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EXECUTIVE SUMMARY

Herpes simplex virus (HSV) 1 and 2 are among the most common viral infections in the U.S., with up to 80% of people between the ages of 14 and 49 infected with HSV-1\(^1\) and more than 10% infected with HSV-2.\(^2\) Infection with HSV can result in a diverse range of symptoms and pathology that can lead to lifelong complications.

To date, there are no HSV vaccines approved by the U.S. Food and Drug Administration (FDA). While research advances have resulted in several therapeutics, the effectiveness of these treatments in reducing symptoms and viral transmission varies widely. In addition, current treatment strategies require active virus replication, making them ineffective against latent HSV infection. The National Institutes of Health (NIH) recognizes that the development of commercially available HSV vaccines, therapeutics and diagnostics to improve public health and well-being requires a multi-pronged effort building upon advances in HSV research.

To advance research to understand and address HSV infection, the NIH has established the Strategic Plan for Herpes Simplex Virus Research. This plan aligns with ongoing national efforts, including the Sexually Transmitted Infections (STI) National Strategic Plan, and provides the framework for HSV research aligned with four priorities (Figure 1):

- **Strategic Priority 1**: Improve fundamental knowledge of HSV biology, pathogenesis, and epidemiology
- **Strategic Priority 2**: Accelerate research to improve HSV diagnosis
- **Strategic Priority 3**: Improve strategies to treat and cure HSV
- **Strategic Priority 4**: Advance research to prevent HSV infection

These strategic priorities encompass interdependent activities that combine the efforts of the research community with those in public health and clinical medicine to develop interventions to reduce the health consequences of HSV.

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\(^2\) [https://www.cdc.gov/std/treatment-guidelines/herpes.htm](https://www.cdc.gov/std/treatment-guidelines/herpes.htm)
The mission of the NIH Strategic Plan for Herpes Simplex Virus Research is to improve diagnostic tools, prevention strategies, and treatment options to end HSV. This mission will be achieved through four strategic priorities:

1. Improve fundamental knowledge of HSV biology, pathogenesis, and epidemiology.
2. Accelerate research to improve HSV diagnosis.
3. Improve strategies to treat and cure HSV.
4. Advance research to prevent HSV infection.

The strategic priorities will be supported by existing tools and resources, such as the current body of research, diagnostics, treatment and prevention strategies, and public health policies.
INTRODUCTION

In the U.S., an estimated 50% to 80% of people ages 14-49 have been infected with HSV-1³ while more than 10% have been infected with HSV-2⁴. Clinical manifestations of HSV infections can result in significant complications. HSV is one of the leading causes of infectious blindness worldwide and can also impact the central nervous system (CNS) resulting in dangerous inflammation of the brain or spinal cord. Neonatal herpes, if left untreated, has a case fatality rate of 60%⁵. Individuals from disadvantaged populations bear a higher burden of HSV infection, which may contribute to disparities in long-term health. Asymptomatic cases of HSV are also extremely common, and those who are asymptomatic continue to shed the virus and can transmit it to close contacts. There is currently no cure for HSV, so individuals remain infected and may need to continue treatment for recurrences and complications for the rest of their lives.

One of the challenges in treating HSV infections is the diverse nature of clinical manifestations of disease. In many cases, symptomatic infection with HSV can lead to the development of herpetic lesions that present as oral labial herpes (cold sores) or genital herpes. These infectious lesions are common sources of disease spread. HSV can also result in diverse and distinct pathology in other tissues of the body, including ocular keratitis, meningitis, or encephalitis. Most cases of HSV encephalitis are due to HSV-1, while most cases of HSV meningitis are due to HSV-2.

HSV infection predominantly occurs through contact with infected tissue of oral or genital mucosal surfaces that are shedding virus. Infection may also occur in other areas of the body if the skin is damaged and comes in contact with infectious virus. Once in the host, the virus can then transition to a quiescent state, called latency, actively suppressing the expression of genes that could lead to detection by the human immune system. In this manner, the virus can exist for extended periods of time in the body without causing symptoms. Once a “trigger” for transition out of latency occurs, HSV reverts into its active, or lytic state. Known triggers for virus reactivation include stress, sunlight, immune suppression, and a variety of other factors.

The vacillating nature of the HSV infection cycle and often asymptomatic nature of infection present challenges in diagnosis and treatment. Recent studies have shown that live virus is shed without the presence of clinically evident classic herpetic lesions. As such, the development and improvement of serologic and point-of-care diagnostics continues to be a research priority. There are currently no licensed vaccines for HSV-1 or HSV-2. HSV infections are primarily treated with antivirals such as acyclovir (or valacyclovir), which can reduce the frequency and intensity of outbreaks of herpetic lesions if started early during the lytic cycle. A prophylactic vaccine that can prevent infection or a therapeutic

³ https://www.cdc.gov/nchs/data/databriefs/db304.pdf
⁴ https://www.cdc.gov/std/treatment-guidelines/herpes.htm
vaccine for individuals who are already infected with HSV that could reduce recurrences and/or shedding would be a crucial tool in mitigating the public health impact of herpes simplex viruses.

The public health impact of HSV-1 and HSV-2 underscores the need for advancing research efforts to understand and thoroughly characterize HSV biology, pathogenesis, and epidemiology toward the development of commercially available vaccines, therapeutics and diagnostics. To address and coordinate efforts to facilitate HSV research, an NIH-wide HSV Working Group, led by the National Institute of Allergy and Infectious Diseases (NIAID), was established. This group consists of scientific and policy experts from NIAID, the National Institute on Mental Health (NIMH), the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute on Aging (NIA), the National Institute on Minority Health and Health Disparities (NIMHD), the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the National Eye Institute (NEI). To seek broad public input on scientific areas of interest in HSV research, NIH issued a Request for Information (RFI). The results of the RFI are summarized in Appendix 3 and suggestions were incorporated into the plan as appropriate.

To advance NIH HSV research objectives, the NIH HSV Working Group organized this plan into four strategic priorities: (1) improving fundamental knowledge of HSV biology, pathogenesis, and epidemiology; (2) accelerating research to improve HSV diagnosis; (3) improving strategies to treat and cure HSV; and (4), advancing research to prevent HSV infection. These interdependent priorities form the framework of the NIH strategy to advance our understanding of HSV-1 and HSV-2 and help accelerate the development of safe and effective interventions to reduce the public health impact of HSV-1 and HSV-2.

**STRATEGIC PRIORITY 1: Improve Fundamental Knowledge of HSV Biology, Pathogenesis, and Epidemiology**

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Although HSV is extremely common worldwide, considerable gaps remain in the fundamental understanding of HSV. These include our understanding of the basic components of HSV biology, pathophysiology, and the host and pathogen drivers that sustain virus latency or drive reactivation. NIH will continue to support research guided by the objectives below toward advancing the understanding of the basic biology of the HSV viruses that will accelerate advances in diagnostics, vaccine development, and efforts toward a cure.
Objective 1.1: Enhance Fundamental Knowledge of HSV Biology

- **Mechanisms of HSV entry into host cells:** HSV can utilize various modes of entry based on cell types infected. HSV can directly fuse with the host plasma membrane, or it can utilize endocytic pathways that are either pH-dependent or -independent. The fusion of the viral envelope with the host cell membrane is a crucial step in infectivity. Continued support for research characterizing this process will be a critical asset for the development of vaccines and therapeutics. If the initial entry of HSV into the host cell can be blocked, infection cannot be established.

