

**The NIH Hepatitis B Cure
Strategic Plan Working Group**

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**STRATEGIC PLAN
FOR NIH
RESEARCH TO
CURE HEPATITIS B
2022 UPDATE**



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Executive Summary

According to the World Health Organization (WHO), approximately 296 million people worldwide are chronically infected with hepatitis B virus (HBV) with 1.5 million infections each year despite the availability of highly effective vaccines for prevention. HBV is transmitted through sex, contact with infected blood or bodily fluids, or from an infected mother to her baby. Infection can range from acute disease that resolves within a few weeks or months to a longer-term chronic infection that may last six months or longer. The vast majority of those individuals who become infected are unaware that they are infected; the WHO estimates this number to be almost 90% worldwide. In the United States, approximately 1.6 million people are living with chronic HBV and in about 20-30% of adults, chronic infection results in life-threatening complications such as cirrhosis (scarring of the liver), liver failure or liver cancer. Chronic hepatitis B infection can be treated with medications, including oral antiviral agents. Treatment can slow the progression of cirrhosis, reduce incidence of liver cancer and improve long term survival. However, there is no intervention that cures HBV infection. An ideal cure would not only eliminate HBV infection and also reduce or eliminate these life-threatening complications.

In 2019, the National Institutes of Health (NIH) released the [*Strategic Plan for Trans-NIH Research to Cure Hepatitis B*](#), which detailed NIH efforts to advance innovative hepatitis B research and improve strategies for vaccination, screening, and follow-up to care. The plan also established a feasible and clinically relevant definition for a hepatitis B cure and included prevention strategies that would contribute to eliminating transmission of HBV.

Recently, the COVID-19 pandemic has impacted all facets of biomedical research, including research on hepatitis B. Since early 2020, hepatitis B researchers have faced the challenge of conducting research with limited access and availability of resources. However, many of the lessons learned and technologies developed during the COVID-19 pandemic may be leveraged to advance hepatitis B research.

Box 1: Strategic Plan for NIH Research to Cure Hepatitis B - 2022 Update

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

Cure definition: 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

The *Strategic Plan for NIH Research to Cure Hepatitis B 2022 Update* reaffirms NIH's commitment to the vision and mission outlined in the 2019 strategic plan to end the hepatitis B epidemic by developing a cure and improving vaccination, screening, and follow-up to care (Box 1). The *2022 Update* incorporates recent advancements and includes updates in three priority areas vital to developing a cure:

- **Strategic Priority 1: Understanding 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: Developing Tools and Resources**—biomarkers, cell culture and animal models, data science tools, diagnostics
- **Strategic Priority 3: Creating Strategies to Cure and Prevent Hepatitis B**—expanded clinical research capacity; 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 provide the comprehensive research base needed to develop a cure and prevention strategies for hepatitis B infection. 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 40 years, [approximately 1.5 million people worldwide get infected with hepatitis B virus each year](#), and [approximately 900,000 die](#) from either fulminant hepatitis (acute liver failure) or complications due to chronic HBV infection. Chronic infection with HBV is the result of a dynamic interaction between the virus and the host. The clinical spectrum of chronic HBV infection is broad, ranging from an inactive carrier state to chronic hepatitis and long-term complications such as cirrhosis (scarring of the liver), liver failure, and hepatocellular carcinoma (HCC), with 25% of people with chronic hepatitis B dying prematurely (Box 2). Worldwide, rates of HCC are also increasing, mostly due to chronic HBV infection.

Box 2: Chronic HBV Infection

People with chronic HBV infection

- 296 million people worldwide
- 1.6 million people in the United States

Transmission

- Perinatal transmission
- Contact with blood
- Sexual activity
- Needle sharing

Outcomes

- Inactive HBV carrier state
- Chronic hepatitis
- Cirrhosis (scarring of liver)
- End stage liver disease
- Liver cancer (hepatocellular carcinoma)
- Premature death in 25% of people with chronic hepatitis B

Hepatitis B is a blood-borne disease. HBV can be transmitted through sexual contact, needle sharing, or other routes of exposure to infected blood or body fluids. In addition, the virus can remain infectious on surfaces for at least seven days. In areas with high levels of infection, HBV infection is most often transmitted perinatally during birth or in early childhood by exposure to infected blood or other body fluids. Among infants infected during the first year of life, 80%–90% will develop chronic infection, while the rate decreases to 30%–50% for children infected between the ages of 1 and 5 years. In contrast to children, about 95% of adults with acute HBV infection recover completely and do not become chronically infected (Figure 1).

