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REVIEW ARTICLE

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

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Genital herpes is caused by infection with herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) and currently has no cure. The disease is the second-most common sexually transmitted infection in the United States, with an estimated 18.6 million prevalent genital infections caused by HSV-2 alone. Genital herpes diagnostics and treatments are not optimal, and no vaccine is currently available. The Centers for Disease Control and Prevention and the National Institute of Allergy and Infectious Diseases convened a workshop entitled "CDC/NIAID Joint Workshop on Genital Herpes." This report summarizes 8 sessions on the epidemiology of genital herpes, neonatal HSV, HSV diagnostics, vaccines, treatments, cures, prevention, and patient advocacy perspective intended to identify opportunities in herpes research and foster the development of strategies to diagnose, treat, cure, and prevent genital herpes.

Genital herpes is caused by herpes simplex virus types 1 and 2 (HSV-1 or HSV-2) and is the leading cause of genital ulcer disease worldwide [1]. Although genital herpes is primarily caused by HSV-2, by 2050 approximately 20% of genital infections will be caused by HSV-1 [2]. Data from the 2015–2018 NHANES (National Health and Nutrition Examination Survey) estimated that there were 18.6 million HSV-2 genital herpes infections in the United States in 2018 in individuals 18 to 49 years of age [3]. Despite an overall decline in HSV-2 seroprevalence among all racial and ethnic groups, NHANES data indicate that racial disparities have increased among US men, with a Black:White ratio of 2.4 between 1988 and 1994 to 4.4 between 2007 and 2010.

On 3 and 4 November 2022, the Centers for Disease Control and Prevention and National Institute of Allergy and Infectious Diseases sponsored a workshop entitled "CDC/NIAID Joint Workshop on Genital Herpes" held at the National Institutes of Health. Presenters and in-person audience participants were members of the herpes research community, industry representatives, public health advocates, and government agency staff. The workshop also had a substantial virtual audience, which included scientists, patient advocates, and, importantly, individuals with genital herpes. This summary reflects the presentations, discussions, and virtual audience contributions, and the topics are presented in order of importance to patients, as indicated by their online commentary.

WORKSHOP TOPICS

Patient and Advocacy Perspective

Three advocacy groups discussed their role in supporting patients with herpes infection and the challenges faced in managing a diagnosis. The American Sexual Health Association (ASHA) has served as an HSV educational resource to patients since 1979 through mechanisms such as a resource center, a hotline, a chat room, newsletters, campaigns, publications, a patient bill of rights, and research. In October 2022, ASHA conducted a survey of approximately 600 patients with herpes regarding their HSV-related perceptions and research priorities (unpublished results). When asked how they would rank HSV research areas, the majority selected improved treatment options. When participants were asked about the most challenging aspect of managing herpes, the top responses were managing intimate relationships and stigma (68.4%) and dealing with symptoms (20.2%). One participant stated, "The stigma behind herpes is my biggest problem . . . being scared you might transmit it to the one you love is scary also." Mental health challenges related to herpes were mentioned by 23.4%; 7.9% specifically mentioned

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suicide. Challenges with symptom management included the lack of treatment options and support from health care providers. Survey data also indicated that patients do not feel adequately supported by the health care system.

AVAC was founded in 1995 to promote increased funding and treatment in HIV research, to identify barriers to the development of a vaccine, and to increase public awareness of the need for a well-funded and coordinated HIV vaccine research program. In coordination with the NIAID and the World Health Organization, AVAC developed a website to track sexually transmitted infection (STI) vaccine development that includes vaccines for genital herpes (https://stiwatch.org/). A goal is to raise awareness and enlist current HIV and sexual and reproductive health advocates to address STIs.

Herpes Cure Advocacy (HCA) shared its mission: to eradicate HSV-1 and HSV-2 from the world and to find a cure and prevent the spread of this chronic infectious disease (https://herpescureadvocacy.com/). HCA is a 501c3 nonprofit organization with nearly 17 000 members and a board of directors that includes HSV researchers. HCA engages with multiple branches of the US government, the World Health Organization, nongovernmental organizations, and industry. HCA goals include prioritizing knowledge, taking action on patient-centered care, and promoting racial and gender equity.

