HSV2VA

Comparative effectiveness of Valacyclovir and Acyclovir for preventing recurrent HSV-2 meningitis: A Randomized Controlled Trial

Sponsored by:

Department of Epidemiology, Department of Biostatistics, Department of Statistics, School of Nursing, University of Washington

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[Final] Version [1.0]
[5/29/2024]

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Sponsored by:

Division of Allergy and Infectious Diseases [DAIDS]
Department of Epidemiology, Department of Biostatistics, Department of Statistics, School of Nursing, University of Washington

[Use the following text for non-IND studies:]

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol. I agree to maintain all study documentation for a minimum of three years after submission of the site's final Financial Status Report to the Division of Infectious Disease (DAID), unless otherwise specified by the DAID Coordinating and Operations Center. DAID policies will govern the publication of the results of this study. Any presentation, abstract, or manuscript will be made available by the investigators to the DAID for review prior to submission.

I have read and understand the information in this protocol and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

_____
Name of Site Investigator of Record

_____ _____
Signature of Site Investigator of Record Date

HSV2VA
Comparative effectiveness of Valacyclovir and Acyclovir for preventing recurrent HSV-2 meningitis: A Randomized Controlled Trial

SCHEMA

Purpose:
To investigate and compare the effectiveness of active antiviral suppression using Acyclovir or Valacyclovir in managing HSV-2 meningitis over one year
Design:
A double-blind, randomized controlled trial (RCT).
Study Population:
Participants selected for this study will be adults aged 18-65 who have had at least one episode of HSV-2 meningitis in the past. Specifically, consecutive patients over 18 years old presenting with symptoms of viral meningitis and cerebrospinal fluid (CSF) pleocytosis levels of greater than 5 × 10^6 cells/L with an HSV-2 infection etiology, confirmed by the detection of HSV-2 DNA in the CSF by PCR and presence of mollaret cells in CSF seen on cytology, will be included.
Study Size:
A sample size of 124 infants, 62 in each arm, is sufficient to detect a clinically significant difference of 20% between groups in curing HSV-2 meningitis using a two-tailed z-test of proportions between two groups with 90% power and a 5% level of significance. This 20% difference represents a 5% recurrence rate using Valacyclovir and 25% recurrence rate using Acyclovir.
Treatment Regimen:
Participants will be randomly assigned to one of two treatment groups:
1. Valacyclovir Group: Participants will receive oral Valacyclovir at a dosage of 1000 mg once daily for up to 12 months.
2. Acyclovir Group: Participants will receive oral Acyclovir at a dosage of 400 mg twice daily for up to 12 months.

Study Duration:
The study duration spans one year from the date participants join the study, with recruitment occurring from January 2025 to December 2026 and continued follow-up until December 2027.
Primary Objectives:
- To compare the effects of active antiviral suppression using Acyclovir or Valacyclovir for one year.
- Outcome measures are (1) the difference in the proportion of patients with at least one verified episode of recurrent HSV-2 meningitis during the 12-month period among patients taking Valacyclovir versus Acyclovir; (2) treatment tolerability during one year.

Secondary Objectives:
- To compare the neurological morbidity of HSV-2 meningitis during one year of active antiviral suppression using Acyclovir or Valacyclovir.
- The outcome measure is the difference in the length of time until symptoms of a recurrence of HSV-2 meningitis among patients taking Valacyclovir versus Acyclovir.

Study Sites:
- General medicine clinics at U.W. Medicine Seattle, WA
- Infectious disease clinics at U.W. Medicine Seattle, WA

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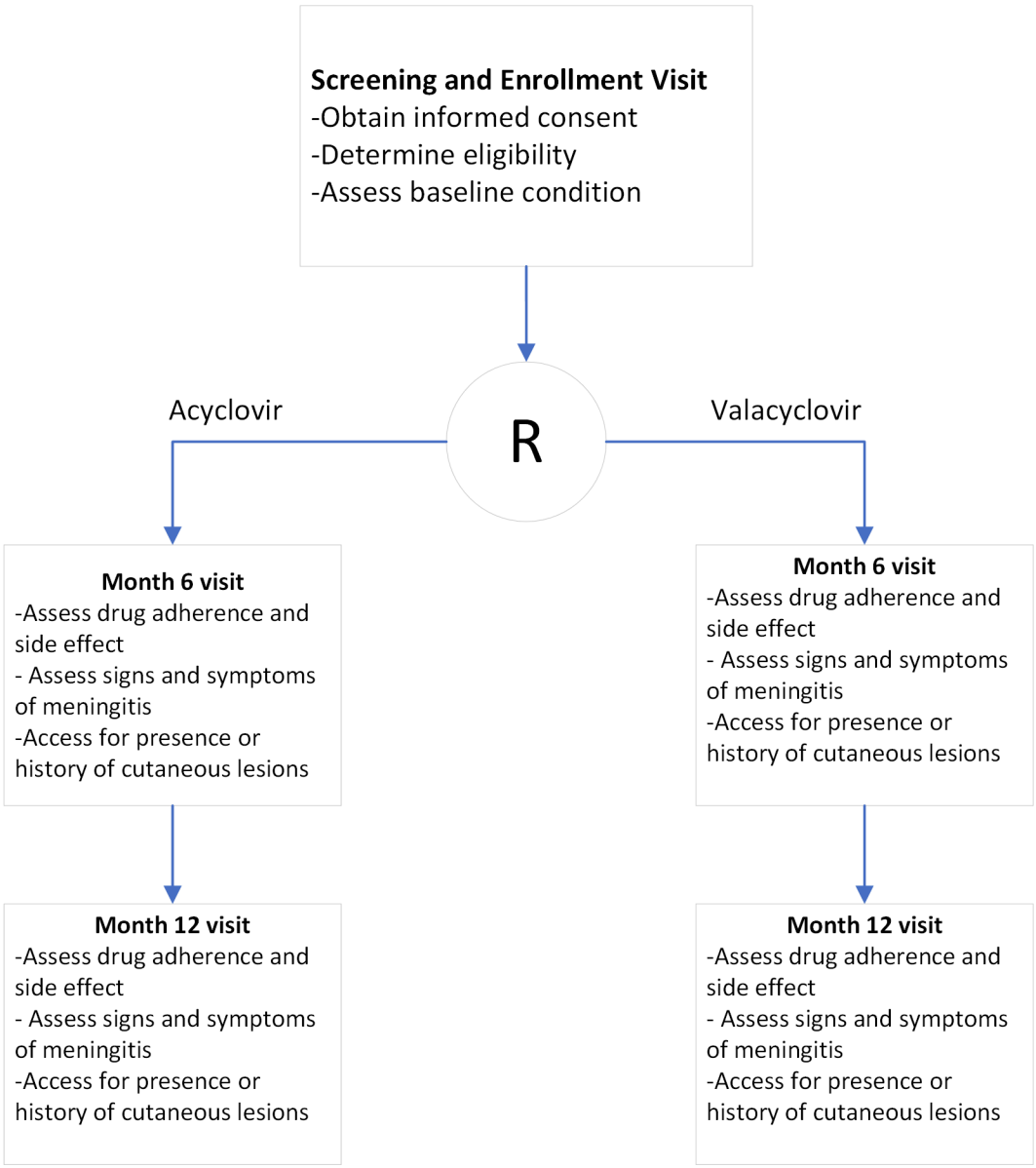
Figure 1: OVERVIEW OF STUDY DESIGN AND RANDOMIZATION SCHEME



1.0 INTRODUCTION

1.1 Background and Prior Research

Herpes genitals can result from either herpes simplex virus type 1 or type 2, which can appear as an initial or recurring infection (1). Most commonly, the virus reproduces in the epithelial cells and then enters a dormant state within sensory neurons, resurfacing intermittently to cause localized recurring lesions (2). It remains prevalent as one of the most widespread sexually transmitted infections, yet its true impact tends to be underestimated due to the unclear manifestation of its symptoms (3). Herpes Simplex Virus type 2 (HSV-2) continues to be a common infection, impacting around 22% of adults aged 12 and above, representing 45 million adults in the United States alone (4). While HSV-1 typically affects the area around the mouth and can lead to genital sores, HSV-2 is usually the primary concern when patients exhibit lesions in the genital region. However, in many cases, infection outbreaks manifest with nonspecific symptoms like genital itching, irritation, and abrasions, potentially leading to delays in diagnosis and treatment (4). Although there's no cure for HSV-2, early recognition of symptoms and swift initiation of medication can help suppress viral replication at an early stage. If left untreated, HSV-2 can result in meningitis, although the virus can impact any part of the nervous system (5).

Aseptic meningitis is a clinical disease characterized by inflammation of the dura, the membranous covering of the spinal cord and cerebrospinal fluid (CSF), and negative bacterial cultures (6). Aseptic meningitis occurs in approximately 36% of women and 13% of men, sometimes necessitating hospitalization (7). In the prodromal phase of genital herpes and during outbreaks, individuals may experience systemic symptoms like headaches, neck stiffness, photosensitivity, and mild fever (7). Prompt investigation typically involves performing a lumbar puncture to analyze CSF, which often shows an increase in lymphocytes (7). Although CSF can be cultured for the virus, diagnosis is established through clinical history and PCR confirmation of viral infection (6). Disease course varies wildly in reported cases, with some patients experiencing only three episodes and others reporting over 20 episodes. HSV-2 meningitis carries the risk of various neurological complications in the future, including recurrent meningitis, myelitis,

and radiculitis (8). In a study involving 40 patients, one-third experienced recurring neurological symptoms within the initial year following HSV-2 meningitis (9). Recurrent lymphocytic meningitis, predominantly attributed to HSV-2, is estimated to arise in approximately 20% to 30% of cases subsequent to primary HSV meningitis (6).

