-021	Advancing Understanding, Prevention, and Management of Infections Transmitted from Women to their Infants
NOT-OD- 19-121	HHS Small Business Innovation Research (SBIR) Program Contract Solicitation (PHS 2020-1) Now Available

Appendix 2. Trans-NIH Hepatitis B Cure Strategic Plan Working Group Members

IC	Last Name	First Name	Position
NIAID	Alston-Smith	Beverly	Chief, Complications and Co-Infections Research Branch, Therapeutics Research Program, Division of AIDS
NIAID	Augustine	Alison	Chief, Basic Immunology Branch, Division of Allergy, Immunology, and Transplantation
NIAID	Ben-Ari	Elia	Scientific Writer/Editor, Strategic Planning and Evaluation Branch, OD
NIAID	Bushar	Nicholas	Chief, Policy, Planning and Reporting Section, Strategic Planning and Evaluation Branch, OD
NIAID	Caviston	Juliane	Health Science Policy Analyst, Strategic Planning and Evaluation Branch, OD
NIAID	Chiou	Christine	Medical Officer, Complications and Co-Infections Research Branch, Therapeutics Research Program, Division of AIDS
NIAID	Farci	Patrizia	Chief, Hepatic Pathogenesis Section, Laboratory of Infectious Diseases, Division of Intramural Research
NIAID	Koshy	Rajen	Viral Hepatitis Program Officer, Division of Microbiology and Infectious Diseases
NIAID	Miers	Sarah	Office of Scientific Coordination and Program Operations, Division of Microbiology and Infectious Diseases
NIAID	Patterson	Jean	Chief, Translational Research Section, Virology Branch, Division of Microbiology and Infectious Diseases
NIAID	Robinson	Daphne	Public Health Analyst, Strategic Planning and Evaluation Branch, OD
NIAID	Schneider	Johanna	Chief, Strategic Planning and Evaluation Branch, OD
NCI	Lam	Tram Kim	Program Director, Environmental Epidemiology Branch, Epidemiology and Genomics Research Program, Division of Cancer Control and Population Sciences
NCI	Nothwehr	Steve	Program Director, Translational Research Program, Division of Cancer Treatment and Diagnosis
NCI	Read-Connole	Betsy	Cancer Etiology Section Chief, Cancer Immunology, Hematology, and Etiology Branch, Division of Cancer Biology
NCI	Rinaudo	Jo Ann	Program Director, Cancer Biomarkers Research Group, Division of Cancer Prevention
NIDDK	Sherker	Averell	Scientific Advisor for Viral Hepatitis and Liver Diseases, Liver Diseases Research Branch

IC	Last Name	First Name	Position
NIDDK	Singh	Megan	Health Science Policy Analyst, Office of Scientific Program and Policy Analysis
NIMHD	Das	Rina	Program Director, Division of Extramural Scientific Programs
NIMHD	Duran	Deborah	Director, Office of Science Policy, Strategic Planning, Analysis, Reporting, and Data
OD	Kukic	Ira	Health Science Policy Analyst, Office of Evaluation, Performance, and Reporting, Division of Program Coordination, Planning, and Strategic Initiatives

Appendix 3. Analysis of Public Comments to Request for Information (RFI)

Introduction

Although a highly effective preventive vaccine for hepatitis B has been available for more than 30 years, infection continues to spread. Globally, more people die annually due to hepatitis B than due to HIV, tuberculosis, or malaria, highlighting the urgent need for better approaches to prevent, diagnose, treat, and cure those infected with HBV.

In 2019, NIH developed the *Strategic Plan for Trans-NIH Research to Cure Hepatitis B* to advance hepatitis B cure research. A trans-NIH working group was convened that included subject matter and policy experts from across NIH, including NCI, NIDDK, NIMHD, NIAID, and the NIH Office of the Director. The working group developed strategic priorities that outline three areas of research: expanding knowledge of hepatitis B biology; establishing tools and resources to advance hepatitis B research; and developing hepatitis B cure and prevention strategies.