- **Mechanisms of replication:** Replication of viral DNA is carried out by several viral-encoded proteins. The newly replicated viral genomes are packaged into preformed capsids in the nucleus, and the viral proteins and the envelope acquired as newly infectious virions exit from the cell. The HSV viral replication process is the target for many of the currently approved HSV therapeutics. Continued investigations of the complex processes of HSV virus replication and viral assembly will be important for the elucidation of new possible targets for HSV therapeutics.

- **Mechanisms of HSV trafficking in the nervous system:** HSV can infect both the peripheral and central nervous systems. After initial infection of epithelial cells, HSV can enter neurons in the skin or mucosa at the primary site of infection. The virus is then transported to clusters of neurons in the peripheral nervous system, called the trigeminal or dorsal root ganglia, where it can establish a life-long latent infection. Upon reactivation in the ganglia, HSV is transported back to the periphery where they cause lesions on the lips or genitals. In rare cases, HSV can also spread from ganglia to the brain which can lead to severe neurological conditions, although the precise mechanisms by which this occurs remain unknown. Additional research to elucidate the basic biological mechanisms of HSV trafficking in the nervous system can lead to novel strategies for preventing HSV dissemination in the nervous system.

- **Fundamental aspects of immune response:** Several components of the HSV virion, including the viral nucleic acid and viral proteins, have been shown to trigger immune responses to HSV, including activation of type 1 interferon (IFN), HSV-specific antibodies, T cells, natural killer (NK) cells, dendritic cells (DC), as well as other immune mechanisms. Investigators are working to define HSV epitopes that are recognized by T cells in the mucosal surface (at the site of infection and reactivation) and to understand the role of these cells in disease prevention, viral reactivation, and pathogenesis. Additional studies are needed to better characterize the complex consequences of the host immune response to HSV in multiple areas of the body including the CNS, where a strong inflammatory response to the virus can be particularly detrimental. Such investigations support the identification of potential correlates of protection and enable researchers to better understand the role of the immune system in viral latency, disease progression, and ultimate severity of disease.

- **HSV transmission:** Transmission of HSV occurs through contact with an individual who is infected and shedding the virus. This may occur in individuals who are either symptomatic or asymptomatic for HSV. In neonatal HSV, transmission can occur either in utero, during delivery, or just after birth. Although many features that lead to HSV transmission are understood,
continued research is needed to further elucidate specific aspects of the transmission process, including the amount of virus required for transmission, and understanding of the specific features of transmission.

- **Identify biomarkers of disease:** Biomarkers have the potential to predict susceptibility to HSV disease states and may be leveraged to predict which patients are more likely to have severe HSV or to have frequent recurrences. To identify new markers of disease, efforts will need to leverage advanced -omics approaches (e.g., transcriptomics, proteomics, metabolomics, etc.) that can compare the level of gene expression, proteins, or metabolites in patients with or without specific manifestations of HSV disease. Applying comprehensive systems biology analyses of the data generated using these approaches can accelerate research and illuminate new mechanisms that may lead to development of novel drugs or therapeutics.

**Objective 1.2: Characterize Host and Pathogen Drivers that Underlie Dynamics of HSV Latency and Reactivation**

- **Strategies of immune evasion:** HSV uses multiple strategies to avoid detection and clearance by the immune system and sustain infection through cycles of latency and reactivation. For example, during active infection, HSV can inhibit presentation of viral proteins to T cells, hampering their ability to respond to the virus. In addition, HSV can express molecules to bind to HSV-specific antibodies, limiting their activity. Once in the latent phase, the HSV genome expresses latency-associated transcripts (LATs) that help establish viral latency and may facilitate avoiding detection by the immune system. Continued advancements to characterize HSV immune evasion during both HSV latency and reactivation will be critical towards the development of strategies that interfere with these immune evasion processes.

- **External and host-derived factors that drive HSV reactivation:** The specific triggers that initiate reactivation of latent HSV to the lytic state continue to be of significant scientific interest. Although the specific triggers of reactivation remain unclear, several factors have been implicated in this process. Stress on a host organism can lead to immune suppression and has been linked to HSV reactivation. In addition, intrinsic host-derived factors related to the immune response may result in a predisposition to reactivation. Cellular transcription factors that are involved in reactivation of HSV, and loss of nerve growth factor (NGF) may also be sources of reactivation of the virus. Identifying specific factors that are responsible for HSV reactivation will help identify individuals at high-risk or predisposed to reactivation as well as strategies to counteract this process and resulting HSV pathology.

**Objective 1.3: Improve Understanding of Diverse Pathophysiology of HSV Infection**

- **Encephalitis and meningitis:** In addition to infecting the skin, mucosa, and peripheral neurons and ganglia, both HSV-1 and HSV-2 can cause inflammation in the brain and spinal cord (the central nervous system or CNS), known as encephalitis and meningitis, respectively (Figure 3). Herpes simplex encephalitis (HSE) accounts for 10-20% of all sporadic encephalopathies, and if it
goes untreated with antiviral agents, the mortality rate is as high as 70%. Neonates and immunosuppressed individuals are at especially high risk for serious HSV-related CNS complications. Previous research has suggested that pathology in HSE may be due to both virus replication and the immune response to the infection. However, the specific roles for each of these mechanisms remain unclear. In addition, the virus or host mechanisms that drive reactivated HSV to spread to the CNS or make people more susceptible to CNS invasion require further characterization. Advancing the understanding of CNS pathology of HSV will be important for intervention strategies that result in better long-term outcomes for patients with HSE.

- **Herpetic Keratitis**: HSV can also infect multiple tissues of the eye. HSV keratitis (HSV-mediated inflammation of the cornea) is a leading cause of blindness worldwide and recurrent HSV keratitis is not uncommon. HSV keratitis can take three primary forms: epithelial, stromal, and rarely, endothelial. Epithelial and stromal keratitis result from infection of specific layers of the cornea and can lead to vision impairment. Endothelial keratitis is caused by an immune response to HSV infection and can have severe adverse effects on vision. HSV can also cause uveitis, retinitis, and progressive retinal necrosis. Continued research is needed to evaluate HSV ocular pathology and investigate strategies to improve these clinical outcomes.

- **Development of neurodegenerative disorders**: HSV, similar to a number of other viral pathogens, has been associated with the future development and/or progression of neurodegenerative disorders that can lead to dementia (i.e., Alzheimer’s Disease and Related Dementias). However, whether these outcomes are directly related to direct viral infection or due to secondary effects of inflammatory responses remain unclear. Brain inflammation triggered by the reactivation of latent HSV may lead to neurodegeneration or accelerate the progression of previously existing neurodegenerative disease states. In addition, several recent epidemiologic studies have suggested that HSV-1 infection may be correlated with an increased risk of Alzheimer’s Disease. Further research is needed to elucidate associations between HSV

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and the development of neurodegenerative disorders and determine pathological mechanisms that lead to more adverse outcomes.