During the workshop, online and in-person attendees participated in several informal electronic polls on patient/provider interactions around a herpes diagnosis. Most individuals with HSV rated the conversation with their providers as *poor* after receiving their HSV diagnosis; they also rated the skill levels of their providers as *poor* in terms of delivering counseling surrounding the social/emotional implications of the diagnosis. Notably, a third of respondents indicated that they did not have any conversation with their providers about their diagnosis. This sentiment was echoed in published data demonstrating a deficit in sexual health training among US nurse practitioners and medical students [4]. Medical and physician assistant students, on average, receive only 3 to 10 and 12 hours of instruction on sexual health, respectively [5, 6]. Increased sexual health training should be considered, given that providers will encounter sexual health issues regardless of chosen specialty.

Also discussed were some key principles and practices that providers could consider when evaluating or treating individuals for HSV: swabbing areas of patient concern, followed by molecular testing; if the patient is asymptomatic but has real concerns, performing type-specific IgG testing (not IgM testing) after counseling the patient about the high probability of false-positive results; confirming all low positive IgG results with a better test; determining HSV type; ensuring that online, phone, and in-person results are given in a sensitive manner; including the natural history of HSV infection when counseling patients; and identifying helpful and accurate resources to dispel stigma.

Panelists discussed that providers need to be aware of the anxiety associated with disclosure of a herpes diagnosis and assist patients with strategies for navigating their sex lives accordingly. Professional counseling may be of assistance to some patients, and there may be differences in how men and women process an HSV diagnosis, especially for women considering pregnancy. Panelists acknowledged the importance of patient-centered approaches but also noted that truly effective interactions would rely on improved diagnostics.

Treatment

The HSV genome replicates through 3 origins of replication with 7 virally encoded replication proteins, including DNA polymerase, which is the primary target of current antiviral therapeutics. Three noncanonical HSV replication proteins were presented that show potential as novel nonpolymerase drug targets. ICP8 is a zinc metalloprotein involved in filament formation and annealing [7]. UL12 is an alkaline nuclease essential for production of infectious virus [8]. PolExo is a proofreading nuclease required for replication fidelity [9]. Small molecules and peptides have been designed to antagonize essential interactions of these 3 targets that limit viral replication [8, 10].

Resistance to acyclovir is low in people with HSV who are immunocompetent; however, the prevalence of resistance in individuals who are immunocompromised can be up to 25%. Many of these patients receive intravenous foscarnet, which has a high potential for side effects and may require hospitalization with close monitoring. In the event of foscarnet resistance, there are limited treatment options. Pritelivir (AiCuris Anti-infective Cures AG) is an inhibitor of the HSV helicase-primase enzyme complex that is active against nucleoside-resistant HSV strains, and it is being developed with an indication to treat resistant HSV infections [11]. In phase 2 clinical trials, pritelivir demonstrated superiority in suppression of HSV shedding and genital lesions as compared with placebo or valacyclovir in healthy people with genital herpes who were immunocompetent [12, 13]. PRIOH-1 (NCT03073967; ClinicalTrials.gov) is a randomized, open-label, and global multicenter phase 3 clinical trial on the efficacy and safety of pritelivir tablets for treatment of acyclovir-resistant HSV infections in those who are immunocompromised. As suggested by the phase 2 clinical trial data among people who were immunocompetent, pritelivir could be considered for maintenance therapy for patients with herpes, and several online audience members expressed interest in the prospect of pritelivir being made available for use by those with genital herpes. Studies indicate that pritelivir may cross the blood-brain barrier in animals, presenting the potential to treat herpes encephalitis.

Therapeutic HSV vaccines would be administered to patients with herpes to reduce recurrent disease and viral shedding [14]. Challenges with clinical study designs for therapeutic vaccines include the variability in the frequency and duration of viral

shedding within and among patients [15]. Despite these challenges, therapeutic vaccines have been tested in phase 1/2 trials [16]. Data suggest that CD4 and CD8T cells targeting the HSV protein VP16 may have a role in prevention of reactivation [17]. Therapeutic vaccination to enrich CD8+ HSV-specific T cells at genital epithelia and skin may help to contain reactivation of the virus [18–20].