NIH sought input from stakeholders in the scientific research community and the general public regarding the proposed priorities through a Request for Information (RFI). The RFI (NOT-AI-19-046) was open for comments from February 28 to March 28, 2019. Comments were submitted through a web-based form or by email. Comments were requested on, but were not limited to, the following three topics regarding hepatitis B cure research:

- Significant research gaps and/or barriers not identified in the strategic priorities above
- Necessary resources critical to advancing research in the three strategic areas
- Emerging scientific advances or techniques that may accelerate research related to the three priorities

NIH staff categorized the responses into cross-cutting themes when possible or otherwise summarized the responses to each of the three topic areas identified above.

NIAID received 34 responses to the RFI. The responses originated from a variety of organizations:

- Academia: 17
- Advocacy organizations: 7
- Private companies: 5
- Government organizations: 2
- Clinical trial networks funded by NIH: 2
- Nonprofit healthcare company: 1

Several of the advocacy groups provided comprehensive, coordinated responses.

Cross-Cutting Themes

Overall, the submissions supported both the overall effort and the specific priorities. No new priorities were suggested. Comments provided further details on what to include within each priority. The following themes emerged from comments submitted across the three questions of the RFI.

The most common response was the need for better animal models (21 responses). Animal models should replicate human disease and be used for basic and preclinical research, including challenge studies. Responses cited the need for novel non-human primate and mouse models, and a few responses suggested specific promising models, including macaques expressing NTCP and some mouse models. Some responses underscored the usefulness of an animal model that enables transmission of HBV from mother to baby. In a related cross-cutting theme, many responses also highlighted the need for *in vitro* models—efficient HBV cell culture infection models supporting the complete HBV replication cycle.

Box 6. Cross-Cutting Themes from RFI Responses

- *Animal and* in vitro *models*
- *Biomarkers*
- *Role of cccDNA in disease, assays to study cccDNA*
- *Comprehensive analysis of immune responses*
- *Basic HBV biology*
- *Pathway to HCC, role of integrated DNA*
- *Low-cost, point of care diagnostics*
- *Expanded clinical research infrastructure, international engagement, multidisciplinary collaboration*

The second common theme was the need for biomarkers that correlate with clinical benefit (17 responses). This includes biomarkers to detect early HBV infection, stages of liver injury (including HCC), viral replication, and reactivation, and biomarkers to predict disease progression, HCC, or response to therapy. Several possible biomarkers were proposed, including extracellular vesicles and microRNAs; pre-genomic RNA (pgRNA) as a circulating quantitative surrogate for cccDNA levels; quantitative HBsAg, HBcrAg, and HBV RNA; circulating liver cells; and cell-free nucleic acids, including those in exosomes.

The third common response (16 responses) was the importance of studying cccDNA biogenesis, homeostasis, and decay in order to understand the role of cccDNA in disease progression and reactivation. Several respondents emphasized that a cure for HBV would require silencing HBV cccDNA. Research on cccDNA will require the development of new methods to quantify, localize, and manipulate HBV cccDNA and transcriptional activity, including assays, culture systems, and surrogate markers to examine cccDNA activity in tissues and in the circulation.

Many responses (15) emphasized the need for in-depth analysis of the heterogeneity of immune responses to HBV in a broad variety of clinical presentations: chronic active and inactive HBV-infected patients (with or without treatment), patients with resolved infections, chronically infected patients with HBsAg loss, and vaccinated healthy individuals. This would

include characterizing the dysfunctional T-cell response, antibody specificity, the role of B cells in resolution or seroconversion, and any mechanisms of immune escape. These mechanisms should be considered across the various phases of HBV infection. The respondents emphasized the need to identify age-dependent differences in immune responses to HBV in newborns and other pediatric populations. These responses often highlighted the importance of identifying robust immunologic correlates to traditional clinical and virologic parameters.

Understanding basic HBV biology more broadly was mentioned in an additional 12 responses. This includes determining the factors that contribute to stabilizing the viral load and factors that drive liver inflammation, including interactions between HBV and hepatocytes and other cell types in the liver. Several responses highlighted the need to characterize the secretion pathways of HBV antigens. One response also mentioned the importance of determining the role of the different spliced forms of HBV DNA and RNA in HBV replication, and their potential use as biomarkers of disease progression and treatment efficacy.