Recurrent HSV-2 meningitis poses a significant clinical challenge, marked by frequent episodes that diminish quality of life and strain healthcare resources. While Acyclovir serves as the primary prophylactic agent, concerns over resistance and suboptimal efficacy have spurred interest in alternative treatments. Valacyclovir, a prodrug of Acyclovir with potentially improved pharmacokinetics, remains underexplored in the context of preventing recurrent HSV-2 meningitis. In a previous study, a randomized controlled trial (RCT) was conducted to determine the impact of antiviral suppression on the recurrence of meningitis and to delineate the full spectrum of neurological complications in both the Valacyclovir and placebo groups. The results showed that suppressive treatment with 0.5 g of Valacyclovir twice daily was not effective in preventing recurrent meningitis and cannot be recommended for this purpose after HSV meningitis in general (8). However, currently, there is no study comparing the difference in effectiveness of Acyclovir and Valacyclovir in preventing recurrent HSV-2 meningitis. Additionally, a comparative investigation between Valacyclovir and Acyclovir is warranted to elucidate their respective roles in managing this condition and optimize therapeutic strategies. This could provide valuable insights into the most effective approach for preventing recurrent HSV-2 meningitis.

1.2 Rationale

The rationale for this proposed trial stems from recognizing a significant gap in treatment options regarding recurrent HSV-2 meningitis. The study aims to provide comprehensive insights into the most effective and cost-efficient prophylactic approach for managing this condition by directly comparing Valacyclovir and Acyclovir. Recurrent HSV-2 meningitis presents a clinical challenge, necessitating effective long-term management strategies. Moreover, understanding the comparative efficacy of these antiviral medications is vital for optimizing patient outcomes and healthcare resource allocation.

Beyond addressing immediate clinical concerns, the study also aims to shed light on broader issues within the realm of antiviral therapy. This includes exploring factors such as antiviral resistance patterns, patient adherence to treatment regimens, and the potential applicability of findings to other HSV-2 infections. Ultimately, this research's outcomes can extend beyond individual patient care, impacting public health by informing evidence-based practices and guiding prophylactic strategies for HSV-2 meningitis. Through rigorous investigation and analysis, this trial seeks to contribute significantly to advancing medical knowledge and improving patient outcomes in this challenging clinical domain.

2.0 STUDY OBJECTIVES AND DESIGN

2.1 Primary Objectives

The primary objective of this study is to compare the effects of active antiviral suppression using Acyclovir or Valacyclovir for one year. Outcome measures are (1) the difference in the proportion of patients with at least one verified episode of recurrent HSV-2 meningitis during the 12-month period among patients taking Valacyclovir versus Acyclovir; (2) treatment tolerability during one year.

2.2 Secondary Objectives

The secondary objective of this study is to compare the neurological morbidity of HSV-2 meningitis during one year of active antiviral suppression using Valacyclovir or Acyclovir. The outcome measure is the difference in the length of time until symptoms of a recurrence of HSV-2 meningitis among patients taking Valacyclovir versus Acyclovir.

2.3 Study Design

A double-blind RCT would be ideal for minimizing bias. The study design involves a prospective, randomized, double-blind, multicenter trial conducted at the General Internal Medicine Clinic and Infectious Disease Clinic at U.W. Medicine, Seattle, Washington,

from January 2025 to December 2027. The population includes individuals with a documented history of at least one episode of HSV-2 meningitis in the past. This trial aims to assess the comparative neurological morbidity of recurrent meningitis resulting from active antiviral suppression using either Acyclovir or Valacyclovir over one year. They will be randomly assigned to one of two treatment groups: the Valacyclovir or Acyclovir group. Randomization will be achieved through a computer-generated randomization scheme to ensure an unbiased allocation process. Blinding procedures will be implemented to maintain the trial's double-blind nature, with participants and researchers unaware of treatment assignments.

Participants will undergo scheduled clinical visits at six and 12 months, during which comprehensive data will be collected. This data includes demographic information, medical history, and details of previous HSV-2 infections to ensure balanced participant groups. The study's primary endpoint includes the difference in the proportion of patients with at least one verified episode of recurrent HSV-2 meningitis during the 12-month period among patients taking Valacyclovir versus Acyclovir. The secondary endpoint is the difference in the length of time until symptoms of a recurrence of HSV-2 meningitis among patients taking Valacyclovir versus Acyclovir.

2.4 Study Sites:

The General Internal Medicine Clinic at U.W. Medicine, Seattle, Washington, provides comprehensive primary care for adult patients, including preventive medicine services, assessment and treatment of acute medical problems, and monitoring and treatment of chronic diseases. It is a dynamic teaching clinic that provides patient-centered care grounded in the best available medical evidence.

Infectious Disease Clinic at U.W. Medicine, Seattle, Washington, provides comprehensive care for patients with bacterial, viral, and parasitic and fungal infections. Commonly treated infections include skin and soft tissue infections, including MRSA; bloodstream infections and endocarditis; bone and joint infections; lung and sinus infections; recurrent or complicated urinary tract infections (UTI); extrapulmonary tuberculosis (T.B.); infections following overseas travel; infections due to primary

immunodeficiencies; zoonotic (animal-associated) infections; infections in patients with certain forms of cancer; and infections in solid organ transplant patients, both pre- and post-transplant.

Both clinics have been used to recruit patients for many clinical trials in the past successfully and have been carefully selected for the HSV2VA clinical trial based on past performance.

3.0 STUDY POPULATION

3.1 Inclusion Criteria

Adults who meet any of the following criteria will be included in this study:

- Aged 18-65
- Have at least one episode of HSV-2 meningitis in the past
- Presenting with symptoms of viral meningitis and cerebrospinal fluid (CSF) pleocytosis levels of greater than 5 × 10^6 cells/L with an HSV-2 infection etiology, confirmed by the detection of HSV-2 DNA in the CSF by PCR, will be included.
- Be able to communicate in English

3.2 Exclusion Criteria

Adults who meet any of the following criteria will be excluded from this study:

- Prior severe drug reaction to Acyclovir or Valacyclovir.
- Prior history of gastrointestinal malabsorption.
- Pregnant women.
- Inability to take oral medication.
- Immunosuppressed individuals or those with HIV infection.
- Intolerance to Acyclovir or Valacyclovir.
- Patients receiving probenecid treatment.
- Individuals undergoing systemic antiviral therapy with antiherpetic effect or immunomodulatory therapy.

- Participants are currently enrolled in ongoing investigational drug treatment.
- Those with medical conditions such as malabsorption.
- Not be able to communicate in English

3.3 Recruitment Process

The recruitment process will involve identifying potential participants from two sites, including the General Internal Medicine Clinic and Infectious Disease Clinic at U.W. Medicine in Seattle, WA, during clinic hours from Monday to Friday. Patient appointments for each day will be reviewed to identify eligible individuals. We will use three techniques in the recruitment process. Firstly, during patient clinic visits, research team members will approach eligible patients to provide information about the study and gauge their interest in participating. Secondly, we will review patients' medical history in the clinic and call the potential participants. Lastly, we will promote the research using flyers, including the QR code so that patients can upload the required clinical information. If the patient expresses interest, informed consent will be obtained, and baseline assessments will be conducted. The research team will then coordinate with the attending physician to devise an appropriate plan for the patient's involvement in the study. Additionally, flyers detailing the study will be displayed in the clinic to attract potential participants who may express interest and contact the research team independently.

3.4 Participant Retention

Efforts to retain participants throughout the study aim to minimize bias associated with loss-to-follow-up. These efforts include comprehensively explaining the study visit schedule and procedural requirements during the informed consent process and re-emphasizing them at each visit. Detailed locator information will be collected and regularly updated at the screening visit, with mapping techniques utilized to establish participant residences and other locator venues. Timely visit reminder mechanisms will be employed, with immediate and multifaceted follow-up on missed visits. Trained outreach workers or "tracers" will be mobilized to contact participants at their homes or other community locations as needed. Regular communication with the study community

will increase awareness about the importance of research and the significance of completing study visits. These measures collectively aim to enhance participant retention and ensure the integrity of study outcomes.

3.5 Participant Withdrawal

Participants may voluntarily withdraw from the study at any time for any reason. Participants' study records will record reasons for withdrawal, and every effort will be made to complete a final evaluation of participants who terminate the study prematurely.

4.0 STUDY TREATMENT/PRODUCT/INTERVENTION

4.1 Treatment/Product/Intervention Formulation/Content

The study will compare two antiviral agents for the prevention of recurrent HSV-2 meningitis: Valacyclovir and Acyclovir. Valacyclovir will be administered orally at a dosage of 1000 mg once daily, while Acyclovir will be administered orally at a dosage of 400 mg twice daily.

4.2 Treatment/Product/Intervention Regimen(s)

Participants will be randomly assigned to one of two treatment groups:

1. Valacyclovir Group: Participants will receive oral Valacyclovir at a dosage of 1000 mg once daily for up to 12 months.
2. Acyclovir Group: Participants will receive oral Acyclovir at a dosage of 400 mg twice daily for up to 12 months.

4.3 Treatment/Product/Intervention Administration

Both Valacyclovir and Acyclovir will be self-administered by participants orally. Participants will be instructed on adequately administering the medications and advised to adhere to the prescribed regimen.

4.4 Treatment/Product/Intervention Supply and Accountability

The study drugs will be supplied to participants by the site pharmacist. Complete records of all study drugs received and dispensed will be maintained. Unused supplies will be returned to the Clinical Research Products Management Center at the conclusion of the study.

4.5 Adherence Assessment

Adherence to the study treatment will be assessed through participant self-reporting and pill counts at study visits. Adherence will be defined as the percentage of prescribed doses taken. If needed, participants will be provided with replacement medications according to predefined treatment criteria.

4.6 Toxicity Management

In the event of observed side effects or adverse events related to the study medications, treatment regimens may be modified or discontinued based on predefined criteria outlined in the study protocol. Participants experiencing significant toxicity may be withdrawn from the study.

4.7 Clinical Management of Pregnancy

Pregnancy testing will be conducted at regular intervals, and participants who become pregnant during the study will be withdrawn from the study treatment.

4.8 HIV Seroconversion

High-risk participants will be followed up regularly for HIV seroconversion every six months. In the event of confirmed HIV seroconversion, appropriate counseling and medical management will be provided. Continued use of study treatment will be discussed on a case-by-case basis.

