HSV

Herpes Simplex Virus Addendum to the Sexually Transmitted Infections

National Strategic Plan

for the United States | 2021–2025

VISION

The United States will be a place where sexually transmitted infections (STI) are prevented and where every person has high-quality STI prevention, care, and treatment while living free from stigma and discrimination.

This vision includes all people, regardless of age, sex, gender identity, sexual orientation, sex characteristics, race, ethnicity, religion, disability, geographic location, or socioeconomic circumstance.

Acknowledgments: The *Herpes Simplex Virus (HSV) Addendum to the Sexually Transmitted Infections National Strategic Plan* (STI Plan) was developed through a robust process that included gathering feedback from colleagues across health care and related fields. Colleagues throughout the federal government, as well as nonfederal colleagues including state, tribal, territorial, and local governments, researchers, health plans and providers, community groups, and national and local organizations that work in STI and related fields, have helped shape the goals, objectives, and strategies in this plan. The Office of the Assistant Secretary for Health (OASH) and its Office of Infectious Disease and HIV/AIDS Policy (OIDP) of the U.S. Department of Health and Human Services (HHS) sincerely thank all those who contributed to making this HSV Addendum a reality, especially staff from the Centers for Disease Control and Prevention (CDC) Division of STD Prevention and the National Institute of Allergy and Infectious Diseases (NIAID) who provided technical support.

Language used in the STI Plan: The HSV Addendum places value on the lived experiences and choices of all people, regardless of age, sex, gender identity, sexual orientation, sex characteristics, race, ethnicity, religion, disability, geographic location, or socioeconomic circumstance. To reflect this vision, a concerted effort was made to use inclusive and person-first language by using CDC Preferred Terms throughout the addendum. Evidence-based, contemporary terminology is also used to convey respect and empowerment and to reduce stigma faced by communities and populations disproportionately impacted by these infections. Despite these efforts, specific terminology or language may be unintentionally offensive or stigmatizing to some individuals or populations. Language is subjective, the meaning and use of language changes over time, and language from local communities can be used in implementation. This approach is intended to help the HSV Addendum's users to identify these societal shifts in preferred terminology and to communicate in a manner that reflects its vision for a collective, inclusive, and respectful national response.

Additional information regarding the STI Plan and associated activities may be accessed at www.hhs.gov/STI.

Suggested citation: U.S. Department of Health and Human Services. 2024. *HSV Addendum to the Sexually Transmitted Infections National Strategic Plan for the United States: 2021–2025.* Washington, DC.

TABLE OF CONTENTS

Executive Summary 1

Introduction 2

The Need for an HSV Addendum to the STI National Strategic Plan 2

Scope, Approach, and Development of the HSV Addendum 3

Overview of HSV 5

Epidemiology 8

Challenges with Prevention and Control of HSV Infections 11

STI Plan Goals for HSV 16

STI Plan Goal 1: Prevent new STIs 17

STI Plan Goal 2: Improve the health of people by reducing adverse outcomes of STIs 19

STI Plan Goal 3: Accelerate progress in STI research, technology, and innovation 21

STI Plan Goal 4: Reduce STI-related health disparities and health inequities 24

STI Plan Goal 5: Achieve integrated, coordinated efforts that address the STI epidemic 25

Federal Action Steps for HSV 27

Appendix A: Process/Methodology for Developing and Adopting the HSV Addendum 34

Appendix B: STI Federal Implementation Working Group 39

Appendix C: Acronyms 40

Appendix D: References 41

Tables, Figures, and Boxes

Tables

Table 1. Potential HSV Surveillance Methods 13

Table 2. Definitions included in the STI Plan 16

Table 3. Federal Action Steps for HSV, 2021–2025 27

Table A1. Composition of STI Federal Implementation Working Group 34

Figures

Figure 1. Percent cases of HSV-1 in persons aged 14–49 by race and Hispanic or Latino origin, United States, 1999–2016 9

Figure 2. Prevalence of HSV-2 in persons aged 14–49 by race and Hispanic or Latino origin, United States, 1999–2016 10

Figure 3. Genital herpes testing guidance 12

Figure 4. The 2023-2028 NIH Strategic Plan for HERPES Simplex Virus Research 22

Figure B1. NIH support for clinical research on HSV prevention and treatment 36

Figure B2. HSV addendum public comments by theme 37

Boxes

Box 1. Notifiable Diseases 3

Box 2. The STI National Strategic Plan and the HSV Addendum 4

Box 3. HSV Snapshot 5

Box 4. Potential Consequences of HSV Infection 6

Box 5. Genital Herpes Testing Guidance 7

Box 6. HSV Surveillance and Fact Sheets 8

Box 7. Stigma 15

Box 8. Addressing HSV Through the Sexual Health Paradigm 17

Box 9. Syndemic 26

EXECUTIVE SUMMARY

In 2020, the Office of Infectious Disease and HIV/AIDS Policy (OIDP) in the Office of the Assistant Secretary for Health (OASH), U.S. Department of Health and Human Services (HHS) published the inaugural *Sexually Transmitted Infections National Strategic Plan for the United States: 2021–2025* (STI Plan). The STI Plan sets forth a vision for the nation with goals, objectives, and strategies to prevent and control sexually transmitted infections (STIs) in the United States, with a focus on chlamydia, gonorrhea, syphilis, and human papilloma virus (HPV). Herpes simplex virus (HSV) was not initially included because the STI Plan, with the exception of HPV, focused on nationally notifiable STIs in the United States for which there are federally funded control programs. Congress directed HHS to amend the STI Plan to address the prevention and treatment of HSV (see House Report 117-96, as reflected in the Joint Explanatory Statement accompanying the Consolidated Appropriations Act, 2022, Pub. L. No. 117-103). In collaboration with subject matter experts from across the federal government and with input from a wide range of community members, including the public, OIDP identified policy, program, and research gaps and priorities to craft a unified national response to HSV, which are described in this *Herpes Simplex Virus Addendum to the Sexually Transmitted Infections National Strategic Plan for the United States: 2021–2025* (HSV Addendum).

HSV is a lifelong condition that spreads primarily from skin-to-skin contact and can cause recurring outbreaks of painful sores on the mouth or genital areas. In addition to physical discomfort, the stigma associated with HSV can significantly impact quality of life. HSV-2 presents almost exclusively as genital lesions, while HSV-1 can present as lesions on the mouth and lips or the genitals. Although rare, pregnant people who are infected with HSV-1 or HSV-2 can transmit HSV-1 or HSV-2 to their infants during birth, which can lead to severe morbidity of HSV and mortality among infants. HSV is one of the most common STIs in the United States, and most people with HSV are asymptomatic and undiagnosed. In 2018, an estimated 18,574,000 people were living with HSV-2 in the United States, and the exact number of genital herpes infections attributed to HSV-1 is unknown. Prevention and control of HSV are extremely challenging because reliable diagnostics for asymptomatic individuals are limited and, currently, there is neither a prophylactic vaccine to prevent acquisition of HSV nor a therapeutic vaccine to provide long-term viral suppression for individuals who have HSV.

The HSV Addendum integrates HSV into the STI Plan's vision, goals, objectives, and strategies to improve HSV diagnostics, prevention, care, and treatment. It also identifies and prioritizes federal action steps for which agencies are encouraged to provide updates in future progress reports for the STI Plan.

INTRODUCTION

The Need for an HSV Addendum to the STI National Strategic Plan

In 2020, the inaugural *Sexually Transmitted Infections National Strategic Plan for the United States: 2021–2025* (STI Plan) was developed by subject matter experts across 20 federal government agencies, with input from a variety of community members, under the direction of the Office of Infectious Disease and HIV/AIDS Policy (OIDP) in the Office of the Assistant Secretary for Health (OASH), U.S. Department of Health and Human Services (HHS). The STI Plan sets forth a vision for the nation with goals, objectives, and strategies to prevent and control STIs in the United States.

The STI Plan is designed to achieve five goals:

Goal 1: Prevent New STIs

Goal 2: Improve the Health of People by Reducing Adverse Outcomes of STIs

Goal 3: Accelerate Progress in STI Research, Technology, and Innovation

Goal 4: Reduce STI-Related Health Disparities and Health Inequities

Goal 5: Achieve Integrated, Coordinated Efforts That Address the STI Epidemic

Although there are more than 30 types of STIs, the STI Plan focuses on four of the STIs with the highest morbidity rates, the most persistent and pervasive inequalities of STI burden according to national data, and the greatest impact on the health of the nation: chlamydia, gonorrhea, syphilis, and human papilloma virus (HPV).

Herpes simplex virus (HSV) is a lifelong infection that spreads from skin-to-skin contact and can cause recurring "outbreaks" of sores on the mouth or genital areas; however, most people with HSV are asymptomatic and undiagnosed.* HSV was not specifically included as one of the STIs of focus within the STI Plan:

> [The] scope of this plan focuses on nationally notifiable STDs in the United States for which there are federally funded prevention and control programs. Chlamydia, gonorrhea, and syphilis are "notifiable" diseases, but other STIs such as genital herpes are not. [HPV is not a nationally notifiable disease but is included in the STI Plan because a safe and highly effective vaccine exists to prevent infection.] … Other common but not nationally notifiable STIs such as genital herpes and trichomoniasis are neither specifically addressed in the STI Plan, nor are emerging sexually transmitted pathogens such as *Mycoplasma genitalium*; however, this should not deter community partners from using available data to identify where their resources will have the most impact. The scope of future iterations of the STI Plan may be broadened to include other common STIs. (p. 11)

* For the purposes of the HSV Addendum to the STI Plan, HSV is primarily considered in the context of sexual transmission. However, HSV is not exclusively transmitted through sexual contact. HSV can also be transmitted through other exposures, including non-sexual contact with saliva, and, in some cases, from physical contact with an HSV lesion that can spread to different areas of the body. Pregnant people can also transmit HSV to their child before birth, but it is more commonly transmitted during delivery. The term "asymptomatic" refers to individuals with no known past or current history of HSV symptoms.

BOX 1
NOTIFIABLE DISEASES

A disease is "notifiable" if health care providers and/or laboratories in all 50 states are required by state law or statute to report the diagnosis or the positive lab test to their state or local health departments. Nationally notifiable diseases are of public interest by reason of their contagiousness, severity, or frequency, as agreed upon by the Council of State and Territorial Epidemiologists. Diseases can also be reported to the public health authority through a law, statute, or regulation, which varies from state to state. Three states have legal mandates for reporting genital HSV: Florida, Washington, and Nebraska. Seven states have legal mandates for reporting neonatal HSV: Connecticut, Delaware, Florida, Louisiana, New York, Massachusetts, and Washington.

Although HSV is not a nationally notifiable disease (see Box 1), it is one of the most prevalent STIs in the United States.[1] Known limitations of some available diagnostic methods challenge surveillance efforts, and current HSV antiviral treatments are not optimal. There is no existing prophylactic vaccine to prevent transmission and no therapeutic vaccine to provide long-term viral suppression for individuals who have HSV. The physical discomfort from recurrent outbreaks and stigma associated with HSV can significantly impact quality of life.[2] The absence of a coordinated national response or strategic plan for HSV may perpetuate stigma associated with HSV and contribute to the lack of advancement and innovation of HSV diagnostics, treatment, and cure. HSV advocates play a critical role in raising awareness and education about the virus—providing support to individuals with HSV and working toward improving health care policies and research to address HSV. Congress directed OASH to develop the first-ever national strategic plan for the treatment and prevention of genital herpes.[†]

Scope, Approach, and Development of the HSV Addendum

The STI Plan is intended to serve as a roadmap for federal and nonfederal colleagues to reverse the upward trends in STI rates in the United States. Its vision, goals, objectives, and strategies are not infection specific and can be used to guide efforts to address HSV. The *STI Federal Implementation Plan* documents the specific actions that federal colleagues are taking to achieve the STI Plan's goals and objectives with regular monitoring and reporting of progress toward meeting the STI Plan's goals. However, acknowledging the need to develop a strategic approach to treat and prevent HSV, detail specific to this infection is provided in this addendum (see Box 2). The Overview of HSV section describes the available epidemiological data for HSV, consequences of HSV infection, and challenges and opportunities for HSV surveillance, prevention, diagnostics, treatment, and cure.

[†] H.R. 117-96; Joint Explanatory Statement, Division H—Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Act, 2022 (stating that H.R. 117-96 should be complied with unless contradicted).

BOX 2
THE STI NATIONAL STRATEGIC PLAN AND THE HSV ADDENDUM

The STI Plan and the HSV Addendum are complementary. Although the inaugural STI Plan focused on four STIs—chlamydia, gonorrhea, syphilis, and HPV—the STI Plan vision, goals, objectives, and strategies are not infection specific. Therefore, the STI Plan can be used to guide efforts to address HSV in the United States.

Development of the HSV Addendum followed a core list of guiding principles that sought to

- integrate the latest science in HSV diagnostics, prevention, care, and treatment;
- identify and prioritize federal actions;
- leverage existing infrastructure, capacity, and resources; and
- recognize the need for coordinated action between national, state, territorial, tribal, and local community organizations and members.

The HSV Addendum lays a foundation for a broad range of collaborators to build upon by bringing additional capacity and resources to bear and providing role models and ideas that can inform other potential partners' actions to further national and local progress. Future iterations of the STI Plan will incorporate HSV within its purview.

The Federal Action Steps section of this addendum highlights federal agency action steps that are specific to HSV and aligned with the STI Plan's goals, objectives, and strategies. Federal agencies will be encouraged to report progress toward HSV action steps in future progress reports for the STI Plan.

Unlike the STI Plan, the HSV Addendum does not identify indicators with quantitative targets to measure progress. Current limitations with HSV diagnostics and therefore data and surveillance render development of HSV-specific indicators both difficult and unreliable (see Overview of HSV section). However, the federal action steps included herein, along with nonfederal activities, can be understood, collectively, to serve as process measures toward advancing HSV priorities, and updates to these federal action steps will be addressed in future progress reports for the STI Plan. As new diagnostics are developed and data and surveillance methods improve, it may become possible to include HSV-specific indicators in future iterations of the STI Plan.

The HSV Addendum was developed through a process that engaged federal leadership, experts, and a variety of nonfederal colleagues who compiled subject matter evidence and recommendations on HSV (see Appendixes A and B). A list of acronyms used throughout the document can be found in Appendix C, and references can be found in Appendix D.

OVERVIEW OF HSV

This section provides an overview of HSV and is informed by current Centers for Disease Control and Prevention (CDC) treatment guidelines, scientific literature, and reported surveillance data, as well as by public input. Box 3 summarizes important facts about HSV.