Eleven responses highlighted the gaps in understanding of the pathway that leads to the development of liver cancer. Several responses also highlighted the need for research on the role and mechanisms of HBV DNA integration, including its impact on the development of HCC post-cure. This similarly will require the development of methods to detect and characterize integrated HBV DNA.

Many responses (10) indicated that diagnostics should be included in the plan. These comments included the need for low-cost diagnostics for assessing and monitoring HBV-related complications. Point-of-care diagnostics for resource-limited settings are particularly needed in the field.

International engagement was also highlighted as a focus in many responses (9). Such collaborations will be necessary to improve the clinical networks needed for discovery, development, and implementation research. Strengthening clinical research was an additional recurring theme (8 responses). This included expanding clinical research capacity and leveraging existing clinical cohorts of virologically and phenotypically well-characterized HBV patients, including cohorts such as the INSIGHT clinical cohorts, NIDDK Hepatitis B Research Network and its repository, cohorts at clinical centers such as Stanford University and other sites, REVEAL Study Cohort in Taiwan, and the Alaska Native Hepatitis B cohort. In particular, clinical research capacity needs to be expanded to include high-risk and underserved populations.

Finally, three responses noted the need for further studies of HBV-infected hepatocytes. This includes determining why some hepatocytes are infected with HBV, how long the HBV-infected cells survive, and which HBV antigens they express. Studies should also determine how many hepatocytes can be destroyed in an individual patient without causing hepatic deficiency, as the primary safety concern with immunotherapy in chronic HBV infection is the induction of fulminant hepatitis.

Significant Research Gaps and/or Barriers

The most commonly mentioned research gap (8 responses) was the role of coinfection with HIV, HCV, or HDV on hepatitis B pathogenesis, disease progression, and treatment. This includes, notably, the mechanisms by which HIV coinfection accelerates progression of chronic hepatitis B liver disease despite suppression of both viral infections, and disease reactivation in the setting of HBV/HCV coinfection.

Box 7. Significant Research Gaps and/or Barriers from RFI Responses

- *Coinfections*
- *Maternal-to-infant transmission and treatment of pregnant women*
- *Improving therapies*
- *Special groups and comorbidities*
- *Implementation research*

Maternal-to-infant transmission of HBV was the next most frequently mentioned barrier for a cure (7 responses). This includes HBV management in pregnant women and effective screening of mothers and children. In addition to pregnant women, a few responses highlighted the importance of examining pediatric populations when developing a cure. Alcohol use, obesity, and IV drug use were also mentioned as important factors to consider, as was immunosuppression – not just due to cancer treatment but also due to treatment with biological response modifiers.

Issues related to improving therapies were commonly mentioned. This includes developing therapies with improved viral suppression rates and time to viral suppression (5 responses) and improving treatment for HCC (4 respondents). Four respondents mentioned that long-acting therapeutics agents currently being developed for HIV may result in long-acting therapies that also are active against HBV infection. The optimal timing of antiviral therapy discontinuation in HBV infection is also unknown, as is the optimal time to begin therapy in patients in the immune tolerant phase (active infection, but no immune response nor liver damage).

Five responses highlighted the fact that a cure would most likely require a combination of various therapeutic approaches and suggested that NIH could facilitate collaborations with industry to accelerate clinical trials of combination therapies.

Responses also indicated the need for implementation research to determine effective strategies to promote screening and vaccination of high-risk and underserved populations, as well as effective strategies to link HBV-infected individuals to care and promote adherence to treatment. Effective strategies to screen and vaccinate or treat individuals are particularly needed in low- and middle-income countries with endemic HBV and pregnant women. A few highlighted the need for research on strategies to decrease disparities and stigmatization. Responses also called for NIH to coordinate the development of guidelines to implement a future cure regimen. One comment indicated the need to assess the role of HBV variability over time and under the pressure of treatment in terms of effects on HBV screening and immunization policies.

Notably, responses pointed out the need for markers to differentiate between "good" and "bad" ALT flares, i.e., flares of liver damage due to effective treatment, loss of HBV-infected cells, or even acceptable levels of drug-induced hepatotoxicity, versus flares of liver damage due to disease progression despite treatment.

