A5383

Randomized, Controlled Trial to Evaluate the Anti-inflammatory Efficacy of Letermovir (Prevymis) in Adults with Human Immunodeficiency Virus (HIV)-1 and Asymptomatic Cytomegalovirus (CMV) Who Are on Suppressive ART and Its Effect on Chronic Inflammation, HIV Persistence, and Other Clinical Outcomes (ELICIT)

A Multicenter Trial of the AIDS Clinical Trials Group (ACTG)

Sponsored by:

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ACTG
AIDS CLINICAL TRIALS GROUP

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Randomized, Controlled Trial to Evaluate the Anti-inflammatory Efficacy of Letermovir (Prevymis) in Adults with Human Immunodeficiency Virus (HIV)-1 and Asymptomatic Cytomegalovirus (CMV) Who Are on Suppressive ART and Its Effect on Chronic Inflammation, HIV Persistence, and Other Clinical Outcomes (ELICIT)

SIGNATURE PAGE

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

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Signed: _____ Date: _____
Name/Title

TABLE OF CONTENTS

TAB LE OF CONTENTS (Cont'd) Page

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STUDY MANAGEMENT

All general questions concerning this protocol should be sent to actg.teamA5383@fstrf.org via e-mail. The appropriate team member will respond with a "cc" to actg.teamA5383@fstrf.org. A response should generally be received within 24 hours (Monday through Friday).

Protocol E-mail Group
Sites should contact the User Support Group at the Data Management Center (DMC) as soon as possible to have the relevant personnel at the site added to the actg.protA5383 e-mail group. Include the protocol number in the e-mail subject line.

- Send an e-mail message to actg.user.support@fstrf.org.

Clinical Management:
For questions concerning entry criteria, toxicity management, concomitant vaccines, and co-enrollment, contact the Clinical Management Committee (CMC).

- Send an e-mail message to actg.CMCa5383@fstrf.org. Include the protocol number, participant identification number (PID), and a brief relevant history.

Laboratory
For questions specifically related to immunologic, virologic, or pharmacologic laboratory tests, contact the Protocol Immunologist, Virologist, or Pharmacologist.

- Send an e-mail message to actg.teamA5383@fstrf.org (ATTENTION: Michael Freeman, Immunologist; Joshua Cyktor, Virologist; Francesca Aweeka and Amelia Deitchman, Pharmacologists).

Data Management

- For nonclinical questions about transfers, inclusion/exclusion criteria, electronic case report forms (eCRFs), randomization/registration, and other data management issues, contact the data manager. Completion guidelines for eCRFs and participant-completed CRFs can be downloaded from the FSTRF website at www.frontierscience.org.
- For transfers, reference the Study Participant Transfer SOP 119, and contact **Summer Oliver** directly.
- For other questions, send an e-mail message to actg.teamA5383@fstrf.org (ATTENTION: **Summer Oliver**).
- Include the protocol number, PID, and a detailed question.

Randomization/Participant Registration
For randomization/participant registration questions or problems and study identification number SID lists:

- Send an e-mail message to rando.support@fstrf.org or call the DMC Randomization Desk at 716-834-0900, extension 7301.

DMC Portal and Medidata Rave Problems
Contact DMC User Support.

- Send an e-mail message to actg.user.support@fstrf.org or call 716-834-0900 x7302.

Protocol Document Questions
For questions concerning the protocol document, contact the Clinical Trials Specialist.
- Send an e-mail message to actg.teamA5383@fstrf.org (ATTENTION: Preeti Dhillon).

Copies of the Protocol
To request a hard copy of the protocol, send an e-mail message to ACTGNCC@dlhcorp.com. Electronic copies can be downloaded from the ACTG website at https://www.actgnetwork.org.

Product Package Inserts and/or Investigator Brochures
To request copies of product package inserts or investigator brochures, contact the DAIDS Regulatory Support Center (RSC) at RIC@tech-res.com or call 301-897-1708.

Protocol Registration
For protocol registration questions, send an e-mail message to Protocol@tech-res.com or call 301-897-1707.

Protocol Activation
For questions related to protocol activation at US sites contact the Clinical Trials Specialist.
- Send an e-mail message to actg.teamA5383@fstrf.org (ATTENTION: Preeti Dhillon).

Study Product
For questions or problems regarding study product, dose, supplies, records, and returns, call Cynthia Parker, Protocol Pharmacist, at 301-496-8213.

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Call the Clinical Research Products Management Center (CRPMC) at 301-294-0741.

IND (Investigational New Drug) Number or Questions
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Expedited Adverse Event (EAE) Reporting/Questions
Contact DAIDS through the RSC Safety Office at DAIDSRSCSafetyOffice@tech-res.com or call 1-800-537-9979 or 301-897-1709; or fax 1-800-275-7619 or 301-897-1710.

Telephone Calls
Sites are responsible for documenting telephone calls made to A5383 team members.
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Protocol-Specific Web Page
Additional information about management of the protocol can be found on the protocol-specific web page (PSWP).

GLOSSARY OF PROTOCOL-SPECIFIC TERMS

alloHSCT	allogeneic hematopoietic stem cell transplant
ART	antiretroviral therapy
CAT-MH	**Computerized Adaptive Testing for Mental Health**
COVID-19	coronavirus disease 2019
CI	confidence interval
CMC	Clinical Management Committee
CMV	cytomegalovirus
CNS	central nervous system
CrCl	creatinine clearance
CSF	cerebrospinal fluid
eGFR	estimated glomerular filtration rate
ECG	electrocardiography
ENT	entry
GAD-7	**Generalized Anxiety Disorder-7**
GM-CSF	granulocyte-macrophage colony-stimulating factor
GTEx	Genotype-Tissue Expression
HIV	human immunodeficiency virus
HOMA-IR	homeostatic model assessment-insulin resistance
HR	heart rate
HSCT	hematopoietic stem cell transplantation
IgG	immunoglobulin G
IOT	initiation of treatment
IP	inducible protein
IRIS	Immune Reconstitution Inflammatory Syndrome
IUD	intrauterine device
KT	kynurenine-to-tryptophan
M-CSF	macrophage colony-stimulating factor
MCP	monocyte chemotactic protein
MIP	macrophage inflammatory protein
NFL	neurofilament light
NIAID	National Institute of Allergy and Infectious Diseases
NRTI	nucleoside reverse transcriptase inhibitors
PAP	plasmin-alpha2-antiplasmin
PHQ-9	Patient Health Questionnaire-9

PK	pharmacokinetics
RANTES	regulated on activation, normal T-cell expressed and secreted
RDW	red blood cell distribution width
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SIV	simian immunodeficiency virus
SMC	safety monitoring committee
suPAR	soluble urokinase plasminogen activator receptor
STD	**sexually transmitted disease**
sTNFRII	soluble receptor for tumor necrosis factor type II
TCR	T cell receptor
TEM	T effector memory cell
TEMRA	terminally differentiated effector memory
TGF	transforming growth factor
TNFα	tumor necrosis factor alpha
VACS	Veterans Aging Cohort Study

SCHEMA

A5383
Randomized, Controlled Trial to Evaluate the Anti-inflammatory Efficacy of Letermovir (Prevymis) in Adults with Human Immunodeficiency Virus (HIV)-1 and Asymptomatic Cytomegalovirus (CMV) Who Are on Suppressive ART and Its Effect on Chronic Inflammation, HIV Persistence, and Other Clinical Outcomes
(ELICIT)

DESIGN	A5383 is a phase II, randomized, open-label, controlled, multicenter trial being conducted at US sites to evaluate anti-inflammatory efficacy of letermovir 480 mg once daily for 48 weeks in adults with HIV and asymptomatic cytomegalovirus (CMV) maintaining antiretroviral therapy (ART)-mediated suppression. A futility analysis will be performed after the first 40 participants reach their 8-week study visit.
DURATION	60 weeks (48 weeks on either letermovir or no anti-CMV treatment with 12 weeks of post-treatment period follow-up).
SAMPLE SIZE	180 participants (90 Arm A: letermovir, 90 Arm B: no anti-CMV treatment).
POPULATION	Adults ≥40 years of age with HIV and asymptomatic CMV, with HIV RNA suppression for ≥48 weeks on combination ART.
STRATIFICATION	Participants will be stratified by sex at birth and use of sex hormones as well as by screening $CD4^+$ T cell count. Our goal is that at least one third (30 participants in each arm) will be individuals assigned female sex at birth not on testosterone or individuals assigned male sex at birth on feminizing sex hormones. Further, we also aim to enroll at least one half (45 participants) in each arm with $CD4^+$ T cell counts <350 cells/mm^3.
REGIMEN	Participants will be randomized 1:1 to receive either letermovir 480 mg once daily (Arm A) or no anti-CMV treatment (Arm B) for 48 weeks.

1.0 HYPOTHESES AND STUDY OBJECTIVES

1.1 Primary Hypothesis

Letermovir will cause a greater reduction in plasma soluble receptor for tumor necrosis factor type II (sTNFRII) levels than no anti-CMV treatment at weeks 46/48.

1.2 Secondary Hypotheses

1.2.1 Letermovir (480 mg once daily) will be generally tolerable over the 48 week study treatment period as compared to no anti-CMV treatment.

1.2.2 Letermovir will reduce the frequency of detection and levels of cytomegalovirus (CMV) DNA in mucosal samples (throat wash, seminal plasma, and cervicovaginal swabs) and in blood plasma compared to no anti-CMV treatment, through 48 weeks of treatment. This effect will persist for 4 weeks following treatment discontinuation (i.e., at week 52), and return to baseline by week 60.

1.2.3 Letermovir will cause a greater reduction in plasma sCD163 levels than no anti-CMV treatment at weeks 8, 46/48, and 52, but not at week 60.

1.2.4 Letermovir will cause greater reductions in plasma sTNFRII than no anti-CMV treatment at weeks 8 and 52, but not at week 60.

1.3 Exploratory Hypotheses

1.3.1 Letermovir will cause a greater reduction in inflammatory and coagulation markers (sCD14, IL-6, hsCRP, and D-Dimer) than no anti-CMV treatment at weeks 8 and 46/48, differences that will persist at week 52, but return to baseline by week 60.

1.3.2 Monocyte activation (cellular markers of monocyte activation, e.g., $CD14^{var}CD16+$): Letermovir will reduce monocyte activation at weeks 8 and 48 compared to no anti-CMV treatment, an effect that will persist for at least 4 weeks after discontinuing study treatment.

