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Status and Future Management of Congenital Cytomegalovirus and Neonatal Herpes Simplex Virus Infections

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ABSTRACT

Congenital cytomegalovirus (CMV) and herpes simplex virus (HSV) infections are among the most common viral infections of the newborn in the developed world. CMV infections can cause sensorineural hearing loss, and both CMV and HSV infections can lead to impaired neurodevelopment. Diagnostic and treatment efforts have been investigated for the past 45 years. With the development of polymerase chain reaction (PCR) for diagnosis and its quantitation as well as studies of the pharmacokinetics and pharmacodynamics of ganciclovir/valganciclovir (CMV) and acyclovir (HSV), significant improvement in outcome has been achieved. For example, studies utilizing ganciclovir and valganciclovir demonstrate improved hearing and Bailey Developmental scores; however, therapy requires six months of treatment with valganciclovir. With neonatal HSV infections, high-dose acyclovir decreases mortality for two classifications of disease - encephalitis and disseminated multiorgan infection. Like congenital CMV infections, neonatal HSV requires long-term suppressive therapy following a course of IV acyclovir. Regardless, outcome for both diseases is unsatisfactory, and improved treatment approaches must be developed.

The current review addresses these two members of the Herpesviridae family: the diseases they cause in the newborn, the current shortcomings and a consideration of future needs. Both viruses establish latency and are reactivated throughout an individual's lifetime, ergo eradication at the present is impossible. The discussion is limited to these two life-threatening diseases. The successful lessons learned from combination therapies of human immunodeficiency virus and hepatitis C virus infections must be applied to these diseases. If improvement can be documented, it will have direct implications for managing diseases caused by both viruses in older individuals. It is the aim of the review to provide the reader with knowledge of the field, providing a reference to future needs and opportunities.

Introduction to Congenital Cytomegalovirus Infection

The diagnosis and management of congenital cytomegalovirus (CMV) introduces unique problems. First, most congenital infections are acquired from maternal transmission across the placenta to the fetus. Second, most infants are born totally asymptomatically, whereas only 10% have clinical evidence of disease at birth. In either case, the outcome can be devastating as hearing loss is a primary problem, even in those children born with an asymptomatic infection. Recognizing that infection is acquired early in gestation, introduces unique therapeutic problems. Namely, is it possible to treat a chronic viral infection acquired early in gestation, particularly when these babies excrete >6 logs of virus in their urine? Similarly, with the advances in therapy that have been developed, can we now treat babies with asymptomatic infection in hopes of preventing subsequent hearing loss? The ideal solution would be the development of a vaccine to prevent both maternal primary infection as well as vertical transmission of infection in the seroimmune woman. Efforts to develop a CMV vaccine have been entertained for decades, but all have failed. We will consider potential future approaches to this problem.

Epidemiology

Congenital cytomegalovirus (CMV) infection is the most common viral infection in the developed world, creating an extensive disease burden.[1,2] The current estimated incidence of vertically infected infants is approximately 3-7/1000 newborns globally, while in the United States (US) nearly 1 in 3 children are infected with CMV by age five.[1,3] Socioeconomic and regional disparities in the prevalence of congenital CMV infection have been documented in the US; for example, non-Hispanic Black newborn infants exhibit significantly higher congenital CMV infection rates (9.5/1000 live births) compared to other racial/ethnic groups.[2,4] Transplacental transmission can occur in women with either primary or preexisting CMV infection by viral reactivation or acquisition of a new strain. Although the time of maternal infection is not related to the risk of congenital infection and clinical presentation, severe sequelae are more commonly identified in women infected early in pregnancy. In addition, most congenital cases in the US occur in infants born to women with a primary infection while the more severe cases in other populations with higher rates of maternal CMV seroprevalence occur in newborns of mothers with preexisting infection. [4]

Disease Burden and Outcomes

At birth, 90% of infants with congenital CMV infection are asymptomatic and the remainder symptomatic, but still being at higher risk for severe complications.[4] CMV infection can affect multiple organs and predisposes infants to reticuloendothelial and central nervous system disease.[5-7] The most common clinical presentation in symptomatic newborns includes jaundice, petechiae, purpura, hepatosplenomegaly, microcephaly, periventricular calcifications and retinitis.[4] Thrombocytopenia, conjugated hyperbilirubinemia and elevated liver enzymes are typical laboratory abnormalities.[4] In terms of neurodevelopmental involvement, sensorineural hearing loss (SNHL) and cognitive delay are the most serious permanent sequelae.[4] Clinical presentation with microcephaly and neurological symptoms, and abnormal neuroimaging findings detected within the first month of life, are considered strong predictors of adverse neurological outcomes in symptomatic infants.[5-7] Of note, SNHL occurs in up to 50% of symptomatic children with congenital CMV infection, while up to 15% of asymptomatic newborns at birth will eventually develop SNHL.[4] Approximately 40% of CMV-related SNHL cases in children have delayed onset that cannot be detected during the first month of life, making management more challenging.[4] Hearing loss might be either unilateral or bilateral and can also deteriorate over time, requiring continuous monitoring.[4-7]

The prevalence of adverse outcomes highlights the chronicity and complexity of congenital CMV infection and indicates the disproportionately higher disease burden and associated disabilities compared to

other well-known conditions of childhood, such as Down's syndrome and fetal alcohol syndrome.[8] In turn, the financial toll of congenital CMV infection is high, attributed to both direct medical costs of managing and treating the condition born by healthcare systems, payers, and parents/caregivers and to indirect and intangible societal costs.[1,9-14]

Diagnosis

Congenital CMV infection can be diagnosed at birth by polymerase chain reaction (PCR) assessment of urine or saliva, with saliva PCR being the preferred method due to the ease of collection and high sensitivity of the assay.[4] Since universal screening is not an established routine yet, some centers perform targeted CMV screening on newborns who fail a hearing test within 3 weeks of birth[14] However, the benefits of a hearing-targeted strategy might be limited because, as noted above, some newborns with congenital CMV infection successfully pass their initial hearing test but develop SNHL later in life[14,15] Otherwise, evaluation is based on clinical criteria.[4,14] Notably, there is a growing trend in the US for routine screening of all live born children. Early detection of CMV in the neonatal period is important since hearing loss might present later in previously asymptomatic children.[5] From a cost-effectiveness perspective, either targeted or universal screening might be superior compared to the clinical diagnosis, considering that early detection and proper treatment could result in improved outcomes at lower costs[5,12,16-18] Despite the limited data on long-term sequelae and costs of congenital CMV infection, existing studies suggest that the implementation of newborn CMV screening is warranted.[5,12,16-18] For that purpose, a saliva real-time PCR on Guthrie card has been proposed as a potential tool for universal congenital CMV screening, exhibiting high sensitivity and specificity.[19]