BOX 3

HSV SNAPSHOT

- HSV is treatable but not currently curable
- Most people with HSV types 1 or 2 have no or mild symptoms; however, stigma and psychosocial burden can be significant for some people
- Currently, routine screening is not recommended for asymptomatic individuals or pregnant people

Epidemiological Data

AN ESTIMATED 18,574,000 PEOPLE ARE LIVING WITH HSV-2 (2018, ages 18–49)

48.1% OF PEOPLE HAVE HSV-1 (2016, ages 14–49); the proportion of genital herpes caused by HSV-1 is unknown

10 PER 100,000 LIVE BIRTHS PRESENT WITH NEONATAL HSV, with an infant mortality rate of 7.9% from 2003 to 2014

Populations Disproportionately Impacted

- Pregnant people
- Newborns and infants
- People who are immunosuppressed
- Racial/ethnic minorities
- Gay, bisexual, and other men who have sex with men

Potential Consequences of Infection

- Transmission from pregnant person to fetus or newborn, which can lead to infant morbidity and mortality
- Discomfort from recurrent outbreaks
- Psychological stress due to stigma
- Increased risk of HIV acquisition and transmission

Current Challenges

- Most people with HSV are asymptomatic and undiagnosed
- Diagnostics for asymptomatic HSV can produce false-positive results in HSV-negative people
- Few prevention strategies exist to limit the spread of HSV
- Available treatments may reduce and shorten duration of symptoms, but there is currently no cure

HSV-1 and HSV-2 are among the most common STIs in the United States.[1] HSV can spread from one individual to another during active herpes outbreaks through direct contact with lesions, saliva or skin in the oral area, or genital secretions or skin in the genital area. HSV can also spread through direct contact with a person who is infected but does not have symptoms if they are shedding the virus from the skin or mucous membranes. Symptoms and consequences of HSV-1 and HSV-2 can range from lesions or sores on the mouth, lips, or genitals, to eye infections, to more severe symptoms including brain and spinal cord complications or death (see Box 4). However, many individuals with HSV have no or mild symptoms. HSV-2 presents nearly exclusively as genital lesions, while HSV-1 can present as lesions on the mouth and lips or the genitals. HSV is a lifelong infection and can result in additional outbreaks at or near the initial site of HSV transmission. These recurrences can be spontaneous or triggered by various factors such as stress, fever, suppression of the immune system, and menstruation.[3] Individuals who are immunosuppressed are more likely to experience more frequent and severe outbreaks and are less likely to respond to antiviral treatments.

BOX 4
POTENTIAL CONSEQUENCES OF HSV INFECTION

Because HSV is a lifelong infection, people with HSV can experience long-term consequences beyond symptom recurrence. For example, HSV-1 can infect the ocular area, causing recurring outbreaks and inflammation of the cornea that can lead to blindness.[4]

HIV INCIDENCE IS NEARLY TRIPLED IN PEOPLE LIVING WITH HSV-2, with the highest acquisition risk following initial HSV-2 infection.[5]

This elevated risk may be due to the fact that the frequency and severity of genital lesions are highest when HSV-2 is first acquired, which could provide more opportunities for HIV to enter the body.[5] However, because most HIV co-infections occur in individuals with HSV-2 who do not have symptoms, researchers should explore how the two viruses interact to facilitate transmission.

Although rare, HSV can move into the central nervous system and cause severe inflammation leading to herpetic encephalitis (inflammation or infection of the brain) and herpetic meningitis (inflammation or infection of the brain covering).[6] Herpetic meningitis is mostly caused by HSV-2, and herpetic encephalitis is primarily caused by HSV-1, although HSV-2 can cause encephalitis in newborns and people who are immunocompromised.[7,8]

Some researchers have proposed a possible association between detection of herpesvirus genetic material in brain specimens and Alzheimer's disease (AD), especially in the setting of the genetic AD risk factor (APOE-ε4 allele of apolipoprotein E).[6,9] Some observational studies have proposed a possible association between history of antiviral treatment and reduced occurrence of AD, although such studies have had variable results and potential for confounding and bias.[10] A few small clinical trials have reportedly been initiated to explore the hypothesis of a potential effect.[6]

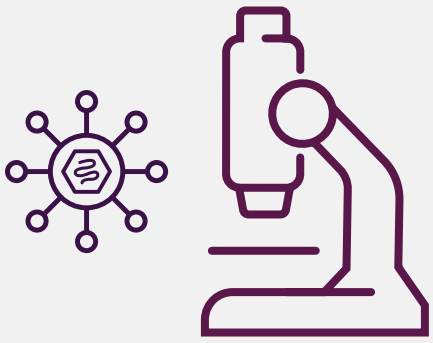
HSV can be detected directly from swab samples taken from active lesions for a nucleic acid amplification test (NAAT) or viral culture.[11] In the absence of lesions, a blood test can detect antibodies indicative of a history of HSV infection. However, Food and Drug Administration (FDA)-cleared HSV-2 blood tests can have low positive predictive value under certain circumstances, which means that a positive result is less likely to be correct.[‡] In addition, HSV-1 blood test results alone cannot distinguish between oral or genital infections and should not be used to diagnose active genital HSV-1 infection. The accuracy of these tests depends on the stage of infection, quality of the sample, and performance of the test itself.[12] The Western blot is the most accurate blood test for diagnosing HSV; however, this test is not widely available for commercial use,[13] and it is expensive and labor intensive,[11] rendering it impractical for large-scale use (see Box 5).

BOX 5
GENITAL HERPES TESTING GUIDANCE

Routine testing for herpes is not recommended.

If a patient has herpes-related symptoms, lesions should be swabbed for subsequent testing:

- Nucleic acid amplification testing (NAAT) is preferred.
- Viral culture is less sensitive than NAAT but may be the only option available.
- Cytologic testing (i.e., Tzanck smear) without additional testing is not recommended.



If a patient does not have herpes-related symptoms but is at increased risk for genital herpes,[a] serologic screening can be considered after an initial assessment.

- Type-common serologic tests cannot distinguish between HSV-1 and HSV-2. Therefore, type-specific serologic testing should be requested.
- Commercial type-specific serologic tests can sometimes provide false-positive results and should be confirmed with a CDC-recommended test, e.g., Western blot.
- HSV-1-positive serology results alone cannot distinguish genital herpes from oral herpes.
  - » These results can be confirmed later via NAAT or viral culture if genital lesions form.
- HSV-2-positive serology results imply genital infection and should be confirmed with a CDC-recommended test, e.g., Western blot.
- When a confirmatory test is unavailable, patients and providers need to be aware of testing limitations and the risks of false-positive results.

[a] Risk factors include sexual intercourse with someone who is positive for genital herpes, presenting for an STI evaluation (especially for persons with ≥10 lifetime sex partners, pregnant persons with no history of genital herpes whose sex partner has HSV infection, and persons with HIV).

[‡] See Food and Drug Administration, *HSV-2 Tests for Genital Herpes Can Produce False Reactive Results—Letter to Clinical Laboratory Staff and Health Care Providers*, https://www.fda.gov/medical-devices/letters-health-care-providers/hsv-2-tests-genital-herpes-can-produce-false-reactive-results-letter-clinical-laboratory-staff-and.

More robust information on HSV epidemiology, surveillance, and screening and treatment guidelines may be found on the CDC website through the links in Box 6.

BOX 6
HSV SURVEILLANCE AND FACT SHEETS

CDC's Sexually Transmitted Disease Surveillance 2018 report presents statistics and trends for HSV in the United States through 2018.

In 2018, CDC revised STI surveillance reports to exclude data points that were not available to be published annually. This change included HSV seroprevalence along with other data points not consistently available every year.

Additional data about HSV are available in the following HSV-specific documents prepared by CDC:

- Genital Herpes Fact Sheet
- 2021 STI Treatment Guidelines—Genital Herpes
- Screening for Genital Herpes

Epidemiology

HSV-1

Although HSV-1 is commonly associated with oral herpes (commonly referred to as cold sores), it is increasingly becoming the cause of genital herpes lesions.[14] Oral HSV-1 infections tend to occur during childhood,[14] but exposure can occur at any point throughout the lifespan. Symptoms may begin 2–12 days after initial infection, although as many as 70% of people with HSV-1 never have symptoms and are unaware of their infection.[15] Symptoms usually occur at the site where the virus first entered the body[16] and present as painful sores on or around the mouth and sore throat for oral herpes and genital lesions if transmitted on the genitalia. In more serious cases, HSV-1 can cause eye infections and inflammation of the brain or liver. Genital lesions caused by HSV-1 may be less severe and less likely to recur than those caused by HSV-2.[17,18]

Globally, the World Health Organization estimates that 3.8 billion people under age 50 have HSV-1. Of these people, an estimated 3.6 billion have oral HSV-1, and 192 million people aged 15–49 have genital herpes caused by HSV-1. This global prevalence differs by age, sex, and geographic region.[1]

CDC estimates through survey data that 48.1% of people aged 14–49 in 2015–2016 in the United States had HSV-1, a decrease from 59.4% in 1999–2000.[19] Prevalence of HSV-1 increases with age, but data are lacking for adults over age 50. HSV-1 is more common among women compared to men and is lowest in the White population compared to Black or African American and Mexican American populations (see Figure 1). The proportion of genital herpes cases caused by HSV-1 is unknown.[20]

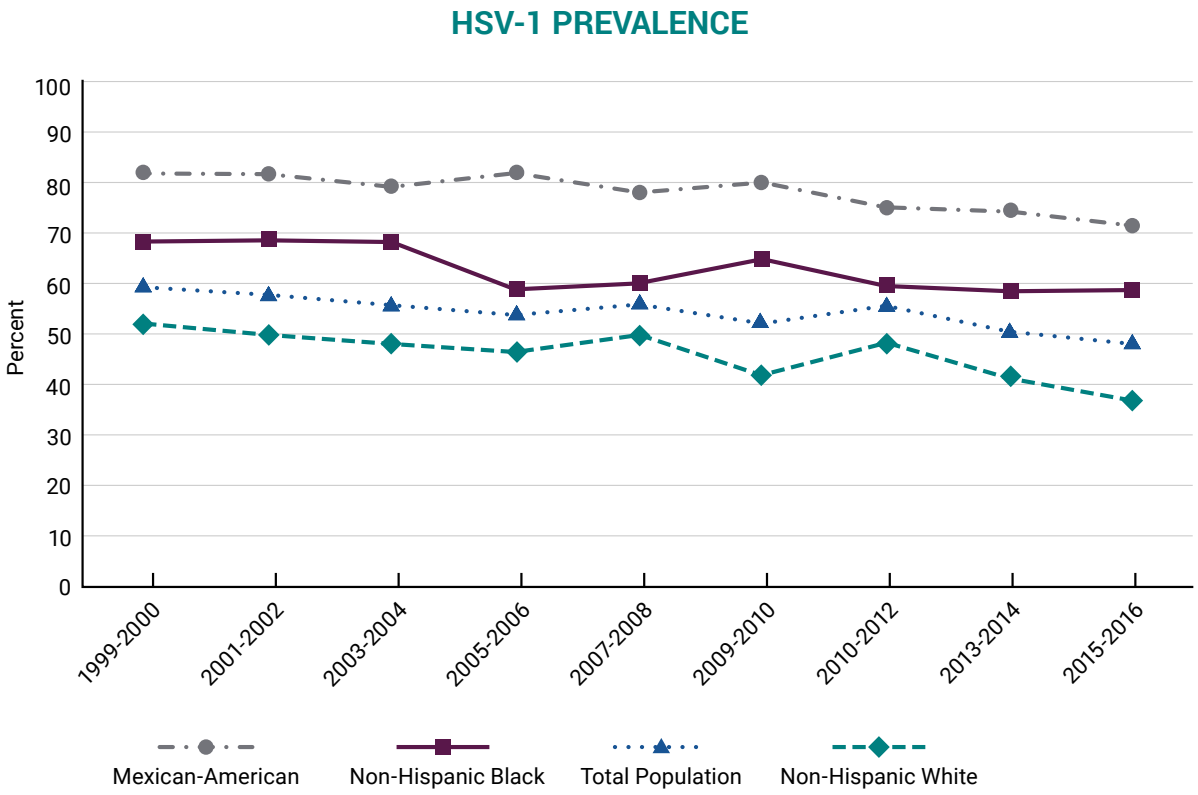


Figure 1. Percent cases of HSV-1 in persons aged 14–49 by race and Hispanic or Latino origin, United States, 1999–2016.[19] For a description of data source and methods, refer to McQuillan et al. (2018).

HSV-2

HSV-2 almost exclusively causes genital herpes and is almost always sexually transmitted. Therefore, the prevalence of HSV-2 infections increases from the start of sexual activity throughout adulthood.[21] However, less than 25% of people with HSV-2 antibodies are aware they have genital herpes, so the spread of genital herpes often occurs through people who are unaware of their status.[22,23] HSV-2 symptom severity can vary and depends on immune status.

Prevalence estimates are calculated using nationally representative survey data. Over the past several decades, HSV-2 infection rates in the United States have declined, but certain populations remain disproportionately affected. Approximately 12.1% of people aged 14–49 had HSV-2 in 2015–2016, compared to 18.0% in 1999–2000 (see Figure 2).[19] Another study estimated that in 2018, 18.6 million people in the United States had HSV-2, with women accounting for 66% of these cases. HSV-2 prevalence was highest among Black or African American persons and lowest among Asian persons. Each year, an estimated additional 572,000 new cases of genital HSV-2 infections among people aged 18–49 occur.[12] As with HSV-1, data for HSV-2 prevalence for adults over age 50 are lacking.

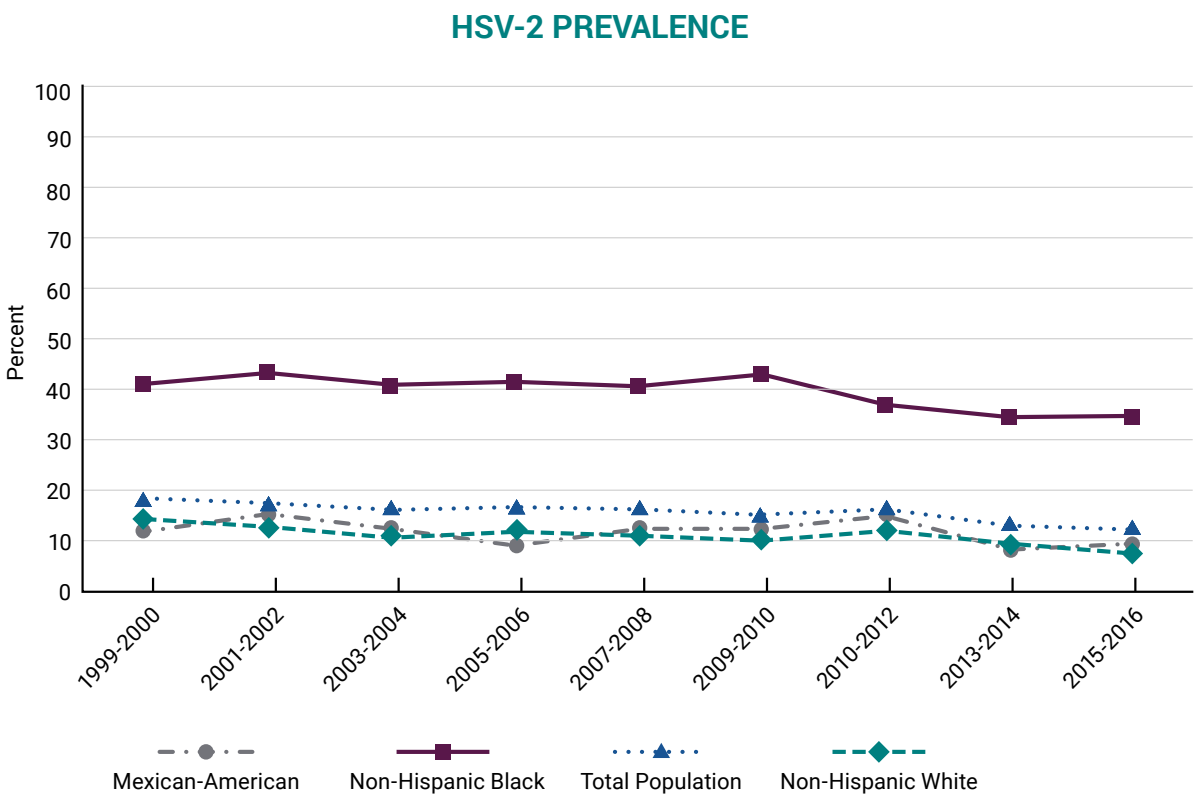


Figure 2. Prevalence of HSV-2 in persons aged 14–49 by race and Hispanic or Latino origin, United States, 1999–2016.[19] For a description of data source and methods, refer to McQuillan et al. (2018).