1.3.3 CMV-specific response: Letermovir will reduce CMV immunoglobulin G (IgG) titer and CMV-specific T cell response (reduced clonality of T cell receptor [TCR]) at week 48 compared to no anti-CMV treatment.

1.3.4 Microbial translocation markers (B-D-Glucan, I-FABP, LBP, Zonulin): Letermovir will reduce biomarkers of microbial translocation at weeks 46/48 compared to no anti-CMV treatment, an effect that will persist for at least 4 weeks after stopping study treatment.

1.3.5 Multiplex-bead-array assay: Letermovir will modulate the cytokines network from baseline to weeks 8 and 46/48, compared to no anti-CMV treatment, an effect that will persist for at least 4 weeks after stopping study treatment.

1.3.6 Detailed markers of coagulation: Letermovir will decrease markers of the coagulation cascade (including soluble urokinase plasminogen activator receptor [suPAR], plasmin-alpha2-antiplasmin complex [PAP], prothrombin fragment 1+2) at weeks 46/48 compared to no anti-CMV treatment.

1.3.7 Letermovir will result in a greater reduction in soluble markers of endothelial activation at weeks 8 and 46/48 than no anti-CMV treatment (sICAM-1, sVCAM-1, sTF, E-selectin, P-selectin), an effect that will persist for at least 4 weeks after stopping study treatment.

1.3.8 T cell dysfunction: Letermovir will reduce T cell dysfunction (including but not limited to decreased activation [$CD38^+$/HLA-DR co-expression], and exhaustion [PD-1] markers) in blood at weeks 8 and 48 and both decrease senescence markers ($CD28^-CD57^+$ T cells) and increase $CD4^+/CD8^+$ ratio at week 48, when compared to those receiving no anti-CMV treatment, differences that will persist for at least 4 weeks after study treatment discontinuation [Freeman et al., 2016; Fromentin et al., 2016; Smith et al., 2016].

1.3.9 Insulin resistance: Letermovir will result in greater reductions in insulin resistance than no anti-CMV treatment at week 46 by homeostatic model assessment-insulin resistance (HOMA-IR) and plasma levels of free fatty acids, differences that will persist for at least 4 weeks after study treatment discontinuation.

1.3.10 Plasma free fatty acids: Letermovir will result in greater reductions in fasting free fatty acids, an indirect measure of adipocyte insulin sensitivity and lipid storage, than no anti-CMV treatment at week 46, differences that may persist for at least 4 weeks after study treatment discontinuation.

1.3.11 Letermovir will result in greater improvements than no anti-CMV treatment in physical function as assessed by chair rise time and frailty score (gait speed, grip strength) at week 46, differences that will persist for at least 4 weeks after study treatment discontinuation.

1.3.12 Veterans Aging Cohort Study (VACS) index: Letermovir will result in greater improvements in VACS index than no anti-CMV treatment at weeks 46 and 60.

1.3.13 HIV Reservoir: Letermovir will reduce the size of the HIV-1 reservoir as measured by cell-associated HIV-1 DNA at weeks 8 and 48 when compared to those receiving no anti-CMV treatment.

1.3.14 HIV Reservoir Sequencing: Letermovir will reduce the clonality of the HIV reservoir in blood at week 48 when compared to those receiving no anti-CMV treatment.

1.3.15 Letermovir will reduce the transcriptional activity of the HIV-1 reservoir as measured by single copy assays of plasma HIV-1 RNA and cell-associated HIV-1 RNA at the week 8 and 48 time points when compared to those receiving no anti-CMV treatment.

1.3.16 Letermovir will not have clinically significant (i.e., requiring dose adjustment) interactions with common ART drugs (i.e., TDF/TAF and integrase inhibitors) **or allowed statins.**

1.3.17 Plasma letermovir levels during treatment will correlate with the extent of reduction in sTNFRII and CMV DNA shedding levels.

1.3.18 Letermovir will alter the plasma proteome as assessed by a modified aptamer assay (SOMAscan), including pathways linked to cardiovascular risk.

1.3.19 Central nervous system (CNS) tolerability of letermovir: Change in neurocognitive performance, mood, sleep quality, concentrations will each be similar to or better than no anti-CMV treatment at week 46. Change in Neurofilament light (NFL) in blood plasma will be similar or better than no anti-CMV treatment at weeks 46/48.

1.3.20 Letermovir resistance: Among letermovir-treated participants with persistent detectable CMV shedding, the emergence of letermovir resistance mutations will be observed in mucosal sites, but not plasma, and will no longer be detected at week 60.

1.3.21 Flu vaccine responsiveness: Letermovir will reduce the humoral response to seasonal influenza vaccination obtained in the course of clinical care compared to no anti-CMV treatment (fold change from the last pre-vaccine time point to the first available time point between 4-12 weeks post-vaccine).

1.4 Primary Objective

To determine whether letermovir 480 mg daily at weeks 46/48 will result in decreased plasma sTNFRII levels compared to no anti-CMV treatment in treated individuals with HIV.

1.5 Secondary Objectives

1.5.1 Tolerability: To determine whether letermovir 480 mg daily for 48 weeks is safe and tolerable in treated individuals with HIV.

1.5.2 CMV DNA levels: To determine if letermovir reduces mucosal and plasma levels of CMV DNA in treated individuals with HIV through 48 weeks of therapy and following treatment discontinuation.

1.5.3 To evaluate if letermovir reduces plasma sCD163 levels at weeks 8, 46/48, 52, and 60.

1.5.4 To evaluate if letermovir reduces plasma sTNFRII levels at weeks 8, 52 and 60.

1.6 Exploratory Objectives

1.6.1 To evaluate if letermovir affects inflammatory and coagulation markers (sCD14, IL-6, hsCRP, and D-Dimer) at weeks 8, 46/48, 52, and 60.

1.6.2 Monocyte activation (cellular markers of monocyte activation): To evaluate if letermovir reduces monocyte activation at weeks 8, 48, 52, and 60.

1.6.3 CMV-specific response: To evaluate if letermovir affects CMV IgG titer and CMV-specific T cell response (reduced clonality of TCR) at week 48.

1.6.4 Microbial translocation markers (B-D-Glucan, I-FABP, LBP, Zonulin): To evaluate if letermovir affects biomarkers of microbial translocation at weeks 8, 46/48, 52, and 60.

1.6.5 Multiplex-bead-array assay: To evaluate if letermovir affects the cytokines network at weeks 8, 46/48, 52, and 60.

1.6.6 Detailed markers of coagulation: To evaluate if letermovir affects the coagulation cascade (including suPAR, plasmin antiplasmin complexes, prothrombin fragment 1+2) at weeks 8, 46/48, 52, and 60.

1.6.7 To evaluate if letermovir reduces soluble markers of endothelial activation at weeks 8, 46/48, 52, and 60.

1.6.8 To evaluate if letermovir affects T cell dysfunction in blood at study weeks 8, 48, 52, and 60.

1.6.9 To evaluate if letermovir reduces insulin resistance at weeks 46 and 60.

1.6.10 To evaluate if letermovir reduces plasma fasting free fatty acids at weeks 46 and 60.

1.6.11 To evaluate if letermovir improves physical function and frailty at weeks 46 and 60.

1.6.12 VACS index: To evaluate if letermovir improves the VACS index at weeks 46 and 60.

1.6.13 HIV Reservoir: To evaluate if letermovir reduces the size of the HIV-1 reservoir as measured by cell-associated HIV-1 DNA at study weeks 8 and 48.

1.6.14 HIV Reservoir Sequencing: To evaluate if letermovir reduces the clonality of the HIV reservoir in blood at study week 48.

1.6.15 To evaluate if letermovir affects the transcriptional activity of the HIV-1 reservoir as measured by single copy assays of plasma HIV-1 RNA and cell-associated HIV-1 RNA at the week 8 and 48 timepoints.

1.6.16 To evaluate interactions between letermovir and common ART drugs **and statins.**

1.6.17 To evaluate correlations between plasma letermovir levels during treatment with the extent of reduction in sTNFRII and CMV DNA shedding levels.

1.6.18 To evaluate if letermovir affects plasma proteome, including pathways linked to cardiovascular risk.

1.6.19 To evaluate the CNS tolerability of letermovir: The tolerability measures will include change in neurocognitive performance, mood, sleep quality, and NFL concentrations in blood plasma.

1.6.20 Letermovir resistance: To evaluate emergence of letermovir resistance mutations in participants with persistent detectable CMV shedding during study period.

1.6.21 Flu vaccine responsiveness: To evaluate if letermovir affects the humoral response to seasonal influenza vaccination obtained in the course of clinical care (fold change from the last pre-vaccine time point to the first available time point between 4-12 weeks post-vaccine).

2.0 INTRODUCTION

2.1 Background

CMV, Inflammation and End-organ Disease in Treated Individuals with HIV

Among all viruses, CMV has one of the most dynamic and comprehensive interactions with the human immune system. In this complex host-virus relationship, the virus elicits and maintains high frequency of CMV-specific T cells that are engaged in a life-long fight to restrict CMV replication and prevent life-threating disease [Sylwester et al., 2005; Waldrop et al., 1997]. As people age with CMV, repeated immune activation and response to CMV can drive T cells toward a more differentiated phenotype [Di Benedetto et al., 2015; Gordon et al., 2017], which may promote replicative exhaustion and senescence [Fletcher et al., 2005]. Senescent T cells frequently bear antigen specificity toward CMV [Appay et al., 2011; Deeks et al., 2012; Looney et al., 1999], and the abundance of senescent T cells has been associated with negative outcomes in older adults including frailty, cardiovascular disease, and systemic infections [Deeks et al., 2009; Kaplan et al., 2011; Nieto et al., 1996; Spyridopoulos et al., 2016]. These inflammatory effector $CD8^+$ T cells typically migrate to tissues where they—along with low-level CMV replication itself—may contribute to local inflammation and chronic disease. In the context of treated individuals with HIV, CMV seropositive adults have higher markers of inflammation that predict morbidity and mortality (e.g., sTNFRII, CXCL10, D-Dimer) as well as profoundly higher $CD8^+$ T cell counts and lower

$CD4^+/CD8^+$ T cell ratios compared to CMV-seronegative adults [Freeman et al., 2016; Limaye et al., 2017; Smith et al., 2016].

sCD163, IL-6, and hsCRP have been associated with CMV infection and predict morbidity and mortality in treated HIV infection. Given that CMV has been shown to stimulate the expression of thrombogenic activity on cells independent of vascular damage, and to promote cell-independent thrombin production, we will also collect citrated plasma samples (collected into conventional blue top tubes containing 3.2% sodium citrate) and measure D-Dimer (among other coagulation markers in exploratory markers).