Treatment

Current treatment guidelines for symptomatic congenital CMV infection include 6 months of oral valganciclovir initiated within the first month of life (32 mg/kg/day in two divided doses), while no treatment is indicated for asymptomatic patients.[4,20,21] Compared to intravenous ganciclovir, valganciclovir is an oral prodrug that provides the same systemic exposure without the challenges of intravenous therapy.[22,23] During treatment, close monitoring of patients receiving valganciclovir is required due to potential serious side effects. Valganciclovir is associated with neutropenia (most commonly presenting within the first 6 weeks), thrombocytopenia, anemia, and elevated liver enzymes. These adverse effects are reversible after discontinuation of the drug. Ganciclovir can theoretically cause long-term effects as observed in animal models and are related to increased risk of carcinogenesis and reproductive organ toxicity.[22,23]

Oral valganciclovir has been successful in treating congenital CMV infection, with the exception of rarely reported, isolated cases of resistance to drug.[24-26] While antiviral treatment decreases the viral load, it does not eliminate CMV, as the virus establishes lifelong persistent infection.[4] The long-term benefits of treatment include the prevention of further hearing loss and neurodevelopmental deterioration.[27] Data from ongoing studies are expected to provide evidence on treatment benefits, but further research on long-term complications is warranted. In addition, new antiviral approaches are being investigated and a phase I clinical trial is currently underway in the US. In this clinical trial, the safety of oral letermovir will be assessed in neonates with symptomatic congenital CMV infection when administered with valganciclovir.[28] Letermovir acts by inhibiting the viral terminase subunit pUL56, subsequently disrupting the production of new virions. The primary goal of this ongoing study will be to determine the pharmacokinetics of oral letermovir in infants, based upon previous observations and data from valganciclovir.[28]

Failure of Late Therapy to Impact Hearing Loss

While current guidelines from the American Academy of Pediatrics recommend the initiation of treatment for symptomatic CMV infection in the

neonatal period, evolving evidence suggests that antiviral treatment might be beneficial for patients without any clinical findings and patients with either isolated or late-onset hearing loss, although the data are limited and uncontrolled.[3,4,29,30] Results from a 2020 study from Israel suggested that treatment of congenital CMV infection initiated after the neonatal period was associated with better outcomes for both symptomatic and initially asymptomatic children who presented with late-onset hearing loss.[31] The results indicated an improvement in hearing during the 1 year follow-up period for most patients, but this study was observational with a small sample, indicating the need for additional and long-term, controlled studies with larger samples.[31] In contrast, results from a recent randomized clinical trial conducted in the US and United Kingdom indicated that oral valganciclovir initiated beyond the neonatal period failed to improve hearing outcomes in children with SNHL associated with congenital CMV infection.[32]

The efficacy of valganciclovir treatment in isolated CMV-related SNHL has been the subject of investigation in recent clinical trials in Europe and the United States, aiming to evaluate the impact both on hearing and developmental evaluations.[33-35] A phase II clinical trial in the US aimed to assess the role of valganciclovir treatment in hearing loss prevention in infants with asymptomatic congenital CMV infection was suspended due to safety concerns.[36] Promising data from another recently published clinical trial suggested a beneficial effect of antiviral treatment in infants with isolated hearing loss in the setting of congenital CMV infection.[37] These discrepancies in results warrant clarification.

To date, only one study has provided data regarding children older than 12 years with symptomatic congenital CMV infection, finding that most symptomatic patients developed severe hearing loss regardless of whether or not they were treated with ganciclovir for 6 weeks.[38] Thus, research to better understand the long-term impact of the standard 6-month valganciclovir regimen is needed.[38]

Maternal –Prevention, Screening, and Treatment

In addition to newborn screening and management, antenatal intervention options have been explored to prevent both primary CMV infection in pregnant women and maternal-to-child transmission.[39,40] The spread of CMV can occur through exposure to saliva and urine from infected individuals, mostly from children in the household and childcare centers to mothers and other caregivers.[4] Thus, hygienic interventions can contribute to preventing seronegative pregnant women from acquiring CMV, while raising awareness regarding maternal CMV infection is also critical to contain CMV burden.[39,41,42] Of note, evidence suggests that the majority of women are not informed about CMV; even healthcare professionals are often not well-equipped to advise pregnant women regarding CMV-related matters, highlighting the need for educational strategies targeting both the public and healthcare professionals.[43-45]. Although serologic screening during pregnancy is useful for detecting primary and non-primary CMV infection, routine screening is not recommended by the official guidelines, as it is not considered to be cost-effective.[20,46,47] Early recognition of maternal CMV cases is important, and currently, different secondary measures have been proposed to prevent maternal-to-child transmission. Passive immunization of pregnant women with hyperimmunoglobulin has been investigated as a secondary prevention measure, but existing studies have yielded mixed results.[48-50] Promising data from observational studies suggested that a high dose of hyperimmunoglobulin biweekly in women with primary CMV infection early in pregnancy decreased maternal-fetal transmission.[48] On the other hand, clinical trials of CMV hyperimmunoglobulin administration in pregnant women with primary CMV infection carried out in Italy and the United States failed to demonstrate benefit and, consequently, is not recommended.[49, 50]