NEONATAL HSV

Pregnant people who are infected with HSV-1 or HSV-2 can transmit HSV-1 or HSV-2 to their infants during birth. People who acquire HSV during pregnancy, especially those who are infected late during pregnancy, are at the highest risk of transmitting HSV during birth. Consequences of neonatal HSV range from mild to fatal, including localized disease on the skin, eyes, or mouth; brain and spinal cord disease; and disseminated disease, which involves infection of multiple organs, although these categories can overlap. HSV-1 is associated more with localized disease, while HSV-2 is associated more with severe brain, spinal cord, and disseminated disease types.[24,25] Hepatitis is also a rare complication of HSV that can occur when pregnant people are infected with HSV for the first time during their pregnancy.[12] Cesarean section is recommended in the presence of active lesions or when there is risk for shedding to reduce the risk of perinatal transmission. Clinical trials have also shown that when pregnant people who have recurrent HSV outbreaks take antivirals beginning at 36 weeks gestational age, they have a decreased risk of viral shedding, recurrences, and Cesarean deliveries.[26] Recommendations have been made for infants with HSV to receive intravenous antiviral treatment for at least 3 weeks after birth, followed by oral antiviral therapy for months.[27]

Greater than 85% of neonatal HSV cases are caused by exposure during delivery, 5% are believed to occur during pregnancy but before birth, and 10% are believed to occur from exposure to caregiver saliva containing HSV-1.[28,29] Improved recognition and treatment of the disease have resulted in improvements in mortality; however, overall mortality of infants with neonatal herpes is still reported to be about 5.6%, though it is 41% for infants with disseminated disease, and 45% of infants with brain and spinal cord disease had notable neurological deficits even at 24 months.[25] Unfortunately, many mothers of infants with neonatal HSV do not have obvious genital lesions, a history of HSV, or risk factors at the time of delivery.[30]

The number of infants who acquire HSV each year in the United States remains unknown, but one report estimated an increase in neonatal HSV from 7.9 per 100,000 live births in 2003 to 10 per 100,000 live births in 2014.[31] Neonatal HSV may occur more frequently in Black or African American infants compared to White infants.[32]

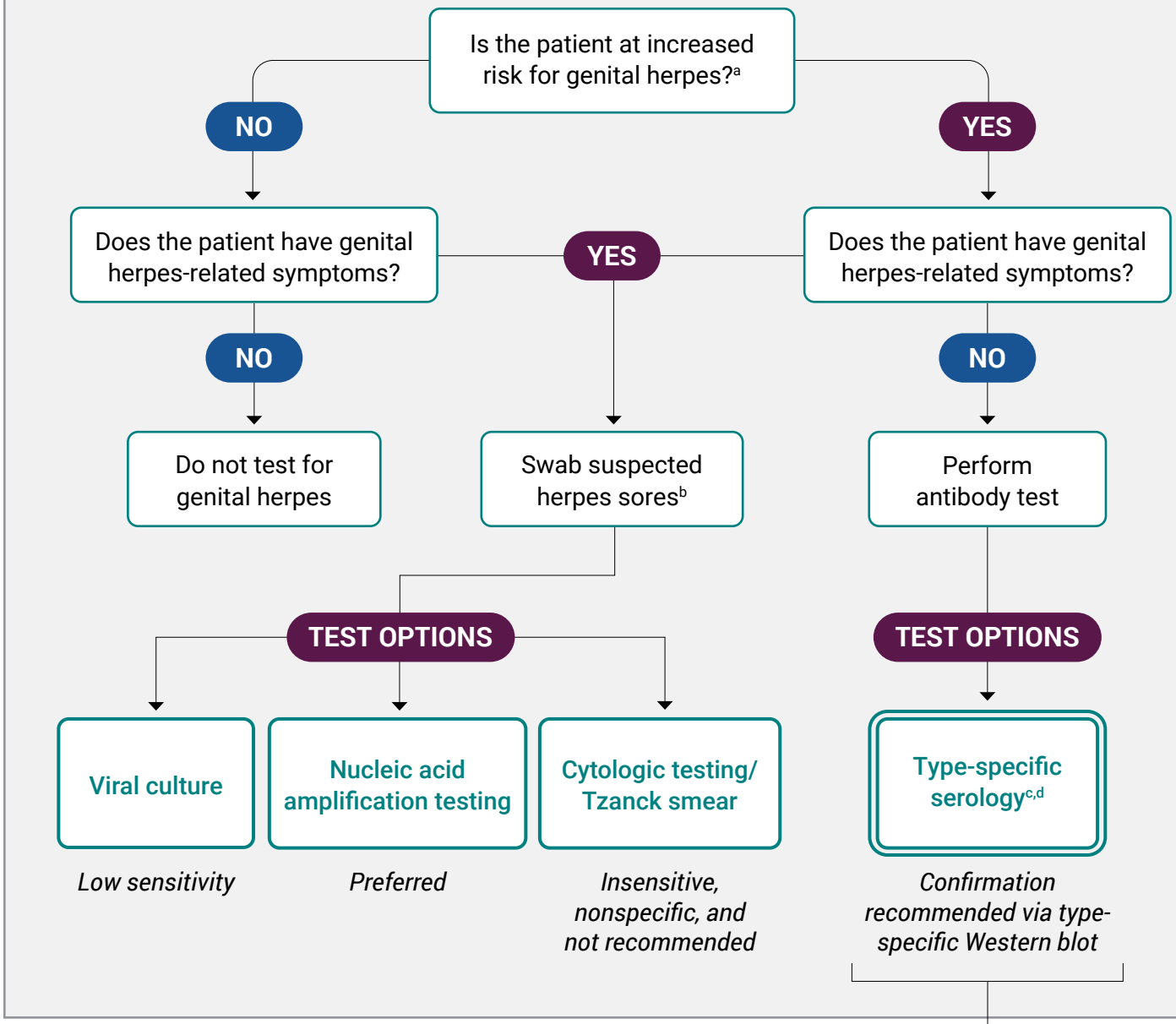
Challenges with Prevention and Control of HSV Infections

Prevention and control of HSV infections are extremely challenging. Detection of the virus or viral DNA in a lesion can aid in the diagnosis of HSV in people experiencing lesions consistent with HSV, but the low specificity of blood tests for HSV antibodies can lead to false positives; therefore, it is difficult to diagnose or screen for HSV when lesions are not present. The lack of robust diagnostics for people without lesions makes it difficult to obtain accurate HSV tracking across populations. Although cases of genital herpes due to HSV-2 infection have declined over time, HSV-1 is an increasing cause of the first episode of genital herpes lesions. However, with current testing technologies, it is impossible to determine the total number of genital herpes cases due to HSV-1.[12]

The U.S. Preventive Services Task Force (USPSTF)[§] recommends against routine blood testing for HSV in people without symptoms, including pregnant people, because the harms associated with false-positive results and unnecessary treatments outweigh the benefits for population-based screening for genital HSV infection.[13,33] CDC recommends blood testing for (1) people with recurrent or atypical genital symptoms or lesions whose lesions originally tested negative for the virus, (2) sexual partners of individuals with genital herpes, and (3) people at increased risk for HSV-2 whose clinical assessment is compatible with genital herpes.[12] Further, while tests for other STIs are used to screen pregnant people, no current HSV blood tests would be suitable for this purpose.[12,34] (See Figure 3.)

[§] USPSTF is an independent, volunteer panel of national experts in disease prevention and evidence-based medicine. It works to improve the health of people nationwide by making evidence-based recommendations about clinical preventive services.

FIGURE 3
GENITAL HERPES TESTING GUIDANCE



Western blot is the most accurate test for confirming a diagnosis of HSV; however, this test is not widely available for use in the U.S. The Western blot is exclusively performed at the University of Washington, where lab specimens can be sent for processing.

[a] Risk factors include sexual intercourse with someone who is positive for genital herpes, presenting for an STI evaluation (especially for persons with ≥10 lifetime sex partners, pregnant persons with no history of genital herpes whose sex partner has HSV infection, and persons with HIV).
[b] Swab newly-formed lesions for the most accurate assay results.
[c] HSV-1-positive serology results alone cannot distinguish genital herpes from oral herpes. Genital herpes can be confirmed later via NAAT or viral culture if genital lesions form.
[d] HSV-2-positive serology results imply genital infection.

HSV is not a nationally notifiable condition, and, therefore, no existing national surveillance system for HSV or neonatal herpes exists. Because HSV surveillance data are not available on an annual basis, CDC does not currently include HSV in STI surveillance reports.[¶] Healthy People 2030's Developmental objective STI-D01 aims to reduce the proportion of adolescents and young adults with genital herpes. It acknowledges that HSV is a high-priority public health issue but does not yet have a reliable data source that can be used to measure progress.

However, different methods could potentially be used to monitor HSV, including population-based surveys, opportunistic surveillance, case-based reporting, and sentinel surveillance. Until tests that yield very few false positives for diagnosing asymptomatic HSV are developed, as well as tests for differentiating a primary or recurrent HSV infection, no surveillance method will fully capture the burden of HSV (see Table 1 for descriptions of HSV surveillance methods and Table 3 for federal action steps that address surveillance challenges).

Table 1. Potential HSV Surveillance Methods

Type of Surveillance

POPULATION-BASED SURVEYS

What It Does	Strengths	Limitations
Randomly samples individuals selected to represent a larger population	• Can estimate HSV seroprevalence and evaluate seroprevalence by sociodemographic characteristics, sexual risk behaviors, and co-infections • Can evaluate seroprevalence trends over time	• Data collection is not timely • Administration is expensive and resource intensive • Accuracy depends on high response rate for a large sample size, and response rates have been declining • Blood tests for HSV antibodies can yield false positives and therefore cannot reliably estimate prevalence • Knowing the timing of infection is not possible
EXAMPLE *A survey that measures the percentage of the U.S. population testing positive for HSV antibodies*		

Type of Surveillance

CASE-BASED REPORTING

What It Does	Strengths	Limitations
Case reports submitted by 59 U.S. jurisdictions	• Can describe the trends in diagnosed and reported cases nationally and by geographic area	• Most infections are asymptomatic; only those reliably diagnosed can be reported • There is no way to tell true incident from recurrent infection because of limitations of current commercial diagnostics
EXAMPLE *Voluntary reporting of diagnosed HSV cases in 59 U.S. jurisdictions*		

[¶] In 2018, CDC revised STI surveillance reports to exclude data points that were not available to be published annually. This change included HSV seroprevalence along with other data points not consistently available every year.

Type of Surveillance

SENTINEL SURVEILLANCE

What It Does	Strengths	Limitations
Collects data on individuals diagnosed with HSV from a "sentinel" or subset of a larger population	• Can enable collection of more detailed information • Can enable longitudinal tracking of patients and evaluation of annual trends	• Administration is expensive and resource intensive • Data represent only the population of interest from which the sample was selected • There is no way to tell true incident from recurrent infection
EXAMPLE *Detailed information about patients diagnosed with HSV from STI clinics*		

Type of Surveillance

OPPORTUNISTIC SURVEILLANCE

What It Does	Strengths	Limitations
Uses data collected for other purposes (e.g., administrative claims data) for disease surveillance	• Can draw from large sample of collected data • Can be less expensive to administer because data collection is outsourced to other entity	• User has no input over what or how the data are collected • Some relevant information might be missing or inconsistent because data are collected for non-surveillance purposes • Some systems may not be timely or include key demographics (e.g., race)
EXAMPLE *Evaluation of health care services related to HSV*		

Source: Kreisel et al. (2022).[1]

Even when accurately diagnosed, HSV cannot currently be cured. Antiviral treatment is often used in symptomatic individuals to reduce the duration and severity of HSV outbreaks, prevent recurrence, and reduce the risk of transmission to a sexual partner. Further studies are needed to determine whether antiviral therapy can be used to prevent HSV transmission from asymptomatic individuals.[12] Because of the lifelong nature of HSV, some people with HSV may experience intense stigma and mental health challenges related to their diagnosis, including depression, anxiety, isolation, fear of rejection, loss of relationships, and shame (see Box 7).[19] This stigma may also hinder testing and disclosure of infection status to sexual partners, contributing to further spread of HSV.[35]

Although a prophylactic and therapeutic vaccine could help control the spread of HSV, there are no approved vaccines for the treatment or prevention of HSV. However, some vaccine candidates are in early clinical development.[36] Genital herpes is most contagious when sores are visible, so abstaining from sexual contact

during recurrences can reduce the risk of transmission, but HSV can still be spread when a person has no symptoms. Consistent and correct condom use can also reduce this risk, although it does not prevent HSV spread due to contact with areas not covered by the condom or other prevention barriers.[12]

BOX 7
STIGMA

Although HSV is one of the most common STIs in the United States, it is also one of the most stigmatizing.[37] For example, a survey of young women's beliefs on HSV found that women often carry negative perceptions of an HSV diagnosis, including sexual promiscuity or deviance and moral weakness and that of being unclean or tainted.[35] HSV genital lesions are an important factor in this stigma; in a study comparing perceptions of various dermatological conditions, greater than 75% of participants indicated discomfort at the prospect of touching or sharing food with someone with a visible HSV lesion.[38]

STIGMA CAN NEGATIVELY AFFECT THE MENTAL HEALTH OF PEOPLE WITH HSV: 47% have reported feeling stigmatized since their diagnosis, and this experience is associated with a lower quality of life.[39]

The initial HSV diagnosis is often accompanied by depression, anxiety, and low self-esteem.[40] Some people with HSV also struggle with a fear of rejection in social and romantic relationships if they disclose their diagnosis, which can lead to social isolation and loneliness.[39]

Although these negative emotions decline with time for many people with HSV, social and emotional support from friends and loved ones is the factor most associated with reducing psychological distress from internalized stigma.[39] Health care providers and health educators also share responsibility for addressing this persistent stigma by countering the misconceptions that fuel it and by delivering diagnoses through a trauma-informed care approach. Empowering people with HSV to self-manage their treatment and to develop successful coping strategies can also help counter the shame and stigma experienced upon diagnosis.[40]

STI PLAN GOALS FOR HSV

The STI Plan sets forth objectives for each goal, and strategies for each objective (see Table 2 for definitions). These objectives and strategies are designed to guide federal partners and nonfederal colleagues in achieving the STI Plan's vision and goals. The objectives provide direction for the attainment of each goal. The strategies recommend approaches to achieve the objectives. The *STI Federal Implementation Plan* details federal agencies' plans and action steps to implement the goals, objectives, and strategies set forth in the STI Plan. The HSV Addendum describes how HSV can be integrated into the STI Plan's five goals.