CMV and HIV DNA Reservoir

Chronic inflammation and immune activation contribute to maintenance of the HIV reservoir during ART [Christensen-Quick et al., 2017; Hatano, 2013]. Recent studies have demonstrated that asymptomatic CMV seminal shedding is associated with higher levels of total HIV DNA in both ART naïve individuals [Gianella et al., 2012] and in individuals suppressed on long-term ART [Gianella et al., 2014]. In a large longitudinal study of individuals followed since the earliest phase of HIV infection, $CD4^+$ T cell associated HIV DNA in blood was associated with the frequency of detectable CMV DNA in blood cells over time [Gianella et al., 2015]. Although the observational design of these studies does not allow causal inference, the findings do support the conclusion that asymptomatic CMV shedding in genital secretions and in blood drives local and systemic immune activation with a subsequent increase in the latent HIV reservoir. For this reason, targeting drivers of chronic inflammation, like CMV, could contribute to HIV curative strategies. We will use longitudinal blood samples collected as part of this trial to determine the effect of suppressing CMV replication with letermovir on HIV persistence, in terms of circulating reservoir size and clonality as well as to explore the mechanisms underlying these changes (assays will be funded through a funded NIAID R01 to Dr. Gianella).

Evidence for a Causal Role of CMV Driving Immune Activation in Treated HIV Infection

The link between CMV shedding and systemic inflammation during HIV infection has been examined in a randomized controlled study conducted by Dr. Hunt that showed a reduction in T cell immune activation when people with HIV were treated with the anti-CMV drug valganciclovir [Hunt et al., 2011]. Recent analysis of samples from this trial further revealed nearly an entire quartile reduction in sTNFRII as well as significant reductions in sCD163 and sCD14 levels in the valganciclovir arm [Beck-Engeser et al., 2019], strongly suggesting an immunologic benefit of treating asymptomatic CMV co-infection in this setting (Refer to Figure 2.2-1). While this study was limited in that only 70% of the participants had HIV RNA suppression with ART (though there was a significant effect on immune activation even in the ART-suppressed subset) and the sample size was small (n=30), it did show a sustained reduction in CMV shedding and immune activation after just 8 weeks that persisted for at least 4 weeks after valganciclovir discontinuation. The findings support our hypothesis about CMV shedding and immune activation. If correct, the anti-inflammatory benefit of reducing CMV replication could accumulate over time, which may support a study of intermittent use of anti-CMV therapy.

While this prior trial of valganciclovir remains one of the few anti-CMV interventional trials that demonstrated improvement in immune activation, the trial had several limitations that precluded moving forward with clinical endpoint trials of anti-CMV therapy. *First*, valganciclovir's toxicity (cytopenias and teratogenicity) creates challenges for long-term use. *Second*, insufficient evidence was generated to definitively conclude that key inflammatory pathways that predict disease outcome (e.g., other inflammatory markers, $CD4^+/CD8^+$ ratio) or cardiovascular surrogate markers were affected. The trial's short 8-week duration also limited the analysis of longer-lived T cell subsets like effector and senescent T cells. For example, terminally differentiated effector memory (TEMRA) $CD4^+$ T cells from ART-suppressed individuals, which are dominated by CMV-specific cells, have an average half-life of nearly 9 months. TEMRA $CD8^+$ T cells also appear quite long-lived in simian immunodeficiency virus (SIV) models using similar direct measures of cellular turnover [Hansen et al., 2013a; Hansen et al., 2013b]. Thus, many months of suppression of CMV replication may be required to stop and/or reverse the negative contribution of CMV-specific effector $CD8^+$ T cells to end-organ disease. Enrollment in the above trial was also limited to individuals with incomplete $CD4^+$ T cell recovery on ART (all $CD4^+<350$). Thus, it remains unclear whether inhibiting CMV shedding would benefit immune activation in individuals with normal $CD4^+$ T cell count recovery on ART. Lastly, there were very few female participants in the valganciclovir trial, and as the effects of chronic viral infections on the immune system may differ by sex [Meier et al., 2009], it is unclear whether treating CMV would have the same or perhaps even greater effects among female participants. These issues will be addressed in the current protocol.

Lastly, it is possible that CMV-mediated interferon-γ expression might actually contribute to more robust humoral responses to influenza. Indeed, in a recent study of healthy young adults without HIV receiving seasonal influenza vaccination, those who were CMV-seropositive had a greater fold-increase in influenza-specific IgG titers following vaccination than those who were CMV-seronegative [Furman et al., 2015]. In that same publication, CMV-induced interferon-γ expression was shown to mediate enhanced protection against influenza challenge in a murine model. While it is unlikely that these CMV-associated differences in flu vaccine response are clinically significant, our trial provides an opportunity to test the hypothesis that asymptomatic CMV replication contributes to influenza vaccine response for the first time in humans.

CMV and Neurocognitive Dysfunction

The CNS is a long-recognized site of CMV end-organ disease in advanced AIDS (e.g., retinitis, periventriculitis). Pathological changes at postmortem in Alzheimer's disease have been linked to CMV. For instance, brain tissue donated by Catholic clergy with few confounding conditions showed that higher lifetime anti-CMV IgG titers were associated with the presence of neurofibrillary tangles at death [Lurain et al., 2013]. CMV-infected individuals in the early stages of multiple sclerosis showed greater generalized brain atrophy over time than CMV-participants [Zivadinov et al., 2014].

Further, Dr. Letendre recently reported that higher anti-CMV IgG titer was associated with greater neurocognitive impairment in the CHARTER study [Letendre et al., 2018], a finding reminiscent of data generated in HIV-uninfected elderly individuals [Roberts et

al., 2010]. While CMV DNA was found in few cerebrospinal fluid (CSF) samples in the small, cross-sectional CHARTER analysis, a role for migrating CMV-specific $CD8^+$ T cells or low-level CMV replication in the brain cannot be excluded.

Similarly, a role of CMV in contributing to psychiatric diseases like depression and sleep disturbance have been debated in the psychiatry field [Simanek et al., 2014] and our own team has generated some data linking the immune activation pathways thought to be driven by CMV to depression in HIV infection [Martinez et al., 2014]. Kiecolt-Glaser and Glaser demonstrated in the 1980s that periods of psychological stress can lead to the reactivation of CMV [Glaser et al., 1985; Kiecolt-Glaser et al., 1984; Kiecolt-Glaser et al., 1988] and this finding has been borne out by more recent studies that have also highlighted the association between psychological stressors and herpesvirus titers [Fagundes et al., 2013; Janicki-Deverts et al., 2014; Shirtcliff et al., 2009]. Several studies have reported higher IgG CMV antibody titers in depressed vs. non-depressed participants with cardiovascular disease [Appels et al., 2000; Miller et al., 2005; Rector et al., 2014] and higher IgM titers were found to be associated with suicide attempts in participants with mood disorders [Dickerson et al., 2017]. Recently, the Detroit Neighborhood Health Study showed that individuals with CMV antibody titers in the top quartile were four times more likely to be depressed than those individuals in the bottom three quartiles of the population [Simanek et al., 2014].

Determining whether inhibiting low-level CMV shedding improves neuroinflammation, neuronal injury, neurocognitive performance, and mood is highly relevant to the ACTG Neurology Collaborative Science Group scientific agenda. We have included brief assessments and a plasma biomarker of brain damage (NFL concentration) as part of this protocol and plan to develop a separate sub-study to perform lumbar punctures and detailed neurocognitive and mood assessment.

CMV and Physical Function and Frailty

In addition to the neurocognitive effects, chronic CMV has also been associated with frailty, in part through greater CMV-associated inflammation [Margolick et al., 2018; Schmaltz et al., 2005; Wang et al., 2010]. Frailty, a key aging-related syndrome of vulnerability, is characterized by a loss of physiologic reserve, resulting in decreased resiliency to stressors and ultimately an increased risk for hospitalization, institutionalization, or death [Fried et al., 2001]. Frailty is commonly defined through a phenotype of weakness (grip strength), slowness (by 4-m walking speed), weight loss, exhaustion, and fatigue.

Even with long-term, effective ART, impairments in physical function and frailty are more common than expected among people aging with HIV [Hawkins et al., 2018], and have been associated with an increased risk of falls, hospitalizations, and mortality [Erlandson et al., 2019; Tassiopoulos et al., 2017]. Furthermore, the combination of both HIV infection and impaired physical function is associated with a greater risk of mortality than the presence of HIV infection or impaired function alone [Greene et al., 2014; Piggott et al., 2015].

While more common than uninfected populations, frailty is relatively uncommon in middle-aged populations of persons with HIV (6% in the ACTG HAILO cohort [Erlandson et al., 2017]), with limited ability to detect change in the categorical scoring due to few frail cases. Individual objective components of frailty score assessing physical function such as the ability to rise from a chair, gait speed, and grip strength have similar clinical outcomes while using continuous outcomes to maximize power and detect changes across a wider range of function. Chair rise time for example, is a well-established measure of lower extremity strength, is associated with morbidity and mortality in the general population, and is a measure that is the most likely to show deficits compared to other physical function components [Cesari et al., 2008; Erlandson et al., 2012; Greene, et al., 2014].

The population of adults aging with HIV is an emerging risk group for the accelerated development of mobility disability, and interventions to delay and prevent physical function impairments and frailty, and improve quality of life, are needed. CMV seropositivity, as measured by qualitative or quantitative CMV IgG or CMV-associated T-cell responses have been associated with frailty in the general geriatric population [Margolick et al., 2018; Schmaltz et al., 2005; Wang et al., 2010], and frailty and physical function impairment in adults with HIV [Erlandson et al., 2015]. Whether CMV-specific therapy can alter physical function or frailty, however, is not known.