- **Neonatal**: Neonatal HSV disease can be caused by HSV-1 or HSV-2. A pregnant person infected with HSV can transmit the virus to the child, and this risk increases with primary infection. Most neonatal transmissions from a pregnant person to a child are caused by HSV-2. Although HSV can be transmitted before, during, and after birth, transmission occurring during birth is the most common cause of neonatal HSV. Neonatal HSV infections can be classified into three primary manifestations: localized skin/eye/mouth disease; disseminated infections with multiple organ system involvement; or CNS disease. In the decades since antivirals became available, morbidity and mortality of neonatal HSV have decreased significantly, but CNS and especially disseminated neonatal HSV may still be devastating. The development of diagnostics for use at labor and delivery combined with vaccines and therapeutics to prevent the neonatal transmission of HSV will be critical tools to combating HSV infection and pathology in neonates.

**Objective 1.4: Explore Epidemiology and Co-infection Associated with HSV Infection**

- **Investigate the prevalence and determinants of HSV susceptibility among populations experiencing health disparities**: Although HSV has been shown to disproportionately affect historically marginalized populations, an understanding of the various determinants of health that influence HSV infection is limited. In the U.S., HSV disparities can exist based on factors related to social determinants of health including race or ethnicity, geography, environment, and socioeconomic status. HSV-1 prevalence is highest among Mexican American persons while Black persons have nearly a 3-fold higher HSV-2 prevalence compared to Mexican American and non-Hispanic White persons. In addition, individuals from intersectional, multiple marginalized identities, including living in rural settings or identifying as a sexual or gender minority, may be at an even higher risk for HSV acquisition. Further research is needed to evaluate the interplay of various determinants of health and contexts that lead to adverse outcomes related to HSV infection in populations experiencing health disparities.

- **Investigate impact of health disparities on HSV prevalence in different populations**: Although HSV has been shown to disproportionately affect certain groups, including historically marginalized populations, the social determinants of these health disparities remain largely unknown and may differ based on HSV subtype. Mexican Americans have a higher prevalence of HSV-1 compared to other racial/ethnic groups, while non-Hispanic Black Americans have nearly a 4-fold higher prevalence of HSV-2 compared to non-Hispanic White Americans. In addition, the prevalence of HSV-2 infection among females is twice that of males. Further research is needed to characterize the disparities in HSV infection prevalence in historically marginalized populations, including sexual and gender minorities and people living in rural areas of the U.S.

- **Address complex epidemiologic synergy of HIV and HSV co-infection**: Prior to the availability of highly active antiretroviral therapy (HAART) for individuals with HIV, genital HSV was widely

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8 https://www.cdc.gov/nchs/data/databriefs/db304.pdf
recognized as a cofactor in enhancing sexual acquisition of HIV. However, people co-infected with HIV and HSV with undetectable HIV viral load due to HAART appear to be no more likely to transmit HIV than those without HSV. Therefore, the impact of HSV as a cofactor expanding the HIV epidemic has been reduced due to the successful implementation of public health strategies to test for and treat HIV. However, genital HSV may continue to amplify HIV transmission in persons not yet recognized to have HIV infection or not engaged in HIV care. New and improved strategies to prevent and treat HSV infection may help to reduce the risk of HIV transmission in HSV serodiscordant couples (one person is HSV positive and one is HSV negative) and may have the additional benefit of mitigating HIV spread globally.

Objective 1.5: Improve and Develop New in vitro and in vivo Models that Reflect Human Disease

- **In vivo animal models:** Although currently available animal models provide valuable insight into HSV infection, many HSV vaccine candidates showing promise in animal models are less successful when tested in humans. The most common animal models in HSV research are the mouse, guinea pig, and rabbit. Lesser used models include the cotton rat and rhesus macaques. Developing and improving animal models that recapitulate human disease is crucial for basic research and for evaluating therapeutics, vaccines, and microbicides.

- **Tissue culture, explant models, and organoids:** Tissue culture and *ex vivo* explant models are valuable tools to characterize critical features of the HSV life cycle. Cell lines have long been used to evaluate the lytic stage of an HSV infection. However, recent advances in explant models, where a small section of tissue can be removed from an organism and multiple differentiated cell types can be studied *ex vivo*, have enabled researchers to explore reactivation of HSV from the latent to the lytic phase. The benefit of this system over a traditional tissue culture model is that multiple tissue types can be investigated under experimental conditions. Advances in the explant models have permitted some modeling of the latent phase of these viruses. Organoids are three dimensional masses of cells derived from stem cells that resemble an organ. These can be used to investigate multiple cell type responses to experimental conditions and are highly valuable in investigating the mechanisms underlying observed or phenotypic effects caused by infection. Continued efforts in developing animal models, *ex vivo*, and *in vitro* tissue culture models and organoid models have the potential to more accurately model HSV infection in humans.

**STRATEGIC PRIORITY 2: Accelerate Research to Improve HSV Diagnosis**

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The lack of reliable and accurate diagnostics continues to be a challenge in the effort to prevent and treat HSV. To address these ongoing challenges, NIH will continue to prioritize the advancement of fundamental research to support the development of better diagnostics. Improvement of serologic tests
and point-of-care diagnostics will be important tools to facilitate the development of treatment and vaccination strategies to prevent HSV transmission. To be most effective, improvements in diagnostics may also need to be paired with strategies to improve communication on the importance of testing and diagnosis of HSV to both individuals and medical providers.

Objective 2.1: Support Innovative Technologies that can be Utilized in Diverse Clinical Settings to Expand Testing Availability

- **Support development of accurate and sensitive serologic tests for screening and diagnosis:** Improving the accuracy of serologic tests is essential for improving diagnosis of infection in both asymptomatic and symptomatic individuals. Serologic tests, which detect antibodies to HSV circulating in the blood, are currently not included in standard sexually transmitted infection (STI) screening panels, due to their potential for indicating a false positive test result. A serologic test that uses the Western blot assay has less potential for false positives and is considered the “gold standard” for HSV infection diagnosis. This test, however, is only commercially available from one source. Historically, the Western blot has not been a technology that is easily amenable to point of care (POC) testing or for conversion to a commercial platform allowing for wide distribution and low cost. Thus, the Western blot assay is mostly used as a confirmatory test for those who can access and afford it. Serologic tests could likely be improved through better understanding of the immune response to HSV and introduction of state-of-the-art technologies and diagnostic platforms. In addition, efforts could be made in the conversion of the Western blot assay into a more accessible and affordable test. Development of novel, accurate serologic tests will likely be the foundation for not only clinical screening to prevent transmission, but also the design of needed surveillance programs for adult HSV infection, neonatal herpes, and other diseases and syndromes associated with HSV infection.