Table 2. Definitions Included in the STI Plan

STI Plan	Federal Implementation Plan
Goals: Broad aspirations that enable a plan's vision to be realized **Objectives:** Changes, outcomes, and impact a plan is trying to achieve **Strategies:** Choices about how to best accomplish objectives	**Action Steps:** Specific activities that will be performed to implement the strategies and achieve the goals of the plan **Progress Reports:** Reports on progress, successes, and challenges

STI PLAN GOAL 1: PREVENT NEW STIS

Goal 1 objectives and strategies from the STI Plan exemplify the use of primary prevention to halt the spread of STIs, specifically by preventing them before they occur, including through raising awareness and education.[#] Primary prevention is uniquely challenging for HSV because of its high prevalence rate, asymptomatic transmission, and limitations of screening and diagnostics for asymptomatic HSV and of prophylactic and therapeutic vaccines. In the absence of these preventive interventions, provider education and public awareness of HSV transmission, symptoms, and risk factors are critical for preventing new cases.

An evidence-based prevention strategy cited in CDC's STI clinical guidelines and applicable to HSV is behavioral counseling about risk-reduction behaviors, such as consistent and correct condom use and reduction in the number of sex partners.[12] (See Box 8.) Disclosure of HSV status to sexual partners has also been shown to reduce transmission, although it is less likely to occur among casual sexual partners.[41,42] Shame and fear of rejection are the primary reasons individuals choose to not disclose their HSV status.[42,43] Individuals should receive appropriate guidance regarding disclosure during patient counseling that includes accurate information regarding transmission risks and messaging to decrease the anxiety and shame associated with diagnosis.

GOAL 1: PREVENT NEW STIS

Objectives

1.1 Increase awareness of STIs and sexual health

1.2 Expand implementation of quality, comprehensive STI primary prevention activities

1.3 Increase completion rates of routinely recommended HPV vaccination

1.4 Increase the capacity of public health, health care delivery systems, and the health workforce to prevent STIs

BOX 8
ADDRESSING HSV THROUGH THE SEXUAL HEALTH PARADIGM

As with other STIs, education is critical to counter misinformation about HSV in the general population, especially among underserved populations. A survey of college-aged women found that 96% believed that HSV infection would result in genital sores and that 68% believed that they would be able to discern whether their partner had HSV. Yet, in fact, the majority of people with HSV are asymptomatic, and transmission can occur during unprotected sex with a partner without genital lesions.[37] Although most of the survey respondents understood that HSV lasts for a lifetime, about one-third believed that HSV infection could either be eliminated with a pill or could not be treated at all. People with HSV can be affected by misinformation; one study found that 38% of people with HSV surveyed believed that the virus could only be passed to a partner during an outbreak, and only 40% were aware of available treatments that could reduce the chance of transmitting the virus.[44] These studies reflect a general lack of knowledge about HSV among the public, which should be addressed.

[#] Primary prevention of STIs includes assessment of behavioral risk (i.e., assessing the sexual behaviors that can place persons at risk for infection) and biologic risk (i.e., testing for risk markers for STI acquisition or transmission). Secondary prevention aims to detect illness through forms of screening or testing. Tertiary prevention aims to reduce the adverse outcomes of illness through treatment and other therapeutic interventions.

HSV can have a significant effect on the sexual health and behavior of people with HSV, particularly within the first year after diagnosis. It is common for people who are newly diagnosed with HSV to initially reduce or abstain from sexual contact, particularly during a recurrence,[40] and to be extremely concerned about transmission of the virus to sexual partners.[44] Although a small percentage of people with HSV report physical discomfort or pain resulting from genital lesions,[40] diminishment of interest or pleasure in sexual behaviors primarily results from the psychological (rather than physical) impact of the diagnosis.[39]

The partnership between health care providers and patients plays a key role in the successful management of HSV. Health care providers should be aware of the profound psychological impact of an HSV diagnosis and be prepared to offer resources to support people newly diagnosed with HSV.[40] Health care providers should also acknowledge patients' concern about transmitting the virus and discuss how condom use and medication can reduce this risk.

Indeed, although health care providers said that 74% of their patients were taking prescription medications for their HSV, ONLY 29% OF PATIENTS REPORTED RECEIVING MEDICATION, WITH MOST NOT ON TREATMENT BELIEVING THEIR OUTBREAKS WERE NOT SEVERE OR FREQUENT ENOUGH.[44]

Because suppressive antiviral therapy can reduce asymptomatic shedding and the risk of transmission, health care providers should consider discussing the benefits of treatment with people with HSV regardless of outbreak frequency or severity.[44] Further, patients should be empowered to navigate conversations regarding disclosure with current and future sexual partners, and be reassured that the HSV diagnosis does not preclude them from engaging in sexual and romantic relationships in the future.

According to CDC, individuals with a history of symptomatic genital HSV can also decrease the risks of transmission to sexual partners by taking daily suppressive antiviral medication to reduce outbreaks and asymptomatic viral shedding, and by abstaining from vaginal, anal, and oral sex during outbreaks, when the risk of transmission is highest.[45] However, no evidence indicates that people without HSV can prevent HSV acquisition by taking antiviral medication prophylactically,[26] which demands further study.

Although many clinical prevention guidelines for STIs also apply to HSV, further education and awareness about prevention is required, because HSV is not exclusively transmitted through sexual contact. HSV can also be transmitted through other exposures, including non-sexual contact with saliva, during childbirth, and, in some cases, from physical contact with an HSV lesion that can spread to different areas of the body. Although HSV is primarily discussed in the context of sexual transmission in the HSV Addendum, other modes of transmission must be considered in primary prevention activities.

Available evidence shows that society holds many misconceptions about HSV, particularly regarding risk reduction strategies, asymptomatic transmission, and suppressive antiviral medications.[46] For example, many individuals underestimate the actual prevalence rates of HSV, particularly given the high rate of individuals who are asymptomatic and undiagnosed, and therefore hold inaccurate risk perceptions.[37] Surveyed college students reported that they believe STI prevention strategies offer more protection against HSV than is evident in the literature,[47] and only slightly more than one-half of Americans are aware that herpes is not curable.[48] An increasing amount of genital herpes infections is attributed to HSV-1,[12] suggesting that many individuals might be unaware of the risks of transmission through oral sex.[49] Indeed, many adults and adolescents perceive

oral sex to be a risk-free behavior.[50] Increasing awareness of individuals' risk for acquiring HSV may increase prevention measures and in turn decrease the proportion of new HSV cases. A greater understanding about HSV prevalence and transmission will enable individuals to navigate sexual encounters with greater awareness of their risks. Patients can then accurately explain those risks to health care providers, who can assess whether HSV testing might be appropriate during behavioral counseling.

HSV incidence is highest among adults aged 18–24,[20] and adolescents and young adults account for the largest population of new HSV-1 cases.[51] Increasing opportunities for HSV awareness in adolescence is critical in preventing HSV prior to early adulthood. It is also important to seek opportunities to target this demographic, such as through strengthening primary prevention activities in comprehensive quality sexual health education programs and social media campaigns.

Many HSV misconceptions are perpetuated by the lack of HSV knowledge among health care providers as well. As stated in the STI Plan, there is a clear need and opportunity to expand overall sexual health education and training among all types of health care providers throughout the stages of their career including during training (e.g., medical school, residency) and once in practice (e.g., through continuing education, certification, and maintenance of certification).

HSV is neglected in many existing STI prevention programs and strategies because of the diagnostic and surveillance limitations discussed in the Overview of HSV section. The HSV Addendum aims to look beyond those limitations and incorporate HSV more into existing STI prevention strategies, and to seek ways to leverage current resources and further engage health care providers, schools, families, and communities about HSV transmission. Additional capacity, resources, incentives, training, partnerships, and integration of efforts are all critical elements to integrating HSV into STI objectives and strategies.

STI PLAN GOAL 2: IMPROVE THE HEALTH OF PEOPLE BY REDUCING ADVERSE OUTCOMES OF STIs

Goal 2 objectives and strategies from the STI Plan exemplify secondary and tertiary prevention approaches to impede the progression from infection to disease and to treat disease when it occurs. Secondary prevention aims to detect illness through forms of screening or testing, and tertiary prevention aims to reduce adverse outcomes through treatment and other therapeutic interventions. Although HSV infection can present as asymptomatic, many individuals with HSV, particularly those who are immunosuppressed, experience adverse physical outcomes, as well as infants, who are at increased risk for severe morbidity and mortality. This Addendum acknowledges that quality of life can be greatly impacted for individuals with HSV because of the physical discomfort from primary and recurrent outbreaks, and the psychological distress following diagnosis and while navigating future sexual and romantic relationships.[2] Improved screening, treatment, and counseling for people with HSV is critical to reducing potential adverse physical and psychological health outcomes and improving their overall quality of life.

GOAL 2: IMPROVE THE HEALTH OF PEOPLE BY REDUCING ADVERSE OUTCOMES OF STIs

Objectives

2.1 Expand high-quality affordable STI secondary prevention, including screening, care, and treatment, in communities and populations most impacted by STIs

2.2 Work to effectively identify, diagnose, and provide holistic care and treatment for people with STIs by increasing the capacity of public health, health care delivery systems, and the health workforce

An accurate HSV diagnosis, which can be informed through detection of the virus in lesions or type-specific blood tests, is important for preventing new infections and initiating treatment. Among data related to patient and provider engagement, 73% of patients reported that their HSV diagnosis was based on clinical suspicion, which can frequently be inaccurate.[12,40] This finding highlights the opportunities to increase provider knowledge and adherence to HSV testing in accordance with CDC's STI Treatment Guidelines.

Most genital herpes infections are transmitted by individuals who are asymptomatic and undiagnosed.[12] USPSTF and CDC do not recommend routine HSV screening for asymptomatic individuals, including pregnant people. Unfortunately, some health care providers are unaware of these testing guidelines and do not always explain the limitations of available diagnostics for asymptomatic patients who request HSV screening. Patients may also be unaware that HSV is often not included in traditional routine STI testing panels, and therefore may falsely assume they are HSV-negative after receiving a negative STI screening. During STI screenings, patients should be informed about all the STI tests they are receiving. Patients should also be made aware of what testing options are available for HSV and why they are not included in general STI screenings.[12] CDC's STI Treatment Guidelines recommends that all individuals with HSV also be tested for HIV, because HSV increases the risk of HIV transmission. As stated in the STI Plan, STI screening is viewed as "an essential and underutilized component of an STD/HIV risk assessment in most clinical settings."[52] When patients seek treatment or evaluation for a particular STI (or pregnancy prevention or testing), health care providers are encouraged to screen for other STIs based on prevalence within their specific community and national recommendations and to perform a comprehensive risk assessment.

After receiving an HSV diagnosis, patients should receive comprehensive counseling on transmission and available therapeutic treatments. Patients often report conflicting guidance from health care providers on risks regarding asymptomatic shedding or when individuals living with HSV infection can pass the virus to others despite not showing any symptoms. Similarly, patients report not being informed about or prescribed antiviral suppressive treatment to manage primary and recurring outbreaks.[40] Dissatisfactory patient counseling occurs in part because health care providers lack knowledge about HSV, as well as time or resources to dedicate to clinical consultations.[37,40] Inadequate counseling may also occur when patients' and health care providers' perceptions about HSV do not align.[40] When health care providers underestimate the psychological and physical burden of HSV, patients may not effectively manage their diagnosis and disclosure of status to current and future sexual partners.[44]

In addition to medical treatment, individuals with HSV may require mental health counseling to cope with psychological distress associated with receiving an HSV diagnosis and living with HSV. Individuals diagnosed with HSV report higher levels of anxiety and depression compared to individuals with other STIs and exhibit minimal improvement in the months following diagnosis.[53] Efforts should be made to integrate psychotherapy as part of initial and longer-term HSV treatment and management protocols, as well as in medical education programs.

Although rare, neonatal herpes can lead to severe long-term morbidity, neurologic impairment, and mortality.[32] Linked birth-death files for infant deaths from 1995 to 2017 from the National Center for Health Statistics show an increase in neonatal herpes deaths that outpaced those caused by HIV and congenital syphilis.[32] It is important to prioritize interventions that enable the public health community and health care providers to prevent mother-to-child HSV transmission and to appropriately recognize neonatal herpes in order to rapidly administer antiviral therapy and prevent infant morbidity and mortality.

As stated in the STI Plan, the COVID-19 pandemic further exposed vulnerabilities in the STI infrastructure and influenced the national response to STIs, as well as other infectious diseases. After the emergence of COVID-19, STI disease intervention specialists and other STI resources were redirected to COVID-19 mitigation efforts, causing disruptions and lags in STI screening and surveillance.[54] Throughout the pandemic, rates of reportable STIs, such as gonorrhea, syphilis, and congenital syphilis, reached record highs.[55] There have also been reports of HSV reactivation in some patients with COVID-19, hypothesized to be attributable to multiple

factors such as psychological stress, fever, immunological suppression, and the possibility that COVID-19 might directly affect neurons harboring dormant HSV.[56,57] The COVID-19 pandemic underscored the importance of investment in public health infrastructure and maintenance of a robust public health workforce that can respond to emerging infectious diseases, while not neglecting current epidemics. As the COVID-19 pandemic wanes, it is uncertain whether long-term investments in the public health workforce, which are also essential to combating current STI epidemics, will continue. Harnessing opportunities to increase resources and implement innovative approaches, during and after public health emergencies such as COVID-19, is necessary to ensure access to and continuity of STI services.

STI PLAN GOAL 3: ACCELERATE PROGRESS IN STI RESEARCH, TECHNOLOGY, AND INNOVATION

The STI Plan acknowledges that a robust innovation agenda is needed to move scientific advances in STIs into clinical practice and communities.[58] Despite the high prevalence of HSV in the United States and globally, the field has seen limited scientific advances regarding innovative preventive measures, improved diagnostics for asymptomatic HSV, and more effective therapeutic treatments. CDC and the National Institutes of Health (NIH) sponsored a workshop titled "Joint Workshop on Genital Herpes" in November 2022 to define the U.S. and global burden and epidemiology of HSV, and to identify gaps and research opportunities in vaccines, therapeutics, prevention, and diagnostics development.[59] Building on the opportunities identified during the workshop, NIH developed the 2023-2028 Strategic Plan for Herpes Simplex Virus Research (see Figure 4), which was coordinated by the National Institute of Allergy and Infectious Diseases (NIAID), *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and National Institute of Neurological Disorders and Stroke (NINDS) with the following priorities: (1) improve fundamental knowledge of HSV biology, pathogenesis, and epidemiology; (2) accelerate research to improve diagnosis; (3) improve strategies to treat and cure HSV; and (4) advance research to prevent HSV infection.