Clinical Data Supporting Letermovir

Letermovir (Prevymis) is a CMV DNA terminase complex inhibitor that is FDA-approved for prophylaxis of CMV infection and disease in adult CMV-seropositive recipients of an allogeneic hematopoietic stem cell transplant (alloHSCT) [Bowman et al., 2017; Maidji et al., 2017; Marty et al., 2017]. Letermovir also has a better safety profile than valganciclovir. To evaluate prophylaxis with letermovir as a preventive strategy for CMV disease in transplant recipients at high risk for CMV reactivation, the efficacy of letermovir was assessed in a multicenter, double-blind, placebo-controlled phase III trial in 565 adult CMV-seropositive recipients of an alloHSCT. Participants were randomized to receive either letermovir at a dose of 480 mg once daily (adjusted to 240 mg when co-administered with cyclosporine), or placebo. Study treatment was initiated shortly after alloHSCT and continued through week 14 post-transplant. Participants were monitored through week 24 post-transplant for the primary efficacy endpoint, with continued follow-up through week 48 post-transplant. The primary efficacy endpoint was the incidence of clinically significant CMV reactivation through 24 weeks post-transplant, defined as the occurrence of either CMV end-organ disease, or initiation of anti-CMV pre-emptive therapy based on documented CMV viremia and the clinical condition of the participant.

Letermovir demonstrated significant benefit compared to placebo in regard to clinically significant CMV disease through week 24 post-hematopoietic stem cell transplantation (HSCT) (18.9% vs. 44.3% cumulative rate; stratified log-rank test, two-sided p-value <0.0001), though this difference narrowed after discontinuation of therapy and longer duration of follow up. Through the week 14 post- HSCT treatment period (during letermovir therapy), 8% of participants in the letermovir group and 39% of participants in the placebo group experienced clinically significant CMV disease. Efficacy results were consistent across high- and low-risk strata for CMV reactivation and was generally

considered safe in terms of safety and tolerability. For the primary efficacy endpoint (risk of clinically significant CMV infection at week 24 post-HSCT), no exposure-response relationship was observed.

Letermovir Safety
While there were fewer adverse events in the letermovir than placebo arms of the registrational trial among HSCT recipients, supporting its overall better safety profile than valganciclovir, cardiac events were more frequent with letermovir than placebo (12.6% versus 6.3%). These events included 15 cases of tachycardia (4%), 4 cases of sinus tachycardia (1.1%), 13 cases of atrial fibrillation (3.5%), 4 cases of atrial flutter (1.1%), and 5 cases of cardiac failure (1.3%). No ischemic events were reported. All of these events were Grade 2 or less and preclinical data do not suggest a clear mechanism by which letermovir might increase tachycardia or atrial arrhythmias. Nevertheless, electrocardiography (ECG) monitoring would be prudent in our planned trial as well as specific monitoring for cardiovascular events.

In a fertility and early embryonic development study in rats, no effects of letermovir on female fertility were observed at letermovir exposures (AUC) approximately 5 times higher than human exposure at the recommended human dose (RHD). In male rat fertility studies, decreased fertility associated with irreversible testicular toxicity was observed at ≥180 mg/kg/day (≥3 times the human exposure at the RHD). No fertility or testicular effects were observed at dose levels resulting in letermovir exposures (AUC) similar to human exposure at the RHD) [Merck Sharp & Dohme Corp. Prevymis-letermovir Prescribing Information, 2017].

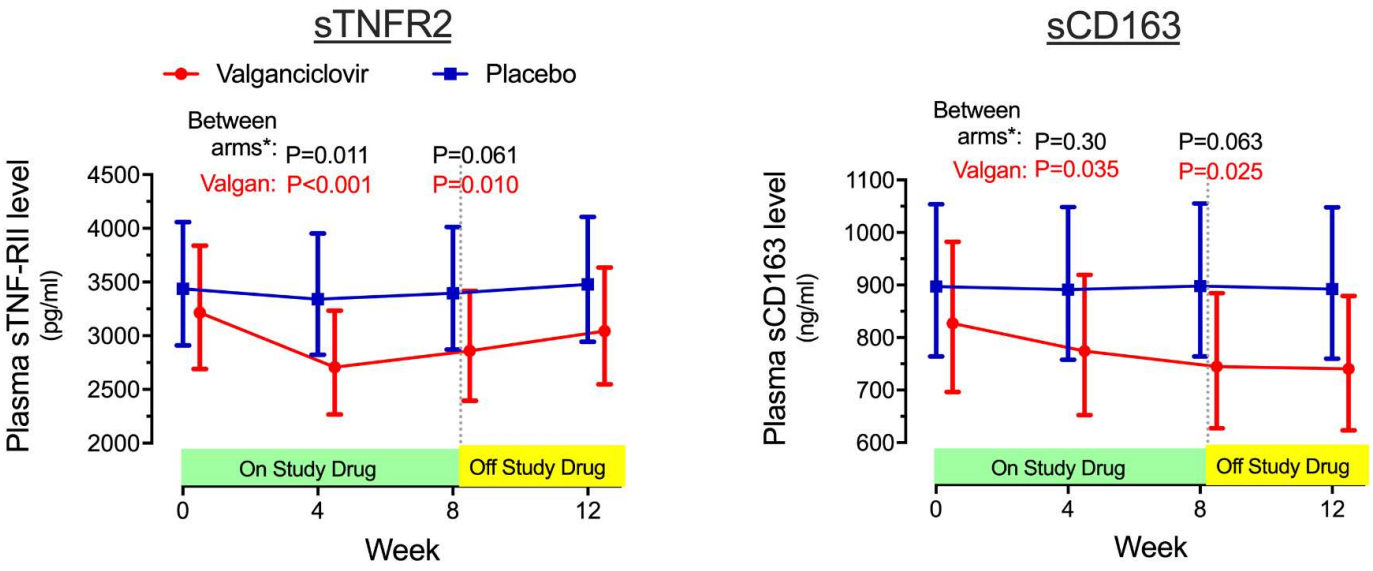
Letermovir Resistance
Of note, letermovir has a lower genetic barrier to resistance as compared to gangiclovir, and is currently approved for CMV prophylaxis. CMV replication in the setting of HIV-infection is mostly intermittent and low level and we expect that the potency of letermovir is enough to control CMV replication without developing CMV resistance in this setting.

Letermovir Pharmacology
See Pharmacology Plan, section 11.0. We propose to obtain plasma for future exploratory analyses to assess for potential PK drug interactions and exposure-response (PK/PD) between letermovir levels and study outcomes.

2.2 Rationale

Rationale for Choice of Primary Inflammatory Endpoint
The primary immunologic endpoint for the trial is the change in sTNFRII in blood from baseline to week 48 (measured by ELISA). This endpoint was chosen since sTNFRII is much higher among CMV-seropositive than CMV-seronegative individuals with HIV maintaining ART-mediated viral suppression [Freeman et al., 2016]. Also sTNFRII strongly predicts all-cause mortality, composite non-AIDS events, and specifically cardiovascular events in this setting [Tenorio et al., 2014; Hoenigl et al., 2019]. After binding with its ligand tumor necrosis factor alpha (TNFα), sTNFRII is shed from the cell surface; therefore, sTNFRII is used as a surrogate marker for TNFα [Valle et al., 2009;

Centers for Disease Control and Prevention (CDC), 2013]. We also prefer to measure sTNFRII as the primary endpoint since TNFα is produced not just by myeloid cells, but also $CD8^+$ T cells, which may be playing an important role in the pathogenesis of cardiovascular disease in treated HIV infection. We elected not to choose T cell activation as a primary endpoint as it has been less useful than innate or inflammatory markers in predicting clinical events in resource-rich settings, particularly in cardiovascular complications [Tenorio et al., 2014]. We also considered making $CD4^+/CD8^+$ ratio a primary endpoint marker as this predicts non-AIDS events and is also profoundly affected by CMV infection but chose sTNFRII as an outcome as it may provide more mechanistic insights. The $CD4^+/CD8^+$ ratio will nevertheless be an important secondary immunologic outcome. Moreover, we also chose 48 weeks as a duration to assess response precisely because the $CD8^+$ T cells that produce TNFα in response to CMV antigens or CMV-associated inflammation may be much longer-lived than previously appreciated. We will also assess earlier time points to determine whether TNFα signaling (i.e., sTNFRII level) or $CD8^+$ T cell counts is affected first by reducing CMV shedding with letermovir.



**P values test difference in the change from baseline between treatment arms at each timepoint (linear mixed model).*

Figure 2.2-1: Reduction of sTNFRII and sCD163 during valganciclovir treatment. Valganciclovir caused greater reductions (~1 quartile) in sTNFRII at 4 and 8 weeks than placebo, and nearly a quartile reduction in sCD163. Both sTNFRII and sCD163 declined to a greater degree with valganciclovir than placebo at week 8 after adjustment for concurrent fluctuations in plasma HIV RNA levels (P=0.027 and P=0.013 respectively).

Preliminary Data for sTNFRII

Dr. Hunt's lab pulled plasma samples from the original valganciclovir trial and assessed sTNFRII levels (R&D Systems, Inc. Kit) and observed significantly greater reductions in the valganciclovir arm than placebo at 4 and 8 weeks (P=0.011 and P=0.061; P values adjusted for concurrent fluctuations in plasma HIV RNA levels both <0.03; see Figure

2.2-1). The magnitude of this reduction in sTNFRII levels corresponded with an approximately 22% decreased risk of subsequent myocardial infarction (MI)/stroke in ACTG NWCS 329 [Tenorio et al., 2014].

In these preliminary data, higher baseline sTNFRII levels were strongly associated with greater frequencies of ($CD38^+HLA\text{-}DR^+$) $CD8^+$ T cells (rho: 0.62, P<0.001), and with lower $CD4^+/CD8^+$ ratios (rho: -0.33, P=0.08). Baseline sTNFRII was also strongly associated with plasma kynurenine-to-tryptophan (KT) ratio (rho: 0.82, P<0.001), which has been linked to mortality, atherosclerosis, and depression in treated HIV infection. These data increase our confidence that baseline sTNFRII is an appropriate primary immunologic endpoint for our trial, and also that we will be able to observe a significant impact on this endpoint early (within the first 4-8 weeks of treatment). Subsequent analyses revealed significantly greater reductions in sCD163 (approximately 2/3 of a quartile reduction) in the valganciclovir arm than placebo at week 8 (unadjusted P=0.063, P=0.013 after adjustment for concurrent fluctuations in low-level plasma HIV RNA levels), supporting this marker's use as a secondary immunologic marker in the planned futility analysis.