- **Support development of diagnostic assays for CNS complications of HSV that do not rely on cerebrospinal fluid (CSF) sampling:** Brain injury caused by HSE proceeds at a rapid pace, and the survival and neurological outcome of patients with HSE is dependent upon immediate treatment with antiviral medication. HSE diagnosis currently involves a polymerase chain reaction for viral DNA in CSF, which requires a painful spinal puncture to patients and sometimes repeated CSF sampling. Further complicating this issue is the fact that HSE symptoms are often nonspecific, which means that many physicians fail to perform CSF testing before permanent brain injury has been observed on magnetic resonance imaging. A sensitive screening test for HSE which utilizes a more accessible blood sample (as opposed to CSF) would substantially reduce morbidity and mortality caused by the CNS complications of HSV infection.
• **Improve performance of point-of-care diagnostic assays:** Current strategies for HSV diagnosis include direct detection of HSV genetic material (usually through a nucleic acid amplification test (NAAT)) or culture of the virus from a clinical specimen. These tests can usually discriminate between HSV-1 and HSV-2. However, HSV can only be detected if the patient is shedding the virus. Therefore, these tests are generally only performed when lesions, such as genital ulcers, are evident and around suspicion for HSV infection. These tests usually require several days turnaround for results. An ideal diagnostic would be one that could be performed at the site where the patient seeks care. These tests are referred to as PoC tests, and can yield an answer in a timely manner, usually in an hour or less (Figure 4). The ideal test would not only be able to detect HSV but would also distinguish between HSV-1 and HSV-2.

**GOALS OF POINT-OF-CARE TESTING**

- Increased access to diagnostic tools
- Decreased time between diagnosis and treatment
- Improved treatment and prevention outcomes

• Continuation of efforts to develop a PoC test that can accurately identify and differentiate between the leading causes of genital ulcers (HSV, *Treponema pallidum* [the cause of syphilis], and mpox virus) would assist in the diagnosis and clinical management of each infection. The development of PoC tests is particularly important to diagnose HSV shedding in a pregnant individual in the delivery room, facilitating earlier treatment of neonates or allowing the choice of a cesarean delivery to minimize the potential for transmission.

**STRATEGIC PRIORITY 3: Improve Strategies to Treat and Cure HSV**

| Strategic Priority 3: Improve Strategies to Treat and Cure HSV |
|---|---|
| **Objective 3.1:** | Advance the Development of Long-Acting Treatment Strategies |
| **Objective 3.2:** | Evaluate the Safety and Efficacy of Treatment Strategies in Diverse Populations and Age Groups |
| **Objective 3.3:** | Identify Strategies for Reducing the Effects of HSV or Functional Cure |

Although existing regimens are relatively effective if started early, there continues to be an urgent need to identify safe and effective treatments across the spectrum of HSV disease. The most promising current therapeutic options require active virus replication, rendering them ineffective against latent infection. In addition, the best available treatments only partially reduce transmission of the virus to uninfected partners. NIH will continue to support efforts to treat and cure HSV, including the development of long-acting treatment strategies and novel strategies to target latent HSV. In addition, NIH will support the
efforts to evaluate treatments through appropriate clinical trials in diverse groups to ensure that research findings can be generalizable to the entire population.

Objective 3.1: Advance the Development of Long-Acting Treatment Strategies

- **Develop novel HSV treatments:** Current strategies to treat HSV rely primarily on the use of nucleoside analogs that function by inhibiting the HSV polymerase during viral replication. Current first line antivirals are acyclovir, valacyclovir, and famciclovir. Second line therapies, cidofovir and foscarnet, are used in cases of drug resistance to the first line therapies, and their use is limited by significant toxicities. Although successful at mitigating some of the damaging sequelae of HSV, current treatment strategies are not effective at elimination of infection and only partially reduce virus shedding. As a result, many individuals still transmit the virus to close contacts despite taking daily antivirals or suffer from relapse after stopping therapy. In addition, long-term use of these treatments in those who are immunocompromised can lead to the development of drug resistance. To combat this, further research is needed towards the development of novel antivirals that can synergize with current regimens to enhance their function and potentially treat resistant infections and reduce shedding. This may include targeting certain viral enzymes important for virus binding, entry, or replication. In addition to antivirals, studies have suggested that individual HSV monoclonal antibodies (mAbs) can confer levels of protection and neutralization of HSV, indicating that mAbs may be a promising strategy to treat or prevent HSV infection. Further studies are needed to identify and evaluate mAbs that may function in synergy with current strategies to treat or prevent HSV infection.

- **Advance treatment strategies for reduced sequelae of HSV encephalitis, including role of anti-inflammatory medications:** The neurological impact of HSV infection has been well documented and can lead to severe organ disease, including brain injury due to herpes simplex encephalitis (HSE). HSV can also cause inflammation of the optic nerve, or optic neuritis, and this can lead to reduced vision or blindness. CNS pathology is attributable to a combination of viral replication and immune mediated responses to the infection. Once HSV infection is established in the brain, components of the adaptive immune response, including T and B cells, drive immune responses that are integral in controlling infection. However, these responses, if not carefully modulated, can lead to dangerous inflammatory responses in the brain. Therefore, in addition to standard treatment strategies for HSV including acyclovir, additional immunomodulatory strategies may be necessary to treat HSV in these circumstances. In animals, multiple broad-acting immunosuppressive treatments have been tested including broad-acting corticosteroids or inhibitors of key inflammatory pathways, such as Toll-like receptor (TLR) pathways. These treatments may be able to modulate the pathophysiology associated with encephalitis and have not been shown to interfere with standard HSV treatments, such as acyclovir.

Objective 3.2: Evaluate the Safety and Efficacy of Treatment Strategies in Diverse Populations and Age Groups

- **Immunocompromised individuals at high-risk for disease:** In individuals who are immunocompromised, such as HIV patients not on Highly Active Antiretroviral Therapy (HAART),
transplant recipients, or people who have severe congenital immune disorders, HSV pathophysiology can be much more severe and potentially life-threatening. Immunocompromised individuals are also much more susceptible to HSV reactivation, with more severe symptoms that are slower to heal or respond to therapy. Although standard treatment regimens including acyclovir are considered viable treatment options for these populations, patients may develop infections that are resistant to acyclovir. Although antivirals can be used for prophylaxis or treatment in these populations, further research is needed to identify and develop additional treatment options for immunosuppressed or immunocompromised individuals. Treatments for this population that could keep the virus in its latent phase could save significant morbidity as lytic lesions in this population are often long lasting and severe.

- **Advance investigation of HSV treatment strategies in populations with health disparities:** Although HSV has been shown to disproportionately affect disadvantaged populations, such as racial or ethnic minorities, the social determinants of these health disparities and their impact on HSV treatment remain largely unknown. Improved understanding of determinants that impact HSV infection will be critical to develop better treatment strategies that are culturally or contextually adapted and to conduct more representative clinical trials as new treatments become available. As part of this effort, developing strategies to improve healthcare access and quality in low-resource clinical and community settings is a priority. Improving the HSV care continuum in diverse populations and settings will enhance the ability to assess individuals at high risk for HSV, evaluate HSV treatment efficacy, and improve dissemination of best practices among populations experiencing health disparities.