Finally, data are emerging to support the use of valacyclovir during pregnancy as an option to prevent congenital CMV infection.[51] In these studies, treatment of primary CMV infection in pregnant

women with valacyclovir (8gr/day orally) was associated with a reduction in congenital CMV infection (defined by amniocentesis) compared to the no-treatment group.[53-55] In addition, secondary outcomes of a study in Italy suggested a reduction in symptomatic congenital CMV infection at birth in infants born to mothers treated with valacyclovir during pregnancy compared to those born to mothers who were not treated.[53] Valacyclovir was overall well tolerated in most cases with minimal but reversible adverse effects after treatment discontinuation.[53] However, these studies included data for pregnant women with primary CMV infection only, in the absence of universal CMV screening strategy during pregnancy and, therefore, they lack generalizability. Moreover, the quality of evidence that prenatal valacyclovir decreases the risk of vertical CMV transmission was deemed very low, highlighting the need for future research.[56]

A randomized clinical trial is currently underway, assessing the role of letermovir, a CVM-specific antiviral drug noted above, in prenatal treatment of first-trimester primary CMV infection cases.[57] Compared to other known antiviral agents licensed for use in immunosuppressed transplant patients (ganciclovir, foscarnet, cidofovir), both letermovir and valacyclovir are safe during pregnancy, not teratogenic, and effectively cross placenta. Investigators hypothesize that letermovir's efficacy will be greater than valacyclovir in inhibiting fetal CMV replication and will result in undetectable CMV viral load in newborns, which is the primary endpoint of this study. Evaluation includes long-term outcome over the first two years of life.[57] Subsequently, if efficacy of maternal treatment for primary CMV infections in the first trimester is proven, the need for early recognition will be intensified and a universal CMV screening approach during pregnancy might be reevaluated.

The development of a maternal vaccine to prevent vertical transmission of CMV has been an urgent priority during the 21st century, according to the US Institute of Medicine (now National Academy of Medicine) of the United States, but none has been licensed to date.[58,59] Various vaccines with different targets have been investigated over the last few decades, and the launch of an effective CMV vaccine is considered feasible in the next 5 to 10 years.[59-61] The development of a vaccine against CMV is challenging since the infection occurs in the presence of both humoral and cell-mediated immune responses.[59-61] Previous attempts with candidate vaccines utilizing recombinant surface protein glycoprotein B (gB) in seronegative women had limited efficacy with waning immunity over time.[62,63] Recently published data showed that an mRNA-based CMV vaccine (mRNA-1647) that codes for the pentamer complex and gB elicited polyfunctional and durable CMV-specific responses, with higher neutralization and antibody-dependent cellular cytotoxicity compared to another gB subunit vaccine, placing it as the most promising candidate.[64] Currently, a Phase 3 clinical trial is underway investigating the efficacy of the mRNA-1647 vaccine focusing on healthy CMV-seronegative women of childbearing age from 16 to 40 years old.[65]The recruitment was completed but the observation period has currently been extended to assess the seroconversion. Results are expected in 2026.[65]

Alternative methods of diagnosis and identifying those at higher risk for vertical CMV transmission and severe permanent sequelae have been explored.[66-69] Identification of potential biomarkers is necessary, as they might guide decision-making. A meta-analysis published in 2022 described the value of amniocentesis results in pregnant women with CMV infection in predicting the risk of fetal infection.[67] A negative amniocentesis result was associated with a lack of severe symptoms at birth and lack of long-term complications, even if vertical transmission had occurred. In addition, a recent randomized controlled trial which was conducted in the US indicated that amniocentesis results can be used as an accurate predictor of congenital CMV infection.[68] An in-progress clinical trial aims to explore non-invasive biomarkers of CMV fetal disease, avoiding amniocentesis when it is not indicated.[70]

Conclusion

While significant progress has been made in the diagnosis and treatment of congenital CMV infection, much remains to be accomplished. Taking lessons learned in the management of human immune deficiency virus infection, combination antiviral therapies must be developed to accelerate the clearance of virus from these babies. The combined use of valganciclovir and letermovir, drugs with different mechanisms of action, offers such a possibility.

Importantly, further research is an urgent priority to guide policymakers about maternal and newborn screening, long-term sequelae, predictors and potential biomarkers, and optimal treatment for women and infants.

Introduction to Neonatal Herpes Simplex Virus Infection

Herpes Simplex virus (HSV) infections are ubiquitous. By the time individuals reach adulthood, as many as 60% of individuals in the developed world and over 90% in the developing world have been infected by this virus. Under rare circumstances, HSV will cause life-threatening disease, namely, herpes simplex encephalitis and neonatal herpes simplex virus infection. While therapies have been developed, specifically acyclovir, that have improved outcome, much remains to be accomplished. Specifically, even with therapy mortality is significant. As with chronic viral infections, mentioned above, combination therapy is warranted to further improve outcome. Clearly drugs with a different mechanism of action that penetrate the central nervous system are essential toward improved neurologic outcome. As with CMV, efforts to develop an HSV vaccine have gone on for nearly a century but again, to no avail. The strengths and weaknesses of advancing the field will be discussed.

Epidemiology

While herpes simplex virus (HSV) infections are ubiquitous and well-documented in adults, neonatal HSV infections are less common but can cause neurologic disability and even death if left untreated.[71,72] Genital herpes, both HSV-1 and HSV-2, in women, can be transmitted to children.[73] Newborns usually contract HSV as they pass through an infected maternal birth canal, but in a few cases, infection can occur earlier in utero as an ascending infection or postnatally horizontally from a parent, sibling, or other caregivers.[4] The risk of maternal-to-child transmission is significantly higher with primary maternal infection during the third trimester of gestation compared to neonates born to mothers previously infected who reactivate the virus during pregnancy (25-60% versus <2%).[4] The use of fetal scalp electrodes has also been identified as a risk factor for maternal-to-child transmission of HSV.[74,75] Due to the lack of symptoms in most maternal infections, it is difficult to distinguish between primary and recurrent infection based on maternal history. Therefore, it is not helpful to assess the risk of transmission to their child.[4]

Disease Burden and Outcome

The incidence of neonatal HSV infection is approximately 1/3000 live births in the United States with increasing incidence noted in the last few years. The global rate is estimated at 10/100,000 births.[4,76-78] HSV infection in newborns can present in three different ways: skin-eye-mouth (SEM) disease – 45%, central nervous system (CNS) disease – 30%, and disseminated – 25%.[4] Typically, initial signs are evident within the first month of life. Furthermore, SEM and disseminated disease usually occur earlier in the neonatal period, as opposed to the CNS infection, which usually presents between the second and third week of life. Any neonate with culture-negative sepsis, severe liver dysfunction, consumptive coagulopathy or suspected viral pneumonia must be evaluated for disseminated HSV infection. More specifically, signs and symptoms such as fever, vesicular rash or seizures with abnormal CSF indices can be indicative of HSV infection. When present, a vesicular rash is typical of SEM disease, but can also occur in CNS or disseminated disease with potentially later onset.[4] Importantly, even though it is uncommon, suspicion is required to diagnose

and promptly treat HSV infection with CNS involvement.[79]