Physical Function and Frailty Measures
Repeat chair stand is a functional test of lower extremity performance that is highly affected by changes in muscle strength and has been proposed as a proxy measure of lower-extremity strength for the clinical setting [Cesari et al., 2008; Dodds et al., 2018]. The test requires minimal equipment (a stopwatch and a chair without arms or wheels), can be completed within approximately 1 minute, and is an assessment that ACTG sites already have experience conducting. Additional frailty measures including gait speed, grip strength, and subjective components of weight loss, exhaustion, and fatigue are already conducted at nearly all ACTG sites through protocol A5322/HAILO and will add minimal additional time.

Changes in muscle or frailty may occur with letermovir therapy and may have important physiologic consequences.

Futility Analysis
The week 8 futility analysis will consist of two immunologic outcomes, sTNFRII and sCD163, since both of these biomarkers were reduced by nearly a quartile in the prior valganciclovir trial. While there is no standard threshold for stopping a clinical trial for futility, we feel that consideration should be given to stopping the trial early if both the sTNFRII and sCD163 futility analyses have conditional power <20% under a range of plausible scenarios. The Study Monitoring Committee (SMC) will determine if the trial should be stopped early. The futility analysis begins after the first 40 participants who initiate study treatment have reached their 8 week study visit. New enrollment will pause after the 40^{th} participant starts treatment and until the results of the futility analysis have been considered.

Rationale for specific design choices:
Age restriction: Enrollment is limited to adults ≥40 years of age as letermovir is indicated for adults [Prevymis package insert, 2017], the risk of multimorbidity is higher with older age, and enrichment for those expected to benefit most from the intervention is desired.

Stratification by CD4 count: Enrollment will be stratified based on screening $CD4^+$ T cell count (<350 cells/mm^3 or ≥350 cells/mm^3). The rationale for this is to have a more direct comparison with the earlier valganciclovir trial (there has been no head to head comparison of letermovir versus valganciclovir for CMV suppression) and to explore whether there may be a role for CMV suppression to reduce immune activation not just among those with incomplete $CD4^+$ T cell recovery, but also among those with preserved $CD4^+$ T cell counts.

Rationale for stratification by gender/sex: Since sex differences in immune response to viral infections have been described (both related to genetics and to hormonal status), we will also stratify by sex assigned by birth and gender-affirming exogenous sex hormone use.

Rationale for observation after treatment discontinuation: Participants will be observed for up to 12 weeks after treatment discontinuation as the prior trial of valganciclovir showed a persistent effect on CMV shedding and immunologic outcomes for at least 4 weeks after treatment discontinuation, which has been hypothesized to be a consequence of the reduction in immune activation (which typically promotes CMV shedding) [Hunt et al., 2011]. Interestingly, a similar 4-week delay in the emergence of CMV end-organ disease was observed in the registrational trial of letermovir following treatment discontinuation.

3.0 STUDY DESIGN

A5383 is a phase II, randomized, open-label, controlled, multicenter trial being conducted at US clinical research sites (CRSs) to evaluate the anti-inflammatory efficacy of letermovir 480 mg once daily for 48 weeks in adults with asymptomatic CMV and HIV-1 with ART-mediated suppression.

A total of 180 participants ≥40 years of age with plasma HIV RNA **<75 copies/ml using an FDA-approved assay and who have been on combination ART** for at least 48 weeks and who meet eligibility criteria will be randomized 1:1 to receive letermovir (Arm A) or no anti-CMV treatment (Arm B) for 48 weeks, followed by 12 weeks of observation on ART alone. The total study duration is 60 weeks. Participants will have evaluations per section 6.1.

Enrollment will be stratified based on sex assigned at birth and use of hormonal therapy and by screening $CD4^+$ T cell count. The goal is to have one third of participants in each arm be individuals assigned female sex at birth who are not using testosterone or individuals assigned male sex at birth on feminizing sex hormones. Further, the study aims to enroll half of all participants in each arm with $CD4^+$ T cell counts <350 cells/mm^3. Special outreach to transgender and gender non-binary persons will be encouraged with a primary stratified analysis conducted based on assigned sex at birth and use of hormonal therapy. Supplemental analyses will be conducted based on self-identified gender identity and by sex assigned at birth.

At study entry (pre-treatment), all participants will have evaluations to establish a stable assessment of biomarkers including genital CMV shedding, IL-6, D-dimer, sCD163, and sTNFRII. Peripheral blood will be drawn, and genital and oral secretion collection will occur. Treatment will be initiated (week 0) after all required pre-treatment evaluations have been completed. Treatment initiation must occur between 2 and 30 days after study entry (pre-treatment). Participants will have blood, genital, and oral secretions collected throughout the study.

An ECG will be performed for all participants at screening and vital signs will be assessed at all visits. Post-screening, if a participant's resting heart rate (HR) is >100 beats per minute (bpm), **the participant has an irregular rhythm or complains of new palpitations,** study clinicians will be instructed to obtain an ECG, particularly to screen for new atrial arrhythmias.

A futility analysis will be conducted after the first 40 participants to initiate study treatment reach their week 8 study visit. Study enrollment will be paused after the 40th participant starts treatment and until the results of the futility analysis have been considered.

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

4.1.1 HIV-1 infection, documented by any licensed rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit at any time prior to study entry and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or by HIV-1 antigen, plasma HIV-1 RNA viral load.

NOTE: The term "licensed" refers to a US FDA-approved kit, which is required for all IND studies.

World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) guidelines mandate that confirmation of the initial test result must use a test that is different from the one used for the initial assessment. A reactive initial rapid test should be confirmed by either another type of rapid assay or an E/CIA that is based on a different antigen preparation and/or different test principle (e.g., indirect versus competitive), or a Western blot or a plasma HIV-1 RNA viral load.

4.1.2 Currently on continuous combination ART for ≥48 weeks prior to study entry. This is defined as continuous ART for **at least** the 48-week period prior to study entry with no ART interruption longer than 7 consecutive days.

4.1.3 Screening plasma HIV-1 RNA **<75 copies/ml** within 90 days prior to study entry using a FDA-approved assay with a quantification limit of **75** copies/mL or lower

performed by any US laboratory that has a Clinical Laboratory Improvement Amendments (CLIA) certification or its equivalent.

4.1.4 Plasma HIV-1 RNA level **<75 copies/ml (using an assay with a quantification limit of 75 copies/mL or lower)** for at least 48 weeks prior to study entry performed by any US laboratory that has a CLIA certification or its equivalent.

NOTE: Single determinations that are between 75 and 500 copies/mL (i.e., "blips") are allowed as long as the preceding and subsequent determinations are <75 copies/ml. The screening value may serve as the subsequent value <75 copies/ml following a blip. **In the 48 weeks prior to study entry, no more than three "blips" are allowed and consecutive values >75 copies/ml during this period are not allowed. If no plasma HIV RNA levels were measured in the 48 weeks prior to screening, participants can still be eligible if their last available plasma HIV RNA level prior to this period was <75 copies/ml and they have not experienced an ART interruption of longer than 7 days in the last 48 weeks.**

4.1.5 $CD4^+/CD8^+$ cell count obtained within 90 days prior to study entry at any US laboratory that has a CLIA certification or its equivalent.

4.1.6 Positive CMV IgG serology, at any time prior to study entry using a FDA-approved assay at any US laboratory that has a CLIA certification or its equivalent.

NOTE: If a prior positive CMV IgG serology test is confirmed in the medical record, a repeat CMV IgG test is not required at screening.

4.1.7 The following laboratory values obtained within 90 days prior to study entry by any US laboratory that has a CLIA certification or its equivalent.

- Hemoglobin >9.0 g/dL
- Platelet count >75,000/mm^3
- Aspartate aminotransferase (AST) (SGOT), alanine aminotransferase (ALT) (SGPT), and alkaline phosphatase ≤3 × ULN
- Total bilirubin ≤2.5 x ULN
- NOTE: If an individual is taking an atazanavir-containing regimen at the time of screening, a total bilirubin of ≤5 x ULN is acceptable.
- Estimated Glomerular Filtration Rate (eGFR) >30 mL/min/1.73m^2 or creatinine clearance (CrCl) >30 mL/min using the Cockcroft-Gault, EPI-GFR, or MDRD equations located on the **A5383 PSWP**.

4.1.8 For individuals assigned female sex at birth and of reproductive potential, negative serum or urine pregnancy test within 24 hours prior to study entry by any US clinic or laboratory that has a CLIA certification or its equivalent or a CLIA Certificate of Waiver for those performing a point of care (POC)/ CLIA-waived test. (Urine test must have a sensitivity of <25 mIU/mL.).

NOTE: Persons of female sex assigned at birth and of reproductive potential are defined as having reached menarche and have not been post-menopausal for at least 24 consecutive months (i.e., have had menses within the preceding 24 months), and have not undergone testosterone therapy for gender alignment or surgical sterilization such as hysterectomy, bilateral oophorectomy, tubal ligation, or salpingectomy. An individual's report is considered acceptable documentation of reproductive status.

4.1.9 All participants **must agree to use at least one of the following types of** contraception throughout the study **when participating in sexual activity that could lead to pregnancy:**

- Diaphragm or cervical cap with spermicide
- Intrauterine device (IUD)
- Hormone-based contraceptive
- Condoms with or without a spermicide

NOTE A: Individuals who are not of reproductive potential are not required to use contraception.

NOTE B: Sperm-producing participants should refrain from donating sperm during the treatment period and for at least 90 days after the last dose of study treatment. **Similarly, ovulating participants should refrain from egg donation during the treatment period and for at least 90 days after the last dose of study treatment.**

4.1.10 Persons age ≥40 years.

4.1.11 Ability and willingness of individual or legal guardian/representative to provide informed consent.

4.2 Exclusion Criteria

4.2.1 Change in the ART regimen within 12 weeks prior to study entry or intended modification of ART during the study.

NOTE: Modifications in the dosage or frequency (i.e., twice a day [bid] to once a day [qd]) of individual antiretroviral (ARV) drugs during the 12 weeks prior to study entry are permitted. In addition, the change in formulation (e.g., from standard formulation to fixed-dose combination) is allowed within 12 weeks prior to study entry. A within class single drug substitution (e.g., switch from atazanavir to darunavir, or tenofovir disoproxil fumarate to tenofovir alafenamide) is allowed within 12 weeks prior to study entry. A switch to any other nucleoside reverse transcriptase inhibitor (NRTI) from abacavir (or vice versa) is not permissible. No other changes in ART within the 12 weeks prior to study entry are permitted.