Increasing the vaccination rate among infants and children is a critical element in controlling the HBV epidemic. Since 1991, the [CDC Advisory Committee on Immunization Practices \(ACIP\) Guidelines](#) has recommended universal hepatitis B vaccination of neonates within 24 hours of birth, followed by 2 additional doses during infancy. However, in the United States, [full vaccination coverage within 7 months is estimated to be 63%](#), well below the target of 90%.

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. Many people with chronic HBV infection are not aware of their status. This leads to a risk of transmission and to reactivation of the liver disease, often following immunosuppression or medical treatment for conditions such as cancer or autoimmune disease. Additionally, the risk of developing cirrhosis and liver cancer is elevated among patients treated for HBV infection compared with uninfected individuals. The CDC ACIP recently recommended [universal hepatitis B vaccination](#) for adults ages 19 through 59 years. In 2017, the U.S. Food and Drug Administration (FDA) approved the 2-dose Heplisav-B vaccine, yet only an estimated [25% of adults](#) in the United States are currently vaccinated for hepatitis B. In 2021, CDC ACIP [guidelines](#) recommended the vaccination of all children and adults up to age 60. That same year, the FDA approved a 3-dose vaccine, [PreHevbrio](#), which has higher response rates in adults. Current HBV vaccines are now nearly 100% effective after three doses in most populations.

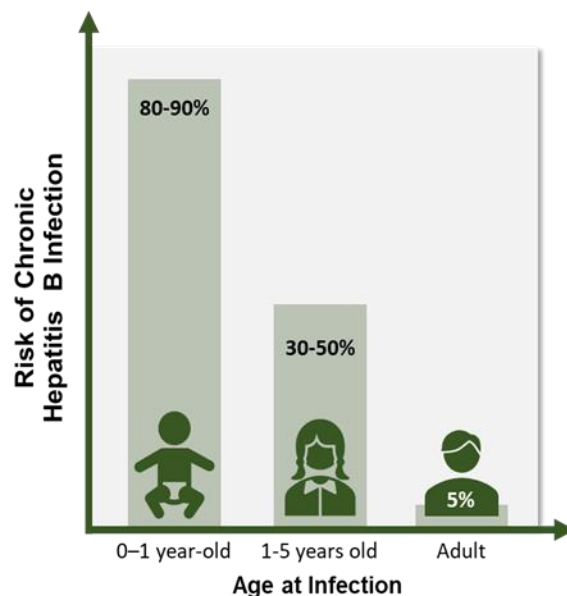


Figure 1: Age at time of HBV infection correlates with risk of developing chronic hepatitis B. Among infants 0–1 year old at time of HBV infection, 80–90% typically develop chronic hepatitis B. This rate drops to 30–50% in children 1–5 years old at time of infection, and 5% for individuals infected as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

In 2020 and 2021, the COVID-19 pandemic impacted all aspects of hepatitis B research and patient care. In the United States, racial and ethnic minority populations were disproportionately impacted by the pandemic, with higher rates of infection, hospitalization, and mortality due to COVID-19. These outcomes caused an unprecedented focus on health disparities in these populations, and underscore the important role that these differences play in contributing to health outcomes. To mitigate the continuing spread of the pandemic, large clinical trials were initiated to test SARS-CoV-2 vaccine candidates. These trials purposefully recruited diverse populations to ensure that vaccine efficacy could be evaluated broadly. Awareness of differences in health outcomes and the importance of inclusive clinical research is shifting focus onto research questions relevant to all people living with hepatitis B and creating better approaches to answer these questions.

The NIH Hepatitis B Cure Working Group, led by the National Institute of Allergy and Infectious Diseases (NIAID), was established to coordinate and facilitate research across the NIH towards a hepatitis B cure. The working group developed the *Strategic Plan for Trans-NIH Research to Cure Hepatitis B* in 2019 and reconvened to update the plan in 2022. This group consists of scientific and policy experts from NIAID, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Cancer Institute (NCI), National Institute on Minority Health and Health Disparities (NIMHD), and NIH Office of the Director (OD). Members from National Institute on Alcohol Abuse and Alcoholism (NIAAA) and National Institute on Drug Abuse (NIDA) also joined in 2022 (Appendix 1). To seek broad public input, NIH issued a [Request for](#)

[Information](#) (RFI) and received several responses from academia, advocacy organizations, industry, government, clinical trial networks, and not-for-profit organizations, as summarized in Appendix 2.