- **Treatment in those who are pregnant and in neonates:** Pregnant individuals are at high risk for passing on infection to their child. Delivery by cesarean reduces risk of transmission from the pregnant individual to the infant, as does treatment to suppress the virus in pregnant people with a history of HSV. In pregnant individuals who are shedding HSV near delivery, it is important to determine whether the individual has a primary or recurrent HSV infection. This distinction may impact the risk of neonatal infection and its management. Identification of pregnant people who are shedding HSV at or near delivery may also allow earlier treatment of neonates and prevent establishment of HSV infection.

**Objective 3.3: Identify Strategies for Working Toward Elimination of HSV or Development of a Functional Cure**

- **Establish strategies to target latent HSV:** While antiviral therapy can reduce HSV reactivation, currently available antiviral drugs have not been shown to completely prevent reactivation or eliminate latent virus. Although full eradication of the virus from the body, or sterilizing cure, may not be feasible in the short-term, efforts to achieve a “functional cure,” or sustained suppression of viral shedding without the need for recurring treatment, may be achievable. During latency, HSV actively suppresses gene expression that render traditional treatment strategies, such as DNA polymerase inhibitors, ineffective. Therefore, strategies need to be advanced to specifically target HSV in the latent state. This may include either directly targeting and inactivating HSV or achieving a similar goal by completely suppressing reactivation of latent
virus through gene editing technologies (e.g., CRISPR/Cas, meganucleases). Advancing these strategies and exploring new mechanisms to decrease HSV reactivation will be key steps towards the goal of functionally reducing the effects of HSV infection.

**STRATEGIC PRIORITY 4: Advance Research to Prevent HSV Infection**

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<th>Strategic Priority 4: Advance Research to Prevent HSV Infection</th>
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<tr>
<td><strong>Objective 4.1:</strong> Advance the Development of Promising Vaccines and Multipurpose Prevention Technologies (MPT)</td>
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<tr>
<td><strong>Objective 4.2:</strong> Support Clinical Trials to Test Therapeutics and Vaccines</td>
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Effective prevention of HSV requires a multi-pronged effort building upon advances in HSV research. Promising HSV prevention strategies must be comprehensively tested in diverse populations and age groups and must be paired with enhanced strategies for diagnosis to target and treat high-risk groups. This is particularly important for infected pregnant individuals, who are at high risk for vertical transmission to the child. NIH will continue to support the development and testing of safe and effective HSV prevention candidates and strategies, including the advancement and testing of prophylactic vaccines to prevent HSV infection.

**Objective 4.1: Advance the Development of Promising Vaccines and Multipurpose Prevention Technologies (MPTs)**

Currently there are no FDA-approved HSV vaccines, though multiple candidates are in development for either prophylactic or therapeutic use. The goal of a prophylactic vaccine is to prevent HSV acquisition. Alternatively, a therapeutic vaccine would be intended for patient with an existing HSV infection to elicit an immune response to reduce the frequency of viral reactivation and lesion outbreaks and to reduce viral shedding. This approach aligns with the WHO Preferred Product Characteristics for Herpes Simplex Virus Vaccines⁹, a document which NIAID helped develop. In addition to vaccines, efforts are also ongoing to advance multipurpose prevention technologies, products developed with multiple active drugs to simultaneously prevent HIV, other STIs or unintended pregnancy. To advance these priorities, research efforts are ongoing to:

- **Identify correlates of protection for HSV-1 and HSV-2:** Characterizing immune responses and correlates of protection can help speed discovery and testing of promising HSV vaccine candidates. While correlates of immune protection have not been conclusively elucidated for either HSV-1 or HSV-2, current studies suggest that neutralizing antibodies specific to proteins on the viral surface correlate with protection against HSV in mice and guinea pigs. Similarly, a recent NIAID-funded Phase 3 vaccine trial identified IgG antibodies specific to HSV-1 glycoprotein D as the first human correlate of protection against genital herpes caused by this virus. Research identifying the correlates of protection observed against both HSV-1 and HSV-2

⁹ [https://www.who.int/publications/i/item/9789241515580](https://www.who.int/publications/i/item/9789241515580)
in humans will facilitate understanding the effectiveness of protection offered in vaccines targeted against both virus types.

- **Advance the development of vaccines:**
  - **Attenuated and replication-deficient virus**: Attenuated and replication-deficient vaccines contain a version of HSV that is weakened in the laboratory to trigger a strong HSV-specific immune response, yet not cause disease. There are currently several different approaches for live attenuated vaccines under development for both HSV-1 and HSV-2, and multiple candidates are being explored as both preventative and therapeutic vaccines.
  - **DNA/RNA**: This strategy employs a multivalent approach wherein the immune system is exposed to multiple HSV antigens. Researchers have previously advanced the use of plasmid DNA (pDNA) vaccines for HSV therapeutic vaccine development, and while preclinical studies were promising, clinical trials were unsuccessful at reducing recurrent outbreaks. Other groups have had initial success with messenger RNA (mRNA) lipid nanoparticle vaccines, a platform similar to those used by some SARS-CoV-2 vaccines to prevent COVID-19.
  - **Protein subunit**: Protein subunit approaches for HSV involve a trivalent subunit vaccine targeting three glycoproteins on the HSV surface and have demonstrated promise in non-human primates and guinea pigs. An intranasal two-component vaccine against two HSV-2 glycoproteins in an oil-in-water nanoemulsion adjuvant has shown both therapeutic and prophylactic potential in animal models.

- **Advance the development of Multipurpose Prevention Technologies (MPTs)**: MPTs are interventions that are being developed for vaginal or rectal use to prevent HIV infections, other STIs including HSV, and unintended pregnancies, if contraception is a desired component. There are a variety of MPT formulations such as gels, films, or intravaginal rings. The active drug products have included antivirals, antimicrobials, and monoclonal antibodies.

**Objective 4.2 Support Clinical Trials to Test Therapeutics and Vaccines**

- **Leverage infrastructure to evaluate efficacy of HSV prevention and treatment strategies**: The development of safe and effective vaccines and treatments for HSV requires comprehensive and rigorous clinical testing. NIH will continue to leverage its robust clinical trial infrastructure to advance clinical research for promising therapeutic and vaccine candidates for HSV (Box 1).