4.2.2 Use of any of the following ARV drugs in current regimen: efavirenz, nevirapine, etravirine, lopinavir/ritonavir, and**/or** once-daily dosing of raltegravir (bid dosing of raltegravir is acceptable).

4.2.3 Two or more HIV-1 RNA determinations >200 copies/mL within **the** 48 weeks prior to study entry.

4.2.4 Any febrile illness (>101°F) within 30 days prior to study entry.

4.2.5 **Symptomatic SARS-CoV-2 or monkeypox infection in the past 30 days, with or without antiviral therapy.**

4.2.6 Use of drugs with anti-CMV activity within 90 days prior to study entry, with the exception of standard-dose valacyclovir and acyclovir.
NOTE: Refer to section 5.4.2 for a list of drugs with anti-CMV activity that are not acceptable. For any anti-CMV activity drug not listed, sites must consult the Clinical Management Committee (CMC).

4.2.7 **Systemic** Immunosuppressive or immunomodulatory drug use **as well as systemic drugs with immunemodulatory effects** within 90 days prior to study entry **(topical, inhaled, and/or intranasal are allowed)**.

NOTE A: Refer to sections 5.4.2 and 5.4.3 for details on prohibited immunomodulatory drugs and the use of statins. Statin use is allowed as long as **the dose is** stable dose for at least **the** 90 days **prior to study entry and within the allowable dosage limits [see section 5.4.3].**

NOTE B: For any immunosuppressive or immunomodulatory drugs **(or drugs of immune modulatory potential)** not listed, sites must consult with the CMC.

4.2.8 Concomitant use of prohibited medications listed in section 5.4.2.

4.2.9 Persons who are **currently** breastfeeding **or** pregnant, or **persons** planning to become pregnant during the study.

4.2.10 Participating in a study where co-enrollment is not allowed (see section 4.4).

4.2.11 Receipt of any vaccination within 14 days prior to study entry

4.2.12 Presence on screening ECG or a known history of atrial tachycardia (other than sinus tachycardia). Ventricular tachycardia is also an exclusion criterion.

4.2.13 History of cardiomyopathy or congenital heart disease or evidence of advanced conduction system disease including second degree heart block Mobitz type II, third degree heart block, AV dissociation or ECG findings that may be suggestive of predisposition to arrhythmia (i.e., delta wave).

4.2.14 Known allergy/sensitivity or any hypersensitivity to components of the study drug or its formulation.

4.2.15 Active drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements.

4.2.16 **S**erious illness requiring systemic treatment and/or hospitalization within 90 days prior to study entry. **Minor illnesses like a sinus infection requiring oral antibiotics or STD exposure requiring antibiotics are not exclusionary. Non-hospitalized but symptomatic SARS-CoV-2 and monkeypox infections are covered separately under exclusion 4.2.5.**

4.2.17 Known active hepatitis B virus infection within the last 24 weeks prior to study entry.

NOTE: **Known currently a**ctive is defined as hepatitis B surface antigen (HBsAg) positive and hepatitis B DNA (HBV DNA) positive. Persons with HBV DNA below level of quantification (BLQ) for >24 weeks prior to study entry are eligible. **If no testing is available in the 24 weeks prior to study entry, and there is no clinical suspicion for currently active hepatitis B virus infection, HBV labs are not necessary to obtain at screening.**

4.2.18 Known active hepatitis C within the last 24 weeks prior to study entry.

NOTE: **Known currently a**ctive is defined as a detectable plasma hepatitis C virus (HCV) RNA level. Persons with HCV RNA BLQ for >24 weeks prior to study entry are eligible. **If no testing is available in the 24 weeks prior to study entry, and there is no clinical suspicion for currently active hepatitis C virus infection, HCV labs are not necessary to obtain at screening.**

4.2.19 Presence or history of conditions that could account for impaired neuropsychological performance, including head injury with prolonged (>1 hour) loss of consciousness, central nervous system infection (e.g., encephalitis), severe learning disability, psychosis, and/or active drug or alcohol use, or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements.

4.2.20 History of multi-class HIV drug resistance or intolerance, such that in the opinion of the investigator, an alternative fully active antiretroviral regimen cannot be constructed should the participant experience loss of viral suppression on their current regimen during the study.

4.3 Study Enrollment Procedures

4.3.1 Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent form(s) approved, as appropriate, by the institutional review board (IRB)/ethics committee (EC) and any

other applicable regulatory entity (RE) responsible for oversight of the study. Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific informed consent forms (ICFs) WILL be reviewed and approved by the DAIDS PRO, and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approvals for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all required documents have been received. Site-specific ICF(s) *WILL NOT* be reviewed and approved by the DAIDS PRO, and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

Once an individual for study entry has been identified, details will be carefully discussed with the participant. The participant will be asked to read and sign the approved protocol consent form.

Participants from whom a signed informed consent has been obtained may be screened and enrolled, if they otherwise qualify. An ACTG Screening Checklist must be entered through the DMC **Study** Enrollment System.

4.3.2 Protocol Activation

Prior to enrollment, sites must complete the Protocol Activation Checklist found on the ACTG Member website. This checklist must be approved prior to any screening of participants for enrollment.

4.3.3 Randomization

For participants from whom informed consent has been obtained, but who are deemed ineligible or who do not enroll into the initial protocol step, an ACTG Screening Failure Results form must be completed and keyed into the database. Participants who meet the enrollment criteria will be registered to the study according to standard ACTG DMC procedures.

4.4 Co-enrollment Guidelines

- Sites are encouraged to co-enroll participants in A5128, “Plan for Obtaining Informed Consent to Use Stored Human Biological Materials (HBM) for Currently Unspecified Analyses.” Co-enrollment in A5128 does not require permission from the A5383 protocol chairs.
- Co-enrollment in CMV Vaccine study A5355 and/or REPRIEVE is not permitted.

  NOTE: Co-enrolled REPRIEVE participants may participate in the A5383 study as long as they are no longer taking REPRIEVE study product (for at least six months) and in follow-up only. Potential A5383 participants must agree not to resume REPRIEVE study product while participating in the A5383 study.

- For specific questions and approval for co-enrollment in other studies, sites should first check the PSWP or contact the protocol team via e-mail as described in the Study Management section.

5.0 STUDY TREATMENT

Study treatment is defined as letermovir, which will be provided by the study.

Required background ART regimens will not be provided by the study.

5.1 Regimens, Administration, and Duration

5.1.1 Regimens

Eligible participants will be randomized (1:1) to either 48 weeks of treatment with letermovir or no study treatment as follows:

- Arm A: letermovir 480 mg orally once daily
- Arm B: no anti-CMV treatment

5.1.2 Administration

Letermovir 480 mg will be administered by one of the following strategies:

- Letermovir 240 mg tablets administered orally as two tablets once daily with or without food.
- Letermovir 480 mg tablets administered orally as one tablet once daily with or without food.

Participants will be able to switch administration strategy during treatment duration based on availability of study supply.

5.2 Study Product Formulation and Storage

Letermovir, labeled as PREVYMIS, will be provided as both 240 mg and 480 mg tablets based on study product availability.

Letermovir 240 mg tablets are yellow, oval tablets debossed with “591” on one side and Merck logo on the other side. Tablets are packaged into a carton containing 2 or 4 Child Resistant (CR) Dosepaks®, each containing a 7-count blister card for a total of 14 or 28 tablets.

Letermovir 480 mg tablets are pink, oval, bi-convex tablets debossed with “595” in one side and Merck logo on the other side. Tablets are packaged into a carton containing 2 or 4 Child Resistant (CR) Dosepaks®, each containing a 7-count blister card for a total of 14 or 28 tablets.

Store Letermovir tablets at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

5.3 Pharmacy: Product Supply, Distribution, and Accountability

5.3.1 Study Product Acquisition/Distribution

Letermovir is manufactured and supplied by Merck and Company, Inc. and is available through the NIAID Clinical Research Products Management Center (CRPMC). The site pharmacist should obtain the study product(s) for this protocol by following the instructions in the manual *Pharmacy* Guidelines and Instructions for DAIDS Clinical Trials Networks.

5.3.2 Study Product Accountability

The site pharmacist is required to maintain complete records of all study products received from the NIAID CRPMC and subsequently dispensed. All unused study products must be returned to the NIAID CRPMC (or as otherwise directed by the sponsor) after the study is completed or terminated. The procedures to be followed are provided in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.*

5.4 Concomitant Medications

Whenever a concomitant medication or study agent is initiated or a dose changed, investigators must review the concomitant medication’s and study agent’s most recent package insert, Investigator’s Brochure, or updated information from DAIDS to obtain the most current information on drug interactions, contraindications, and precautions.

Additional drug information may be found on the ACTG Precautionary and Prohibited Medications Database located at http://tprc.pharm.buffalo.edu/home/di_search/.

5.4.1 Required Medications

All participants will be requested to continue their ongoing ART regimen for the duration of the study. ART will not be provided by the study. Refer to inclusion criterion 4.1.2 and exclusion criteria 4.2.1 and 4.2.2 for ART regimen requirements.

5.4.2 Prohibited Medications

- Pimozide, ergotamine, dihydroergotamine, and nafcillin.
- Anti-convulsants: phenytoin, carbamazepine, phenobarbital.
- Antimycobacterials: rifabutin, rifampin.
- Anti-psychotics: thioridazine.
- Endothelin antagonists: bosentan.
- Herbal products: St. John's Wort.
- Wakefulness-Promoting agents: modafinil.
- Other CMV drugs including valganciclovir, ganciclovir, foscarnet, and cidofovir.
- Other ARV drugs including efavirenz, nevirapine, etravirine, lopinavir/ritonavir and once-daily dosing of raltegravir (bid dosing of raltegravir is acceptable).
- **Systemic i**mmunomodulatory or immunosuppressive therapies. **Examples include but are not limited to: c**yclosporine, sirolimus, tacrolimus, Interferons, Interleukins, **growth hormone agonists,** systemic cytotoxic. chemotherapy, and systemic glucocorticoids. **T**opical, inhaled, and intranasal **immunomodulatory or immunosuppressive therapies** are allowed.
- Statins: pitavastatin (**see section 4.4 for** REPRIEVE trial participation) and simvastatin are not allowed at any dose. See precautionary medications below (5.4.3.) for allowable dosing of other statins.