A virologic cure for herpes would need to remove the HSV genome from latently infected cells. Gene-editing enzymes can be targeted to specific sequences of the HSV genome, which can lead to deletions within the viral genome that may knock out essential viral functions [21]. Latent HSV is a potential candidate for gene editing because the virus is limited to the neurons in the ganglia, of which only a subset is infected with HSV. Three HSV-specific meganucleases introduced into an adeno-associated virus vector and administered to mice showed reduction of ganglionic HSV shedding in a dose-dependent manner [22, 23]. The intent of gene editing is to target the long-lived reservoir of cells in latent HSV rather than acute disease, and researchers are hoping to learn from ongoing gene-editing clinical trials against other pathogens, which are being conducted in the United States and Europe.

Neonatal HSV

Neonatal HSV (nHSV) affected 1 in almost 2000 infants in 2015. Five percent of nHSV infections are acquired in utero, whereas 85% of nHSV infections are acquired by passage through an infected birth canal. The most severe manifestation of nHSV is disseminated disease, which occurs in 25% of all cases. Localized nHSV may manifest as encephalitis (central nervous system disease) in 30% of cases or as skin, eye, and mouth disease [24]. Infants born to persons with recently acquired genital herpes are at much higher risk of becoming infected than those born to persons with a history of genital HSV before pregnancy, suggesting that focusing on pregnant persons with a history of genital herpes will not capture the population that is most at risk [25]. Several discussants called for making nHSV a reportable condition to increase understanding and awareness.

A new model that may aid in the development of treatments for nHSV was presented. A paired associative learning behavioral test given to mice infected with HSV at birth showed that HSV-infected animals performed significantly poorer over time and had increased cerebral protein aggregates when compared with their uninfected counterparts (D. Leib, unpublished data). In addition, mouse studies have demonstrated that maternal immunization provides protection to neonates [26].

Diagnostics

The standard approach to diagnosis of genital ulcer disease relies on molecular detection assays. In general, HSV molecular assays are highly sensitive, but HSV *must* be present in the collected sample. This proves difficult if no lesions are present or if a patient is not shedding the virus at the time of sample collection. A 1999 study showed that 81% of individuals with new HSV-2 infections who were symptomatic were correctly diagnosed, yet only 40% of these new cases had lesions. This demonstrates the limitations of relying solely on clinical presentation of lesions or symptoms to diagnose a patient with HSV, and it emphasizes the value of accurate serologic diagnostic tests [27].

Serologic assays detect IgM between 7 and 30 days or IgG approximately 2 to 6 weeks after infection. The Western blot is considered the gold standard for serologic diagnosis of HSV; however, this test is labor intensive, provided by a single source in the United States, and not widely utilized. Type-specific enzyme immunoassays are available commercially, but HSV-2 specificity can be quite low in these tests [28], especially in patients with low index values [29, 30]. The positive predictive value of serology for screening among asymptomatic individuals is low, as false-positive results are common, and it is of limited utility for diagnostic use unless the patient is tested at least 2 months after exposure or if confirmatory testing by Western blot is conducted. The US Preventive Services Task Force recommends against routine screening for genital HSV infection among asymptomatic adolescents and adults, including pregnant persons [31].

Further discussion noted a global lack of access to HSV testing. In Kenya, only 9 sites offer testing, it is costly, and results can be significantly delayed. Panelists agreed that novel diagnostic solutions are needed and, if developed, may prove useful for screening and diagnosis among asymptomatic people. The importance of the patient perspective on diagnostic needs was discussed extensively. Providers stated that patients presenting with symptoms greatly desire rapid and accurate tests for initial diagnosis. Additionally, patients may not be aware that regular STI screening does not include testing for HSV, and many patients with negative results for an STI screen wrongly consider themselves as not having a genital HSV infection.

Prevention

Prophylactic vaccines that have undergone clinical testing were subunit vaccines composed of surface glycoproteins D and B from HSV-2 (gD2 and gB2, respectively). These elicited neutralizing antibody titers and protection in animal models but showed limited efficacy in the clinic [32–35]. A large phase 3 trial demonstrated protection against HSV-1 genital infection, and IgG titers were correlated with the protection [36].