GOAL 3: ACCELERATE PROGRESS IN STI RESEARCH, TECHNOLOGY, AND INNOVATION

Objectives

3.1 Support research and investments to develop STI vaccines and bring them to market

3.2 Support the development and uptake of STI multipurpose prevention technologies, antimicrobial prophylaxis regimens, and other preventive products and strategies

3.3 Support the development and uptake of innovative STI diagnostic technologies, therapeutic agents, and other interventions for the identification and treatment of STIs, including new and emerging disease threats

3.4 Identify, evaluate, and scale up best practices in STI prevention and treatment, including through translational, implementation, and communication science research

FIGURE 4

THE 2023-2028 NIH STRATEGIC PLAN FOR HERPES SIMPLEX VIRUS RESEARCH[60]

This plan outlines the commitment of the NIH to support 4 research priorities on Herpes Simplex Virus (HSV)

As addressed throughout the Addendum, HSV is not a nationally notifiable disease, partially because of known limitations of technology employed by HSV blood tests that can lead to false-positive results. Detection of the virus through direct methods, such as molecular testing or culture, are the most sensitive methods to aid the diagnosis of HSV, but they can only be conducted when an individual has an active lesion or sore. Current blood tests for HSV antibodies can yield false-positive results for asymptomatic individuals, and the serological Western Blot test is not widely accessible for confirmatory testing for the general population.[13]

The lack of a reliable diagnostic test for asymptomatic individuals is a barrier to creating a national surveillance system for HSV and neonatal herpes, which is necessary for accurate estimation of HSV prevalence and overall burden of disease and enhancement of primary and secondary prevention activities. New diagnostic technologies should be widely available, easy to conduct and interpret, cost-effective, and accurate in identification of HSV infection. Ideally, diagnostic tests should be able to accurately differentiate between HSV-1 and HSV-2 infections. Some investigators have also suggested that differentiating primary and recurring outbreaks can be useful in understanding the relative likelihood of viral shedding and recurrent symptoms, as well as incident infections and prevalence. Patients can then be more effectively counseled on how they may have obtained the virus and minimize risks for transmission to sexual partners.[17] Oral antiviral medications, the standard HSV treatment, can be used episodically and suppressively; however, there are limitations to their efficacy. Unless initiated at the start of an outbreak, they have demonstrated to have minimal effect on the duration of an outbreak, specifically with immunocompetent individuals.[61] Relatedly, antiviral medications have been shown to reduce transmission by 50% when used as suppressive treatment,[62] although further studies are needed to understand how antiviral medications affect transmission, particularly among persons with a history of asymptomatic HSV-2 infection identified by a positive HSV-2 serologic test. Although several antivirals have been available for decades, subsequent therapeutics development for HSV has been limited and safety questions have arisen with some candidate products.[63] More optimal antiviral treatments, particularly for long-term suppressive use, should be prioritized for development because they will help improve the overall health and wellbeing of individuals with HSV by reducing the duration and recurrence

of outbreaks. New treatments should also seek to maximize "treatment as prevention,"[‖] as has been explored with HIV, to effectively reduce or prevent HSV transmission among people living with HSV to partners living without HSV. This could also help reassure people with HSV that they will not transmit the virus to sexual partners, which is cited as the primary concern for patients after initial HSV diagnosis and a contributor to the psychological stress and depression that some people living with HSV experience.[44]

The STI Plan calls for the development and exploration of other innovative preventive products against STIs. Condoms are an effective—and the most common—tool to prevent transmission of genital herpes, but to prevent transmission they must cover the anatomic locations of HSV shedding, which can vary for different individuals.[64] More research is also needed on the efficacy and usage of dental dams as a preventative product for oral to genital HSV-1 transmission.[65] Microbicides, which are topical substances that contain drugs designed to reduce the risk of STI and HIV transmission, offer potential as an HSV prevention tool. Intravaginal gels or rings that contain antiviral medications should be further explored as a means for preventing HSV transmission. Given the strong syndemic interaction between HSV and HIV (described further in Goal 5), it would be useful to develop preventive interventions that deliver both HSV and HIV antiviral medications in combination.[66,67] While some aspects of viral latency are known, more effort is needed to identify key factors that can be targeted to prevent the virus from reactivating. Blocking the initial steps of reactivation could potentially reduce the spread of the virus more effectively than current antivirals do. Creating lab systems that accurately mimic viral latency could enhance the understanding of the critical elements that control it. Ultimately, finding ways to eliminate the virus from its hidden state in neurons or to keep it permanently suppressed will require a deep understanding of viral latency and HSV's genetic state.

The STI Plan also calls for innovation in vaccine development, which aligns with Goal 1 of the *Vaccines National Strategic Plan: 2021–2025* (Vaccine Plan) to "Foster Innovation in Vaccine Development and Related Technologies." As mentioned throughout this addendum, no cure for HSV currently exists. Because of its high prevalence, the development of both a prophylactic vaccine to prevent primary HSV infections and a therapeutic vaccine to reduce the duration and recurrence of outbreaks for people with HSV[68] should be prioritized. Ideally, prophylactic and therapeutic vaccines would be effective for both HSV-1 and HSV-2 subtypes. Mathematical modeling shows that even an imperfect therapeutic vaccine for HSV-2 of 75% efficacy could reduce HSV-2 incidence by 55% over the course of a decade.[69,70]

The STI Plan also calls for innovative service delivery models and comprehensive communication strategies that emphasize the importance of sexual health and reducing stigma. These strategies should be informed by behavioral, social, clinical, and epidemiologic science as well as health economics. Such strategies should consider the target demographic for rolling out the vaccine, whether it would be most effective as a preventive option when administered in infants, or in adolescents, such as the HPV vaccine. Community-based involvement, particularly for identifying acceptable intervention and prevention methods in disproportionately impacted communities, is also crucial for HSV innovation. Regulatory support, commercial investment, and academic, public, and private partnerships are all needed to successfully accelerate progress in these areas.

Investment in research, commercialization, and translation into practice will lead to more innovative, evidence-based prevention models, technologies, and products to decrease the prevalence of HSV and to work toward achieving the goals of the STI Plan.

[‖] Treatment as prevention is a highly effective prevention method in which people with HIV take HIV medication daily as prescribed and get and keep an undetectable viral load. As a result, they have effectively no risk of sexually transmitting HIV to their HIV-negative partners. This is often referred to as U=U or "undetectable=untransmittable."

STI PLAN GOAL 4: REDUCE STI-RELATED HEALTH DISPARITIES AND HEALTH INEQUITIES

As is true for other STIs, HSV disproportionately impacts certain communities and populations who are often underserved. Women account for 66% of HSV-2 infections,[19] and an estimated 22% of pregnant women are positive for HSV-2.[71] Women are at higher risk of infection because HSV is more easily transmitted from men to women than from women to men during penile-vaginal sex.[19,28] HSV-1 prevalence is highest among Mexican American persons, and Black or African American persons have the highest prevalence of HSV-2 infections by nearly three-fold when compared to Mexican American and White persons.[19] Disparities also exist in neonatal herpes, with incidence highest among births in Black or African American people. Although trends in HSV-2 seroprevalence have decreased overall, racial disparities have continued to increase.[1,72] HSV seroprevalence is also higher among people with lower incomes and with lower educational attainment.[73] These social and structural determinants of health (SDOH) may contribute to further health disparities because HSV forms a syndemic with other infections, such as HIV and other STIs. Indeed, racial and ethnic disparities in HSV-2 infection predate the HIV/AIDS epidemic in the United States[21] and potentially helped to contribute to disparities in HIV rates.[74]

GOAL 4: REDUCE STI-RELATED HEALTH DISPARITIES AND HEALTH INEQUITIES

Objectives

- 4.1 Reduce stigma and discrimination associated with STIs
- 4.2 Expand culturally competent and linguistically appropriate STI prevention, care, and treatment services in communities disproportionately impacted by STIs
- 4.3 Address STI-related social determinants of health and co-occurring conditions

Further research on racial and ethnic disparities in awareness and recognition of HSV symptoms, as well as access to STI preventive and treatment services, should be conducted to inform appropriate and culturally competent interventions for disproportionately affected populations. More demographic research is needed to understand HSV disparities based on sexual orientation and gender identity. As new treatments and vaccines are developed, racial, ethnic, gender, and sexual minorities must be adequately represented in clinical trials as new therapeutics and vaccines become available. Such developments should include engagement of those impacted most by HSV and the inclusion of their voices to understand their needs, preferences, and attitudes. This input could help shape education and promotion campaigns for future therapeutics and vaccines.

Compared to younger age groups, there is limited epidemiological data on HSV in older adults, although it is known that HSV prevalence increases with age because it is a lifelong infection.[75] It is also known that other STIs have increased in older adults, with a nearly 9-fold increase in syphilis, more than 5-fold increase in gonorrhea, and more than 3-fold increase in chlamydia in adults over age 65 between 2012 and 2022.[76] As with other age demographics, significant racial and ethnic disparities exist in STI rates among older adults.[75] Although younger adults still account for higher rates of STIs than older adults, it is important to address these increased trends and disparities and to correct misconceptions and biases about sexual health in older adults, which contribute to this demographic being overlooked for STI screening and other interventions. Given HSV's potential association with Alzheimer's disease (see Box 4), it is especially important to improve our understanding of HSV in older adults and to create appropriate strategies for minimizing risk and treatment for this population.

The STI Plan also states that the negative impacts of stigma and discrimination must be recognized to address the STI epidemic. For example, 11 states have laws that criminalize behavior that potentially exposes others to STIs, some of which explicitly include genital herpes.[77] Criminalization laws are another tangible,

negative result of stigma that often do not reflect scientific evidence. Federal agencies have a role in reducing STI-related health disparities by supporting communities to engage in local solutions and training health care providers to deliver culturally competent, trauma-informed, and compassionate comprehensive sexual health care, free of judgment and discrimination.

Health equity is achieved when everyone has an equal chance to be healthy and thriving. However, STI health disparities, or differences in health outcomes and their causes, exist among certain populations and across different regions of the United States. The STI Plan's tailored objectives and strategies support the goal of reducing STI-related health disparities and health inequities by, for example, emphasizing patient-centered improvements such as reducing stigma associated with STIs and fostering treatment service environments that are more conscious of the needs of affected populations. Efforts to advance health equity for all includes centering the needs of people of color and others who have been historically underserved, under-resourced, marginalized, and adversely affected by persistent poverty, inequality, and other SDOH.

STI PLAN GOAL 5: ACHIEVE INTEGRATED, COORDINATED EFFORTS THAT ADDRESS THE STI EPIDEMIC

STIs, viral hepatitis, HIV, substance use disorders, and SDOH, such as violence, have the potential to form syndemics and are priorities for action in the STI Plan as well as the HSV Addendum (see Box 9). Indeed, HSV has been found to be syndemic with HIV. Co-infection of HSV and HIV has been shown to increase HIV viral load, risk of HIV transmission, and disease progression.[78] It has also been shown to increase the frequency and severity of HSV symptoms;[79] therefore, improved testing and treatment for HSV could help improve outcomes of people with HIV.[5] Likewise, people with HIV and HSV with undetectable HIV viral load due to HIV treatment are no more likely to transmit HIV than those without HSV.** The 2022 Mpox outbreak was also syndemic with STIs, including HIV. Mpox lesions and other symptoms can mirror those of HSV. In addition, research from CDC shows that about 40% of people diagnosed with Mpox in the United States also have HIV. As a result, clinical guidelines recommend testing potential Mpox lesions for other STIs as well, including HIV and HSV.[80,81]

GOAL 5: ACHIEVE INTEGRATED, COORDINATED EFFORTS THAT ADDRESS THE STI EPIDEMIC

Objectives

5.1 Integrate programs to address the syndemic of STIs, HIV, viral hepatitis, and substance use disorders

5.2 Improve quality, accessibility, timeliness, and use of data related to STIs and social determinants of health

5.3 Improve mechanisms to measure, monitor, evaluate, report, and disseminate progress toward achieving national STI goals

** See National Institute of Allergy and Infectious Disease. 2023-2028 Strategic Plan for Herpes Simples Virus Research. https://www.niaid.nih.gov/sites/default/files/nih-herpes-simplex-strategic-plan-2023.pdf.

BOX 9
SYNDEMIC

Syndemics happen when two or more diseases or health conditions cluster and interact within a population because of social and structural factors and inequities, leading to an excess burden of disease and continuing health disparities.

Not all areas, individuals, or populations are affected by syndemics similarly or at the same time. Different populations or geographic areas may experience different clustering of disease or different social and structural determinants of health. Further, syndemics may change over time.

Ultimately, a syndemic approach aims to achieve greater reductions in disease and related stigmas by addressing syndemic conditions including related SDOH at the same time, rather than if addressed separately.

Syndemic disease clustering and interactions, including HIV, HSV, and mental health and substance use, are facilitated by social and structural determinants of health.[82–85] This recognition requires the need to understand and address the root causes of STI transmission and acquisition. Some of these facilitating factors include poverty, lack of health care access, limited sexual health education, criminalization of substance use, stigma and discrimination, and disproportionate clustering of STIs within populations.

Responding to HSV and other STIs, including HIV, through a coordinated, syndemic approach centers the focus on the needs of populations served and engages populations in agenda setting; promotes the conditions necessary for thriving and optimal health; encourages integrated, transdisciplinary partnerships to provide more holistic service delivery; enables flexibility to respond to continuously evolving conditions; and supports increased efficiency and cost-effectiveness.

The federal government is taking steps to integrate HSV activities across portfolios. To help drive a coordinated response to the syndemic, the HSV Addendum complements the *National HIV/AIDS Strategy for the United States 2022–2025* and the *Viral Hepatitis National Strategic Plan for the United States: A Roadmap to Elimination (2021–2025)*. These plans mutually recognize that both the specific health conditions and syndemics present opportunities to conduct relevant research and analyses, develop evidence-based interventions and policy options, and allocate resources to respond efficiently and effectively. As described in Goal 3, in 2023, NIH released the first-ever *Strategic Plan for HSV Research*. This event highlights an example of an inter-agency effort across multiple NIH institutes to advance understanding of herpes virology and to accelerate development of diagnostics, vaccines, and therapies. Future federal efforts to better address HSV through existing efforts may include reviewing and updating policies with the latest science, developing education opportunities on HSV diagnosis for health care providers (including the need for trauma-informed approaches), and increasing awareness of the syndemic interactions between HSV and other health conditions.

FEDERAL ACTION STEPS FOR HSV

Table 3 lists previous, ongoing, and planned HSV-specific action steps for the federal agencies corresponding to the goals and relevant objectives and strategies from the STI Plan, which were developed by each agency for FY 2021—2025. These HSV-focused action steps will be incorporated into future progress reports for the STI Plan. The years indicate the fiscal year (FY) in which the action begins and ends within the context of the STI Plan (2021–2025). Ongoing action steps that extend beyond FYs 2021–2025 only list the years within this timeframe. The actions are described as succinctly as possible; it should be noted that the action steps are supported by a level of detail for their conceptualization and implementation not captured in a summary document such as this. When more than one agency will collaborate on an action, the lead agency is listed first in boldface, followed by the federal agencies in alphabetical order.

These action steps are intended to inform and inspire the policy development and program planning process for federal and nonfederal colleagues. This is not a budget document and does not imply approval for any specific action under Executive Order 12866 or the Paperwork Reduction Act. All activities included in this document are subject to budgetary constraints and other approvals, including the weighing of priorities and available resources by the Administration in formulating its annual budget and by Congress in legislating authorizations and appropriations.