4.9 Concomitant Medications

Enrolled study participants do not permit the use of the following concomitant medications: Probenecid, Zidovudine, and high-dose NSAIDs. All concomitant medications taken or received by participants within the two weeks prior to study enrollment will be reported on applicable study case report forms. In addition to prescribed and over-the-counter medications, vitamins, herbal remedies, and other traditional preparations will be recorded. Alcohol and recreational or street drug use will be recorded in clinical progress notes if needed for interpretation/documentation of observed participant health status. Medications used for the treatment of A.E.s that occur during study participation will also be recorded on applicable study case report forms.

5.0 STUDY PROCEDURES

An overview of the study visit and procedures schedule is presented in Figure I. Additional information on visit-specific study procedures is presented below. The study-specific procedures manual will provide detailed instructions to guide and standardize all study procedures across sites.

The study procedures encompass several key stages. Firstly, during the screening visit, participants will provide written informed consent before undergoing a comprehensive medical history review, physical examination, and laboratory tests to confirm eligibility. Following the screening, eligible participants proceed to the enrollment visit, where randomization to either the Valacyclovir or Acyclovir treatment group occurs, alongside detailed instructions on the treatment regimen.

Throughout the study period, participants attend follow-up visits at regular intervals to assess treatment adherence, monitor adverse events, and evaluate study outcomes. These visits include physical examinations, laboratory tests, and assessments of recurrent HSV-2 meningitis episodes. In case of participant withdrawal before the scheduled end date, a final study visit will be arranged to collect the remaining study medications and assess study outcomes and adverse events.

The study procedures aim to ensure a standardized and comprehensive assessment of participants' responses to treatment and overall study outcomes. By adhering to these procedures, we can effectively evaluate the comparative effectiveness of Valacyclovir and Acyclovir in preventing recurrent HSV-2 meningitis, contributing valuable insights to clinical practice and patient care.

6.0 SAFETY MONITORING AND ADVERSE EVENT REPORTING

6.1 Safety Monitoring

Effective safety monitoring is important for ensuring participant's safety and maintaining the integrity of the study. To achieve this, the cooperation between different team members (chairs, principal investigators, SDMC Biostatistician, NIAID Medical/ Program Officer, CORE Protocol Coordinator, and other study team members) is crucial.

Before the study starts, the team should establish a schedule of regular conference calls to discuss participants' safety and any issues observed during an interval of the study. According to this feedback, the study design will be modified. In order to ensure data safety and monitoring board oversight, the DSMB will review the study at regular intervals. The reviews should be taken seriously to assess safety data and overall study integrity.

During the study, planned interim analyses will be conducted to evaluate the safety and efficacy of the data. These analyses are detailed in 7.5 of the protocol. The study would be paused or stopped according to the predefined criteria. The stopping rules are shown as follows:

- If two or more participants experience a Grade 3 or higher adverse event, as defined by the DAIDS standard toxicity table, that is judged by possibly, probably, or definitely related to the study medications, then the accrual should be suspended.

- The protocol team should review all pertinent data and decide whether to resume or terminate the study based on a thorough risk-benefit analysis.

In addition to the DSMB, a Protocol Safety Review Team should be established, especially given the study's phase I/II nature, which involves significant safety considerations.

6.2 Adverse Event Definitions and Reporting Requirements

6.2.1 Adverse Event

An adverse event (A.E.) is defined as any untoward medical occurrence in which a clinical research participant administered an investigational product and which does not necessarily have a causal relationship with the investigational product. As such, an A.E. can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with using an investigational product, whether or not considered related to the product.

Study participants will be provided a 24-hour telephone number and instructed to contact the studied clinician to report any A.E.s they may experience, except for life-threatening events, for which they will be instructed to seek immediate emergency care. Where feasible and medically appropriate, participants will be encouraged to seek evaluation where the study clinician is based and to request that the clinician be paged or otherwise contacted upon their arrival. With the participant's appropriate permission, records from all non-study medical providers related to A.E.s will be obtained, and required data elements will be recorded on study case report forms. All participants reporting an A.E. will be followed clinically until the A.E. resolves (returns to baseline) or stabilizes.

Study site staff will document on study case report forms all A.E.s reported by or observed in enrolled study participants regardless of severity and presumed relationship to the study product. All A.E.s will be graded using the DAIDS Table for the Grading Severity of Adult and Pediatric Adverse Experiences (also referred to as the "Toxicity Table"), which is available on the RSC website: http://rsc.tech-res.com/safetyandpharmacovigilance/. The Investigator or designee will assess the relationship of all A.E.s to the study product based on the Investigator's Brochure, Package Insert, DAIDS Drug Risk List, and their clinical judgment. These documents are all available at http://rsc.tech-res.com/

6.2.2 Serious Adverse Event

Serious adverse event (SAE) will be defined per U.S. Code of Federal Regulations (CFR) 312.32 and International Conference on Harmonization (ICH), "Good Clinical Practice: Consolidated Guidance" (E6) and "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" (E2A), as A.E. occurring at any dose that:

- Results in death
- Is life-threatening
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/congenital disability
- Requires inpatient hospitalization or prolongation of existing hospitalization

This includes important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or require intervention to prevent one of the above outcomes.

Per ICH SAE definition, hospitalization itself is not an adverse event but is an outcome of the event. The following types of hospitalization do not require expedited reporting to DAIDS:

- Any admission unrelated to an A.E. (e.g., for labor/delivery, cosmetic surgery, administrative, or social admission for temporary placement for lack of a place to sleep)
- Protocol-specified admission (e.g., for procedure required by protocol)
- Admission for diagnosis or therapy of a condition that existed before receipt of study agent(s) and has not increased in severity or frequency as judged by the clinical Investigator

6.2.3 Expedited Adverse Event Reporting

6.2.3.1 Adverse Event Reporting to DAIDS

According to the DAIDS EAE Manual, Version 2.0:

- Expedited Adverse Event(EAE): An EAE is defined as any adverse event that is both unexpected and related to the investigational product and meets any of the following criteria: results in death, is life-threatening, requires or prolonged hospitalization, results in a significant disability, involves a congenital anomaly, or requires intervention to prevent one of the aforementioned outcomes.
- Serious Adverse Event(SAE): This includes any medical-scientifically significant event, even if the event does not meet the immediate criteria for an EAE. However, the event may jeopardize the participant and require medical or surgical intervention.

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must expedite A.E. reporting to DAIDS. In case of system outages or technical difficulties, expedited A.E.s may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov or from within the DAERS application.

Sites where DAERS has not been implemented, will submit expedited A.E.s by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website: http://rsc.tech-res.com/safetyandpharmacovigilance/. For questions about EAE reporting, please contact the RSC (DAIDSRSCSafetyOffice@tech-res.com).

6.2.3.2 Reporting Requirements for this Study

This study will adhere to the Serious Adverse Event (SAE) or Suspected Unexpected Serious Adverse Reaction (SUSAR) EAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual. This category requires expedited reporting for all A.E.s that are unexpected, related to the investigational product, and meet any of the criteria for serious adverse events as previously outlined.

The study agents for which expedited reporting is required are:

- Valacyclovir
- Acyclovir
- Placebo for Valacyclovir (if applicable)
- Placebo for Acyclovir (if applicable)

For clarity and ease of reporting, the following abbreviations will be used:

- Valacyclovir (VCV)
- Acyclovir (ACV)

It is critical that all A.E.s associated with these agents, whether considered related to the study drug or not, are subject to the expedited reporting requirements.

In addition to the EAE Reporting Category, the following additional adverse events must be reported in an expedited manner:

- All instances of hepatic failure
- All severe allergic reactions, including anaphylaxis
- Any adverse events leading to prolonged hospitalization
- All occurrences of thrombotic events (e.g., deep vein thrombosis, pulmonary embolism)
- All cases of severe neutropenia (absolute neutrophil count < 500 cells/mm^3)
- Reporting Procedures

Initial Report: All expedited A.E.s must be initially reported to DAIDS within 24 hours of the study staff becoming aware of the event.

Follow-Up Report: Comprehensive follow-up reports must be submitted within 15 days of the initial report. These reports should include additional details obtained during the ongoing investigation of the event.

Documentation: Accurate and complete documentation of all A.E.s is mandatory. This includes detailed descriptions of the event, treatments administered, outcomes, and an assessment of the relationship to the study drug.

Training: All study personnel involved in patient management will receive training on the recognition and reporting of A.E.s, using resources provided by DAIDS to ensure consistency and compliance with reporting standards..].

6.2.3.3 Grading Severity of Events

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event **NOT** identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

Table 1. Estimating Severity Grade for Parameters Not Identified in the Grading Table. The functional table below should be used to grade the severity of an A.E. that is not specifically identified in the grading table. In addition, all deaths related to an A.E. are to be classified as grade 5.

6.2.3.4 Expedited A.E. Reporting Period

After the protocol-defined A.E. reporting period, unless otherwise noted, only SUSARs, as defined in Version 2.0 of the EAE Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

The expedited A.E. reporting period for this study is defined as the duration from the participant's first dose of the study medication until 30 days after the completion of their treatment, as per the DAIDS EAE Manual guidelines. This period reflects the typical window during which most treatment-related adverse events are likely to occur and can be causally associated with the study agents.

In addition to the standard reporting period specified in the EAE Manual, this study mandates further vigilance:

Extended Surveillance for Specific A.E.s: For severe adverse events such as hepatic failure, severe allergic reactions, and other potentially life-threatening conditions, an extended reporting period up to 90 days post-treatment will be enforced. This additional surveillance period is crucial given the potential for delayed onset of severe reactions associated with systemic treatments.

SUSAR Reporting: Only Suspected Unexpected Serious Adverse Reactions (SUSARs), as defined in Version 2.0 of the DAIDS EAE Manual will continue to be reported to DAIDS. This reporting will occur if the study staff becomes aware of such events passively, from publicly available information or other non-active surveillance methods.

Method of Reporting: Such reports should be compiled and submitted quarterly to DAID unless a specific SUSAR necessitates immediate action based on its severity and potential implications for participant safety across the study.