For diagnostic purposes, the Tzanck test, a histologic examination of lesions for presence of multinucleated giant cells, was previously used, but it is not currently recommended due to low sensitivity.[4] At present, PCR or culture (if available) is being used for the diagnosis of neonatal HSV infection. The samples used can be "surface specimens" from the mouth, nasopharynx, conjunctivae, and anus, specimens of skin vesicles, CSF sample or whole blood. To avoid false-positive results due to contamination after intrapartum exposure, specimens should be obtained 12-24 hours after birth. In addition, HSV viremia can be present in all manifestations of neonatal infection (SEM, CNS, disseminated), therefore a positive PCR result does not necessarily mean that the neonate has disseminated disease, so these results cannot be used to determine disease severity and guide the treatment duration.[4]

The prognosis of neonatal HSV infection varies widely based on multiple factors, including disease classification, the time of transmission and the extent of organ involvement.[71] SEM disease exhibits better outcomes compared to the other disease types from a morbidity and mortality perspective, but it is usually followed by frequent skin recurrences.[71] Infants presenting with severe symptomatology, especially with CNS involvement, are at increased risk for long-term neurodevelopmental deficits.[71] Ocular complications can occur and lead to visual impairment or blindness.[71] Due to the advances in antiviral therapy, the prognosis has been improved, and mortality rates have declined, but continuous efforts in this direction are needed.[71,80-83]

Treatment

The adverse and potentially detrimental outcomes of neonatal HSV infection and the emotional burden placed on patients and their families, render the management of the condition more challenging and require collaborative approaches of a multidisciplinary team.[71,81] Early recognition of the disease and initiation of treatment is critical to contain disease burden and manage the infection.[80] Treatment with high-dose intravenous acyclovir (20 mg/kg/tid) is the standard of care, with a 14-day course for SEM cases and a 21-day course for CNS or disseminated disease. In CNS involvement, repeat CSF near the end of treatment is needed to determine that the PCR is negative. In the event of a positive result, treatment for 7 more days is required, with repeat lumbar puncture until the PCR is negative. After completion of IV treatment, suppressive therapy with oral acyclovir is initiated in all cases for a 6-month duration.[4,71] In theory, suppressive treatment can address low-level replication of the virus and prevent or at least decrease the number of future recurrences, while also being associated with improved neurodevelopmental outcomes in infants with CNS involvement.[84]

Intravenous acyclovir has been successful in treating HSV infections, but it can have adverse effects such as neutropenia and renal tubular dysfunction; thus, close monitoring is warranted.[85] Acyclovir resistance has been observed, but the prevalence in neonates is unknown.[85,86] Treatment resistance should be suspected in cases with persistent symptoms or positive CSF PCR results. Oral acyclovir is not used as an alternative treatment option due to poor bioavailability. In contrast, oral valacyclovir has better bioavailability, but its use has not been adequately studied.[85] Unfortunately, shortage of acyclovir supply is common, particularly over the past few years, with limited options for alternative regimens.[85] Intravenous ganciclovir is the first-line option in case of acyclovir shortage, with intravenous foscarnet as the second-line alternative.[4] More importantly, IV acyclovir should be reserved for proven neonatal HSV disease and encephalitis.[4]

Future Approaches

Current studies focus on new treatment options and evaluate different potential targets for drug development.[87] A new agent for inhibiting HSV replication is the helicase-primase inhibitor, IM-250, which has shown high potency and crosses the blood-brain barrier.[88] This new drug is promising,

particularly for severe HSV cases resistant to nucleoside analogs such as acyclovir.[89] A combination strategy of a new inhibitor with acyclovir could also maximize efficacy, leading to improved clinical outcomes. [88] In addition, a recent clinical trial is evaluating valacyclovir pharmacokinetics and pharmacodynamics in neonates, in comparison to intravenous acyclovir, which is currently the standard of care.[90] Continuous research is required, as an orally bioavailable treatment of neonatal HSV infection could potentially decrease the emotional burden on families and the healthcare costs of intravenous therapy and long hospital stays in those babies with non-life threatening disease.[76]

Given the evidence that neonates born to mothers with non-primary, recurrent genital HSV infection have a lower risk of infection, and assuming they have protection by the antibodies transferred through the placenta, an antibody-based therapy might have a place in future approaches.[95] HSV-specific monoclonal antibodies have shown promising results in animal models, but further human-based research is warranted.[95] Based on this rationale, another step towards long-term prevention of recurrent HSV infection or initial infection is the development of a vaccine against HSV, which is one of the 2023-2028 goals in the strategic plan for HSV research, according to NIH.[77,96] Finally, the huge burden of HSV and the existing scientific needs require persistent efforts and innovation in drug development exploring alternative mechanisms of action or other interventions to treat or prevent HSV infections.

Prevention

Focusing on pregnant women to prevent HSV transmission to their child is a significant component in the effort to reduce the disease burden.[91] Serologic testing for HSV is currently available in commercial labs, and it can reliably detect type-specific antibodies in pregnant women, but there is no evidence for routine screening.[92] For pregnant women with recurrent genital herpes, suppressive antiviral treatment should be offered beyond 36 weeks of gestation. PCR screening of women in the delivery suite can also be an excellent tool in HSV management.[93] According to the American Academy of Pediatrics, current evaluation and management algorithms for newborns are based on the mother's classification of HSV infection.[94] Cesarean section is recommended for mothers with active genital HSV lesions to prevent newborn exposure during delivery.[92] In addition, careful hand hygiene is important postnatally in mothers with active lesions while handling their infants.[4]

Conclusion

Neonatal HSV infection, like CMV, requires combination therapy with drugs having different mechanisms of action. Perhaps IM-250 plus acyclovir will help address this important need. Further, an oral formulation of valacyclovir, the prodrug of acyclovir with improved bioavailability, would make ambulatory care significantly easier for families and the child. At the present, valacyclovir has to be compounded before it can be administered.