Table 3. STI Plan Core Indicators

Goal 1: Prevent New STIs

Action Step	Timeframe	Federal Agency
Strategy 1.1.2 Support a non-stigmatizing, comprehensive approach to sexual health education and sexual well-being, especially in adolescents and young adults, that promotes healthy sexual development and relationships and includes both risk-avoidance and risk-reduction messaging at the community level in schools, faith-based organizations, and other community-based organizations.		
Ensure that STI prevention education delivered through the Teen Pregnancy Prevention program includes education about HSV.	2023–2025	OPA
Strategy 1.2.1 Ensure that prevention programs are accessible, comprehensive, and culturally, linguistically, and age appropriate.		
Educate adolescents on adulthood preparation subjects through the Adolescent Pregnancy Prevention Program's Personal Responsibility Education Program on age-appropriate and medically accurate information on both abstinence and contraception for the prevention of pregnancy and STIs, including HIV/AIDS, HSV, and syphilis.	2023–2025	ACF

Action Step	Timeframe	Federal Agency
Strategy 1.2.2 Implement STI prevention activities in a broad range of health care delivery, education, and community-based settings through innovative, evidence-based approaches.		
Identify additional technical assistance/support opportunities for health centers on STIs (to include HSV) as part of comprehensive STI treatment and prevention program development. Proposed activities include engaging community members, social service organizations, and state/local health departments to coordinate care, prevention, and treatment services.	Ongoing	**HRSA/BPHC**, BHW; CDC; IHS
Strategy 1.4.1 Provide resources, incentives, training, and technical assistance to expand health workforce and systems capacity. and community centers.		
Provide trainings on genital HSV diagnosis/evaluation, management, and prevention through the CDC-funded National Network of STD Clinical Prevention Training Centers.	Ongoing	CDC

Goal 2: Improve the Health of People by Reducing Adverse Outcomes of STIs

Action Step	Timeframe	Federal Agency
Strategy 2.1.1 Integrate STI screening, diagnosis, care, and treatment as a routine part of a wide variety of programs and settings including those that screen, diagnose, and treat people for other whole health and public health issues such as primary care, urgent care, emergency departments, pediatrics, family planning, HIV, viral hepatitis, substance use disorders, correctional facilities, and school-based health centers.		
Deliver patient education, testing, and treatment for STIs, including HSV, to clients in Title X settings in accordance with CDC Guidelines.	Ongoing	OPA
Strategy 2.2.1 Expand workforce knowledge and experience in STI prevention, screening, diagnosis, and treatment through education and training, maintenance of certification, and continuing education programs for health professionals and paraprofessionals.		
Update FAQ on HSV Screening to remove outdated information and reflect plain language best practices/principles.	2022	CDC

Action Step	Timeframe	Federal Agency
Issue letter to clinical laboratory staff and health care providers about the potential for false-positive results in HSV-2 blood tests, including recommendations for conducting HSV-2 blood tests and guidance for reporting false-positive results to FDA.	2023	FDA
Conduct training through the Ryan White HIV/AIDS Program Part F AIDS Education and Training Centers on individuals co-infected with HSV and HIV that includes HSV testing considerations during the National Ryan White Clinical Conference.	2024	HRSA/HAB
Conduct health care provider training on HSV diagnostic testing and treatment guidelines and the physical and emotional aspects of an HSV diagnosis.	2024	VA
Strategy 2.2.2 Expand the capacity of the health workforce to provide STI screening, testing, and care through innovative, evidence-based models such as Project ECHO, mentoring programs, telehealth, express visits, and other models.		
Work with the Northwest Portland Area Indian Health Board's Indian Country ECHO to train IHS, tribal, and urban Indian health care providers on HSV diagnostic testing and treatment guidelines and the physical and emotional aspects of an HSV diagnosis.	2024	IHS

Goal 3: Accelerate Progress in STI Research, Technology, and Innovation

Action Step	Timeframe	Federal Agency
Strategy 3.1.1 Increase research to improve understanding of STI pathogenesis, immunity, and correlates of protection.		
Support work to identify the molecular basis of HSV pathogen-induced pathology and evasion of host immunity to develop mechanisms to induce immunological protection from infection.	2023–2025	NIH
Support work to utilize in vivo and in vitro models to understand the basis of pathogenicity, discover virulence factors, and identify targets for therapy and prevention of HSV.	2023–2025	NIH

Action Step	Timeframe	Federal Agency
Leverage HSV pathogenesis and immunology research to develop new diagnostics for HSV infection.	2023–2025	NIH
Strategy 3.1.2 Develop and leverage academic, public, and private partnerships for vaccine development, approval, and manufacture.		
Identify and evaluate lead prophylactic and therapeutic vaccine candidates for HSV.	2023–2025	NIH
Strategy 3.3.4 Develop and leverage academic, public, and private partnerships for the development, approval, and manufacture of new, as well as short supplied and/or high cost existing, STI diagnostic technologies, therapeutic agents, and other interventions.		
Solicit white papers and proposals for the "Development of a Confirmatory Serologic Assay for Herpes Simplex Virus (HSV-1/2) Diagnosis."	2023	CDC
Convene a joint workshop on genital herpes to define the U.S. and global burden and epidemiology of HSV, and identify gaps and research opportunities in vaccines, therapeutics, prevention, and diagnostics development.	2022	CDC, NIH
Provide advice, guidance, and review related to sponsor proposals and data submissions.	2021–2025	FDA
Convene Trans-NIH HSV NIH Working Group of members from NIAID, NICHD, and NINDS to develop NIH Strategic Plan for Herpes Simplex Virus Research, 2023-2028, and meet quarterly to discuss research updates and developments.	2022–2025	NIH
Release Small Business Innovation Research (SBIR) award for development of a highly specific and sensitive HSV-1 and HSV-2 diagnostic test.	2024	NIH
Convene federal and nonfederal colleagues to discuss the current landscape of HSV diagnostic testing and surveillance.	2024–2025	OIDP

Goal 4: Reduce STI-Related Health Disparities and Health Inequities

Action Step	Timeframe	Federal Agency
Strategy 4.1.2 Work with communities to address misconceptions and reduce stigmas that negatively affect STI prevention, screening, testing, care, and treatment.		
Convene federal and nonfederal colleagues to discuss how health care providers, educators, and researchers can reduce HSV stigma.	2024–2025	OIDP
Strategy 4.2.1 Train providers, including primary care, specialty, and nontraditional providers, to deliver high-quality, culturally and linguistically appropriate, nondiscriminatory, nonjudgmental, compassionate, and comprehensive sexual health services to populations disproportionately impacted by STIs.		
Leverage new and existing strategic partners to increase technical assistance/support on comprehensive STI treatment and prevention (to include HSV) to health centers on recruitment/ retention efforts and continued training and education for providers and staff.	Ongoing	**HRSA/BPHC**, BHW; CDC
Collaborate and disseminate a webinar for health departments and community-based organizations on STI clinical guidelines, including testing for HSV antibodies.	2021–2025	**HRSA/BPHC**, CDC
Conduct literature review on HSV research and survey a sample of health centers on HSV knowledge and testing to identify opportunities for technical assistance.	2022	HRSA/BPHC
Enhance provider awareness of the latest treatment guidelines for STIs (to include HSV). Incorporate multifaceted approaches including ECHO webinars, grand rounds, resource sharing, and site-specific didactics to expand to nontraditional providers.	2021–2025	IHS

Goal 5: Achieve Integrated, Coordinated Efforts That Address the STI Epidemic

Action Step	Timeframe	Federal Agency
Strategy 5.1.2 Integrate STI prevention, screening, testing, care, and treatment in funding opportunities that address other components of the syndemic.		
In collaboration with the Syndemic Steering Committee, explore the braiding of multiple funding sources to support syndemic approaches to address HIV, STI, viral hepatitis, mental health, and substance use.	2024–2025	OIDP
Strategy 5.2.1 Strengthen and expand existing surveillance infrastructure and methods including the capacity for more real-time data sharing between public health authorities and health care providers.		
Conduct evaluation of neonatal HSV to determine feasibility as a candidate for being made nationally notifiable.	2024–2025	CDC
Strategy 5.2.2 Incorporate novel scientific approaches for monitoring, identifying, and responding to trends in STIs and STI sequelae and social determinants of health related to STIs.		
Identify methods to regularly estimate the annual prevalence of HSV and incidence of neonatal HSV using laboratory data and/or administrative claims data.	2023–2024	CDC
Strategy 5.2.6 Ensure timely dissemination of data and analyses related to STI surveillance, public health, and health care data to inform decision-making.		
Conduct an HSV literature review to update the herpes section of the STI Treatment Guidelines.	2023–2024	CDC
Lead a study to evaluate the impact of the neonatal HSV infection in the United States by estimating the incidence, rate, cost, and mortality by using data from the 2019 Healthcare Cost and Utilization Project (HCUP) Kids' Inpatient Database (KID), a nationally representative sample of all-payer pediatric discharges.	2023–2024	CDC

Action Step	Timeframe	Federal Agency
Monitor genital HSV incident cases and trends, gathered by the Armed Forces Health Surveillance Division, for publication in the Medical Surveillance Monthly Report.	Ongoing	DOD
Strategy 5.3.3 Develop and implement recommendations promoting policies, programs, and activities that accomplish goals and address areas for improvement.		
Lead the development through the STI Federal Implementation Working Group of an *HSV Addendum* and integration of HSV into future iterations of the STI Plan and STI Progress Reports.	2023–2025	OIDP

APPENDIX A: PROCESS/METHODOLOGY FOR DEVELOPING AND ADOPTING THE HSV ADDENDUM

The process for developing the *HSV Addendum to the Sexually Transmitted Infections National Strategic Plan* included engaging federal leadership, experts, and a variety of nonfederal colleagues to compile evidence and recommendations on herpes simplex virus (HSV). It also included conducting a literature review to identify the latest research in HSV diagnostics, prevention, care, and treatment. These data were then synthesized and integrated into the HSV Addendum.

FEDERAL LEADERSHIP

The STI Federal Implementation Working Group, which set the vision, goals, and priority populations and discussed key challenges to be addressed in the *Sexually Transmitted Infections National Strategic Plan* (STI Plan) and companion *STI Federal Implementation Plan*, was convened to develop the HSV Addendum to the STI Plan. This Working Group consists of senior representatives and subject matter experts from four federal departments and 15 U.S. Department of Health and Human Services (HHS) agencies and offices (see Table A1).

Table A1. Composition of STI Federal Implementation Working Group

Federal Departments	HHS Agencies and Offices
• Department of Defense • Department of Health and Human Services • Department of Housing and Urban Development • Department of Veterans Affairs	• Administration for Children and Families • Administration for Community Living • Centers for Disease Control and Prevention • Centers for Medicare & Medicaid Services • Food and Drug Administration • Health Resources and Services Administration • Indian Health Service • National Institutes of Health • Office of the Assistant Secretary for Health » Office of Infectious Disease and HIV/AIDS Policy » Office of Minority Health » Office of Population Affairs » Office of the Surgeon General » Office on Women's Health • Substance Abuse and Mental Health Services Administration

With coordinating support from the Office of Infectious Disease and HIV/AIDS Policy (OIDP), this Working Group developed individual and collaborative action items for the HSV Addendum, both within and across agencies, and considered comments and suggestions from interested parties and the public.

Between January and April 2023, OIDP conducted an inventory survey of all Working Group members' funded and unfunded activities related to HSV-1, HSV-2, and neonatal herpes among Working Group participants that occurred during fiscal years (FY) 2018–2022. The survey captured the breadth of activities related to HSV, and results were analyzed to identify potential gaps in data, policy, funding, and programming. Although HSV-related projects were within the scope of several agencies represented on the Working Group, only the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) reported dedicating specific funding to support HSV programs and activities. CDC estimates allocating $900,000 annually for FYs 2018–2022 to HSV activities related to surveillance, research for diagnostics, and development of diagnostics and treatment protocols. NIH funding increased from $6.11 million in FY 2016 to $14.39 million in FY 2022 for HSV clinical research (see Figure B1).

FIGURE B1

NIH SUPPORT FOR CLINICAL RESEARCH ON HSV PREVENTION AND TREATMENT[86]

In addition to a robust portfolio of basic research to advance the understanding of HSV1 and 2 biology, pathogenesis, and epidemiology, NIH supports the development of HSV prevention and treatment strategies from preclinical research through early-stage clinical trials. Below is an overview of the NIH portfolio of preclinical and clinical research toward the development of HSV prevention and treatment strategies.[a]

FUNDING

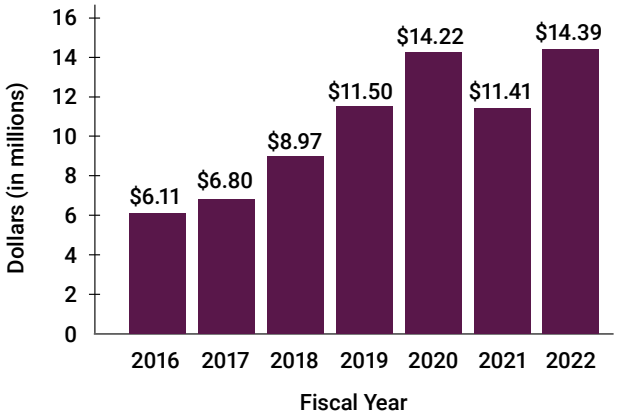


Figure 1. NIH funding for preclinical and early clinical research on HSV prevention and treatment strategies from FY 2016 to FY 2022.

PROJECTS

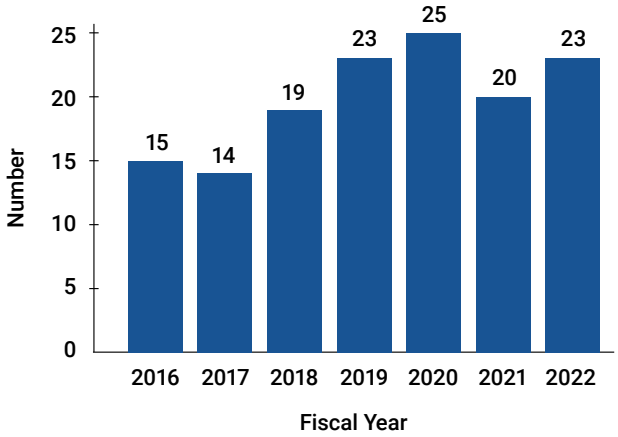
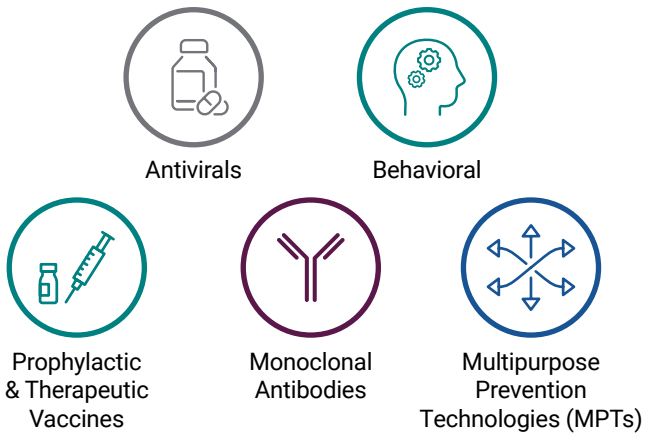
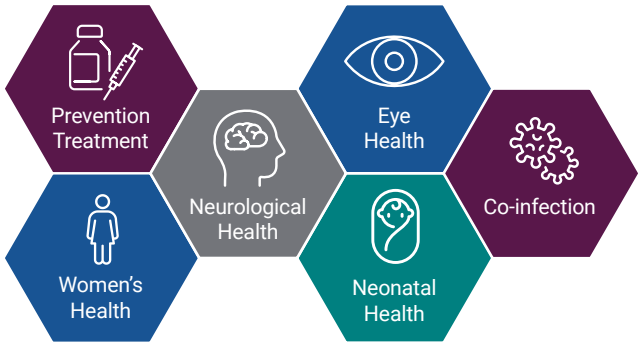


Figure 2. Number of preclinical and early clinical research projects for HSV prevention and treatment strategies from FY 2016 to FY 2022.