7.0 STATISTICAL CONSIDERATIONS

7.1 Review of Study Design

This study is a double-blind, randomized controlled trial to compare the efficacy of Valacyclovir versus Acyclovir in preventing recurrent HSV-2 meningitis. Participants with a history of at least one episode of HSV-2 meningitis are divided into two groups. One group is treated with Valacyclovir orally at a dosage of 1000 mg once daily, with a maximum duration of 12 months, while the other group is treated with Acyclovir orally at 400 mg twice a day, with a maximum duration of 12 months.

7.2 Endpoints

7.2.1 Primary Endpoints

Consistent with the primary study objective to find the most effective approach to managing HSV-2 meningitis, the following endpoint(s) will be assessed:

- The difference in the proportion of patients with at least one verified episode of recurrent HSV-2 meningitis during the 12-month period among patients taking Valacyclovir versus Acyclovir

Consistent with the primary study objective to analyze the practicality of each treatment, the following endpoint(s) will be assessed:

- Assessment of adverse effects associated with each medication
- How each treatment affects the well-being of participants.
- Long-term treatment effect

7.2.2 Secondary Endpoints

Consistent with the secondary study objective to assess the safety profile, the following endpoint(s) will be assessed:

- The difference in the length of time until symptoms of recurrent HSV-2 meningitis during the 12-month period among patients taking Valacyclovir versus Acyclovir

Consistent with the secondary study objective to analyze the impact on quality of life, the following endpoint(s) will be assessed:

- Patient adherence to prophylactic regimen
- Cost-effectiveness analysis

7.3 Accrual, Follow-up, and Sample Size

The expected recurrence rate in the Acyclovir group is 25%. And the expected recurrence rate in the Valacyclovir group is 5%. The sample size for this study was predicated on the detection of a difference of 20% in recurrences of HSV-2 meningitis between the Valacyclovir and Acyclovir groups. Based on a calculated power of 90% and a significance level of 5%, we estimated that a sample size of 62 patients per group would be needed.

A sample size of 124 infants, 62 in each arm, is sufficient to detect a clinically significant difference of 20% between groups in curing HSV-2 meningitis using a two-tailed z-test of proportions between two groups with 90% power and a 5% level of significance. This 20% difference represents a 5% recurrence rate using Valacyclovir and 25% recurrence rate using Acyclovir.

$$P_1 = 0.25,\ P_2 = 0.05, Z_{\frac{\alpha}{2}} = 1.96,\ Z_{\beta} = 1.28$$

$$N = \frac{(Z_{\frac{\alpha}{2}}+Z_{\beta})^2\ \ [P_1(1-P_1)+P_2(1-P_2)]}{(P_1-P_2)^2} \approx 62$$

Site-Specific Accrual Targets: Assuming the study will be conducted across two sites: General Internal Medicine Clinic (Site A) and Infectious Disease Clinic (Site B) at U.W. Medicine

1. Site A: 62 participants (31 per group)
2. Site B: 62 participants (31 per group)

For the accrual plan of this study, each site aims to recruit approximately 10 participants per month, reaching the total recruitment target within 12 months. We will use three techniques to recruit participants: approaching potential participants in person at clinics, calling, and promoting flyers at clinics. The total number of participants will not exceed 150 to control study costs and manage resources efficiently. Each site will have a cap of approximately 70 participants to avoid overburdening any single site. Monthly reviews of recruitment progress will be conducted. If any site is significantly underperforming or exceeding expectations, site-specific targets may be adjusted accordingly to ensure balanced recruitment across sites.

7.4 Random Assignment / Study Arm Assignment

The randomization of participants into the Valacyclovir and Acyclovir groups will be conducted using a randomized block design. This approach ensures a balanced allocation of participants across the two treatment arms while accounting for potential confounding factors that could influence the trial outcomes. Participants will be stratified based on key

demographic and clinical characteristics that might affect the treatment outcome. As for block randomization, within each stratum, participants will be randomly assigned to one of the two treatment groups using blocks of a fixed size, maintaining the balance in sample size between the groups.

Drug Allocation Based on Stratified Block Design:

Site A:

Age Stratification:	18-30 years: 21 participants
	31-50 years: 21 participants
	51-65 years: 20 participants
Gender Block:	Equal distribution of males and females

Site B:

Age Stratification:	18-30 years: 21 participants
	31-50 years: 21 participants
	51-65 years: 20 participants
Gender Block:	Equal distribution of males and females

Within each age and gender group, participants are randomly assigned to either Valacyclovir or Acyclovir.

Example Allocation (Site A):

- 18-30 years males: Approximately 10 participants receive Valacyclovir, approximately 10 participants receive Acyclovir
- 18-30 years females: Approximately 11 participants receive Valacyclovir, approximately 10 participants receive Acyclovir
- 31-50 years males: Approximately 10 participants receive Valacyclovir, approximately 11 participants receive Acyclovir
- 31-50 years females: Approximately 10 participants receive Valacyclovir, approximately 11 participants receive Acyclovir
- 51-65 years males: Approximately 10 participants receive Valacyclovir, approximately 10 participants receive Acyclovir
- 51-65 years females: Approximately 10 participants receive Valacyclovir, approximately 10 participants receive Acyclovir

Allocation for Site B follows a similar pattern to ensure an approximately equal distribution of Valacyclovir and Acyclovir within each age and gender group. This allocation strategy ensures a balanced distribution of Valacyclovir and Acyclovir within each stratum, mitigating potential biases inherent in the stratified block design.

The actual randomization will be performed using a computer-generated random number sequence, which will be created by an independent statistician not otherwise involved in the trial. The sequence will determine the assignment of participants to either the Valacyclovir or Acyclovir group. At the time of enrollment, after obtaining informed consent and completing baseline assessments, participants will be assigned to their respective groups based on the following position in the randomization sequence corresponding to their stratification category. To maintain the integrity of the double-blind design, neither the participants nor the clinical staff administering the interventions will be aware of the group assignments.

7.5 Blinding

The trial will employ a double-blinded design, where both the participants and the clinical staff administering the treatments and assessing the outcomes will be blinded to the treatment assignments. Valacyclovir and Acyclovir will be provided in identical, indistinguishable capsules in shape, size, color, and taste to maintain blinding. This preparation will be handled by a third-party pharmacist who is not involved in the assessment or treatment of participants. Treatment allocation will be managed by an independent statistician using a randomization schedule. The allocation details will be kept in sealed, opaque envelopes that are only accessible by this independent party. Each participant's treatment assignment will be concealed until the end of the study or in cases where unblinding is necessary for safety reasons. All study investigators, staff, and participants will remain unaware of the treatment assignments. Data collected during the study will be coded in such a way that treatment assignment is not revealed. Only the independent statistician will have access to the unblinded data.

Unblinding will occur at the end of the study once the primary data analysis is complete. At this point, participants will be informed of their treatment assignment, especially if

knowledge of their treatment is relevant for their subsequent care. If a participant experiences severe adverse effects that require intervention, a predetermined emergency unblinding protocol will be followed. This protocol involves the participant's primary Investigator contacting the independent statistician to request the unblinding of the specific participant's treatment.

7.6 Data Analysis

Preliminary work

Purpose of the study: To evaluate the effectiveness of Valacyclovir and Acyclovir in curing HSV-2

- Null Hypothesis (H_0): There is no difference in recurrence rate between Valacyclovir and Acyclovir.
- Alternative Hypothesis (H_1): Valacyclovir and Acyclovir have a significant difference in recurrence rate.

Calculate the recurrence rate:

Let $\hat{p}_1$ be the recurrence rate of Acyclovir, and $\hat{p}_2$ be the recurrence rate of Valacyclovir.

Compute the Test Statistic:

$$Z = \frac{\hat{p}_1 - \hat{p}_2}{\sqrt{\hat{p}\,(1-\hat{p}\,)\left(\frac{1}{n_1}+\frac{1}{n_2}\right)}}$$

Using the pooled proportion $\hat{p} = \frac{x_1+x_2}{n_1+n_2}$, where x_1 and x_2 are the number of recurrent objects in each group, and n_1 and n_2 are the sample sizes in each group.

We will compare the calculated -value to the critical value from the standard normal distribution (1.96 for a two-tailed test at the 5% significance level). If $|Z| > 1.96$, we will reject the null HypothesisH_0; otherwise, we will not reject H_0.

7.6.1 Primary Analyses

Primary objectives

To compare the effects of active antiviral suppression using Acyclovir or Valacyclovir for one year. Outcome measures are (1) the difference in the proportion of patients with at least one verified episode of recurrent HSV-2 meningitis during the 12-month period among patients taking Valacyclovir versus Acyclovir; (2) treatment tolerability during one year. The statistics used in this objective are explained below.

1. The difference in recurrent rate of HSV-2 Meningitis: A Cox proportional hazards model will also be used to calculate the hazard ratio(HR). If HR = 1, there is no difference in risk between the two groups. If HR > 1, the event is more likely to occur in the Valacyclovir group than in the Acyclovir group. If HR < 1, The event is less likely to occur in the Valacyclovir group than in the Acyclovir group.

   Cox proportional hazards model

   The stratification by age is handled by allowing different baseline hazards for each age group. Separate models for each gender would be run.

   $$h_i(t) = h_0^k(t)exp(\beta_1 X_{1i} + \beta_2 X_{2i} + \beta_3 (X_{1i} * X_{2i}) + \ldots + \beta_p X_{pi})$$

   - X_{1i} is the treatment variable, Valacyclovir is 1 and Acyclovir is 0. X_{2i} is the gender, $X_{1i} * X_{2i}$ is the interaction between treatment and gender.
   - $h_i(t)$ is the hazard function for the i-th individual at time t.
   - $h_0^k(t)$ is the baseline hazard function for the k-th age group, allowing each age group to have its own baseline hazard.
   - $X_{1i}, X_{2i}, \ldots X_{pi}$ are the covariates for the i-th individual which include treatment, gender, and possibly other relevant variables.
   - $\beta_1, \beta_2 \ldots \beta_p$ are the coefficients to be estimated.
   - HR=exp{β_t}, β_t is the coefficient for treatment.

2. Assessment of Adverse Effects: The frequency and type of adverse effects will be compared between the two groups using chi-square tests for categorical outcomes.
3. Impact on Quality of Life: Quality of life will be measured using descriptive statistics to identify any significant deviations from baseline within each group.