Several vaccine candidates were discussed, including a prophylactic trivalent (gC2/gD2/gE2) mRNA–lipid nanoparticle vaccine (BioNTech SE) that is in a phase 1 clinical trial (NCT05432583; ClinicalTrials.gov). An intranasal vaccine composed of HSV-2 gD2/gB2 in an oil-in-water emulsion adjuvant (BlueWillow Biologics, Inc) demonstrated protection from challenge and a reduction of lesions in previously infected animals in

a guinea pig model [37]. gD2 is also immunodominant in HSV-2 human and animal infections and may result in less-than-optimal immune responses to other HSV antigens. To augment non-gD2 immune responses, a vaccine consisting of an HSV-2 strain deleted for gD was developed, which resulted in a single-cycle virus that elicited high antibody and T-cell responses and was protective in several animal models [38–40]. Another HSV-1 live-attenuated vaccine (Thyreos, Inc) includes deletion of the pUL37 tegument protein, producing strain that can replicate locally in the mucosa but does not disseminate to the nervous system [41]. Several animal models demonstrated that this vaccine prevented viral shedding, as well as gross pathology and infection of the sensory nerves and brain following challenge [42].

Discussion featured the involvement and importance of neutralizing antibody, various cell types used in neutralization assays, and the overall ability of the assay to predict success in vivo. The importance of local immune responses, including antibodies and T cells, was also stressed. Other topics included the need for serologic tests that can identify infection in those immunized with a live-attenuated vaccine and, most important, the gap that still exists in identifying a correlate (or correlates) of protection.

The impacts of effective HSV vaccines were also discussed [43]. One study showed that a reduction in HSV-2 incidence following the introduction of prophylactic vaccination of uninfected 15- to 49-year-olds would have an immediate impact on newly acquired HSV-2 infections [44]. Although health economic modeling studies estimate the lifetime cost of HSV-2, it was noted that these costs usually do not include the severe psychosocial costs experienced by many people with genital herpes [45]. Quantifying the burden of genital herpes based only on direct medical costs greatly underestimates the true burden of the disease.

Analysis of previous vaccine experiences indicates that adolescent sexual health and behavior and vaccine safety can help to inform vaccine acceptance of potential HSV-2 vaccines. Overall vaccine hesitancy is influenced by a range of factors, and the most significant predictor of vaccine acceptance is the perception of the vaccine's importance [46–50].

Multipurpose prevention technologies (MPTs) are devices that combine protection against unintended pregnancy, HIV, and other STIs. They have the potential to address overlapping risks, synergize prevention approaches, increase motivation for adherence, and destigmatize STIs. The optimal MPT is efficacious, safe, and multidrug loading; it has sustained-release or on-demand characteristics, a wide active pharmaceutical ingredient range, and limited side effects; and it is easy to use. A list of MPTs shows 14 with activity against HSV, but only about half of those are advancing [51].

SUMMARY

This workshop allowed the herpes research community, industry representatives, public health advocates, patients, and government agency staff to work together to define the status of genital herpes and to identify gaps and challenges to advance the field. The diagnosis of a genital herpes infection can have important psychosocial impacts for the patient, result in stigma, and affect sexual health and quality of life. This workshop offered a forum for patient advocates to describe their methods of advocacy, list priorities and specific items and technologies that could be addressed by the research community, and express how the disease affects their lives. Approximately 160 comments and questions were posted by the online audience, and a large proportion of the submitted questions began with the word "When," clearly indicating the urgency of patients to obtain new treatments and preventative products. By far the most important patient concern is the development of new treatments that would allow for better management of the disease and for a decrease in shedding such that the patient is untransmissible. To achieve this goal, it was acknowledged that HSV is relatively rich in targets for new drugs and that therapeutic vaccination is a possibility. A virologic cure for HSV infection is in its infancy, although evidence was presented for at least one mechanism to achieve that goal.

It was highlighted that a clear challenge in the field is suboptimal diagnostics. Patients often present without lesions that would enable direct detection of the virus; thus, diagnosis of genital herpes must rely on examination, sexual history, and serology. However, clinicians do not often recommend HSV serologic testing, even to patients who request it, to avoid the real possibility of a false diagnosis. Suboptimal serologic test performance has affected the lack of recommendations for HSV screening. Suboptimal technologies also influence the ability to perform rigorous epidemiology and modeling studies and to design clinical trials for the testing of new vaccines and therapeutics. Thus, the development of effective, reliable, and widely available diagnostics for genital herpes is a clear gap. Overall, the workshop identified areas of that research that could improve the overall future for HSV control and prevention.

Notes

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