5.4.3 Precautionary Medications

When letermovir is co-administered with a CYP3A substrate, refer to the prescribing information for dosing of the CYP3A substrate with a moderate CYP3A inhibitor.

When letermovir is co-administered with cyclosporine or any moderate CYP3A inhibitor, the combined effect on CYP3A substrates may be similar to a strong CYP3A inhibitor. Refer to the prescribing information for dosing of the CYP3A substrate with a strong CYP3A inhibitor.

An expanded list of precautionary medications is included below:

- Anti-arrhythmic agents: amiodarone, quinidine
- Anti-coagulants: warfarin
- Antidiabetic agents: glyburide, repaglinide, rosiglitazone
- Antifungals: voriconazole
- Benzodiazepines: midazolam
- Opiates: alfentanil, fentanyl

- Proton pump inhibitors: omeprazole, pantoprazole
- Statins: statin use is allowed, but may not exceed allowable doses. **Atorvastatin is allowed but may not exceed doses of 20 mg/day**; any dose of rosuvastatin, lovastatin, fluvastatin, or pravastatin is allowed, but participants should be monitored closely for myopathy and rhabdomyolysis and statin dose reductions may be required. Simvastatin and pitavastatin are not allowed at any dose (see section 5.4.2).

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Evaluations

Table 6.1-1: Schedule of Evaluations

Evaluation	Screening	Study Entry (Pre-Treatment Evaluations) 0 ENT	Treatment Initiation	Post-Treatment Initiation Evaluations (Weeks)											
			(0 IOT)	4	8	16	24	32	40	46	48	52	60	**Conf. of** *VF*	*Disc. Evals*
Visit Windows	*Within 90 days prior to Entry*	*2-30 days prior to Treatment Initiation*	*2-30 days after Study Entry*	*±10 days*						*-10/+5 days*	*-5/+10 days*	*±10 days*			
Documentation of HIV	X														
Medical History	X	X													
Medication History	X	X													
Clinical Assessment **(see section 6.3.4)**	X	X	X	X	X	**X**	X	**X**	**X**	X	X	X	X		X
Complete Physical Exam	X														
Targeted Physical Exam		X	X	X	X		X			X	X	X	X		X
ECG	X	If applicable **(see section 6.3.5)**													
Hematology	X	X	X	X	X		X			X	X	X	X		X
Liver Function Tests (C=conditional; see section 6.3.6 for visits marked C)	X		X		X		X			X	C	X	X		
Chemistry (C=conditional; see sections 6.3 & 6.3.6 for visits marked C)	X		X				**X**			X	C		X		
Pregnancy Testing (see section 6.3.6)	X	X	X	If otherwise indicated											
CMV Serology (historical positive result can be used)	X														
$CD4^+/CD8^+$	X		X		X						X		X		X
Plasma HIV-1 RNA	X		X		X		X				X		X	X	X

Evaluation	Screening	Study Entry (Pre-Treatment Evaluations) 0 ENT	Treatment Initiation	Post-Treatment Initiation Evaluations (Weeks)											
			(0 IOT)	4	8	16	24	32	40	46	48	52	60	***Conf. of** VF*	*Disc. Evals*
Visit Windows	*Within 90 days prior to Entry*	*2-30 days prior to Treatment Initiation*	*2-30 days after Study Entry*	*±10 days*						*-10/+5 days*	*-5/+10 days*	*±10 days*			
Stored Plasma/PBMC/Serum		X	X	X	X		X			X	X	X	X	X	X
Plasma PK Sampling (C=conditional; see section 6.7)			X	X	X					X	C		X		
Adherence Assessment			**X**	X	X	X	X	X	X	X	X				
Genital and Oral Secretion Collection		X	X		X					X	X	X	X		X
Rectal Swab Collection **(C=conditional; see section 6.10 for visits marked C)**		X	**C**		X					**X**	**C**		X		
Physical function testing (C=conditional; see section 6.11 for visits marked C)		**X**	**C**							X	C		X		
Brief NP testing **& Limited Neurophysiological Evaluations** (C=conditional; see section 6.12 for visits marked C)		X	**C**							X	C		X		
Brief mood testing (mental health/substance abuse disorders; **CAT-MH**, PHQ-9 & GAD-7) (C=conditional; see section 6.13 for visits marked C)		X	**C**		X					X	C	X	X		
Brief sleep assessment (C=conditional; see section 6.13 for visits marked C)		**X**	**C**							X	C		X		

Evaluation	Screening	Study Entry (Pre-Treatment Evaluations) 0 ENT	Treatment Initiation	Post-Treatment Initiation Evaluations (Weeks)											
			(0 IOT)	4	8	16	24	32	40	46	48	52	60	***Conf. of** VF*	*Disc. Evals*
Visit Windows	*Within 90 days prior to Entry*	*2-30 days prior to Treatment Initiation*	*2-30 days after Study Entry*	*±10 days*						*-10/+5 days*	*-5/+10 days*	*±10 days*			
Sexual & Gender Identity Questionnaire **(C=conditional; see section 6.13 for visits marked C)**		X	**C**												
Telephone, text message, or e-mail contact	Between visits as needed **(see section 6.2.4)**														

6.2 Timing of Evaluations

6.2.1 Screening

Screening evaluations must occur prior to the **Study Entry visit**.

Screening evaluations to determine eligibility must be completed within 90 days prior to the Study Entry (Pre-Treatment) visit unless otherwise specified.

In addition to data being collected on participants who enroll into the study, demographic, clinical, and laboratory data on screening failures will be captured in a Screening Failure Results form and entered into the ACTG database.

6.2.2 Study Entry (Pre-Treatment) Visit (0 ENT) Evaluations

All screening evaluations must be complete prior to the Study Entry (Pre-Treatment) visit. The Study Entry visit should occur within the time window outlined in section 6.1. The participant will be randomized to study treatment at the Study Entry visit.

Timing of all study visits (Study Entry and all subsequent visits)
Participants are encouraged to receive standard vaccinations, including influenza vaccination (i.e., flu vaccine) and COVID-19 vaccination, in the course of their clinical care, but the timing of these vaccinations should occur at least 14 days prior to any given study visit (or be administered after the study collections are completed). Furthermore, participants experiencing inflammatory conditions at the time of a scheduled visit (e.g., a febrile illness, acute infection **including SARS-CoV-2**) should be instructed to wait 7 days after resolution of the inflammatory condition before returning for the scheduled visit.

NOTE: **In cases where study visits need to be rescheduled due to illness or vaccination, postponement is allowed as long as the participant's visit window does not overlap with the next one.**

The presence and resolution of an inflammatory condition is based on participant symptoms (i.e., fever, chills, swelling, redness) and at the judgement of the study clinician.

Because of the diurnal variation in biomarkers that may be measured as part of the study (e.g., $CD4^+$ and $CD8^+$ T-cell counts and other biomarkers that may be measured on stored samples), blood draws for individual participants should be performed consistently in either the morning or the afternoon throughout the study, if possible. Furthermore, since fasting status can affect inflammatory biomarkers, metabolic, and lipid measurements, all blood draws should be obtained in the fasting state. Please note that height will only be recorded at the Study Entry visit.

6.2.3 Treatment Initiation Visit Evaluations **(0 IOT/DAY 0)**

The Treatment Initiation visit (0 IOT) should only occur after all required Pre-Treatment Visit evaluations have been completed at Study Entry. The Treatment Initiation visit must occur within 2-30 days after Study Entry visit evaluations have been completed. If more than 30 days have elapsed after the Study Entry visit, the Study Entry visit must be repeated prior to the Treatment Initiation visit. Participants must begin treatment within 2 days after the Treatment Initiation visit. **The rationale for separate entry and treatment initiation visits is to establish a stable baseline level for biomarker levels, which tend to fluctuate within individuals, to enhance power to detect treatment-associated changes. Thus, the treatment initiation visit is a required visit for both the letermovir and "no CMV treatment" arms.**

6.2.4 Post-Treatment Initiation Evaluations

All post-Treatment Initiation evaluations will occur per the time windows outlined in section 6.1. **The timing of all the subsequent post-treatment initiation visits are based on the date of the treatment initiation visit (i.e., Week 4 is 4 weeks after the treatment initiation visit).**

On-Treatment Evaluations (Weeks 4-48)
Evaluations must occur after the Treatment Initiation visit as shown in section 6.1. If any of the evaluation visits are missed, they should be conducted at the next visit. This is particularly important for evaluations that may have been missed at the week 46 visit. Visits on weeks 16, 32, and 40 are **primarily** designated for **assessments of adverse events, changes in concomitant medications, adherence,** and for participants to pick up refills for study treatment, **but if the participant does not report interim adverse events and has sufficient supply of study medication, these visits can be conducted remotely by telephone at the discretion of the site investigator. In addition to these visits, clinical assessments for adverse events and adherence should be conducted at all study visits as shown in section 6.1.**

Post-Treatment Evaluations (Weeks 52 and 60)
Evaluations must occur as shown in section 6.1. If any of the evaluation visits are missed, they should be conducted at the next visit. If the week 60 visit is missed, it should be rescheduled at the next and most convenient time, **but not greater than 14 days after the originally scheduled visit.**

Study Completion Evaluations
Week 60 will be the participant's final visit on-study.

Remote Data Collection
Study visits may be conducted remotely (e.g., telephone, telehealth) in the following situations:

- A participant is unable to attend a visit because of personal illness, illness among others in their home, or local conditions or guidelines restricting travel to the clinic.
- The site is temporarily unable to conduct non-essential visits in the clinic; the site must inform the core team (actg.CMCa5383@fstrf.org) when it has to stop non-essential visits.
- At the discretion of the A5383 study team.
- **Visits would not be conducted remotely if the participants needs to travel to the clinic to refill study medication or report any new side effects or health problems that require medical attention. This is at the discretion of the site investigator (see criteria listed above as noted under [On-Treatment Evaluations Weeks 4-48]).**

Regardless of the situation, sites should document which visits were conducted remotely, attempt to obtain as much of the visit-specific required information, based on section 6.1, as possible, and record it. The impacted visits and rationale must be reported and documented, following instructions provided by the team or network leadership.