Interim Analyses

Purpose

Monitor early signs of effectiveness and tolerability.

Methods

Effectiveness: Use a simplified interim analysis of the Cox proportional hazards model to evaluate the hazard ratio (HR) between the two groups at the midpoint of the study period. This analysis will provide an early indication of any significant differences in the recurrence rate between the treatments.

Safety and Tolerability: Review adverse event reports collected up to the midpoint to assess any significant differences in the tolerability between the two drugs.

Criteria for Action

Consider modifying or halting the study if the interim HR indicates a significantly higher risk of recurrence in one group (e.g., HR significantly greater than one or less than one with a predefined confidence level). We need to address safety concerns if the interim safety analysis shows a substantial difference in adverse effects between the groups.

Final Analyses

Purpose

The purpose of the Final Analysis is to comprehensively evaluate the research hypothesis, providing detailed information about the effects and safety of the study treatments, forming the basis for scientific conclusions and publications.

Methods

Statistical Model: Implement the full Cox proportional hazards model with all collected data to calculate the final HR. This will conclusively show whether the recurrence of HSV-2 meningitis is more likely in one group over the year.

Outcome Measure: Compare the proportion of patients with at least one episode of recurrent HSV-2 meningitis over 12 months in each group.

Assessment of Adverse Effects:The frequency and type of adverse effects will be compared between the two groups using chi-square tests for categorical outcomes.

Key Outputs

Comprehensive evaluation of the treatment effects, detailed safety report, and detailed clinical study report are suitable for regulatory submission and scientific publication.

7.6.2 Secondary Analyses

Secondary objectives: To compare the neurological morbidity of HSV-2 meningitis during one year when active antiviral suppression was performed using Acyclovir or Valacyclovir. The outcome measure is the difference in the length of time until symptoms of a recurrence of HSV-2 meningitis among patients taking Valacyclovir versus Acyclovir. The statistics used in this objective are explained below.

1. Length of time of a recurrence of HSV-2 meningitis: Kaplan-Meier survival curves will be plotted to visually compare the time to recurrence (Using R).
2. Cost-Effectiveness: The incremental cost-effectiveness ratio (ICER) will be calculated to determine the cost per QALY gained.

   $$ICER = \frac{\Delta C}{\Delta E}$$

   $$\Delta C = Costs_A - Costs_B$$

   $$\Delta E = QALY_A - QALY_B$$

   Costs: Collect all relevant costs for each treatment, including drug costs, healthcare visits, hospitalizations, and any other related medical or indirect costs.

   QALYs: Determine the effectiveness of each treatment in terms of QALYs. This requires data on the quality of life and survival estimates for each treatment. Often, these are derived from clinical trials or secondary research.

   Example:

   Treatment A: Costs = $10,000, QALYs = 2.0

   Treatment B: Costs = $12,000, QALYs = 2.5

   Using the example above:

   Incremental Cost = $12,000 - $10,000 = $2,000

   Incremental QALYs = 2.5 - 2.0 = 0.5

The ICER value of $4,000 per QALY gained means that Treatment B costs an additional $4,000 for every extra QALY gained compared to Treatment A.

Patient Adherence

Adherence will be measured based on patient self-reports and pill counts.

Plan for Non-adherence: Establish a clear protocol for addressing non-adherence, which may include additional counseling, peer support groups, or even revisiting educational materials.

Key Point - Adherence correction term-sample size formula, a squared function.

$2n = \sigma^2(z_\alpha + z_\beta)^2/(\mu_1 - \mu_2)(1 - p)^2$ p=Reduction in Adherence

Interim Analyses

Purpose

Evaluate early indicators of neurological outcomes and adverse effects.

Methods

- Neurological Morbidity: Conduct an early assessment using the Kaplan-Meier survival curves to compare the preliminary time to the first recurrence of HSV-2 meningitis between the two groups.

Criteria for Action

Consider adjustments to the study protocol if early results show unexpected trends in safety or efficacy that could ethically justify modifying or halting the study.

Final Analyses

Purpose

The final analysis will comprehensively assess the effectiveness of Acyclovir versus Valacyclovir in extending the time to the first recurrence of HSV-2 meningitis and their impact on the neurological morbidity of patients over one year. This analysis forms the basis for the study's conclusions and recommendations for clinical practice.

Methods

Neurological Morbidity: Plot Kaplan-Meier survival curves to visually present the time to recurrence, providing a clear graphical representation of the survival function across both groups.

Cost-Effectiveness Evaluation: Use all gathered data on treatment costs and effectiveness in terms of quality-adjusted life years (QALYs). Determine the incremental cost-effectiveness ratio to ascertain the cost per QALY gained for each treatment. This analysis will help identify which treatment offers the best value for money.

Key Outputs

A comprehensive report detailing the efficacy of each drug in extending the time to first recurrence of HSV-2 meningitis, comprehensive evaluation of the treatment effects, detailed safety report and detailed clinical study report suitable for regulatory submission and scientific publication.

8.0 HUMAN SUBJECTS CONSIDERATIONS

8.1 Ethical Review

This protocol and the template informed consent form(s) contained in Appendix I — and any subsequent modifications — will be reviewed and approved by the U.W. Human Subject Division Review Committee with respect to scientific content and compliance with applicable research and human subjects regulations.

The protocol, site-specific informed consent form, participant education and recruitment materials, and other requested documents — and any subsequent modifications — also

will be reviewed and approved by the ethical review bodies responsible for oversight of research conducted at the study site.

Subsequent to initial review and approval, the responsible IRBs/E.C.s will review the protocol at least annually. The Investigator will make safety and progress reports to the IRBs/E.C.s at least annually and within three months of study termination or completion. These reports will include the total number of participants enrolled in the study, the number of participants who completed the study, all changes in the research activity, and all unanticipated problems involving risks to human subjects or others. [In addition, all open DSMB reports will be provided to the IRBs/E.C.s.] Study sites will submit documentation of continuing review to the U.W. Human Subject Division.

8.2 Informed Consent

Written informed consent will be obtained from each study participant (or the parents or legal guardians of participants who cannot consent for themselves). Each study site is responsible for developing a study informed consent form for local use, based on the template in Appendix I, that describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation in accordance with all applicable regulations. The study site also is responsible for translating the template form into local languages and verifying the accuracy of the translation by performing an independent back-translation.

Literate participants will document their provision of informed consent by signing their informed consent forms. Non-literate participants will be asked to document their informed consent by marking their informed consent forms (e.g., with an X, thumbprint, or another mark) in the presence of a literate third-party witness. (Further details regarding U.W. Human Subject Division requirements for documenting the informed consent process with both literate and non-literate participants are provided in the U.W. Human Subject Division Standard Operating Procedure for Source Documentation.) Any other local IRB/EC requirements for obtaining informed consent from non-literate persons will also be followed. Participants (or their parents or legal guardians) will be provided with a copy of their informed consent forms if they are willing to receive them.

8.3 Risks

Common side effects include headache, nausea, vomiting, rash, and abdominal pain. There is a potential for more severe adverse reactions such as renal impairment, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS) in patients with compromised renal function, and neurological reactions like confusion, hallucinations, and decreased consciousness, particularly in the elderly or those with renal impairment. Besides, there is a risk of allergic reactions.

Procedures like health questionnaires or interviews can cause discomfort or psychological distress, especially if sensitive or private health information is discussed. Although strict measures are taken to ensure confidentiality, there is always a risk that personal health information could be inadvertently disclosed. This could lead to discrimination, loss of employment, or insurance coverage issues.

8.4 Benefits

Participating in this trial provides the opportunity to contribute to medical research that may benefit others in the future by improving the understanding and treatment of HSV-2 meningitis. Specifically, the findings from this study could lead to better prophylactic strategies to prevent the recurrence of HSV-2 meningitis, potentially benefiting future patients at risk of this condition.

8.5 Incentives

Pending IRB/EC approval, participants will be compensated for their time and effort in this study, and/or be reimbursed for travel to study visits and time away from work. Participants will receive a $75 Amazon gift card after completing the study.

8.6 Confidentiality

We will utilize Microsoft SharePoint as the primary online secure platform for storing all documents and recordings. Regular backups will be performed to prevent data loss, and

measures will be implemented to anonymize participant information to safeguard confidentiality throughout the research process. Access to the data will be restricted to the primary investigator and designated research team members, who will maintain the integrity and security of the research data.

Participant's study information will not be released without the participant's written permission, except as necessary for monitoring by the NIAID and/or its contractors.

8.7 Communicable Disease Reporting Requirements

Study staff will comply with all applicable local requirements to report communicable diseases identified among study participants to local health authorities. Participants will be informed of all reporting requirements during the study informed consent process.

8.8 Study Discontinuation

The study also may be discontinued at any time by NIAID.

9.0 LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT

9.1 Local Laboratory Specimens

As described in Section 5, the following types of specimens will be collected for testing at the local laboratory (L.L.): CSF samples obtained through lumbar puncture

Local laboratories will perform Chemistry, Cell count, Cytology, and HSV PCR on CSF samples obtained via lumbar puncture. Laboratories performing these tests will be monitored by Patient Safety Monitoring and International Laboratory Evaluation (pSMILE) and must demonstrate successful participation in the relevant External Quality Assurance (EQA) programs. Local laboratories may also perform cell count testing and quantitative HSV PCR testing. Laboratories performing these tests will be monitored by the Immunology Quality Assurance (IQA) and /or Virology Quality Assurance (VQA) programs and must demonstrate successful participation in the relevant EQA programs. Each study site will adhere to standards of good clinical laboratory practice and local standard operating procedures for specimen management, including proper collection,

processing, labeling, transport, and storage of specimens to the L.L. Specimen collection, testing, and storage at the L.L. will be documented using the U.W. Laboratory Data Management System (LDMS) as described in the study-specific procedures manual.

9.2 Network Laboratory Specimens

As described in Section 5, the following types of specimens will be collected for testing at the HPTN Network Laboratory (N.L.): CSF samples obtained through lumbar puncture

Each study site will adhere to good clinical laboratory practice standards and the U.W. Network Laboratory Manual for proper collection, processing, labeling, and transport of specimens for the N.L. All specimens will be shipped in accordance with IATA specimen shipping regulations. All shipments will be documented using the UW LDMS as described in the study-specific procedures manual.