Conflicts of Interest Statement:

The authors have no conflicts of interest to declare.

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References:

1. Grosse SD, Leung J, Lanzieri TM. Identification of congenital CMV cases in administrative databases and implications for monitoring prevalence, healthcare utilization, and costs. *Curr Med Res Opin*. 2021;37 (5):769-779. doi:10.1080/03007995.2021.1890556

2. Fowler K, Mucha J, Neumann M, et al. A systematic literature review of the global seroprevalence of cytomegalovirus: possible implications for treatment, screening, and vaccine development. *BMC Public Health*. 2022;22(1):1659. Published 2022 Sep 1. doi:10.1186/s12889-022-13971-7

3. Clinical overview of CMV and congenital CMV. Centers for Disease Control and Prevention. Accessed September 25, 2024. https://www.cdc.gov/cytomegalovirus/hcp/clinical-overview/.

4. American Academy of Pediatrics. Red Book. 2024-2027 Report of the Committee on Infectious Diseases. 33rd Edition.

5. Kabani N, Ross SA. Congenital Cytomegalovirus Infection. *J Infect Dis*. 2020;221 (Suppl 1):S9-S14. doi:10.1093/infdis/jiz446

6. Pinninti SG, Rodgers MD, Novak Z, et al. Clinical Predictors of Sensorineural Hearing Loss and Cognitive Outcome in Infants with Symptomatic Congenital Cytomegalovirus Infection. *Pediatr Infect Dis J*. 2016;35(8):924-926. doi:10.1097/INF.0000000000001194

7. Dreher AM, Arora N, Fowler KB, et al. Spectrum of disease and outcome in children with symptomatic congenital cytomegalovirus infection. *J Pediatr*. 2014;164(4):855-859. doi:10.1016/j.jpeds.2013.12.007

8. Cannon MJ. Congenital cytomegalovirus (CMV) epidemiology and awareness. *J Clin Virol*. 2009;46 Suppl 4:S6-S10. doi:10.1016/j.jcv.2009.09.002

9. Diaz-Decaro J, Myers E, Mucha J, et al. A systematic literature review of the economic and healthcare resource burden of cytomegalovirus. *Curr Med Res Opin*. 2023;39(7):973-986. doi:10.1080/03007995.2023.2222583

10. Meyers J, Sinha A, Samant S, Candrilli S. The Economic Burden of Congenital Cytomegalovirus Disease in the First Year of Life: A Retrospective Analysis of Health Insurance Claims Data in the United States. *Clin Ther*. 2019;41(6):1040-1056.e3. doi:10.1016/j.clinthera.2019.04.022

11. Lucas A, Sinha A, Fowler KB, et al. A framework for assessing the lifetime economic burden of congenital cytomegalovirus in the United States. *Cost Eff Resour Alloc*. 2019;17:21. Published 2019 Oct 3. doi:10.1186/s12962-019-0189-0

12. Grosse SD, Dollard SC, Ortega-Sanchez IR. Economic assessments of the burden of congenital cytomegalovirus infection and the cost-effectiveness of prevention strategies. *Semin Perinatol*. 2021; 45(3):151393. doi:10.1016/j.semperi.2021.151393

13. Stephan AJ, de Lepper M, Wölle R, et al. Healthcare costs of congenital cytomegalovirus (cCMV) disease in infants during the first two years of life: a retrospective German claims database analysis. *Cost Eff Resour Alloc*. 2023;21(1):8. Published 2023 Jan 23. doi:10.1186/s12962-022-00411-x

14. Newborn Screening. National CMV Foundation. Accessed September 25, 2024. https://www.nationalcmv.org/overview/newborn-screening

15. Fowler KB, McCollister FP, Sabo DL, et al. A Targeted Approach for Congenital Cytomegalovirus Screening Within Newborn Hearing Screening. *Pediatrics*. 2017;139(2):e20162128. doi:10.1542/peds.2016-2128

16. Gantt S, Dionne F, Kozak FK, et al. Cost-effectiveness of Universal and Targeted Newborn Screening for Congenital Cytomegalovirus Infection. *JAMA Pediatr*. 2016;170(12):1173-1180. doi:10.1001/jamapediatrics.2016.2016

17. Phillips VL, Xu J, Park A, Gantt S, Dedhia K. The cost-effectiveness of targeted screening for congenital cytomegalovirus in newborns compared to clinical diagnosis in the US. *Int J Pediatr Otorhinolaryngol*. 2023;166:111450.

doi:10.1016/j.ijporl.2023.111450

18. Chen K, Zhong Y, Gu Y, et al. Estimated Cost-effectiveness of Newborn Screening for Congenital Cytomegalovirus Infection in China Using a Markov Model. *JAMA Netw Open*. 2020;3 (12):e2023949. doi:10.1001/jamanetworkopen.2020.23949

19. Pasternak Y, Oikawa MT, Mendelson E, Osovsky M, Klinger G, Bilavsky E. Diagnosing congenital cytomegalovirus by saliva on Guthrie paper. *J Clin Virol*. 2020;126:104337. doi:10.1016/j.jcv.2020.104337

20. Rawlinson WD, Boppana SB, Fowler KB, et al. Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. *Lancet Infect Dis*. 2017;17(6):e177-e188. doi:10.1016/S1473-3099(17)30143-3

21. Shim GH. Treatment of congenital cytomegalovirus infection. *Clin Exp Pediatr*. 2023; 66(9):384-394. doi:10.3345/cep.2022.01032

22. Kimberlin DW, Lin CY, Sánchez PJ, et al. Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. *J Pediatr*. 2003;143(1):16-25. doi:10.1016/s0022-3476(03)00192-6

23. Kimberlin DW, Acosta EP, Sánchez PJ, et al. Pharmacokinetic and pharmacodynamic assessment of oral valganciclovir in the treatment of symptomatic congenital cytomegalovirus disease. *J Infect Dis*. 2008;197(6):836-845. doi:10.1086/528376