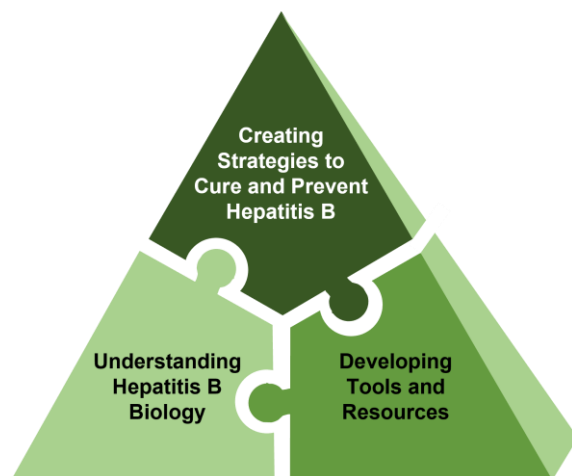


Figure 2: Strategic Plan for NIH Research to Cure Hepatitis B is built on three priority areas that are vital to developing a cure: 1. Understanding hepatitis B biology, 2. Developing tools and resources to advance HBV research, and 3. Creating strategies to cure and prevent hepatitis B.

The *Strategic Plan for NIH Research to Cure Hepatitis B 2022 Update* is focused on three interdependent and complementary priority areas (Figure 2). Improving our understanding of the biology of HBV and developing new tools and resources for HBV research are fundamental to creating strategies to cure and prevent hepatitis B. Furthermore, to effectively address the global public health challenges posed by HBV infection, a curative treatment will need to go hand in hand with better approaches for prevention, screening, and follow-up to care.

Strategic Priority 1: Understanding Hepatitis B Biology

Developing a cure for HBV will require continued advances in understanding the complex molecular and immune mechanisms underlying infection and disease. Clinical manifestations of chronic hepatitis B can vary greatly and can transition between different phases (immune-tolerant, immune-active, and inactive). These phases are differentiated using markers of viral replication (hepatitis B e antigen [HBeAg], hepatitis B surface antigen [HBsAg], and HBV DNA), and markers of liver disease such as alanine aminotransferase (ALT) levels. Studies that elucidate the viral lifecycle and host responses to infection can identify potential targets for intervention in HBV infection and disease. Successful cure therapies will likely require two strategies: one that directly inhibits viral activity and a second that prevents viral spread to uninfected cells.

The HBV life cycle is unique in that during replication, genomic DNA is converted to a molecular template DNA, called covalently closed circular DNA (cccDNA), that is used to amplify all viral

RNAs. Silencing HBV cccDNA is considered essential for a cure. Developing assays to quantify cccDNA and assess its transcriptional activity is also a critical component in curing HBV. Continuing to advance our understanding of the function of various viral proteins and host factors is necessary for improving the assays, models, and other resources needed to move toward a cure.

The clinical outcomes of HBV infection are affected by many factors, including age, sex, race, 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 clinical studies are needed to provide insights into the complexity and range of host-pathogen interactions. Results from these investigations will 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.

Box 3. Strategic Priority 1 — Understanding Hepatitis B Biology

- 1.1 Identify viral factors that control infection and disease
- 1.2 Understand immune responses 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

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 nucleoside and nucleotide 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. Investigations into understanding each step of the HBV lifecycle and the role of various viral factors in the progression of disease are necessary to develop 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 into the mechanisms of the HBx protein in viral replication, its regulatory function in the transcription of cccDNA, and its role in HBV pathogenesis may also 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 elucidate 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 underpinning this process and identify targets essential to halt its progression.

Objective 1.2 Understand immune responses and other host factors of HBV infection

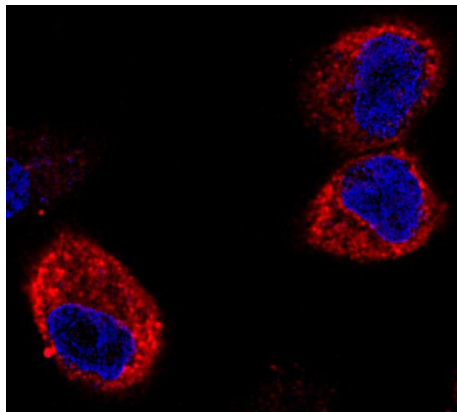


Figure 3: Hepatitis B core antigen (HBcAg, red) in the cytoplasm of human liver cancer cells (HepG2) transfected with HBV. Cell nuclei are labelled in blue. Credit: NIAID

HBV infection resolves in 95% of adults, indicating 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. Continued research to understand the nature of such effective host immune responses are crucial for harnessing them therapeutically.

To accomplish this, the roles of both the adaptive and the innate immune responses to HBV infection need to be better characterized. Extensive analyses of systemic and tissue specific (liver) T-cell and B-cell responses, T-cell exhaustion in HBV persistence, and T-cell recovery, as well as mechanisms by which HBV proteins impact antiviral

innate and adaptive immunity, are still needed to better understand immune control of the virus. These studies should 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

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 requires the identification of age-related differences in the immune response to HBV.