9.3 Quality Control and Quality Assurance Procedures

The clinical sites will document that their clinical laboratories are certified under the Continuous Laboratory Improvement Act of 1988 (CLIA-certified) and/or participate in DAID-sponsored EQA programs. N.L. staff will conduct periodic visits to each site to assess the implementation of on-site laboratory quality control (Q.C.) procedures, including proper maintenance of laboratory testing equipment and the use of appropriate reagents. N.L. staff will follow up directly with site staff to resolve any Q.C. or quality assurance (Q.A.) problems identified through proficiency testing and/or on-site assessments. Throughout the course of the study, the HSV2VA will select a random sample of stored specimens to test for Q.A. purposes. NL staff will follow up directly with site staff to resolve any QA problems identified through this process. All of the assays to be used in this study have been approved for use in HSV2VA studies by the cross-network CPQA program. The quality of the assays is also continuously evaluated by a twice yearly proficiency testing program administered by the CPQA. Satisfactory scores are required for the laboratory to be able to continue to use assays in support of HSV2VA studies. The Pharmacology Core Lab will adhere to Good Laboratory Practice (GLP) for processing all samples.

9.3.1 QC for HSV-2 diagnostic testing

The UW NL will perform CSF HSV PCR diagnostic testing for QC. Before performing HSV diagnostic testing, all sites must validate their testing algorithm, and the validation study must be approved by the UW NL. Local laboratories will perform testing for HSV diagnosis at symptoms onset of meningitis. Algorithms for HSV-2 diagnostic testing are provided in the SP Manual. Participants will be tested for HSV infection status using two standard PCR tests, one of which must be FDA-cleared. Participants with one non-reactive HSV test result at initial testing will be retested within 48 hours.

9.4 Specimen Storage and Possible Future Research Testing

Study site staff will store all CSF specimens collected in this study at least through the end of the study. In addition, study participants will be asked to provide written informed consent for their CSF specimens to be stored after the end of the study for possible future testing. The specimens of participants who do not consent to long-term storage and additional testing will be destroyed at the end of the study.

9.5 Biohazard Containment

As the transmission of HSV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of CSF Samples during lumbar puncture and shipping and handling of all specimens for this study, as currently recommended by the United States Centers for Disease Control and Prevention. All infectious specimens will be transported in accordance with United States regulations (42 CFR 72).

10.0 Organization and ADMINISTRATIVE PROCEDURES

10.1 Protocol Registration

Before implementing this protocol or any subsequent full-version amendments, each site must have the protocol and consent forms approved by the Human Subject Division, UW and Division of Allergy and Infectious Disease (DAID). Once final approval is obtained,

sites must submit all necessary protocol registration documents to the DAID Protocol Registration Office (DAID PRO) at the Regulatory Services Center (RSC). The DAID will review the submission to ensure all required documents are included.

Initial Registration:

- The DAID PRO will review and approve the site informed consent form.
- Sites will receive an Initial Registration Notification from the DAID PRO, indicating successful completion of the registration process. This notification should be kept in the site's regulatory files.

10.2 Study Activation

Prior to the implementation of this protocol and any subsequent full version amendments, each site must have the protocol and the protocol consent form approved, as appropriate, by the Human Subject Division, UW and DAID. Upon receiving final approval, sites will submit all required protocol registration documents to the DAID PRO at the RSC. The DAID PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Pending successful protocol registration and submission of all required documents, CORE staff will "activate" the site to begin study operations. Study implementation may not be initiated until a study activation notice is provided to the site.

10.3 Recruitment and Enrollment

Recruitment will be carried out by a clinical research coordinators (CRCs) team based at General medicine clinics and Infectious disease clinics at UW Medicine Seattle, WA. Coordinators will collaborate with infectious disease specialists, primary care providers and nurses to identify potential participants with a history of HSV-2 meningitis. Three techniques will be used in the recruitment process. Firstly, during patient clinic visits, CRCs will approach eligible patients to provide information about the study and gauge their interest in participating. Secondly, CRCs will review the medical history of patients in the clinic and will call the potential participant. Lastly, CRCs will promote the research

by using flyers, which will include the QR code for the patient to upload the required clinical information. Additionally, social media and online platforms can help with recruitment, enabling us to attract and reach potential participants efficiently.

At each site, CRCs will handle data collection. They will conduct initial screenings, obtain informed consent, and gather baseline data. This includes demographic information, medical history, and details of any previous HSV-2 infections. Follow-up data, such as meningitis recurrence and adverse effects, will be collected during clinical visits and through patient diaries at six and twelve months.

10.4 Management of Resources and Coordination

A research administrative team will oversee the study. We will manage the budget, allocate resources, and coordinate the overall study. Regular meetings will be held to ensure smooth communication among all participating sites and address any logistical challenges.

We will develop a standardized enrollment protocol to ensure consistent and efficient enrollment at all sites. This protocol will detail the inclusion and exclusion criteria, screening procedures, and the informed consent process. The research administrative team will monitor enrollment progress and offer support to the sites as needed.

Close coordination between the research administrative team members and CRCs will be necessary to track study progress, respond to queries about proper study implementation, and address other issues in a timely manner. The team will closely monitor rates of accrual, adherence, follow-up, and AE incidence. The Protocol Chair, DAID Medical Officer, and Protocol Biostatistician will address issues related to study eligibility and AE management and reporting as needed to ensure consistent case management, documentation, and information-sharing across sites.

10.5 Study Monitoring

A dedicated monitoring plan will be established to ensure the integrity and quality of the trial. This will include regular site visits by clinical monitors to review source documents, verify data accuracy, and ensure compliance with the study protocol. An independent

Data Safety Monitoring Board (DSMB) will document and review adverse events and protocol deviations.

On-site study monitoring will align with DAID policies. Study monitors will visit the site to ensure compliance with human subjects and other research regulations and guidelines. They will evaluate adherence to the study protocol, the study-specific procedures manual, and local counseling practices and confirm the quality and accuracy of the data collected at the study site and entered into the study database.

- Verification of Compliance: Study monitors will ensure that the study meets all ethical standards and regulatory requirements. This includes verifying that informed consent has been properly obtained and documented for all participants and that their confidentiality is maintained throughout the study.
- Adherence to Protocol: Monitors will check whether the study is being conducted exactly as outlined in the approved protocol, the study-specific procedures manual, and local counseling practices. This includes verifying that interventions are administered as specified—Valacyclovir 1000 mg once daily for the Valacyclovir group and Acyclovir 400 mg twice daily for the Acyclovir group—and that participants are followed up at the scheduled six and twelve-month intervals.
- Data Quality and Accuracy: Monitors will review source documents and case report forms (CRFs) to ensure the data entered into the study database is accurate and complete. This involves checking clinical visit records, laboratory test results, and participant diaries for consistency and correctness.

Site investigators will allow study monitors to inspect study facilities and documentation, including informed consent forms, clinic and laboratory records, other source documents, and CRFs. Monitors will also observe study procedures to ensure they are conducted correctly and safely.

10.6 Protocol Compliance

The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the Protocol Chair and NIAID Medical Officer. All protocol amendments must be submitted to and approved by the Human Subject Division, UW, and the DAID Regulatory Support Center (RSC) prior to implementing the amendment.

10.7 Investigator's Records

The Investigator is responsible for keeping thorough, accurate, and up-to-date study records throughout the duration of the study. Federal regulations require that all records related to the investigational products being tested—Valacyclovir and Acyclovir—must be securely stored. These records need to be kept for at least two years after the study product receives marketing approval for the specific indication it was studied for. If there is no marketing application or if the application is not approved, the records should be retained for two years after the FDA is informed that the Investigational New Drug (IND) application has been discontinued.

The study records include a range of documents such as administrative paperwork like protocol registration documents, all study-related reports, and correspondence. Additionally, there must be detailed documentation for each participant who is screened or enrolled in the study. This includes informed consent forms, locator forms, case report forms, records of all participant interactions, and any other relevant source documents. Maintaining these records is crucial to ensure compliance with study protocols and regulatory requirements, thereby supporting the integrity and validity of the study data.

10.8 Use of Information and Publications

The results of this study will be shared widely to maximize impact. We'll publish our findings in peer-reviewed journals, present at conferences, and engage in public health forums. Our central administrative team will oversee the preparation of all manuscripts, ensuring proper recognition for every contributor. To facilitate further research, we will

establish data-sharing agreements that allow other researchers to access de-identified data, all in accordance with ethical guidelines and participant consent.

10.9 Funding for Recruitment and Workforce

Funding for our recruitment efforts and the study's workforce comes from a mix of the NIH and the DAID, UW. We've meticulously planned our budget to ensure comprehensive coverage of all study-related expenses, including salaries for personnel, compensation for participants, and operational costs. To ease the burden of travel for study visits, we will either reimburse travel expenses or provide transportation services as needed.

11. FACILITIES, RESOURCES, AND EQUIPMENT

11.1 Facilities

The clinical trial will be conducted at two prestigious medical institutions: the Infectious Disease and General Medicine clinics at the University of Washington in Seattle, and the Northwest Medical Center in Seattle.

11.1.1University of Washington Infectious Disease Clinic

The Infectious Disease Clinic at the University of Washington is a renowned center of excellence in infectious disease management and research. Staffed by a multidisciplinary team of infectious disease specialists, nurses, and support staff, the clinic offers comprehensive care to patients with infectious diseases. Services include diagnosis, treatment, and management of a wide range of infectious conditions, as well as specialized care for patients with complex infectious disease issues.

11.1.2 University of Washington General Medicine Clinic

The General Medicine Clinic at the University of Washington provides primary care services to patients with a focus on preventive care, chronic disease management, and

health promotion. The clinic is staffed by primary care physicians, nurse practitioners, and other healthcare professionals who work collaboratively to deliver high-quality, patient-centered care. Services offered include routine physical exams, management of chronic conditions, and coordination of care with specialists as needed.