24. Torii Y, Horiba K, Kawada JI, et al. Detection of antiviral drug resistance in patients with congenital cytomegalovirus infection using long-read sequencing: a retrospective observational study. *BMC Infect Dis*. 2022;22(1):568. Published 2022 Jun 22. doi:10.1186/s12879-022-07537-6

25. Garofoli F, Lombardi G, Angelini M, Campanini G, Zavattoni M, Baldanti F. Onset of valganciclovir resistance in two infants with congenital cytomegalovirus infection. *Int J Infect Dis*. 2020;98:150-152. doi:10.1016/j.ijid.2020.06.087

26. Morillo-Gutierrez B, Waugh S, Pickering A, Flood T, Emonts M. Emerging (val)ganciclovir resistance during treatment of congenital CMV infection: a case report and review of the literature. *BMC Pediatr*. 2017;17(1):181. Published 2017 Aug 22. doi:10.1186/s12887-017-0933-6

27. Kimberlin DW, Jester PM, Sánchez PJ, et al. Valganciclovir for symptomatic congenital cytomegalovirus disease. *N Engl J Med*. 2015;372(10):933-943. doi:10.1056/NEJMoa1404599

28. A safety assessment of oral letermovir in infants with symptomatic congenital cytomegalovirus. ClinicalTrials.gov ID NCT06118515. Updated September 23, 2024. Accessed September 25, 2024. https://clinicaltrials.gov/study/NCT06118515

29. Lanzieri TM, Pesch MH, Grosse SD. Considering Antiviral Treatment to Preserve Hearing in Congenital CMV. *Pediatrics*. 2023;151 (2):e2022059895. doi:10.1542/peds.2022-059895

30. De Cuyper E, Acke F, Keymeulen A, Dhooge I. The Effect of (Val) ganciclovir on Hearing in Congenital Cytomegalovirus: A Systematic Review. *Laryngoscope*. 2022;132(11):2241-2250. doi:10.1002/lary.30027

31. Dorfman L, Amir J, Attias J, Bilavsky E. Treatment of congenital cytomegalovirus beyond the neonatal period: an observational study. *Eur J Pediatr*. 2020;179(5):807-812. doi:10.1007/s00431-019-03558-7

32. Kimberlin DW, Aban I, Peri K, et al. Oral Valganciclovir Initiated Beyond 1 Month of Age as Treatment of Sensorineural Hearing Loss Caused by Congenital Cytomegalovirus Infection: A Randomized Clinical Trial. *J Pediatr*. 2024;268:113934. doi:10.1016/j.jpeds.2024.113934

33. Congenital Cytomegalovirus: Efficacy of Antiviral Treatment (CONCERT 2). ClinicalTrials.gov ID NCT02005822. Updated June 3, 2021. Accessed September 25, 2024. https://clinicaltrials.gov/study/NCT02005822

34. Valganciclovir Therapy in Infants and Children With Congenital CMV Infection and

Hearing Loss. ClinicalTrials.gov ID NCT01649869. Updated June 2, 2021. Accessed September 25, 2024. https://clinicaltrials.gov/study/NCT01649869

35. Randomized Controlled Trial of Valganciclovir for Cytomegalovirus Infected Hearing Impaired Infants (ValEAR). ClinicalTrials.gov ID NCT03107871. Updated February 24, 2022. Accessed September 25, 2024. https://clinicaltrials.gov/study/NCT03107871

36. Asymptomatic Congenital CMV Treatment. ClinicalTrials.gov ID NCT03301415. Updated January 26, 2023. Accessed September 25, 2024. https://clinicaltrials.gov/study/NCT03301415

37. Chung PK, Schornagel FAJ, Soede W, et al. Valganciclovir in Infants with Hearing Loss and Clinically Inapparent Congenital Cytomegalovirus Infection: A Nonrandomized Controlled Trial. *J Pediatr*. 2024;268:113945. doi:10.1016/j.jpeds.2024.113945

38. Lanzieri TM, Caviness AC, Blum P, Demmler-Harrison G; Congenital Cytomegalovirus Longitudinal Study Group . Progressive, Long-Term Hearing Loss in Congenital CMV Disease After Ganciclovir Therapy. *J Pediatric Infect Dis Soc*. 2022;11(1):16-23. doi:10.1093/jpids/piab095

39. Leruez-Ville M, Ville Y. Secondary prevention of congenital cytomegalovirus infection. *Lancet*. 2020;396(10253):739-741. doi:10.1016/S0140-6736(20)31903-6

40. Kadambari S, Evans C, Lyall H. Congenital Infections: Priorities and Possibilities for Resource-limited Settings. *Pediatr Infect Dis J*. 2023;42 (2):e45-e47. doi:10.1097/INF.0000000000003710

41. Barber V, Calvert A, Vandrevala T, et al. Prevention of Acquisition of Cytomegalovirus Infection in Pregnancy Through Hygiene-based Behavioral Interventions: A Systematic Review and Gap Analysis. *Pediatr Infect Dis J*. 2020;39(10):949-954. doi:10.1097/INF.0000000000002763

42. Revello MG, Tibaldi C, Masuelli G, et al. Prevention of Primary Cytomegalovirus Infection in Pregnancy. *EBioMedicine*. 2015;2(9):1205-1210. Published 2015 Aug 6. doi:10.1016/j.ebiom.2015.08.003

43. Benou S, Dimitriou G, Papaevangelou V, Gkentzi D. Congenital cytomegalovirus infection: do pregnant women and healthcare providers know enough? A systematic review. *J Matern Fetal Neonatal Med*. 2022;35(25):6566-6575. doi:10.1080/14767058.2021.1918088

44. Vena F, D'Ambrosio V, Pajno C, et al. Pregnant women's knowledge and behaviour to prevent cytomegalovirus infection: an observational study. *J Perinat Med*. 2020;49(3):327-332. Published 2020 Oct 23. doi:10.1515/jpm-2020-0301

45. Castillo K, Hawkins-Villarreal A, Valdés-Bango M, et al. Congenital Cytomegalovirus Awareness and Knowledge among Health Professionals and Pregnant Women: An Action towards Prevention. *Fetal Diagn Ther*. 2022;49(5-6):265-272. doi:10.1159/000525528