- **Advance and test treatment strategies for pregnant individuals**: Studies suggest that some pregnant individuals with primary HSV infections develop protective responses against HSV transmission. Researchers are investigating whether giving HSV-specific antibodies to pregnant people provides additional benefit to prevent neonatal HSV when combined with other current strategies. The development of new antivirals or vaccines for HSV prevention, treatment, or both that can be safely administered to pregnant individuals are additional avenues of research to protect the neonate.
Develop strategies to vaccinate and treat diverse populations: A successful vaccination campaign will depend not only on the development of safe and effective vaccines, but also reliable strategies to facilitate equitable vaccination uptake among all populations. This is particularly important in areas with high risk of HSV disease acquisition and transmission. Lessons learned from previous vaccination efforts, including COVID-19, can inform strategies for deploying and encouraging uptake of HSV vaccines when new vaccine candidates become available. These lessons include collaborative community partnership, appropriate representation, information communication and dissemination strategies for vaccine safety and efficacy to facilitate access to vaccines among populations experiencing health disparities. NIH will continue to support efforts to improve the future availability and uptake of HSV vaccines to diverse populations.
Box 1. A portfolio analysis describing NIH support for HSV prevention and treatment strategies from fiscal year (FY) 2016 – 2022. NIH funding (in millions) shows a steady increase from $6.11m in FY 2016 to $14.39m in FY 2022 with a slight decrease in FY 21. Number of preclinical and early clinical research projects for HSV prevention and treatment strategies for FY 2016 – 2022 followed the same trend. Types of interventions supported are prophylactic and therapeutic vaccines, antivirals, monoclonal antibodies, behavioral, and multipurpose prevention technologies (MPTs). Clinical research topics focused on prevention treatment, women’s health, neurological health, eye health, neonatal health, and co-infection. The method and analysis used for this search criteria are described below.*

*Data for this analysis were collected from NIH REPORTER on 7/31/2023. Search criteria were: Fiscal Year: 2022, 2021, 2020, 2019, 2018, 2017, 2016; Text Search: (“genital herpes” OR “herpes simplex virus” OR “herpes simplex viruses” OR “herpes simplex” OR “HSV” OR “HSV-1” OR “HSV-2” OR “HSV-1” OR “HSV-2”) AND (treat OR treats OR treatment OR treatments OR prevent OR prevents OR prevention OR preventions OR preventing OR therapy OR therapies OR therapeutic OR therapeutics OR vaccine OR vaccines OR vaccine OR vaccines OR vaccination OR vaccinations OR antiviral OR antivirals OR antimicrobial OR antimicrobials OR antibody OR antibodies OR drug OR drugs OR medicine OR medicines OR medication OR medications OR cure OR cures OR remedy OR remedies) NOT (“herpes zoster” OR cancer OR glioblastoma OR glioma OR gliomas OR oncolytic OR “oHSV” OR zoster OR “high-speed videoendoscopy” OR “dysphonia” OR “human greater saphenous vein” OR “voice tremor”); Limit To: Project Title, Project Abstracts; NIH Spending Category: Bioengineering, Biotechnology, Clinical Research, Clinical Trials and Supportive Activities, Immunization, Infectious Diseases, Sexually Transmitted Infections, Nanotechnology, Vaccine Related, Eye Disease and Disorders of Vision, Pediatric, Mental Health, Behavioral and Social Science, Social Determinants of Health, Neurosciences, Prevention, Women’s Health.
CONCLUSION

The NIH Herpes Simplex Virus Strategic Plan establishes research priorities for NIH in its efforts to respond to the ongoing threat of HSV. This plan serves as a framework for research efforts to address this critical public health threat and aligns with goals and priorities in the Sexually Transmitted Infections National Strategic Plan. NIH will continue to support basic research and advance translational studies toward the development and testing of improved diagnostics, therapeutics, and vaccines to detect, treat, and prevent HSV. NIH also will continue to work with partners to advance these efforts and to enhance health communication and outreach strategies to support availability and uptake, particularly in high-risk populations. Through this combined effort of improving the reliability and availability of diagnostics and the development and testing of safe and effective vaccines and therapeutics, NIH is leading the biomedical research response to reduce the persistent personal and public health impacts of HSV.
## APPENDICIES

### APPENDIX 1: NIH HSV Working Group Members

<table>
<thead>
<tr>
<th>IC</th>
<th>Last Name</th>
<th>First Name</th>
<th>Position</th>
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</thead>
<tbody>
<tr>
<td>NIAID</td>
<td>Azeez</td>
<td>Olumayowa</td>
<td>Health Science Policy Analyst, Policy, Planning and Evaluation Branch, OD</td>
</tr>
<tr>
<td>NIAID</td>
<td>Bushar</td>
<td>Nicholas</td>
<td>Chief, Policy, Planning and Evaluation Branch, OD</td>
</tr>
<tr>
<td>NIAID</td>
<td>Challberg</td>
<td>Mark</td>
<td>Health Scientist Administrator</td>
</tr>
<tr>
<td>NIAID</td>
<td>Chen</td>
<td>Ray</td>
<td>Physician</td>
</tr>
<tr>
<td>NIAID</td>
<td>Cohen</td>
<td>Jeffrey</td>
<td>Physician</td>
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<tr>
<td>NIAID</td>
<td>Connolly</td>
<td>Kristie</td>
<td>Health Scientist Administrator</td>
</tr>
<tr>
<td>NIAID</td>
<td>Davis</td>
<td>Mindy</td>
<td>Health Science Administrator</td>
</tr>
<tr>
<td>NIAID</td>
<td>Deal</td>
<td>Carolyn</td>
<td>Chief, Enteric and Sexually Transmitted Infections Branch</td>
</tr>
<tr>
<td>NIAID</td>
<td>Deckhut</td>
<td>Alison</td>
<td>Chief, Basic Immunology Branch</td>
</tr>
<tr>
<td>NIAID</td>
<td>Dempsey</td>
<td>Walla</td>
<td>Program Officer</td>
</tr>
<tr>
<td>NIAID</td>
<td>Drew</td>
<td>Jessi</td>
<td>Contractor, Policy, Planning and Evaluation Branch, OD</td>
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<tr>
<td>NIAID</td>
<td>Gautam</td>
<td>Rajeev</td>
<td>Health Scientist, Program Officer</td>
</tr>
<tr>
<td>NIAID</td>
<td>Glock</td>
<td>Jonathan</td>
<td>Program Officer</td>
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<tr>
<td>NIAID</td>
<td>Grace</td>
<td>Beth</td>
<td>Senior Financial Analyst</td>
</tr>
<tr>
<td>NIAID</td>
<td>Greenstone</td>
<td>Heather</td>
<td>Health Scientist Administrator</td>
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<tr>
<td>NIAID</td>
<td>Hiltke</td>
<td>Thomas</td>
<td>Program Officer</td>
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<tr>
<td>NIAID</td>
<td>Miers</td>
<td>Sarah</td>
<td>Program Analyst</td>
</tr>
<tr>
<td>NIAID</td>
<td>Mulach</td>
<td>Barbara</td>
<td>Director, Office of Scientific Coordination and Program Operations</td>
</tr>
<tr>
<td>NIAID</td>
<td>Newman</td>
<td>Lori</td>
<td>Medical Officer</td>
</tr>
<tr>
<td>NIAID</td>
<td>Schmit</td>
<td>Ginny</td>
<td>Health Science Policy Analyst, Policy, Planning and Evaluation Branch, OD</td>
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<tr>
<td>NIAID</td>
<td>Shaffer</td>
<td>Meredith</td>
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<tr>
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<td>Sheryl</td>
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<td>Chai</td>
<td>Mindy</td>
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</tr>
<tr>
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<td>Fox</td>
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<tr>
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<td>Rao</td>
<td>Vasudev</td>
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<tr>
<td>NIMHD</td>
<td>Herren</td>
<td>Olga</td>
<td>Program Officer</td>
</tr>
<tr>
<td>NINDS</td>
<td>Daley</td>
<td>Will</td>
<td>Program Director, Neuronal Environment Cluster</td>
</tr>
<tr>
<td>NINDS</td>
<td>Torborg</td>
<td>Christine</td>
<td>Health Science Policy Analyst</td>
</tr>
<tr>
<td>NEI</td>
<td>McKie</td>
<td>George</td>
<td>Program Officer</td>
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## APPENDIX 2: NIH-Supported HSV Research Resources