Some of the variety in clinical outcomes is related to genetics. For instance, 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, response to therapy, and vaccine responsiveness.

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 with or 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.

In addition to genetics, many factors influence 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 coinfecting 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 must be considered, particularly as they relate to important comorbidities and coinfections. Alcohol misuse 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 needle sharing, can lead to coinfection with either HIV, HDV, or HCV. Furthermore, substance use disorders may have effects on the outcome of viral infections. Additional research is necessary to study the mechanisms whereby substance use affects viral pathogenesis, antiviral immunity and disease progression of HBV mono-infection or coinfection with HIV, HDV, or HCV.

Clinical pathology studies need to focus on persons in and from HBV-endemic countries, to examine biological, environmental, social, or cultural factors that might affect the immune 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 protect certain populations may also be identified, such as the contribution of diet or microbiome to the enhancement of natural immunity

Strategic Priority 2: Developing Tools and Resources

Achieving the research objectives outlined in Strategic Priority 1 to advance understanding of hepatitis B biology requires standardized tools and resources including reagents, laboratory methods, animal models, and assays. This effort also includes the application of novel technology such as comprehensive systems biology analyses of patient data, laser capture microdissection, digital droplet polymerase chain reaction (PCR), and deep sequencing. Use of biorepositories and online platforms allow investigators to share resources, tools, data, and samples for basic research, product testing, and clinical evaluation. The development of new data science tools can accelerate research, illuminating new potential mechanisms of disease and possible drug effects, or interactions. Improved cell culture systems, including human organoid cultures, to support fundamental research and product development, and new animal models that better reflect human HBV infection and related diseases, are also necessary. Finally, biomarkers for various stages of disease, and improved and validated diagnostic, monitoring, and assessment tools will advance fundamental and clinical HBV research.

Box 4. Strategic Priority 2 — Developing Tools and Resources

- 2.1 Share and standardize data, 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

Objective 2.1 Share and standardize data, 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. Such efforts include 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, are important. Together, these steps will facilitate the exchange of standardized samples and data between investigators and expand the hepatitis B knowledge base.

Artificial intelligence and data science have emerged as increasingly powerful tools to address questions in HBV research. Applying these tools to large clinical data sets can identify factors

linked to infection and disease progression, revealing important biological mechanisms to be explored and suggesting possible avenues for a cure. Such analyses depend on validated, standardized biological and clinical data sets, including standardized measures of factors that can affect health outcomes. Improving data science tools and the availability of hepatitis B biological and clinical data will accelerate the development of a hepatitis B cure. Augmented reality (AR) technology is an example of a method for researchers to communicate and learn about structural and functional features of biomolecules and viruses. NIAID added a module about HBV to its public virtual reality application [PathogensAR](#) to educate researchers, clinicians, and the public about HBV.

NIH will leverage existing clinical/epidemiological cohorts, (Appendix 3) such as [the Hepatitis B Research Network \(HBRN\) 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 \(INSIGHT\)](#) to advance hepatitis B cure research and continue to support the development of new standardized reagents, protocols, and assays. NIH is facilitating the sharing of key resources through biorepositories such as [BEI](#), a repository supported by NIAID. The new [NIH Policy on Data Management and Sharing](#), effective January 2023, aims to increase openness and facilitate sharing. The NIH Office of Data Science Strategy is developing data science educational opportunities for biomedical researchers as well as data science tools and databases, such as the [Generalist Repository Ecosystem](#), to facilitate access to standardized data.

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 sodium taurocholate co-transporting polypeptide (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 necessary 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 will also be useful for advancing fundamental knowledge of HBV biology and host-pathogen interactions, and for developing and screening potential new therapies.

Platform technologies that are easily adapted to various diseases or conditions have shown promise for other diseases, such as mRNA-based vaccines for COVID-19. The combination of these emerging technologies and new possible targets may lead to new strategies to prevent or treat and possibly cure chronic hepatitis B. New validated, 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 to evaluate hepatitis B virology, liver pathogenesis, and novel cure strategies

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

In vivo studies on HBV 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 it 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. These new or improved models are essential to test potential cure strategies.

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 is difficult to measure. Surrogate serum markers of cccDNA and HBV replication within liver cells are needed. Recent reports suggest that the hepatitis B core-related antigen (HBcrAg) is a reliable indicator of cccDNA transcription and may also be useful in distinguishing the different phases of chronic hepatitis B. Similarly, serum HBV RNA has also been shown to be a potential biomarker for chronic hepatitis B infection and treatment response. Further studies are needed to explore the usefulness and validation of these biomarkers in guiding clinical management and predicting the outcome of antiviral therapy.