46. Xie M, Tripathi T, Holmes NE, Hui L. Serological screening for cytomegalovirus during pregnancy: A systematic review of clinical practice guidelines and consensus statements. *Prenat Diagn*. 2023;43(7):959-967. doi:10.1002/pd.6397

47. Fisher SA, Miller ES, Yee LM, Grobman WA, Premkumar A. Universal first-trimester cytomegalovirus screening and valaciclovir prophylaxis in pregnant persons: a cost-effectiveness analysis. *Am J Obstet Gynecol MFM*. 2022;4(5):100676. doi:10.1016/j.ajogmf.2022.100676

48. Kagan KO, Enders M, Schampera MS, et al. Prevention of maternal-fetal transmission of cytomegalovirus after primary maternal infection in the first trimester by biweekly hyperimmunoglobulin administration. *Ultrasound Obstet Gynecol*. 2019; 53(3):383-389. doi:10.1002/uog.19164

49. Hughes BL, Clifton RG, Rouse DJ, et al. A Trial of Hyperimmune Globulin to Prevent Congenital Cytomegalovirus Infection. *N Engl J Med*. 2021; 385(5):436-444. doi:10.1056/NEJMoa1913569

50. Revello MG, Lazzarotto T, Guerra B, et al. A randomized trial of hyperimmune globulin to

prevent congenital cytomegalovirus. *N Engl J Med*. 2014;370(14):1316-1326. doi:10.1056/NEJMoa1310214

51. Chatzakis C, Shahar-Nissan K, Faure-Bardon V, et al. The effect of valacyclovir on secondary prevention of congenital cytomegalovirus infection, following primary maternal infection acquired periconceptionally or in the first trimester of pregnancy. An individual patient data meta-analysis. *Am J Obstet Gynecol*. 2024;230(2):109-117.e2. doi:10.1016/j.ajog.2023.07.022

52. Zammarchi L, Tomasoni LR, Liuzzi G, et al. Treatment with valacyclovir during pregnancy for prevention of congenital cytomegalovirus infection: a real-life multicenter Italian observational study. *Am J Obstet Gynecol MFM*. 2023;5(10):101101. doi:10.1016/j.ajogmf.2023.101101

53. Shahar-Nissan K, Pardo J, Peled O, et al. Valaciclovir to prevent vertical transmission of cytomegalovirus after maternal primary infection during pregnancy: a randomised, double-blind, placebo-controlled trial [published correction appears in Lancet. 2020 Oct 10;396(10257):1070. doi: 10.1016/S0140-6736(20)32075-4]. *Lancet*. 2020;396(10253):779-785. doi:10.1016/S0140-6736(20)31868-7

54. Faure-Bardon V, Fourgeaud J, Stirnemann J, Leruez-Ville M, Ville Y. Secondary prevention of congenital cytomegalovirus infection with valacyclovir following maternal primary infection in early pregnancy. *Ultrasound Obstet Gynecol*. 2021;58(4):576-581. doi:10.1002/uog.23685

55. D'Antonio F, Marinceu D, Prasad S, Khalil A. Effectiveness and safety of prenatal valacyclovir for congenital cytomegalovirus infection: systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. 2023;61(4):436-444. doi:10.1002/uog.26136

56. Prenatal Treatment of Congenital Cytomegalovirus Infection with Letermovir Versus Valaciclovir (CYMEVAL3-step2). ClinicalTrials.gov ID NCT05446571. Updated September 4, 2024. Accessed September 25, 2024. https://clinicaltrials.gov/study/NCT05446571

57. Institute of Medicine (US) Committee to Study Priorities for Vaccine Development, Stratton KR, Durch JS, Lawrence RS, eds. *Vaccines for the 21st Century: A Tool for Decisionmaking*. Washington (DC): National Academies Press (US); 2000.

58. CMV Vaccines and clinical trials. National CMV Foundation. Accessed September 25, 2024. https://www.nationalcmv.org/overview/vaccine-development

59. Boppana SB, van Boven M, Britt WJ, et al. Vaccine value profile for cytomegalovirus. *Vaccine*. 2023;41 Suppl 2:S53-S75. doi:10.1016/j.vaccine.2023.06.020

60. Plotkin SA, Boppana SB. Vaccination against the human cytomegalovirus. *Vaccine*. 2019;37(50):7437-7442. doi:10.1016/j.vaccine.2018.02.089

61. Pass RF, Zhang C, Evans A, et al. Vaccine prevention of maternal cytomegalovirus infection. *N Engl J Med*. 2009;360(12):1191-1199. doi:10.1056/NEJMoa0804749

62. Bernstein DI, Munoz FM, Callahan ST, et al. Safety and efficacy of a cytomegalovirus glycoprotein B (gB) vaccine in adolescent girls: A randomized clinical trial. *Vaccine*. 2016;34(3):313-319. doi:10.1016/j.vaccine.2015.11.056

63. Hu X, Karthigeyan KP, Herbek S, et al. Human Cytomegalovirus mRNA-1647 Vaccine Candidate Elicits Potent and Broad Neutralization and Higher Antibody-Dependent Cellular Cytotoxicity Responses Than the gB/MF59 Vaccine. *J Infect Dis*. 2024;230(2):455-466. doi:10.1093/infdis/jiad593

64. A Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1647 Cytomegalovirus (CMV) Vaccine in Healthy Participants 16 to 40 Years of Age. ClinicalTrials.gov ID NCT05085366. Updated April 24, 2024. Accessed September 25, 2024. https://clinicaltrials.gov/study/NCT05085366

65. Rouse DJ, Fette LM, Hughes BL, et al. Noninvasive Prediction of Congenital Cytomegalovirus Infection After Maternal Primary Infection. *Obstet Gynecol*. 2022;139(3):400-406.

doi:10.1097/AOG.0000000000004691

66. Chatzakis C, Sotiriadis A, Dinas K, Ville Y. Neonatal and long-term outcomes of infants with congenital cytomegalovirus infection and negative amniocentesis: systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. 2023;61(2):158-167. doi:10.1002/uog.26128

67. Dinsmoor MJ, Fette LM, Hughes BL, et al. Amniocentesis to diagnose congenital cytomegalovirus infection following maternal primary infection. *Am J Obstet Gynecol MFM*. 2022;4(4):100641. doi:10.1016/j.ajogmf.2022.100641

68. Bourgon N, Fitzgerald W, Aschard H, et al. Cytokine Profiling of Amniotic Fluid from Congenital Cytomegalovirus Infection. *Viruses*. 2022;14(10):2145. Published 2022 Sep 28. doi:10.3390/v14102145

69. Biomarkers of Cytomegalovirus Fetal Infection and Disease (BIO-CCMV). ClinicalTrials.gov ID NCT03090841. Updated November 7, 2022. Accessed September 25, 2024. https://clinicaltrials.gov/study/NCT03090841

70. Fernandes ND, Arya K, Syed HA, Ward R. Congenital Herpes Simplex. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; April 21, 2024.