<table>
<thead>
<tr>
<th>Resource Name</th>
<th>Description</th>
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<tbody>
<tr>
<td>BEI Resources Repository</td>
<td>Central repository that supplies organisms and reagents to the broad community of microbiology and infectious diseases researchers</td>
</tr>
<tr>
<td>Bioinformatics Resource Centers</td>
<td>Collects, archives, updates, and integrates research data with user-friendly interfaces and computational analysis tools</td>
</tr>
<tr>
<td>NIAID Clinical Genomics Program</td>
<td>Provides centralized resources to be used for genomics and related research</td>
</tr>
<tr>
<td>Genomic Centers for Infectious Disease Resources</td>
<td>Provides innovative application of genomic technologies and rapid, cost-efficient production of high-quality genome sequences for pathogens and hosts</td>
</tr>
<tr>
<td>Infectious Disease Clinical Research Consortium</td>
<td>A clinical trials research consortium that prioritizes vaccines, diagnostics, and other interventions to test in clinical trials</td>
</tr>
<tr>
<td>ImmPort</td>
<td>Platform to share and analyze immunology data generated from human and animal models</td>
</tr>
<tr>
<td>Immune Epitope Database and Analysis Resource Immune Epitope Database and Analysis Resource</td>
<td>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</td>
</tr>
<tr>
<td>ImmuneSpace</td>
<td>Powerful data management and analysis engine for the HIPC program that enables integrative analyses and visualization of human immunological data</td>
</tr>
<tr>
<td>Interventional Agent Development</td>
<td>Services to facilitate preclinical development of therapeutics and new <em>in vivo</em> diagnostics for infectious disease–causing pathogens and/or toxins</td>
</tr>
<tr>
<td>NIAID Adjuvant Development Program</td>
<td>The goal of the adjuvant development program is to establish and expand the availability of novel vaccine adjuvants that researchers can use for preclinical vaccine development in both infectious and immune mediated diseases</td>
</tr>
<tr>
<td>NIAID Adjuvant Discovery Program</td>
<td>NIAID plays a leading role in the discovery, development, and characterization of new vaccine adjuvants that may be used to: improve the efficacy of current vaccines; design new or improved vaccines for existing and emerging infectious diseases; and develop vaccines to treat allergies, autoimmune diseases, and cancer</td>
</tr>
<tr>
<td>NIH Tetramer Core Facility</td>
<td>Produces and distributes major histocompatibility complex tetramers and related reagents to the research community</td>
</tr>
<tr>
<td>Phase I Clinical Trial Units for Therapeutics</td>
<td>Supports design, development, implementation, and conduct of Phase I clinical trials against viral (other than HIV), bacterial, parasitic, and fungal pathogens</td>
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<tr>
<td>Resource Name</td>
<td>Description</td>
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<tr>
<td><strong>Preclinical Models of Infectious Disease Program</strong></td>
<td>Provides development, screening, and efficacy testing in preclinical infectious diseases models, including traditional lab species, nonhuman primates, and non-traditional models</td>
</tr>
<tr>
<td><strong>Structural Genomics Centers for Infectious Diseases</strong></td>
<td>Applies state-of-the-art technologies/methodologies to characterize 3-D atomic structures of molecules to support infectious disease research</td>
</tr>
<tr>
<td><strong>Therapeutic Development Services: Biopharmaceutical Product Development Services</strong></td>
<td>Offers services for biotechnology products, such as planning, product characterization, process development, formulation, Good Manufacturing Practice, and Chemistry, Manufacturing and Control documentation</td>
</tr>
<tr>
<td><strong>Therapeutic Development Services: Interventional Agent Development Services</strong></td>
<td>Facilitates development of therapeutics, including lead identification and development, chemistry and manufacturing, toxicology, and pharmacokinetics</td>
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<tr>
<td><strong>Vaccine Adjuvant Compendium</strong></td>
<td>Displays adjuvant characteristics or metadata defined through NIAID-supported adjuvant studies, helps vaccine developers identify suitable adjuvants for vaccine indications</td>
</tr>
<tr>
<td><strong>Vaccine Development Services: Vaccine Testing Services</strong></td>
<td>Offers services for vaccine and adjuvant development such as assay development, non-clinical immunogenicity and efficacy studies, clinical and non-clinical sample testing and safety and toxicity testing</td>
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APPENDIX 3: Analysis of Public Comments to Request for Information (RFI)

The National Institutes of Health (NIH) developed the Strategic Plan for Herpes Simplex Virus Research to serve as a foundation for the research and medical communities to continue to work together to develop interventions that will enable us to reduce the health consequences of HSV infection.

To solicit input from the public, NIH released the Request for Information (RFI): Inviting Comments and Suggestions on a Framework for the NIH HSV Strategic Plan (NOT-AI-23-042), which was open for comments from April 21, 2023, to June 21, 2023. The RFI gathered input from the research community, advocacy groups, the public, and other interested stakeholders on significant knowledge gaps and barriers, resource deficiencies, and areas of emerging technologies relevant to HSV research. The responses to the RFI were reviewed and incorporated in the plan as appropriate.

Comments were requested on, but not limited to, the following topics in HSV research:

- Significant research gaps and/or barriers not identified in the outlined strategic priorities
- Necessary resources critical to advancing research in the outlined strategic areas
- Emerging scientific advances or techniques that may accelerate research related to the outlined priorities
- Approaches to advance treatment and prevention, and identify future priority areas for new clinical research

In response to the RFI, NIH received 105 submissions, underscoring the significant interest in advancing HSV research. Overall, the respondents indicated support of the plan’s outlined priorities, suggested new or adapted scientific priorities, and offered personal experiences providing insight into living with HSV infection. To respect the personal nature of many of these submissions, a summary of themes that emerged from an analysis of the RFI responses is provided. Figure 5 shows the top ten most frequently cited topics from the RFI responses.
Specific Themes from RFI Responses

Basic HSV Biology, Pathogenesis and Epidemiology
Respondents supported continued investigations into HSV epidemiology and basic HSV biology, including viral mechanisms of entry, viral replication, viral assembly and egress, immune response to infection, as well as investigation into whether HSV pathogenesis differs by gender. Respondents also suggested the need for research to further identify and explain differences in HSV infectivity, shedding and transmission.