Using state-of-the art technologies, including data science tools, 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 and validate 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 broad 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, need to be developed in parallel with candidate therapies. The last few years have seen the application of machine learning to develop new approaches to diagnose people with hepatitis B and to identify those at high risk of disease progression. Developing, standardizing, and validating affordable point-of-care diagnostics suitable for use in all settings and in all geographic locales where chronic HBV infection is prevalent is a priority.

NIH supports 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 is important. Such monitoring is 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.

Strategic Priority 3: Creating Strategies to Cure and Prevent Hepatitis B

Developing strategies to cure chronic HBV infection will include interventions to reduce related morbidity and mortality and will build on insights gained from 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, are critical for testing potential new therapies and advancing the most promising approaches into clinical studies. Increased clinical research capacity and collaborations between academic and industry partners are required to learn more about the disease in humans and to test cure and prevention strategies.

Box 5. Strategic Priority 3 — Creating Strategies to Cure and Prevent Hepatitis B

- 3.1 Create cure strategies that suppress viral replication and/or stimulate the immune response
- 3.2 Expand clinical research capacity
- 3.3 Evaluate curative approaches in all populations
- 3.4 Develop effective strategies to screen and vaccine vulnerable populations and ensure follow-up to care and adherence to treatment

In addition to curing hepatitis B, improving prevention strategies is essential to ending the hepatitis B epidemic. Implementation of the [new guidelines](#) to vaccinate all children and adults would make significant progress toward eliminating transmission of HBV. Developing culturally appropriate, multi-level prevention strategies that reach those most likely to become infected with HBV, and those with limited English proficiency, would also accelerate the elimination of HBV transmission by addressing barriers at the individual, community, and structural levels.

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

As outlined in Strategic Priority 1, multiple approaches are required for blocking viral entry into uninfected hepatocytes, preventing viral replication, and silencing or eradicating cccDNA. Individual drugs, and drug combinations to target each of the viral proteins are in various

stages of development, and some are currently being evaluated in clinical trials. NIH is stimulating research to develop these approaches, including advancing small molecule drugs that target essential HBV proteins and 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.

NIH is promoting 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 already are being used to treat a wide range of cancers, as well as agents that modulate innate immunity.

Combination therapies that 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. As potential therapeutics are being developed, such as HBx protein, capsid inhibitors, siRNAs, nucleic acid polymers/ S-antigen transport-inhibiting oligonucleotide polymers (NAPs/STOPs), antisense oligonucleotides (ASOs), and entry inhibitors, additional effort is needed to systematically design and test combinations of these candidates in new and improved animal models before evaluating them in humans.

Objective 3.2 Expand clinical research capacity

Testing putative cure regimens, new diagnostics, and improved prevention strategies will require expanded clinical research capacity, with a particular emphasis on involving those most likely to become infected with HBV, including vulnerable and minority populations and children. Building clinical research capacity includes multiple infrastructure resource components, from identifying clinical research sites and recruiting relevant populations, to training staff and deploying new tools at clinical sites. The COVID-19 pandemic enabled the large-scale application of innovative strategies, such as telehealth visits for clinical research, expanded involvement of community leaders, and enrollment of minority populations. Applying these approaches to hepatitis B clinical research could lead to the development of more relevant and easier-to-use interventions to cure and prevent hepatitis B. NIH will build on its existing investments in clinical research infrastructure and resources (Appendix 3) 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 coinfecting 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. An 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. Encouraging multidisciplinary collaborations helps draw on expertise across disciplines, including virology, immunology, systems biology, data science, genetics, and epidemiology. Pursuing the research opportunities described in this plan should enable an increased focus on HBV research, improve the design and impact of clinical studies, and expand the cadre of HBV researchers across NIH.

NIH will continue to leverage existing research activities, resources, and human cohorts. For example, researchers continue to analyze data from the NIDDK, which conducted clinical studies of disease characteristics and treatment approaches in both adults and children, in collaboration with several industry partners. The HBRN and its [repository](#) help researchers explore the mechanisms of viral pathogenesis, including immunology and HBV/HIV co-infection. A new Liver Cirrhosis Network, supported by the NIDDK in collaboration with the NCI and NIAAA, is building upon this work by establishing a longitudinal cohort of people with cirrhosis, including those with chronic hepatitis B. This Network plans to test new therapeutic approaches to cirrhosis, such as the use of statin drugs.