71. Slutsker JS, Schillinger JA. Assessing the Burden of Infant Deaths Due to Herpes Simplex Virus, Human Immunodeficiency Virus, and Congenital Syphilis: United States, 1995 to 2017. *Sex Transm Dis*. 2021;48(8S):S4-S10. doi:10.1097/OLQ.0000000000001458

72. James SH, Kimberlin DW. Neonatal herpes simplex virus infection: epidemiology and treatment. *Clin Perinatol*. 2015;42(1):47-viii. doi:10.1016/j.clp.2014.10.005

73. Samies NL, James SH. Prevention and treatment of neonatal herpes simplex virus infection. *Antiviral Res*. 2020;176:104721. doi:10.1016/j.antiviral.2020.104721

74. Pinninti SG, Kimberlin DW. Neonatal herpes simplex virus infections. *Pediatr Clin North Am*. 2013;60(2):351-365. doi:10.1016/j.pcl.2012.12.005

75. Mahant S, Hall M, Schondelmeyer AC, et al. Neonatal Herpes Simplex Virus Infection Among Medicaid-Enrolled Children: 2009-2015. *Pediatrics*. 2019;143(4):e20183233. doi:10.1542/peds.2018-3233

76. Herpes Simplex Virus. World Health Organization (WHO). Accessed September 25, 2024. https://www.who.int/home/search-results?indexCatalogue=genericsearchindex1&searchQuery=neonatal%20herpes&wordsMode=AnyWord

77. 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

78. 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

79. Thompson C, Whitley R. Neonatal herpes simplex virus infections: where are we now?. *Adv Exp Med Biol*. 2011;697:221-230. doi:10.1007/978-1-4419-7185-2_15

80. 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 Pediatric Infect Dis Soc*. 2022;11(3):94-101. doi:10.1093/jpids/piab105

81. Kimberlin DW, Lin CY, Jacobs RF, et al. Natural history of neonatal herpes simplex virus infections in the acyclovir era. *Pediatrics*. 2001;108(2):223-229. doi:10.1542/peds.108.2.223

82. Kimberlin DW, Lin CY, Jacobs RF, et al. Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infections. *Pediatrics*. 2001;108(2):230-238. doi:10.1542/peds.108.2.230

83. Kimberlin DW, Whitley RJ, Wan W, et al. Oral acyclovir suppression and neurodevelopment after neonatal herpes. *N Engl J Med*. 2011;365(14):1284-1292. doi:10.1056/NEJMoa1003509

84. Harris JB, Holmes AP. Neonatal Herpes Simplex Viral Infections and Acyclovir: An Update.

J Pediatr Pharmacol Ther. 2017;22(2):88-93. doi:10.5863/1551-6776-22.2.88

85. Frobert E, Burrel S, Ducastelle-Lepretre S, et al. Resistance of herpes simplex viruses to acyclovir: an update from a ten-year survey in France. *Antiviral Res*. 2014;111:36-41. doi:10.1016/j.antiviral.2014.08.013

86. James SH, Prichard MN. Current and future therapies for herpes simplex virus infections: mechanism of action and drug resistance. *Curr Opin Virol*. 2014;8:54-61. doi:10.1016/j.coviro.2014.06.003

87. James SH, Larson KB, Acosta EP, Prichard MN. Helicase-primase as a target of new therapies for herpes simplex virus infections. *Clin Pharmacol Ther*. 2015;97(1):66-78. doi:10.1002/cpt.3

88. Uhlig N, Donner AK, Gege C, Lange F, Kleymann G, Grunwald T. Helicase primase inhibitors (HPIs) are efficacious for therapy of human herpes simplex virus (HSV) disease in an infection mouse model. *Antiviral Res*. 2021;195: 105190. doi:10.1016/j.antiviral.2021.105190

89. Valacyclovir in Neonatal Herpes Simplex Virus Disease. ClinicalTrials.gov ID NCT04448392. Updated September 19, 2024. Accessed September 25, 2024. https://clinicaltrials.gov/study/NCT04448392

90. James SH, Sheffield JS, Kimberlin DW. Mother-to-Child Transmission of Herpes Simplex Virus. *J Pediatric Infect Dis Soc*. 2014;3 Suppl 1(Suppl 1):S19-S23. doi:10.1093/jpids/piu050

91. Management of Genital Herpes in Pregnancy: ACOG Practice Bulletinacog Practice Bulletin, Number 220. *Obstet Gynecol*. 2020;135(5):e193-e202. doi:10.1097/AOG.0000000000003840

92. Gardella C, Huang ML, Wald A, et al. Rapid polymerase chain reaction assay to detect herpes simplex virus in the genital tract of women in labor. *Obstet Gynecol*. 2010;115(6):1209-1216. doi:10.1097/AOG.0b013e3181e01415

93. Kimberlin DW, Baley J; Committee on infectious diseases; Committee on fetus and newborn. Guidance on management of asymptomatic neonates born to women with active genital herpes lesions. *Pediatrics*. 2013;131(2):e635-e646. doi:10.1542/peds.2012-3216

94. Backes IM, Leib DA, Ackerman ME. Monoclonal antibody therapy of herpes simplex virus: An opportunity to decrease congenital and perinatal infections. *Front Immunol*. 2022;13:959 603. Published 2022 Aug 9. doi:10.3389/fimmu.2022.959603

96. 2023-2028 NIH Strategic plan for Herpes Simplex Virus Research. Accessed September 25, 2024. https://www.niaid.nih.gov/sites/default/files/nih-herpes-simplex-strategic-plan-2023.pdf