These clinics provide state-of-the-art facilities and specialized expertise essential for the successful implementation of the trial. All trial activities, including participant recruitment, assessments, and follow-up visits, will take place within these clinical settings. The coordination of data collection and management will be centralized within the clinical trial team housed within the Infectious Disease department at the University of Washington. All collected data will be securely collated by the clinical trial team and stored on a dedicated drive accessible only to authorized personnel, ensuring confidentiality and data integrity throughout the trial.

11.2 Resources

An array of resources stands ready to support the study's objectives within the outpatient clinics. From essential medical supplies to administrative infrastructure, these resources are meticulously organized to facilitate efficient study operations. Administrative personnel play a vital role in coordinating participant appointments, managing study documentation, and ensuring adherence to regulatory requirements. Additionally, access to comprehensive medical records and databases enables researchers to glean valuable insights into participant histories, thus enhancing the quality of clinical care and research outcomes. The resources will be provided by the University of Washington in collaboration with the Infectious Disease Department and the NIH.

11.2.1 University of Washington

The University of Washington (UW) stands as a beacon of academic excellence and innovation in the heart of Seattle. As one of the top public research universities in the United States, UW is renowned for its commitment to scholarly inquiry, interdisciplinary collaboration, and community engagement. With a rich history spanning over 150 years,

UW serves as a hub of intellectual discovery and societal impact, empowering students, faculty, and staff to address the most pressing challenges facing our world today.

11.2.2 University of Washington Infectious Disease Department

Within the esteemed confines of the University of Washington resides the Infectious Disease department, a leading center of expertise in infectious disease management, research, and education. The department comprises a diverse team of infectious disease specialists, scientists, clinicians, and support staff dedicated to advancing knowledge and improving patient outcomes in the field of infectious diseases. Through innovative research, compassionate patient care, and community outreach initiatives, the department plays a pivotal role in combating infectious diseases locally, nationally, and globally.

11.2.3 National Institutes of Health (NIH)

The National Institutes of Health (NIH) is the nation's premier medical research agency, dedicated to improving health and saving lives through groundbreaking scientific discoveries. Comprising 27 Institutes and Centers, NIH supports a vast array of research initiatives spanning basic, translational, and clinical research domains. With a mission to seek fundamental knowledge about the nature and behavior of living systems and to apply that knowledge to enhance health, lengthen life, and reduce illness and disability, NIH serves as a catalyst for scientific innovation and biomedical progress on a global scale.

The resources necessary for conducting the clinical trial will be generously sponsored by the University of Washington Infectious Disease department through funding provided by the National Institutes of Health (NIH). The partnership between the NIH and the University of Washington Infectious Disease department represents a commitment to advancing scientific knowledge and improving patient care. Through this collaboration, the trial will have access to essential resources such as personnel, medical supplies, administrative support, and funding, ensuring the seamless execution of the trial's objectives.

11.3 Equipment

The Infectious Disease and General Medicine clinics at the University of Washington and Northwest Medical Center will provide all necessary equipment for participant assessments, medical procedures, and data collection activities. Additionally, laboratory supplies for sample collection and processing will be sourced from the University of Washington Virology Laboratory, a renowned center of excellence in clinical diagnostics and research. The virology lab is equipped with state-of-the-art instrumentation and staffed by highly trained personnel capable of conducting a wide range of diagnostic tests with precision and accuracy. Laboratory samples collected from the research sites will be securely transported to the University of Washington Virology Laboratory for analysis and testing via a secure and efficient transportation process, ensuring the integrity and reliability of study results. The following equipment and supplies will be use for sample collection and analysis:

11.3.1 CSF Collection Kit

The Cerebrospinal Fluid (CSF) Collection Kit is a specialized set of instruments and supplies designed for the safe and sterile collection of cerebrospinal fluid from patients. This kit typically includes items such as sterile needles, syringes, collection tubes, and specimen containers, as well as materials for skin preparation and local anesthesia. CSF collection kits are essential for obtaining samples of cerebrospinal fluid for diagnostic purposes, such as the detection of infections, inflammatory conditions, or other neurological disorders.

11.3.2 Clinic Supplies

Clinic supplies encompass a broad range of medical consumables and equipment utilized in clinical settings to support patient care, examination, and treatment. These supplies may include but are not limited to examination gloves, gauze pads, bandages, disposable syringes and needles, alcohol swabs, adhesive tapes, and wound care products. Additionally, clinic supplies may comprise medical instruments such as stethoscopes, blood pressure cuffs, thermometers, otoscopes, and examination tables. These essential

supplies ensure the provision of safe, efficient, and high-quality healthcare services within clinic environments.

11.3.3 Blood Sample Collection Kit

The Blood Sample Collection Kit consists of specialized equipment and supplies designed for the aseptic and safe collection of blood specimens from patients. This kit typically includes items such as evacuated blood collection tubes, sterile needles, syringes, tourniquets, alcohol swabs, and bandages. Blood sample collection kits are essential for obtaining blood samples for diagnostic testing, such as complete blood counts, biochemical analyses, and infectious disease screening. Proper collection techniques and adherence to safety protocols are crucial to ensuring the integrity and accuracy of blood specimens.

11.3.4 Laboratory Supplies

Laboratory supplies encompass a diverse array of consumables, reagents, and equipment utilized in laboratory settings to support scientific research, diagnostic testing, and analytical procedures. These supplies may include laboratory glassware, plasticware, pipettes, test tubes, centrifuge tubes, microscopes, balances, and pH meters. Additionally, laboratory supplies may comprise biochemical reagents, culture media, buffers, enzymes, and molecular biology kits. These essential supplies enable researchers and laboratory personnel to conduct experiments, analyze samples, and generate data critical for advancing scientific knowledge and improving patient care.

11.3.5 PCR Analysis Machine

The Polymerase Chain Reaction (PCR) Analysis Machine is a sophisticated instrument used for amplifying and analyzing DNA sequences in biological samples. PCR machines employ thermal cycling to repeatedly heat and cool the reaction mixture, facilitating the amplification of specific DNA regions through enzymatic replication. These machines are equipped with precise temperature control systems, fluorescence detection modules, and software for data analysis. PCR analysis machines are essential tools in molecular

biology research, genetic testing, and infectious disease diagnosis, enabling the detection and quantification of nucleic acids with high sensitivity and specificity.

11.3.6 CSF Analysis Machine

The Cerebrospinal Fluid (CSF) Analysis Machine is a specialized instrument used for analyzing the biochemical and cellular composition of cerebrospinal fluid samples obtained from patients. These machines employ various analytical techniques, including spectrophotometry, microscopy, and immunoassays, to assess parameters such as cell counts, protein concentrations, glucose levels, and the presence of pathogens or biomarkers. CSF analysis machines play a crucial role in the diagnosis and management of neurological disorders, infectious diseases, and inflammatory conditions affecting the central nervous system.

12. BUDGET & BUDGET JUSTIFICATION

The budget below is provided for the one-year estimated budget that will be use in this project. All personnel listed below will be UW employees. Fringe benefits are 22.7% for faculty, 17% for hourly student support, and 27.7% for professional staff. Salaries are calculated at a 2% increase each year after the first year.

12.1 Salaries

12.1.1 Salaries for Scientists and Senior Personnel

1. Chineme Nwaichi, PI

Chineme, as the Principal Investigator (PI) and master's student coordinating the study, will take on the primary responsibility for the overall scientific and fiscal integrity of the entire research project. In this role, Chineme will ensure the study's integrity by supervising data extraction and analysis, coordinating team meetings, and leading the preparation of the final report and scientific publications.

This position demands a significant commitment, with 90% of Chineme's time dedicated to these tasks, equivalent to 8.1 calendar months. Chineme's monthly salary is $4,500, amounting to a total of $37,908 for the 8.1 months. Including fringe benefits, which total $8,074, the overall salary expense for this period will be $45,982.

2. Cynthia Zhao, Co-PI

   Cynthia, serving as Co-Principal Investigator (Co-PI), will take on the role of master's student coordinating the study and assisting with data analysis. Her primary responsibilities include the development and maintenance of the study database, conducting data analysis, preparing safety reports, and contributing to the interpretation and dissemination of findings.

   Cynthia will dedicate 75% of her time to these tasks, equivalent to 6.75 calendar months. With a monthly salary of $4,500, her total earnings for this period will be $31,590. Including fringe benefits, which amount to $7,613, the overall compensation for this period will be $39,203.

3. Rinlita Itthikomolsil, Co-PI,

   Rinlita, serving as Co-Principal Investigator (Co-PI), holds the position of a predoctoral student coordinating the study. She will take primary responsibility for the conduct of the study, which includes all reporting and ensuring the protection of human subjects. Rinlita will also be responsible for developing and implementing the study's recruitment strategy, ensuring a diverse and representative sample. Furthermore, she will coordinate the training of research assistants and manage the study's compliance with ethical guidelines.

   Rinlita will dedicate 75% of her time to these responsibilities, equivalent to 6.75 calendar months. With a monthly salary of $4,500, her total earnings for this period will be $31,590. Including fringe benefits at 16%, which amount to $6,729, the overall compensation for this period will be $38,319.

4. Ruyue Wang, Co-PI,

   Ruyue Wang, serving as Co-Principal Investigator (Co-PI), holds the position of a master's student coordinating the study and assisting with data analysis. She will dedicate 75% of her time to these responsibilities, which amounts to 6.75 calendar months. With a monthly salary of $4,500, her total earnings for this period will be $31,590. Including fringe benefits, which total $7,613, the overall compensation for this period will be $39,203.

5. Gary Chen

Gary Chen, as the biostatistician, will assist with the data analysis plan and the data analysis process. He will dedicate 25% of his time to these tasks, which equates to 1.25 calendar months. With a monthly salary of $7,000, his total earnings for this period will be $9,100. Including fringe benefits, which amount to $2,894, the overall compensation for this period will be $11,994.

12.1.2 Salaries for other personnel

1. Research Assistant 1

   Research Assistant 1 is a PhD candidate student who will have primary responsibility for outcome assessment. This graduate student will also communicate with subjects and manage study-related data. Additionally, they will assist research coordinators with manuscript preparation, materials management, and arranging study team meetings. This role requires a commitment of 4.5 calendar months in the first year. The regular salary for this period is $27,135, with fringe benefits amounting to $5,780, bringing the total salary to $32,915. Additionally, tuition costs are $20,175.