Neurological Impacts of HSV
Support for further investigations of the neurological impacts of HSV was a common theme across responses. This included investigations into the link between HSV and Alzheimer's disease/dementia and other conditions. Comments mentioned the importance of treating acute and chronic HSV infection to reduce the risk of progression to other conditions including neurodegenerative diseases. Neuropathic pain and neuropathic itch were frequently suggested as areas that may benefit from more investigation.

Mental Health Impacts of HSV
For people living with HSV, there can be significant impacts on mental health such as depression and the societal stigma surrounding infection. Numerous comments noted a lack of recognition by the medical community of these impacts. Respondents offered suggestions to assess the mental and social impact of the viruses on those living with HSV such as measuring the mental health cost (e.g., quality-adjusted life year QALY). Many expressed interest in the research community investigating how reducing the prevalence of HSV could impact the prevalence and cost of HIV burden of disease. Another suggestion was to model the impact of HSV infection on social well-being (e.g., how many working days/months/years lost to stress, anxiety, and pain).

HSV Models of Infection
Another area that was highlighted in the comments was the need for continued development of robust models of human peripheral ganglia or other human neuronal models. Respondents felt that investigators’ work in this area has not been sufficiently coordinated, and that researchers have not received sufficient support. As such, there are few efforts to directly compare infection models or to invest in the development of models to better recreate the complex cellular environment where HSV establishes latency. Others suggested that the development of improved, reliable animal models for predicting immunological outcomes should be developed and emphasized the importance of rigorous comparisons between models.

HSV Diagnostics
Several respondents commented on the need for improved sensitivity and specificity of diagnostic tests, including decreasing the high number of false positives/negatives. In addition, respondents supported efforts to improve access to the current Western Blot test and increased emphasis on developing specific and sensitive at-home tests. Respondents were also interested in the development of point of care (PoC) diagnostics that can detect HSV from sampling of skin and mucosal sites without evidence of herpetic lesions (i.e., asymptomatic individuals). One commenter noted that universal screening of people of childbearing age would help determine the risk for neonatal infection. Additionally screening of neonates for both symptomatic or asymptomatic infection would be important since subclinical infection could result in short- or long-term neurological sequelae in a newborn.

As part of an overall emphasis on improving HSV diagnosis, several respondents indicated that HSV testing should be included in routine STI screening panels. There was sentiment that the current United States Preventive Services Task Force (USPSTF) recommendations to not test asymptomatic people for
HSV, and the subsequent adverse impact on routine screening for HSV has led to poor clinical care and the deprioritization of HSV as a health issue.

**HSV Preventative and Therapeutic Treatments**
Respondents indicated that development of an HSV cure should be the highest priority for the field. As part of this effort, commenters noted that there is a need to increase resources for clinical trials investigating interventions. Specifically, more funding should be allocated for investigations into prophylactic vaccine candidates.

Preventing HSV shedding was also an area of significant focus. Many indicated that the treatment, pritelivir, should be available for all, not just those who are immunocompromised. In addition, respondents suggested that therapeutic approaches for those for whom current therapies have little to no effect be expanded and barriers of access to all therapies be decreased. Commentors also suggested that multipurpose prevention therapies (MPTs) containing acyclovir or a monoclonal antibody that prohibits HSV transmission, should be further developed and brought to market.

Many respondents suggested that there is also a need for research on HSV suppression during pregnancy, including epidemiological studies that demonstrate the effectiveness of treating HSV infection during pregnancy to improve maternal and fetal outcomes. It also was suggested that researchers investigate outbreaks triggered by hormonal changes in women. Resources for coupling evaluation of PoC diagnostics for pregnant individuals during delivery with post-exposure prophylaxis (PEP) in exposed newborns should be prioritized.

**HSV Clinical Research**
Several respondents noted that clinical trials should be broadly advertised, engaging community members to promote inclusive participation. Incorporating social sciences into HSV research was also suggested to help identify issues related to vaccine hesitancy, burden of disease, appropriate education for physicians providing counseling to HSV positive individuals, etc. Some respondents suggested implementation of community advisory boards consisting of people living with herpes and other stakeholders for all HSV clinical trials.

**Cross-cutting Themes**

**HSV Research Funding and Support**
Many comments stated that funding for HSV research across all areas should be increased. Respondents noted the need for additional government funding for the development of prophylactic vaccines, pointing out that pharmaceutical companies are working extensively on therapeutic HSV vaccines. Other commenters noted that funding should be provided to small organizations in areas that recruit for diverse clinical trial participants. Another response indicated that funding opportunities should be provided to researchers and trainees from underrepresented groups across all disciplines to better understand HSV.

**HSV Research Collaborations**
Enhanced research collaboration was another theme that emerged from the responses. There was interest in improving and emphasizing scientific collaboration in the HSV field, including the sharing and depositing of reagents in existing NIAID or other reagent repositories and coordinating workshops/meetings that bring HSV researchers together. Respondents also expressed the importance of collaborative efforts in improving strategies to manage HSV diagnoses (e.g., holistic practitioners, mental health providers, etc.). Further, results from clinical studies investigating other infections, such as HIV, should be shared to provide data on virologic outcomes for those coinfected with HSV.
Additionally, responders indicated that more NIH programs and staff should be dedicated to HSV research and treatment, and that a program dedicated to a single virus and its diseases be modeled after the Division of AIDS. Respondents also requested more collaboration across NIH Institutes, Centers, and Offices (ICOs) and noted the need for multidisciplinary expertise in virology, immunology, epidemiology, statistics, mathematical modeling, and clinical trial design to stimulate advances in the HSV field. Because there are few clinical researchers dedicated to the study of HSV, some suggested it would be beneficial to implement novel and other funding strategies (e.g., Request for Applications (RFAs) and Request for Proposals (RFPs) across NIH ICOs to encourage participation. Junior and new researchers should also be incentivized to join the field.

**HSV Public Health Education**

Respondents suggested clinical advances in diagnosis need to be accompanied by the development of new and widely disseminated educational materials for providers. These materials would enable them to provide more effective and compassionate counseling for those who test positive for HSV and support referral of patients to mental health providers. Several individuals stated that physicians regard HSV as a mere skin condition rather than a complex disease with nervous system involvement. Neuropathic pain and neuropathic itch are frequently unrecognized as HSV symptoms by physicians, and many respondents suggested education among physicians in these areas. Others expressed the need for education for providers and the public on asymptomatic transmission of HSV.

Many respondents indicated that HSV-related stigma amongst the patient, professional, and scientific communities and has stymied scientific progress. The burden of HSV impact disproportionately affects women and minorities, and because of the stigma around this disease, there are screening guidelines that are paternalistic and not patient-centered. Respondents suggested that herpes should be rebranded as a public health epidemic. Increasing awareness is critical for public health education and reducing stigma.

**HSV surveillance**

Finally, respondents indicated the need for improved HSV surveillance. Surveillance tools that could provide the scientific and medical communities with a clearer, more nuanced picture of the burden of HSV include population-based surveys, opportunistic and sentinel surveillance, and case-based reporting.