TYPES OF INTERVENTIONS



CLINICAL RESEARCH TOPICS



[a] 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 vaccinate OR vaccinates 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.

When asked about internal unmet resource needs, limitations, or challenges about working on HSV-related projects, Working Group members primarily cited lack of funding and staffing resources to dedicate to HSV specifically.

PUBLIC INPUT

A crucial component in developing the HSV Addendum was engagement and input from nonfederal colleagues. Community members from all sectors and at all levels (i.e., community, state, regional, national) and people whose lives have been affected by HSV were encouraged to provide input on the HSV Addendum.

Solicitation of Public Input

To assist development of the HSV Addendum, OIDP solicited input from the public. Between April and May 2023, three listening sessions were held; two via webinar and one in-person during a national conference. The combined listening sessions drew more than 250 participants from across the country. The HSV Addendum was also informed by the findings from the CDC and the National Institute of Allergy and Infectious Diseases (NIAID) "Joint Workshop on Genital Herpes," which convened in November 2022.[59] In addition, a request for written public comment submissions was posted on the OIDP website on February 6, 2024. A total of 76 individual commenters were identified and categorized into various respondent types. Comments were received from health care providers (n=6) and researchers from academia, nonprofits, and private industries (n=17). However, the overwhelming majority of comments received were from people with HSV (n=53). These numbers reflect the overarching theme addressed in this Addendum regarding the disconnect between the general public and the health care and public health community about the prioritization of HSV as an urgent public health issue (see Figure B2).

Summary of Findings

Methods used and findings from the public input, from both the listening sessions and written public comment period, including prominent themes and sub-themes along with supporting comments, were presented to the STI Federal Implementation Working Group. Input received through the listening sessions and written public comments was extremely valuable, and comments addressed a broad range of HSV-related topics and personal experiences that are reflected in the HSV Addendum, including federal action steps. Dominant themes from the written public comments are listed in Figure B2.

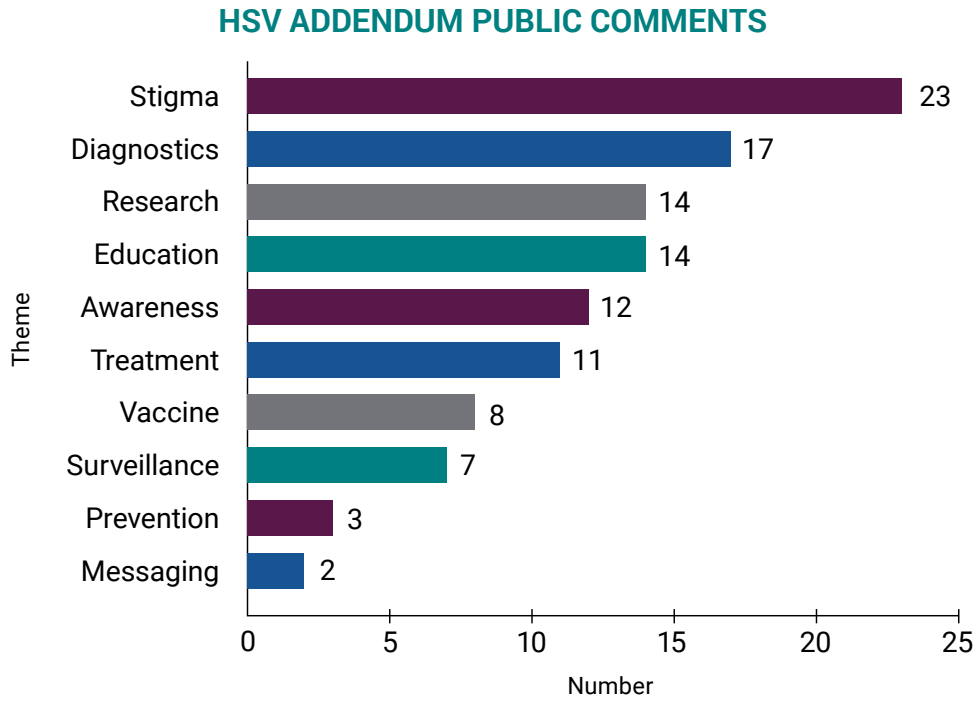


Figure B2. HSV addendum public comments by theme.

Awareness, Education, Messaging, and Prevention

Participants in the listening sessions and written public comment period stated that many health care providers and medical students are underinformed about HSV. Multiple participants shared that upon initial diagnosis, health care providers were unable to provide basic information on HSV transmission, whether patients should disclose their diagnosis to sexual partners, or potential risks associated with HSV, such as herpes encephalitis and neonatal HSV. Many participants took offense to a common perception that HSV is "benign" and believed that medical support for HSV patients who do not have "textbook" HSV symptoms is insufficient. Participants also described difficulties finding relevant support groups and other HSV resources. Multiple participants highlighted the need for greater awareness and education regarding HSV among the public as well. Participants also highlighted the stigmatizing language and messaging of current HSV education and awareness campaigns and emphasized that people with HSV can still have sexual relationships, while minimizing risk.

Stigma

Participants in the listening sessions and written public comment period highlighted HSV stigma as a major issue, suggesting that it is the greatest contributor to morbidity and reduced quality of life. They also described the limitations of HSV diagnostics in perpetuating stigma because the true prevalence of HSV is underestimated. Participants with symptomatic HSV stated that they feel unfairly stigmatized merely because of their symptoms, whereas under current testing guidelines, individuals who are asymptomatic may never get tested for HSV or disclose their status to sexual partners. Several participants expressed interest in promoting social and behavioral research to reduce stigma. Many participants also identified the role of health care providers in perpetuating stigma. For example, health care providers might be less likely to discuss HSV with their patients because of their own limited knowledge, which underscores the need to strengthen provider education.

Surveillance and Diagnostics

Participants in the listening sessions and written public comment period addressed surveillance barriers in the context of designating HSV as a nationally notifiable disease. They identified a lack of widespread, accurate testing as the primary barrier. Participants cited the insufficiencies of current diagnostic technologies and frustration that HSV is not part of routine STI testing panels. Participants questioned delays in reporting HSV seroprevalence rates and urged for more timely reporting. In the listening sessions, participants recommended the use of large health care data sets to conduct research into HSV. These data sets could include medical visits and prescription records for antiviral medications. However, several participants also acknowledged that the high volume of HSV cases makes it unclear how state and local health departments would manage the logistics and costs of monitoring cases. Participants stressed the importance of reporting neonatal HSV cases; because neonatal cases are rare, they could be monitored more closely to connect patients with timely access to care.

Research and Development of Treatment and Vaccines

Participants in the listening sessions and written public comment period highlighted the importance of involving community members in federal research endeavors and strategic planning. Several participants recommended greater efforts to support research into the possible connections between HSV and neurological diseases. Participants also recommended harnessing research networks that host HIV clinical trials to conduct HSV vaccine research, acknowledging the syndemic between HIV and HSV. They noted that HIV research networks helped conduct rapid research into COVID-19 vaccines. Overall, participants appreciated the federal government's commitment to more HSV research but sought more prioritization and urgency in developing better treatment options, because many are dissatisfied with the results of current antiviral therapies, and a cure. In addition, some written comment participants perceived that research efforts and current clinical trials disproportionately addressed HSV-2 instead of HSV-1, which should also be a priority.

APPENDIX B: STI FEDERAL IMPLEMENTATION WORKING GROUP

Department of Defense

Department of Health and Human Services

Administration for Children and Families (ACF)

Administration for Community Living (ACL)

Centers for Disease Control and Prevention (CDC)

Centers for Medicare & Medicaid Services (CMS)

Food and Drug Administration (FDA)

Health Resources and Services Administration (HRSA)

Indian Health Service (IHS)

National Institutes of Health (NIH)

Office of the Assistant Secretary for Health (OASH)

- Office of Infectious Disease and HIV/AIDS Policy (OIDP)
- Office of Minority Health (OMH)
- Office of Population Affairs (OPA)
- Office of the Surgeon General (OSG)
- Office on Women's Health (OWH)

Substance Abuse and Mental Health Services Administration (SAMHSA)

Department of Housing and Urban Development (HUD)

Department of Veterans Affairs (VA)

APPENDIX C: ACRONYMS

ACF	Administration for Children and Families
AD	Alzheimer's disease
BHW	Bureau of Health Workforce (HRSA)
BPHC	Bureau of Primary Health Care (HRSA)
CDC	U.S. Centers for Disease Control and Prevention
DOD	U.S. Department of Defense
ECHO	Extension for Community Healthcare Outcomes
FDA	U.S. Food and Drug Administration
FY	fiscal year
HAB	HIV/AIDS Bureau (HRSA)
HHS	U.S. Department of Health and Human Services
HPV	human papilloma virus
HRSA	Health Resources and Services Administration
HSV	herpes simplex virus
IHS	Indian Health Service
NIAID	National Institute of Allergy and Infectious Diseases (NIH)
NICHD	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NIH)
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke (NIH)
OASH	Office of the Assistant Secretary for Health
OIDP	Office of Infectious Disease and HIV/AIDS Policy (OASH)
OPA	Office of Population Affairs (OASH)
SDOH	social and structural determinants of health
STI	sexually transmitted infection
USPSTF	U.S. Preventive Services Task Force
VA	U.S. Department of Veterans Affairs

APPENDIX D: REFERENCES

1 Kreisel KM, Spicknall IH, Gargano JW, et al. Sexually transmitted infections among US women and men: Prevalence and incidence estimates, 2018. *Sex Transm Dis.* 2021;48(4):208-214. doi:10.1097/OLQ.0000000000001355

2 You S, Yaesoubi R, Lee K, et al. Lifetime quality-adjusted life years lost due to genital herpes acquired in the United States in 2018: A mathematical modeling study. *Lancet Reg Health - Am*. 2023;19:100427. doi:10.1016/j.lana.2023.100427

3 Doerr H, Gurtler L, Wittek M. Biology of sexually transmitted herpes viruses. In: Gross G, Tyring SK, eds. *Sexually Transmitted Infections and Sexually Transmitted Diseases.* Springer; 2011:285-312.

4 Ahmad B, Patel BC. Herpes simplex keratitis. In: *StatPearls.* StatPearls Publishing; 2024. Accessed March 27, 2024. http://www.ncbi.nlm.nih.gov/books/NBK545278/

5 Looker KJ, Elmes JAR, Gottlieb SL, et al. Effect of HSV-2 infection on subsequent HIV acquisition: An updated systematic review and meta-analysis. *Lancet Infect Dis.* 2017;17(12):1303-1316. doi:10.1016/S1473-3099(17)30405-X

6 Protto V, Marcocci ME, Miteva MT, et al. Role of HSV-1 in Alzheimer's disease pathogenesis: A challenge for novel preventive/therapeutic strategies. *Curr Opin Pharmacol*. 2022;63:102200. doi:10.1016/j.coph.2022.102200

7 Ak AK, Bhutta BS, Mendez MD. Herpes simplex encephalitis. In: *StatPearls*. StatPearls Publishing; 2024. Accessed March 27, 2024. http://www.ncbi.nlm.nih.gov/books/NBK557643/

8 Tyler KL. Herpes simplex virus infections of the central nervous system: Encephalitis and meningitis, including Mollaret's. *Herpes J IHMF*. 2004;11 Suppl 2:57A-64A.

9 Ge T, Yuan Y. Herpes simplex virus infection increases beta-amyloid production and induces the development of Alzheimer's disease. *BioMed Res Int*. 2022;2022:8804925. doi:10.1155/2022/8804925

10 Itzhaki RF. Overwhelming evidence for a major role for herpes simplex virus type 1 (HSV1) in Alzheimer's disease (AD); Underwhelming evidence against. *Vaccines.* 2021;9(6):679. doi:10.3390/vaccines9060679

11 Nath P, Kabir MA, Doust SK, Ray A. Diagnosis of herpes simplex virus: Laboratory and point-of-care techniques. *Infect Dis Rep*. 2021;13(2):518-539. doi:10.3390/idr13020049

12 Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. *MMWR Recomm Rep*. 2021;70(4):1-187. doi:10.15585/mmwr.rr7004a1

13 US Preventive Services Task Force, Mangione CM, Barry MJ, et al. Serologic screening for genital herpes infection: US Preventive Services Task Force reaffirmation recommendation statement. *JAMA*. 2023;329(6):502-507. doi:10.1001/jama.2023.0057

14 James C, Harfouche M, Welton NJ, et al. Herpes simplex virus: Global infection prevalence and incidence estimates, 2016. *Bull World Health Organ*. 2020;98(5):315-329. doi:10.2471/BLT.19.237149

15 Tuddenham S, Hamill MM, Ghanem KG. Diagnosis and treatment of sexually transmitted infections: A review. *JAMA*. 2022;327(2):161-172. doi:10.1001/jama.2021.23487

16 Whitley R, Kimberlin DW, Prober CG. Pathogenesis and disease. In: Arvin A, Campadelli-Fiume G, Mocarski E, et al., eds. *Human Herpesviruses: Biology, Therapy, and Immunoprophylaxis*. Cambridge University Press; 2007. Accessed August 2, 2023. http://www.ncbi.nlm.nih.gov/books/NBK47449/

17 Johnston C, Magaret A, Son H, et al. Viral shedding 1 year following first-episode genital HSV-1 infection. *JAMA*. 2022;328(17):1730-1739. doi:10.1001/jama.2022.19061

18 Benedetti JK, Zeh J, Corey L. Clinical reactivation of genital herpes simplex virus infection decreases in frequency over time. *Ann Intern Med.* 1999;131(1):14-20. doi:10.7326/0003-4819-131-1-199907060-00004

[19] McQuillan G, Kruszon-Moran D, Flagg EW, Paulose-Ram R. Prevalence of herpes simplex virus type 1 and type 2 in persons aged 14-49: United States, 2015-2016. *NCHS Data Brief*. 2018;(304):1-8.