2. Research Assistant 2

   Research Assistant 2 is another PhD student who will assist with participant recruitment and data collection. This role requires a 50% effort over 4.5 calendar months. The regular salary for this period is $25,253, with fringe benefits amounting to $5,379, resulting in a total salary of $30,632. Tuition costs for this role are also $20,175.

1. Project manager

   The Project Manager will be responsible for subject recruitment, communication with subjects, and data management. This role includes overseeing run-in procedures, subject randomization, and protocol implementation. The project manager will prepare IRB applications in consultation with the PI and assist with meetings, manuscript preparation, materials management, and arranging study team meetings. This position requires a 20% effort, equivalent to 1.8 calendar months in Year 1. The monthly salary is $4,000, amounting to $7,488 for 1.8 calendar months. Fringe benefits are $2,381, making the total compensation $9,869.

12.2 Equipment purchase

The budget includes an allocation of $1,000 for office supplies, ensuring that the research team has the necessary tools for everyday administrative tasks. Additionally, an estimated $50,000 is earmarked for the purchase of laboratory equipment. This substantial investment is crucial for conducting accurate and reliable tests and analyses essential to the study.

12. 3 Equipment rental

To support the research activities, $1,000 is allocated for the rental of a printer and $3,000 for the rental of a computer. These rentals will provide the necessary technology to facilitate data collection, analysis, and communication among the research team.

12.4 Supplies

Lab supplies are budgeted at $1,000 per person, totaling $124,000 for all participants. These supplies include essential items such as medical supplies, sample bottles, blood sample collection kits, CSF sample collection kits, laboratory supplies, laboratory kits, and PCR testing equipment. These materials are critical for the accurate and efficient collection and analysis of biological samples throughout the study.

12.5 Travel (domestic only)

The budget includes $15,000 for conference travel for the research team, allowing them to present findings and collaborate with other experts in the field. An additional $5,000 is allocated for travel expenses related to data collection by research assistants. This travel is necessary to ensure comprehensive data collection from all study sites.

12.6 Publication costs

An allocation of $3,000 is dedicated to covering publication costs. This funding will support the dissemination of research findings through scientific journals and conferences, ensuring that the knowledge gained from the study reaches a wide audience.

12.7 Other direct costs

To encourage participation, the study will provide Amazon gift cards valued at $300 per person. With 124 participants, the total cost for these incentives amounts to $37,200. These incentives are crucial for maintaining participant engagement and ensuring high retention rates throughout the study period.

12.8 Total cost

The summary of all categories includes $215,694 for salaries, $20,000 for travel expenses, $37,200 for participant incentives, $181,000 for supplies and equipment, $49,589 for fringe benefits, and $44,385 for student aid. These direct costs sum up to $547,868. Additionally, indirect costs (F&A) are calculated at $281,681, bringing the total final budget to $829,549. This comprehensive budget ensures that all aspects of the study are adequately funded, from personnel and travel to supplies and dissemination of results.Student aid $44,385

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14. APPENDICES

14.1 Appendix I: Sample Informed Consent Form

INFORMATION ABOUT A UNIVERSITY OF WASHINGTON RESEARCH STUDY

Comparative effectiveness of Valacyclovir and Acyclovir for preventing recurrent HSV-2 meningitis: A Randomized Controlled Trial

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We are asking you to be part of a research study. This form gives you information to help you decide whether or not to be in the study. Participation in the study is voluntary. Please read the form carefully. You may ask any questions about the study. Then, you can decide whether or not you want to be in the study.

PURPOSE OF THE STUDY

Recurrent HSV-2 meningitis poses a significant clinical challenge, marked by frequent episodes that diminish quality of life and strain healthcare resources. While Acyclovir serves as the primary prophylactic agent, concerns over resistance and suboptimal efficacy have spurred interest in alternative treatments. Valacyclovir, a prodrug of Acyclovir with potentially improved pharmacokinetics, remains underexplored in the context of preventing recurrent HSV-2 meningitis. However, there is no study comparing the difference in effectiveness of Acyclovir and Valacyclovir in preventing recurrent HSV-2 meningitis. The purpose of this study is to investigate and compare the effectiveness of active antiviral suppression using Acyclovir or Valacyclovir in managing HSV-2 meningitis over a one-year period. We are conducting this research to gain insight into the most effective and

cost-efficient prophylactic approach for managing this condition. You are invited as a possible parent participant if you are aged between 18-65 years old, have at least one episode of HSV-2 meningitis in the past, and are proficient in the English language.

STUDY PROCEDURES

- If you choose to participate in this study, you will be asked to undergo several procedures throughout the study period. Firstly, there will be a screening visit where your eligibility for the study will be confirmed through a review of your medical history, a physical examination, and various laboratory tests. Once deemed eligible, you will attend an enrollment visit where you will be randomly assigned to one of two treatment groups: either Group A or Group B. At this visit, you will receive detailed treatment regimen instructions. Following enrollment, you will attend regular follow-up visits, typically at Month 6 and Month 12. During these visits, your adherence to the treatment regimen will be assessed, any adverse events will be monitored, and the study outcomes will be evaluated. These visits will involve assessments such as physical examinations and laboratory tests. The estimated time commitment for each visit is approximately 1-2 hours.

Procedure	**Group A**	**Group B**
Screening Visit	Eligibility confirmation, medical history review, physical examination, and laboratory tests.	Eligibility confirmation, medical history review, physical examination, and laboratory tests.
Enrollment Visit	Randomization to treatment group (Valacyclovir), treatment initiation, and detailed instructions on treatment regimen.	Randomization to treatment group (Acyclovir), treatment initiation, and detailed instructions on treatment regimen.
Follow-up Visits (Month 6)	Assessment of treatment adherence, monitoring of adverse events, and evaluation of study outcomes.	Assessment of treatment adherence, monitoring of adverse events, and evaluation of study outcomes.
Follow-up Visits (Month 12)	Assessment of treatment adherence, monitoring of adverse events, and evaluation of study outcomes.	Assessment of treatment adherence, monitoring of adverse events, and evaluation of study outcomes.

RISKS, STRESS, OR DISCOMFORT

Psychological discomfort: Psychological discomfort stemming from discussing personal experiences with HSV-2, including symptoms, treatment, and the impact on daily life, may arise during participation in the study. Participants may experience anxiety, embarrassment, or stigma associated with disclosing their HSV status and discussing sensitive health-related topics with researchers.

Adverse effect of drug: Participants in this study may experience potential risks associated with antiviral medication, such as Acyclovir or Valacyclovir. Common side effects of these medications may include nausea, headache, and diarrhea. In some cases, individuals may experience more severe adverse effects, such as renal impairment or allergic reactions. Additionally, there may be risks associated with the recurrence of HSV-2 meningitis despite antiviral suppression, including neurological complications and discomfort associated with symptoms.

Medical procedure discomfort: Participation in the study may also entail risks related to medical procedures, such as blood draws for monitoring purposes, which can lead to discomfort, bruising, or infection at the site of venipuncture.

BENEFITS OF THE STUDY

Participation in this study may not directly benefit individual participants; however, it will significantly contribute to the advancement of knowledge surrounding HSV-2 infection and its management, particularly in preventing recurrent meningitis. The findings from this research have the potential to inform and improve guidelines for prophylaxis treatment, ultimately leading to better outcomes for individuals living with HSV-2 and reducing the risk of recurrent meningitis.

SOURCE OF FUNDING

The National Institutes of Health (NIH)

CONFIDENTIALITY OF RESEARCH INFORMATION

All research team members involved in this study will receive training on the importance of privacy and confidentiality when interacting with study participants. Personal identifying information collected during the study will be kept separate from research data to minimize the risk of unauthorized access. Measures will be taken to ensure that participants' identities remain confidential in any publications or presentations resulting from the study. Furthermore, to enhance anonymity, subject ID numbers will be used instead of personal identifiers when discussing participant issues within the research team. Participants will also have the option to specify their preferred communication methods to maintain their comfort and privacy. Lastly, individual identities will not be disclosed in any study reports or publications, thus ensuring the confidentiality of participants' information throughout the research process.

USE OF INFORMATION

The information and samples collected as part of this research may be used for future studies related to HSV infection. Identifiable information will be removed from data and samples whenever possible to protect participants' privacy. Any future use of data or samples will be subject to review by a research ethics board to ensure compliance with ethical standards.

STUDY-RELATED INJURY

If you think you have a medical problem or illness related to this research, contact the Project Director right away at (432)-3524307. He will provide information to you about services that may help you.

OTHER INFORMATION

Participation in this study is entirely voluntary, meaning you have the choice to decline participation. Furthermore, if you choose to participate, you retain the right to withdraw from the study at any time without facing any penalties or consequences.

Talk to the study team. We are here to help you understand the study. Please ask us any questions you may have, even about things that are not in this document. It is our responsibility to give you the information you need to make a decision and to give you time to think about whether or not you want to sign up.

Talk to someone else. If you want to talk about the study with someone who is not part of the study team, talk about your rights as a research subject, or to report problems or complaints about the study, contact the UW Human Subjects Division.

Study Team	PI: Chineme Nwaichi 432-3524307 Co-PI: Cynthia Zhao 206-7342715 Co-PI: Rinlita Itthikomolsil 541-6509578 Co-PI: Ruyue Wang 206-8416461
UW Human Subjects Division	206.543.0098 hsdinfo@uw.edu

Consent presenter statement

By printing my name on this form, I am attesting that I have provided the subject with information about this study. The participant has been given sufficient time to consider participation and I have answered any questions they had. The participant indicated that they understand the nature of the study, including risks and benefits of participating.

Printed name of study staff obtaining consent	Date

Subject's statement

By signing this consent form, I confirm that the study has been explained to me and I volunteer to participate in the research. I have had a chance to ask questions. If I have questions later about the research or feel I have been harmed by participating in the study, I can contact a member of the research team or the UW Human Subjects Division using the information listed above. I will receive a copy of this consent form.

Printed name of subject	Signature of subject	Date