Necessary Resources Critical to Advancing Research in the Three Strategic Areas

Three resources were frequently named as crucial to advancing research: funding, biorepositories, and shared reagents and protocols. The most common resource requested was additional funding for HBV research, be it large collaborative clinical research networks or individual research projects.

Box 8. Necessary Resources Identified in RFI Responses
• *Funding* • *Repositories of blood and liver samples* • *Shared, standardized HBV reagents and protocols*

The second most frequently requested resource was access to repositories of liver samples and blood from a broad range of clinically well-characterized persons with HBV. Access to these resources would enable the detailed immune analyses and basic biology studies mentioned as cross-cutting themes. These repositories could also include data on HBV genotype and any liver cancer that develops.

The third most requested resource was access to standardized HBV reagents and protocols. This included a broad variety: viral DNA, RNA, and protein standards; peptide libraries; monoclonal antibodies against HBV proteins; HBV clones of various genotypes; cell lines, either stably transfected or susceptible to HBV infection and replication; chemical libraries for studies in experimental models; and validated protocols for ELISPOT and flow cytometry assays.

In addition, a few responses included the need for less- or noninvasive technologies to examine the liver, e.g., improved versions of fine needle aspiration or *in vivo* imaging. One responder noted the use of developing health-related quality of life measures to assess stigma.

Emerging Scientific Advances or Techniques that May Accelerate Research Related to the Three Priorities

The advances most mentioned focused on new sequencing technologies such as deep sequencing, digital droplet PCR, and single cell analysis. All of these technologies could enable a more detailed understanding of HBV biology.

Box 9. Emerging Scientific Advances or Techniques
• *Single cell analysis, deep sequencing, digital droplet PCR* • *Advances in cancer therapies, vaccine technology* • *Laser capture microdissection* • *Systems biology, omics analysis*

New therapeutic approaches were mentioned as frequently as sequencing, especially immunotherapy approaches being used for cancer. This included T-cell transfer therapy and checkpoint inhibitor blockade used for cancer; long-acting direct-acting antivirals

similar to those currently used to treat hepatitis C; and advances in vaccine technology such as virus-like particles, antisense oligonucleotides, and fusion protein–based vaccines. These technologies could be used both to develop a cure and to dissect the virus and host factors underlying HBV pathogenesis.

The usefulness of laser capture microdissection and of omics technologies (genomics, transcriptomics, proteomics, and metabolomics) were also frequently mentioned. A comprehensive systems biological characterization of the tissues and blood from large, well-characterized cohorts of patients with HBV infection could provide significant insights on the disease process.

Summary and Conclusions

Overall, the respondents strongly supported the strategic priorities identified by the NIH working group. The responses further emphasized the need for increased research coordination that stimulated the development of a strategic plan to cure hepatitis B. The most needed elements mentioned were better animal models that can be used for preclinical testing; methods to study and understand the role of cccDNA; access to biospecimens from large, well-characterized, diverse clinical cohorts; shared, standardized research resources, reagents, and protocols; clinical networks; and multidisciplinary research collaborations. The NIH working group incorporated the RFI responses in the *Strategic Plan for Trans-NIH Research to Cure Hepatitis B*.