Objective 3.3 Evaluate curative approaches in all populations

Any cure strategy developed, whether a single or a combination approach, will need to be evaluated among all populations. Factors such as sex, race and ethnic background, socioeconomic status, and country of birth need to be considered when evaluating potential cures and the long-term clinical residual risk of liver disease progression and HCC. For example, 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. Furthermore, many people with chronic hepatitis B are immigrants from Africa or Asia and are often not perceived as at-risk for infection due to lack of awareness among clinicians. 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. Examination of interactions between therapies is 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 sociocultural variables also affect the clinical impact of a cure. For example, 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 those who engage in injection drug use, who are at increased risk of HBV infection, may be particularly difficult to reach with potentially curative therapies. Furthermore, 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 listed in Strategic Priority 2 and existing NIH-sponsored networks such as the HIV clinical trial networks.

Objective 3.4 Develop effective strategies to screen and vaccinate vulnerable populations and ensure follow-up to care and adherence to treatment

Innovative, effective strategies to screen those most likely to become infected with HBV, including underserved and hard-to-reach populations, must be devised and implemented. Improved access to the existing and highly effective HBV vaccine is 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.

In 2017, the U.S. Food and Drug Administration (FDA) approved the HepBisav-B vaccine—which requires only two shots over one month instead of three shots over six months and that may facilitate the implementation of the new guidelines and protect more adults from hepatitis B and liver cancer. Despite this advancement, the CDC estimates that only [25% of adults](#) in the United States are currently vaccinated for hepatitis B. As of November 2021, CDC ACIP [guidelines](#) recommend the vaccination of all children and adults up to age 60. Current HBV vaccines are nearly 100% effective after three doses in most populations, especially children. In 2021, the FDA approved an HBV vaccine, [PreHevbrion](#), that has higher response rates with three doses in adults, who are more likely to be poor responders due to complicating comorbidities or coinfections (e.g., obesity, HIV, renal failure, transplantation). Implementing the new U.S. recommendations to vaccinate adults should decrease the incidence of both infection and transmission.

Implementation of the current guidelines for HBV prevention is a particularly important issue for underserved and hard-to-reach populations in the United States. Improved approaches are needed to vaccinate and screen people from HBV-endemic countries who have moved to the United States, and to treat infected individuals. Strategies are needed to overcome vaccine hesitancy and improve vaccine uptake, especially among those most likely to become infected

with HBV. New strategies to decrease infection could be considered, such as free mobile vaccination clinics, or screening clinics for adults. Screening will also serve to inform people and communities about HBV infection and limit further transmission. Other strategies will need to be tailored to reach specific groups. For instance, systematically screening patients for HBV infection prior to cancer chemotherapy or immunosuppressive treatment would decrease the risk of HBV reactivation, which in some cases may lead to acute liver failure.

Interventions are needed to better implement HBV treatment guidelines and to facilitate clinical follow-up and adherence to treatment in vulnerable 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 need to address the stigma of chronic HBV infection in some populations, which poses challenges for achieving effective screening and follow-up to care. Long-term adherence to treatment to control HBV infection is challenging, especially in hard-to-reach populations, and 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 strategies for implementation at both the U.S. and global levels. These strategies may need to be modified to address 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.

This *Strategic Plan for NIH Research to Cure Hepatitis B 2022 Update* aligns with the HHS [Viral Hepatitis National Strategic 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 [HHS](#) and [WHO](#) goals 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 to build on the existing portfolio of resources and investments in

biomedical research to strengthen the NIH hepatitis B research program. These efforts will continue to strengthen hepatitis B research, 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. 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	Azeez	Olumayowa	Health Science Policy Analyst, Policy, Planning and Evaluation Branch, OD
NIAID	Bushar	Nicholas	Chief, Policy, Planning and Reporting Section, Policy, Planning and Evaluation Branch, OD
NIAID	Caviston	Juliane	Health Science Policy Analyst, Policy, Planning and Evaluation Branch, OD (now at NIH Office of Research on Women's Health)
NIAID	Challberg	Mark	Chief, Virology Branch, Division of Microbiology and Infectious Diseases
NIAID	Chiou	Christine	Medical Officer, Complications and Co-Infections Research Branch, Therapeutics Research Program, Division of AIDS
NIAID	Deckhut	Alison	Chief, Basic Immunology Branch, Division of Allergy, Immunology, and Transplantation
NIAID	Farci	Patrizia	Chief, Hepatic Pathogenesis Section, Laboratory of Infectious Diseases, Division of Intramural Research
NIAID	Koshy	Rajen	Viral Hepatitis Program Officer, Virology Branch, Division of Microbiology and Infectious Diseases
NIAID	Miers	Sarah	Program Analyst, 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	Health Science Policy Analyst, Policy, Planning and Evaluation Branch, OD (now at NIH's National Institute of Arthritis and Musculoskeletal and Skin Diseases)