[20] Spicknall IH, Flagg EW, Torrone EA. Estimates of the prevalence and incidence of genital herpes, United States, 2018. *Sex Transm Dis*. 2021;48(4):260-265. doi:10.1097/OLQ.0000000000001375

[21] Fleming DT, McQuillan GM, Johnson RE, et al. Herpes simplex virus type 2 in the United States, 1976 to 1994. *N Engl J Med*. 1997;337(16):1105-1111. doi:10.1056/NEJM199710163371601

[22] Schillinger JA, McKinney CM, Garg R, et al. Seroprevalence of herpes simplex virus type 2 and characteristics associated with undiagnosed infection: New York City, 2004. *Sex Transm Dis*. 2008;35(6):599-606. doi:10.1097/OLQ.0b013e3181666fb1

[23] Bernstein DI, Bellamy AR, Hook EW, et al. Epidemiology, clinical presentation, and antibody response to primary infection with herpes simplex virus type 1 and type 2 in young women. *Clin Infect Dis.* 2013;56(3):344-351. doi:10.1093/cid/cis891

[24] Cruz AT, Freedman SB, Kulik DM, et al. Herpes simplex virus infection in infants undergoing meningitis evaluation. *Pediatrics*. 2018;141(2):e20171688. doi:10.1542/peds.2017-1688

[25] Melvin AJ, Mohan KM, Vora SB, Selke S, Sullivan E, Wald A. Neonatal herpes simplex virus infection: Epidemiology and outcomes in the modern era. *J Pediatr Infect Dis Soc*. 2022;11(3):94-101. doi:10.1093/jpids/piab105

[26] Johnston C. Diagnosis and management of genital herpes: Key questions and review of the evidence for the 2021 Centers for Disease Control and Prevention Sexually transmitted infections treatment guidelines. *Clin Infect Dis*. 2022;74(Supplement_2):S134-S143. doi:10.1093/cid/ciab1056

[27] Kimberlin DW. *Red Book (2018): Report of the Committee on Infectious Diseases*. American Academy of Pediatrics; 2018. doi:10.1542/9781610021470

[28] Corey L, Wald A. Maternal and neonatal herpes simplex virus infections. *N Engl J Med*. 2009;361(14):1376-1385. doi:10.1056/NEJMra0807633

[29] Looker KJ, Magaret AS, May MT, et al. First estimates of the global and regional incidence of neonatal herpes infection. *Lancet Glob Health*. 2017;5(3):e300-e309. doi:10.1016/S2214-109X(16)30362-X

[30] Caviness AC, Demmler GJ, Selwyn BJ. Clinical and laboratory features of neonatal herpes simplex virus infection: A case-control study. *Pediatr Infect Dis J*. 2008;27(5):425-430. doi:10.1097/INF.0b013e3181646d95

[31] Donda K, Sharma M, Amponsah JK, et al. Trends in the incidence, mortality, and cost of neonatal herpes simplex virus hospitalizations in the United States from 2003 to 2014. *J Perinatol*. 2019;39(5):697-707. doi:10.1038/s41372-019-0352-7

[32] Matthias J, du Bernard S, Schillinger JA, Hong J, Pearson V, Peterman TA. Estimating neonatal herpes simplex virus incidence and mortality using capture-recapture, Florida. *Clin Infect Dis*. 2021;73(3):506-512. doi:10.1093/cid/ciaa727

[33] Feltner C, Grodensky C, Ebel C, et al. Serologic screening for genital herpes: An updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2016;316(23):2531-2543. doi:10.1001/jama.2016.17138

[34] Tita ATN, Grobman WA, Rouse DJ. Antenatal herpes serologic screening: An appraisal of the evidence. O*bstet Gynecol*. 2006;108(5):1247-1253. doi:10.1097/01.AOG.0000236433.29679.9a

[35] Bickford J, Barton SE, Mandalia S. Chronic genital herpes and disclosure.... The influence of stigma. *Int J STD AIDS*. 2007;18(9):589-592. doi:10.1258/095646207781568484

[36] Awasthi S, Friedman HM. An mRNA vaccine to prevent genital herpes. *Transl Res*. 2022;242:56-65. doi:10.1016/j.trsl.2021.12.006

[37] Royer HR, Falk EC, Heidrich SM. Genital herpes beliefs: Implications for sexual health. *J Pediatr Adolesc Gynecol*. 2013;26(2):109-116. doi:10.1016/j.jpag.2012.11.007

[38] Donigan JM, Pascoe V, Kimball A. Psoriasis and herpes simplex virus are highly stigmatizing compared with other common dermatologic conditions: A survey-based study. *J Am Acad Dermatol*. 2015;73(3). doi:10.1016/j.jaad.2015.06.035

[39] Bennett C, Rebafka A, Carrier J, Cook S, Edwards D. Impact of primary and recurrent genital herpes on the quality of life of young people and adults: A mixed methods systematic review. *JBI Evid Synth*. 2022;20(6):1406-1473. doi:10.11124/JBIES-21-00057

[40] Alexander L, Naisbett B. Patient and physician partnerships in managing genital herpes. *J Infect Dis*. 2002;186 Suppl 1:S57-65. doi:10.1086/342964

[41] Wald A, Krantz E, Selke S, Lairson E, Morrow RA, Zeh J. Knowledge of partners' genital herpes protects against herpes simplex virus type 2 acquisition. *J Infect Dis*. 2006;194(1):42-52. doi:10.1086/504717

[42] Green J, Ferrier S, Kocsis A, et al. Determinants of disclosure of genital herpes to partners. *Sex Transm Infect*. 2003;79(1):42-44. doi:10.1136/sti.79.1.42

[43] Myers JL, Buhi ER, Marhefka S, Daley E, Dedrick R. Associations between individual and relationship characteristics and genital herpes disclosure. *J Health Psychol*. 2016;21(10):2283-2293. doi:10.1177/1359105315575039

[44] Romanowski B, Zdanowicz YM, Owens ST. In search of optimal genital herpes management and standard of care (INSIGHTS): Doctors' and patients' perceptions of genital herpes. *Sex Transm Infect*. 2008;84(1):51-56. doi:10.1136/sti.2007.027631

[45] About genital herpes. Centers for Disease Control and Prevention. February 20, 2024. Accessed October 17, 2023. https://www.cdc.gov/herpes/about/?CDC_AAref_Val=https://www.cdc.gov/std/herpes/stdfact-herpes.htm

[46] Patel R. Educational interventions and the prevention of herpes simplex virus transmission. *Herpes J IHMF*. 2004;11 Suppl 3:155A-160A.

[47] Hirschler C, Hope A, Myers JL. College students' perceptions of and experiences with human papillomavirus and herpes: Implications for college sexual health education. *Am J Sex Educ*. 2015;10(4):298-315. doi:10.1080/15546128.2015.1091760

[48] Kirzinger A, Muñana C, Brodie M, et al. Public knowledge and attitudes about sexually transmitted infections: KFF polling and policy insights. KFF. February 18, 2020. Accessed October 18, 2023. https://www.kff.org/womens-health-policy/issue-brief/public-knowledge-and-attitudes-about-sexually-transmitted-infections/

[49] Looker KJ, Magaret AS, Turner KME, Vickerman P, Gottlieb SL, Newman LM. Global estimates of prevalent and incident herpes simplex virus type 2 infections in 2012. *PLoS ONE*. 2015;10(1):e114989. doi:10.1371/journal.pone.0114989

[50] Strome A, Moore-Petinak N, Waselewski M, Chang T. Youths' knowledge and perceptions of health risks associated with unprotected oral sex. *Ann Fam Med*. 2022;20(1):72-76. doi:10.1370/afm.2761

[51] Ayoub HH, Chemaitelly H, Abu-Raddad LJ. Characterizing the transitioning epidemiology of herpes simplex virus type 1 in the USA: Model-based predictions. *BMC Med*. 2019;17(1):57. doi:10.1186/s12916-019-1285-x

[52] Workowski KA, Bolan GA, Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep*. 2015;64(RR-03):1-137.

[53] Singh S, Singh SK. Psychological health and well-being in patients with sexually transmitted infections: A prospective cross-sectional study. *Indian J Sex Transm Dis AIDS*. 2021;42(2):125. doi:10.4103/ijstd.IJSTD_77_19

[54] Wright SS, Kreisel KM, Hitt JC, Pagaoa MA, Weinstock HS, Thorpe PG. Impact of the COVID-19 pandemic on Centers for Disease Control and Prevention-funded sexually transmitted disease programs. *Sex Transm Dis*. 2022;49(4):e61. doi:10.1097/OLQ.0000000000001566

[55] Sexually transmitted disease surveillance, 2021. Centers for Disease Control and Prevention. April 11, 2023. Accessed October 17, 2023. https://www.cdc.gov/std/statistics/2022/2021-STD-Surveillance-Report-PDF_ARCHIVED-2-16-24.pdf

[56] Shanshal M, Ahmed HS. COVID-19 and herpes simplex virus infection: A cross-sectional study. *Cureus*. 2021;13(9):e18022. doi:10.7759/cureus.18022

[57] Giacobbe DR, Di Bella S, Lovecchio A, et al. Herpes simplex virus 1 (HSV-1) reactivation in critically ill COVID-19 patients: A brief narrative review. *Infect Dis Ther*. 2022;11(5):1779-1791. doi:10.1007/s40121-022-00674-0

[58] America Leading the World in Science and Technology – The White House. Accessed October 17, 2023. https://trumpwhitehouse.archives.gov/articles/america-leading-world-science-technology/

[59] Connolly KL, Bachmann L, Hiltke T, et al. Summary of the Centers for Disease Control and Prevention/National Institute of Allergy and Infectious Diseases joint workshop on genital herpes: 3–4 November 2022. *Open Forum Infect Dis*. 2024;11(5):ofae230. doi:10.1093/ofid/ofae230

[60] NIH releases strategic plan for research on herpes simplex virus 1 and 2. National Institute of Allergy and Infectious Diseases. September 18, 2023. Accessed November 9, 2023. https://www.niaid.nih.gov/news-events/nih-releases-strategic-plan-research-herpes-simplex-virus-1-and-2

[61] Birkmann A, Zimmermann H. HSV antivirals – current and future treatment options. *Curr Opin Virol*. 2016;18:9-13. doi:10.1016/j.coviro.2016.01.013

[62] Reichman RC, Badger GJ, Mertz GJ, et al. Treatment of recurrent genital herpes simplex infections with oral acyclovir. A controlled trial. *JAMA*. 1984;251(16):2103-2107.

[63] Whitley R, Baines J. Clinical management of herpes simplex virus infections: Past, present, and future. *F1000Research*. 2018;7:F1000 Faculty Rev-1726. doi:10.12688/f1000research.16157.1

[64] Magaret AS, Mujugira A, Hughes JP, et al. Effect of condom use on per-act HSV-2 transmission risk in HIV-1, HSV-2-discordant couples. *Clin Infect Dis*. 2016;62(4):456-461. doi:10.1093/cid/civ908

[65] Gutierrez D, Tan A, Strome A, Pomeranz MK. Dental dams in dermatology: An underutilized barrier method of protection. *Int J Womens Dermatol*. 2022;8(1):e008. doi:10.1097/JW9.0000000000000008

[66] Mesquita PMM, Rastogi R, Segarra TJ, et al. Intravaginal ring delivery of tenofovir disoproxil fumarate for prevention of HIV and herpes simplex virus infection. *J Antimicrob Chemother*. 2012;67(7):1730-1738. doi:10.1093/jac/dks097

[67] Moss JA, Malone AM, Smith TJ, et al. Simultaneous delivery of tenofovir and acyclovir via an intravaginal ring. *Antimicrob Agents Chemother*. 2012;56(2):875-882. doi:10.1128/AAC.05662-11

[68] Stanfield BA, Kousoulas KG, Fernandez A, Gershburg E. Rational design of live-attenuated vaccines against herpes simplex viruses. *Viruses*. 2021;13(8):1637. doi:10.3390/v13081637

[69] Ayoub HH, Chemaitelly H, Abu-Raddad LJ. Epidemiological impact of novel preventive and therapeutic HSV-2 vaccination in the United States: Mathematical modeling analyses. *Vaccines*. 2020;8(3):366. doi:10.3390/vaccines8030366

[70] Spicknall IH, Looker KJ, Gottlieb SL, et al. Review of mathematical models of HSV-2 vaccination: Implications for vaccine development. *Vaccine*. 2019;37(50):7396-7407. doi:10.1016/j.vaccine.2018.02.067

[71] Xu F, Markowitz LE, Gottlieb SL, Berman SM. Seroprevalence of herpes simplex virus types 1 and 2 in pregnant women in the United States. *Am J Obstet Gynecol*. 2007;196(1):43.e1-6. doi:10.1016/j.ajog.2006.07.051

[72] Fanfair RN, Zaidi A, Taylor LD, Xu F, Gottlieb S, Markowitz L. Trends in seroprevalence of herpes simplex virus type 2 among non-Hispanic blacks and non-Hispanic whites aged 14 to 49 years—United States, 1988 to 2010. *Sex Transm Dis*. 2013;40(11):860-864. doi:10.1097/OLQ.0000000000000043

[73] Stebbins RC, Noppert GA, Aiello AE, Cordoba E, Ward JB, Feinstein L. Persistent socioeconomic and racial and ethnic disparities in pathogen burden in the United States, 1999-2014. *Epidemiol Infect*. 2019;147:e301. doi:10.1017/S0950268819001894

[74] Des Jarlais DC, Arasteh K, McKnight C, Perlman DC, Cooper HLF, Hagan H. HSV-2 infection as a cause of female/male and racial/ethnic disparities in HIV infection. *PloS ONE*. 2013;8(6):e66874. doi:10.1371/journal.pone.0066874

[75] Van Epps P, Musoke L, McNeil CJ. Sexually transmitted infections in older adults: Increasing tide and how to stem it. *Infect Dis Clin North Am*. 2023;37(1):47-63. doi:10.1016/j.idc.2022.11.003

[76] NCHHSTP AtlasPlus. Centers for Disease Control and Prevention. Accessed August 12, 2024. https://www.cdc.gov/nchhstp/about/atlasplus.html?CDC_AAref_Val=https://www.cdc.gov/nchhstp/atlas/index.htm

[77] HIV and STD criminalization laws. March 29, 2023. Accessed October 18, 2023. https://www.cdc.gov/hiv/policies/law/states/exposure.html

[78] Freeman EE, Weiss HA, Glynn JR, Cross PL, Whitworth JA, Hayes RJ. Herpes simplex virus 2 infection increases HIV acquisition in men and women: Systematic review and meta-analysis of longitudinal studies. *AIDS Lond Engl*. 2006;20(1):73-83. doi:10.1097/01.aids.0000198081.09337.a7

[79] Schacker T, Zeh J, Hu HL, Hill E, Corey L. Frequency of symptomatic and asymptomatic herpes simplex virus type 2 reactivations among human immunodeficiency virus-infected men. *J Infect Dis*. 1998;178(6):1616-1622. doi:10.1086/314486

[80] Macneil A, Reynolds MG, Braden Z, et al. Transmission of atypical varicella-zoster virus infections involving palm and sole manifestations in an area with monkeypox endemicity. *Clin Infect Dis Off*. 2009;48(1):e6-8. doi:10.1086/595552

[81] Potential risk for new Mpox cases. Centers for Disease Control and Prevention. May 15, 2023. Accessed October 18, 2023. https://emergency.cdc.gov/han/2023/han00490.asp

[82] Hogben M, Leichliter JS. Social determinants and sexually transmitted disease disparities. S*ex Transm Dis*. 2008;35(12 Suppl):S13-18. doi:10.1097/OLQ.0b013e31818d3cad

[83] Seiler N, Pearson WS, Organick-Lee P, et al. Medicaid, sexually transmitted infections, and social determinants of health. *Sex Transm Dis*. 2024;51(1):33-37. doi:10.1097/OLQ.0000000000001887

[84] Cohn T, Harrison CV. A systematic review exploring racial disparities, social determinants of health, and sexually transmitted infections in Black women. *Nurs Womens Health*. 2022;26(2):128-142. doi:10.1016/j.nwh.2022.01.006

[85] Carlson JM, Tannis A, Woodworth KR, et al. Substance use among persons with syphilis during pregnancy - Arizona and Georgia, 2018-2021. *MMWR Morb Mortal Wkly Rep*. 2023;72(3):63-67. doi:10.15585/mmwr.mm7203a3

[86] National Institutes of Health. *Strategic Plan for Herpes Simplex Virus Research 2023-2028*. Published online September 2023. Accessed August 12, 2024. https://www.niaid.nih.gov/sites/default/files/nih-herpes-simplex-strategic-plan-2023.pdf