Appendix 4. NIH-Supported Research Resources

Resource Name	Description
AIDS Reagent Program	Acquires, develops, and produces state-of-the-art reagents and provides these reagents at no cost to qualified investigators throughout the world
BEI Resources Repository	Central repository that supplies organisms and reagents to the broad community of microbiology and infectious diseases researchers
Bioinformatics Resource Centers	Collects, archives, updates, and integrates research data with user-friendly interfaces and computational analysis tools
NIAID Clinical Genomics Program	Provides centralized resources to be used for genomics and related research
Cooperative Centers on Human Immunology	Conduct mechanistic studies to advance understanding of human immunity; also supports technology development to improve immunologic analyses of human samples
Genomic Centers for Infectious Disease Resources	Provides innovative application of genomic technologies and rapid, cost-efficient production of high-quality genome sequences for pathogens, and hosts
Hepatitis B Research Network (HBRN)	NIDDK-funded network conducts research on chronic hepatitis B to better understand the pathobiology of the disease and develop effective treatment strategies with currently available therapies, accompanied by a resource for data and biosamples related to HBV, through the NIDDK HBRN repository
HIV/AIDS Clinical Trials Networks	Group of clinical trials networks addressing HIV scientific priorities, including therapeutics for coinfections
Human Immunology Project Consortium (HIPC)	Conducts detailed immune profiling/systems immunology analyses of human immune system at steady state and before/after infection, vaccination, or adjuvant treatment. HIPC-generated datasets and analyses are publicly available through ImmuneSpace.
ImmPort	Platform to share and analyze immunology data generated from human and animal models
Immune Epitope Database and Analysis Resource	Database with detailed information for more than 100,000 unique immune epitopes (antibody/B cell and T cell) related to infectious and immune-mediated diseases
ImmuneSpace	Powerful data management and analysis engine for the HIPC program that enables integrative analyses and visualization of human immunological data
Interventional Agent Development	Services to facilitate preclinical development of therapeutics and new *in vivo* diagnostics for infectious disease–causing pathogens and/or toxins

Resource Name	Description
International Clinical Sciences Support Center	Support services, including consultation and protocol development, site assessment, and data management for clinical investigators supported by NIAID
International Epidemiology Databases to Evaluate AIDS Cohort Consortium (IeDEA)	Generates large, harmonized HIV/AIDS data sets from seven international regional data centers to help address high-priority research questions
International Network for Strategic Initiatives in Global HIV Trials (INSIGHT)	International network conducting HIV treatment trials
Liver Tissue Cell Distribution System	Provides human liver tissue from regional centers for distribution to scientific investigators throughout the United States
NCI AIDS Cancer Specimen Resource	Provides biospecimens from persons with a wide spectrum of HIV/AIDS-related diseases, particularly cancers
NCI Developmental Therapeutics Program	Provides services and resources to research communities worldwide to facilitate the discovery and development of new cancer therapeutic agents
NIH Tetramer Core Facility	Produces and distributes major histocompatibility complex tetramers and related reagents to the research community
Phase I Clinical Trial Units for Therapeutics	Support design, development, implementation, and conduct of Phase I clinical trials against viral (other than HIV), bacterial, parasitic, and fungal pathogens
Preclinical Models of Infectious Disease Program	Provides development, screening, and efficacy testing in preclinical infectious diseases models, including traditional lab species, nonhuman primates, and non-traditional models
REVEAL cohort in Taiwan	Community-based prospective study of hepatitis B and hepatitis C
Structural Genomics Centers for Infectious Diseases	Applies state-of-the-art technologies/methodologies to characterize 3-D atomic structures of molecules to support infectious disease research
Therapeutic Development Services: Biopharmaceutical Product Development Services	Offers services for biotechnology products, such as planning, product characterization, process development, formulation, Good Manufacturing Practice, and Chemistry, Manufacturing and Control documentation
Therapeutic Development Services: Interventional Agent Development Services	Facilitates development of therapeutics, including lead identification and development, chemistry and manufacturing, toxicology, and pharmacokinetics
Vaccine and Treatment Evaluation Units	Support efforts to develop new and improved vaccines and therapies against infectious diseases
Virus Pathogen Resource	Database, bioinformatics analysis and visualization tools to support the research of viral pathogens

Appendix 5. Abbreviations

Abbreviation	Definition
ALT	Alanine aminotransferase
cccDNA	Covalently closed circular DNA
DNA	Deoxyribonucleic acid
GWAS	Genome-wide association studies
HBcAg	Hepatitis B core antigen
HBcrAg	Hepatitis B core-related antigen
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HBx	Hepatitis B protein x
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDV	Hepatitis D virus
HIV	Human immunodeficiency virus
NCI	National Cancer Institute
NIAID	National Institute of Allergy and Infectious Diseases
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIMHD	National Institute of Minority Health and Health Disparities
NTCP	Sodium taurocholate co-transporting polypeptide
OD	Office of the Director
PCR	Polymerase chain reaction
RNA	Ribonucleic acid
WG	Working Group
WHO	World Health Organization