IC	Last Name	First Name	Position
NIAID	Schneider	Johanna	Chief, Policy, 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
NIAAA	Wang	Joe	Program Director, Division of Metabolism & Health Effects
NIDA	Cotto	Jessica	Health Science Policy Analyst, Science Policy Branch
NIDA	Hartsock	Peter	Research Scientist Officer, Epidemiology Research Branch
NIDDK	Sherker	Averell	Scientific Advisor for Viral Hepatitis and Liver Diseases, Liver Diseases Research Branch
NIDDK	Singh	Megan	Health Science Policy Analyst, Office of Scientific Program and Policy Analysis
NIMHD	Das	Rina	Program Director, Division of Integrative Biological and Behavioral Sciences
NIMHD	Farhat	Tilda	Director, Office of Science Policy, Planning, Evaluation, and Reporting, Reporting, and Data
OD	Kuhn	Ira	Health Science Policy Analyst, Office of Evaluation, Performance, and Reporting, Division of Program Coordination, Planning, and Strategic Initiatives

Appendix 2. Analysis of Public Comments to Request for Information (RFI)

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-22-018](#)) was open for comments from December 27, 2021 to January 31, 2022. Comments were submitted through a web-based form or by email. Comments were requested on, but were not limited to, the following four topics regarding hepatitis B cure research:

- Recent significant research advances in hepatitis B as well as in other areas that could have implications for the development of a hepatitis B cure
- Impact of COVID-19 pandemic on hepatitis B research, and possible solutions
- Emerging research questions and/or barriers
- Resources necessary to advance basic, translational, and clinical research to cure hepatitis B.

NIH received 5 responses to the RFI, including a detailed, coordinated response from 23 advocacy groups. Other responses originated from academia and private companies, representing 27 organizations in total. Overall, the submissions supported both the effort to update the plan and the specific priorities. No new priorities were suggested. Comments provided further details on what to include within each priority.

Strategic Priority 1 – Understanding Hepatitis B Biology

- Understand HBV cccDNA biology
- Explore the roles of HBx, HBsAg, HBcAg, and HBeAg in pathobiology
- Characterize the variety of immune responses to HBV
- Understand the impact of various HBV genotypes
- Address the role of HBV DNA integration in HCC development, and improve HCC treatment

Strategic Priority 2 – Developing Tools and Resources

- Consider the impact and treatment of co-infection with HDV and HIV, including systematically assessing drug interactions
- Develop biomarkers of disease, especially to reflect disease reactivation and flare-ups
- Improve and create new animal models that enable evaluation of potential therapies

Strategic Priority 3 – Creating Strategies to Cure and Prevent Hepatitis B

- Explore new strategies for prevention as well as immune-therapeutic intervention and ways of producing therapeutic proteins in target organs, such as mRNA vaccines
- Systematically design and evaluate potential combination therapies
- Incorporate more patient-friendly strategies, such as telehealth visits for clinical research

- Conduct research to understand the barriers to linkage to care, especially among immigrants from Africa and Asia and those with limited English proficiency
- Coordinate with community partners (community leaders and people living with HBV) to develop evidence-based, culturally appropriate interventions for HBV screening, vaccination, and treatment
- Explore the possibility of an Undetectable=Untransmittable approach for hepatitis B

The NIH working group members carefully considered all the suggestions and incorporated them in the updated plan as appropriate. Many of the RFI responses mentioned research areas included in the original plan that underscored the importance of understanding hepatitis B biology, developing animal models and identifying biomarkers. RFI responses related to Priority 3 reflected an increased awareness of health disparities and new approaches to research developed during the COVID-19 pandemic. These are reflected in the updated plan.

Appendix 3. NIH-Supported Research Resources

Resource Name	Description
<u>AIDS Reagent Program</u>	Acquires, develops, and produces state-of-the-art reagents and provides these reagents at no cost to qualified investigators throughout the world
<u>BEI Resources Repository</u>	Central repository that supplies organisms and reagents to the broad community of microbiology and infectious diseases researchers
<u>Bioinformatics Resource Centers</u>	Collects, archives, updates, and integrates research data with user-friendly interfaces and computational analysis tools
<u>NIAID Clinical Genomics Program</u>	Provides centralized resources to be used for genomics and related research
<u>Cooperative Centers on Human Immunology</u>	Conduct mechanistic studies to advance understanding of human immunity; also supports technology development to improve immunologic analyses of human samples
<u>Genomic Centers for Infectious Disease Resources</u>	Provides innovative application of genomic technologies and rapid, cost-efficient production of high-quality genome sequences for pathogens, and hosts
<u>Hepatitis B Research Network (HBRN)</u>	NIDDK-funded network conducts ongoing analyses of completed 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 <u>NIDDK HBRN repository</u>
<u>HIV/AIDS Clinical Trials Networks</u>	Group of clinical trials networks addressing HIV scientific priorities, including therapeutics for coinfections
<u>Human Immunology Project Consortium (HIPC)</u>	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 <u>ImmuneSpace</u> .

Resource Name	Description
<u>ImmPort</u>	Platform to share and analyze immunology data generated from human and animal models
<u>Immune Epitope Database and Analysis Resource</u> <i>Immune Epitope Database and Analysis Resource</i>	Database with detailed information for more than 1,000,000 unique immune epitopes (antibody/B cell and T cell) related to infectious and immune-mediated diseases
<u>ImmuneSpace</u>	Powerful data management and analysis engine for the HIPC program that enables integrative analyses and visualization of human immunological data
<u>Interventional Agent Development</u>	Services to facilitate preclinical development of therapeutics and new <i>in vivo</i> diagnostics for infectious disease-causing pathogens and/or toxins
<u>International Clinical Sciences Support Center</u>	Support services, including consultation and protocol development, site assessment, and data management for clinical investigators supported by NIAID
<u>International Epidemiology Databases to Evaluate AIDS Cohort Consortium (IeDEA)</u>	Generates large, harmonized HIV/AIDS data sets from seven international regional data centers to help address high-priority research questions
<u>International Network for Strategic Initiatives in Global HIV Trials (INSIGHT)</u>	International network conducting HIV treatment trials
<u>Liver Cirrhosis Network (LCN)</u>	Network funded by the NIDDK, in collaboration with the NCI and NIAAA, to establish a longitudinal cohort of adults with cirrhosis, including those with chronic hepatitis B, and test new therapeutic approaches.
<u>NCI AIDS Cancer Specimen Resource</u>	Provides biospecimens from persons with a wide spectrum of HIV/AIDS-related diseases, particularly cancers
<u>NCI Developmental Therapeutics Program</u>	Provides services and resources to research communities worldwide to facilitate the discovery and development of new cancer therapeutic agents
<u>NIH Tetramer Core Facility</u>	Produces and distributes major histocompatibility complex tetramers and related reagents to the research community

Resource Name	Description
<u>NIH Webinar Series on Moving from Hepatitis Discovery to Elimination</u>	This series, led by NCI and the Coalition for Global Hepatitis Elimination in partnership with other NIH Institutes and Centers, has featured webinars on HBV and HDV.
<u>Phase I Clinical Trial Units for Therapeutics</u>	Support design, development, implementation, and conduct of Phase I clinical trials against viral (other than HIV), bacterial, parasitic, and fungal pathogens
<u>PhenX Toolkit</u>	Example of standardized measures for social determinants of health
<u>Preclinical Models of Infectious Disease Program</u>	Provides development, screening, and efficacy testing in preclinical infectious diseases models, including traditional lab species, nonhuman primates, and non-traditional models
<u>REVEAL cohort in Taiwan</u>	Community-based prospective study of hepatitis B and hepatitis C
<u>Structural Genomics Centers for Infectious Diseases</u>	Applies state-of-the-art technologies/methodologies to characterize 3-D atomic structures of molecules to support infectious disease research
<u>Therapeutic Development Services: Biopharmaceutical Product Development Services</u>	Offers services for biotechnology products, such as planning, product characterization, process development, formulation, Good Manufacturing Practice, and Chemistry, Manufacturing and Control documentation
<u>Therapeutic Development Services: Interventional Agent Development Services</u>	Facilitates development of therapeutics, including lead identification and development, chemistry and manufacturing, toxicology, and pharmacokinetics
<u>Vaccine and Treatment Evaluation Units</u>	Support efforts to develop new and improved vaccines and therapies against infectious diseases
<u>Virus Pathogen Resource</u>	Database, bioinformatics analysis and visualization tools to support the research of viral pathogens

Appendix 4. Abbreviations

Abbreviation	Definition
ACIP	Advisory Committee on Immunization Practise
ALT	Alanine aminotransferase
ASOs	Antisense oligonucleotides
cccDNA	Covalently closed circular DNA
CDC	Centers for Disease Control and Prevention
COVID-19	Coronavirus disease 2019
DNA	Deoxyribonucleic acid
FDA	Food and Drug Administration
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
NAPs/STOPS	Nucleic acid polymers/ S-antigen transport-inhibiting oligonucleotide polymers
NASH	Non-alcoholic steatohepatitis
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
pgRNA	Pre-genomic RNA
RNA	Ribonucleic acid
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
siRNAs	Small interfering RNA
WHO	World Health Organization
WHV	Woodchuck hepatitis virus