Study drug supplies may be mailed/delivered to participants' homes to assure continuous drug supply, if needed. The site PoR can ship oral study product to the participant by following the instructions under "Shipping Study Product to a Participant" in the manual entitled Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks as well as complying with institutional requirements. The PoR must comply with shipping requirements including documentation of chain of custody as detailed in the DAIDS pharmacy manual as well as institutional requirements. The PoR must reach out to the protocol pharmacist for any shipping deviations, challenges and/or questions.

Week 8 Visit (only for the first 40 participants enrolled)
Enrollment will be paused after the first 40 participants have enrolled so that week 8 immunologic activity can be assessed for futility. During this first phase of enrollment, a blood draw at the week 8 visit is critical to complete the interim analysis of immunologic activity. Thus, if the participant is unable to attend an in-person clinic visit at the scheduled time, the week 8 visit can be postponed for up to **6** weeks so that they can contribute to the interim analysis. All subsequent visits will be completed as scheduled (i.e., a postponement of the week 8 visit will not extend the duration of study drug treatment or result in the postponement of any of the subsequent scheduled visits). If the SMC allows enrollment to resume after the week 8 interim analysis on the first 40 participants, all subsequent enrollees in this second phase (i.e., enrollees 41 through 180) will no longer be required to have their week 8 visits performed in person and the standard remote data collection guidance would apply.

Week 46 and 48 Visits
Participants who complete the treatment course will perform the evaluations listed

while on study drug. If the participant is unable to attend at least one in-person clinic visit at the scheduled time (week 46 or 48), the week 48 visit can be postponed for up to 8 weeks with an extension of study drug treatment during this time so that the primary outcome, which requires a blood draw, can be ascertained while still receiving study medication. Should a need for postponement of the week 48 visit appear likely, the site should inform the core team (actg.CMCa5383@fstrf.org) as soon as possible so that the necessary increase in drug supply can be accommodated without an interruption of treatment. The week 46 and 48 visits should not be conducted as a Remote Data Collection visit. If the week 48 visit is postponed, the weeks 52 and 60 visits will also be postponed accordingly (i.e. the off-treatment phase of the study should always be 12 weeks).

6.2.5 Confirmation of Virologic Failure

Confirmed virologic failure is defined as two consecutive HIV-1 RNA levels ≥200 copies/mL by real-time HIV-1 RNA testing. Participants with a plasma HIV-1 RNA ≥200 copies/mL at any visit will have a confirmatory viral load obtained as soon as possible but within 14 days after the first sample was drawn, if possible. If this visit coincides with a regularly scheduled visit, the evaluations should be combined. If the consecutive measurement of HIV-1 RNA is also ≥200 copies/mL, the participant will be considered to have confirmed virologic failure and the CMC must be notified via e-mail actg.CMCa5383@fstrf.org within 72 hours.

Participants will have premature study treatment discontinuation evaluations performed as noted in section 6.1. These participants will remain on study, off study treatment and have all evaluations performed per section 6.1.

6.2.6 Discontinuation Evaluations

Evaluations for Randomized Participants Who Do Not Complete the Treatment Initiation visit (and for Arm A, those who do not start letermovir)
Participants who are randomized, but withdraw from the study prior to completing the treatment initiation visit (and for Arm A, those who do not start letermovir), should have discontinuation evaluations performed and off-study eCRFs completed and keyed. No further follow-up is required for these participants. Participants who do not complete the treatment initiation visit (and for Arm A, those who do not start letermovir) should be replaced.

Premature Study Treatment Discontinuation Evaluations
Participants who prematurely permanently discontinue study treatment will have discontinuation evaluations performed as noted in the Schedule of Events within 7 days of discontinuation. They will have evaluations performed as per section 6.1. After completion of the premature treatment discontinuation evaluations and until week **60** participants will follow the clinical assessment and laboratory schedules as per section 6.1, except that pregnancy testing **is** not required. Plasma/PBMCs/Serum for biomarkers **should continue to be collected as per section 6.1 through the**

week 60 visit as participants who discontinue treatment prematurely will still contribute to the secondary intention-to-treat analyses.

Study drug will not be dispensed nor will adherence assessments **to study drug** be performed **(though adherence assessments for ART will continue).** More frequent clinical and laboratory evaluations may be clinically indicated.

Participants who permanently discontinue study treatment due to toxicity should remain in study follow-up to study completion or until the toxicity resolves to a Grade 2 or less (whichever is first). See section 8.1 for specific toxicity management instructions and evaluations to be performed.

Premature Study Discontinuation Evaluations
Participants who prematurely discontinue from the study will have the study discontinuation evaluations performed as soon as possible prior to being taken off the study.

6.3 Instructions for Evaluations

Each study site and laboratory involved in this study will comply with the DAIDS policy on Requirements for Laboratories Performing Testing for DAIDS-Supported and/or Sponsored Clinical Trials, which is available at https://www.niaid.nih.gov/sites/default/files/laboratorypolicy1.pdf.

All clinical and laboratory information required by this protocol is to be present in the source documents. Sites must refer to the Source Document Guidelines on the DAIDS website for information about what must be included in the source document: https://www.niaid.nih.gov/sites/default/files/daids-sourcedocpolicy.pdf.

All stated evaluations are to be recorded on the eCRF unless otherwise specified. Refer to section 7.0 for information on the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), and AE reporting of adverse events requirements.

Fasting Instructions
With the exception of the screening visit and visits for confirmation of virologic failure and discontinuation evaluations, all study visits with blood draws (i.e., entry; treatment initiation; and weeks 4, 8, 24, 46, 48, 52, and 60) must be conducted when participants are fasting. Because fasting status can affect inflammatory biomarkers, metabolic, and lipid measurements, all blood draws should be obtained in the fasting state.

Fasting is defined as nothing to eat or drink except oral medications and plain water for at least 8 hours before the evaluations. If participants are in a non-fasting state, they should come back to the clinic in a fasting state within 7 days of the originally scheduled study visit for a fasting blood draw and evaluation, unless otherwise indicated.

Participants should be instructed with the exact time beyond which they are to be fasting, such as: “Your visit is scheduled for 8:00 a.m. You should not have any food or drink by mouth except water and medication after 12 a.m.” See below for timing of blood draws.

Timing of Blood Draws
Because of the diurnal variation in biomarkers that may be measured as part of the study (e.g., CD4+ and CD8+ T cell counts and other biomarkers that may be measured on stored samples), blood draws for individual participants should be performed consistently in either the morning or the afternoon throughout the study, if possible.

6.3.1 Documentation of HIV-1

Section 4.1.1 specifies assay requirements for HIV-1 documentation. HIV-1 documentation is not recorded on the eCRF.

6.3.2 Medical History

The medical history must include all signs and symptoms regardless of grade and all diagnoses identified by the ACTG criteria for clinical events and other diagnoses regardless of grade within the past 30 days. In addition, the following diagnoses should be recorded regardless of when the diagnosis was made:

- AIDS-defining conditions
- Bone fractures (verbal history accepted)
- Coronary heart disease
- Cancer (exclusive of basal/squamous cell skin cancer)
- Diabetes
- Tuberculosis
- Chronic hepatitis C
- Chronic hepatitis B
- Documented CMV end-organ disease (e.g., retinitis, colitis, ventriculitis, etc.)
- Any diagnosis of SARS-CoV-2 infection within the past year (including any positive SARS-CoV-2 test regardless of symptoms)

Any allergies to any vaccines and medications and their formulations must also be documented.

6.3.3 Medication History

A medication history must be present, including start and stop dates. The table below lists the medications and vaccines that must be included in the history.

Table 6.3.3-1: Medication History

Medication Category	Complete History or Timeframe
Antiretroviral therapy	Within 1 year prior to study entry
Immune-based therapy	Complete History
Blinded study treatment	Within 1 year prior to study entry
HIV-1-related vaccines and bNAbs	Complete History
Prescription drugs for treatment of opportunistic infections	Within 30 days prior to study entry
Prescription drugs for prophylaxis of opportunistic infections	Within 30 days prior to study entry
Previous anti-CMV vaccines	Complete History
Drugs with anti-CMV activity	Within 90 days prior to **study entry**
All other previous vaccines	Within 90 days prior to study entry
Prescription drugs (other)	Within 30 days prior to study entry
Alternative therapies	Within 30 days prior to study entry
Dietary supplements	Within 30 days **prior to** study entry
Sex-hormone drugs or sex-hormone analogues or antagonists*	Last 12 months except as noted below
Substance use/IV Drug use	Within 30 days prior to study entry

*Includes: hormone-releasing IUDs (e.g., Mirena inserted in the last 7 years); oral, injectable, implanted, or patch contraceptives; vaginal ring, creams, or inserts; estrogen, progesterone, or testosterone therapy; leuprolide or other synthetic gonadotropin-releasing hormone; tamoxifen, raloxifene, aromatase inhibitors or any other androgen, estrogen, or progesterone analogue or antagonist therapy.

6.3.4 Clinical Assessments

Clinical Assessments are conducted at the specified time points in section 6.1 specifically to collect information on adverse events, concomitant medications, and study treatment modifications. These assessments can be performed remotely at weeks 16, 32, and 40 (see section 6.2.4). Refer to section 7.2 for AE collection requirements.

NOTE: Sites should ask participants about tobacco use. This includes the participant's history of smoking tobacco, including the number of cigarettes smoked per day and the number of years the participant smoked. This information should be recorded on the eCRF at study entry. If not obtained at study entry, it can be recorded at the initiation of treatment visit. If participants have already completed their initiation of treatment visit, then perform a one-time collection of tobacco use data at the next scheduled visit.

Complete Physical Examination
A complete physical examination is to be performed at screening and is to include at a minimum an examination of the skin, head, mouth, and neck; auscultation of the chest; cardiac examination; abdominal examination; and examination of the lower extremities for edema. The complete physical examination will also include signs and symptoms, diagnoses, and vital signs (weight, temperature, pulse, respiration rate, and blood pressure).

Targeted Physical Examination
Post-screening, a targeted physical examination will be completed at every study visit **(with the exception of weeks 16, 32, and 40 as noted above under Clinical Assessments)** and will include vital signs (weight, temperature, pulse, respiration rate, and blood pressure), and is to be driven by any previously identified or new adverse event/targeted event, that the participant has experienced since the last visit. Height will be recorded at the study entry visit only. Weight should be recorded at every study visit. **A targeted physical exam is not required as part of a confirmation of virologic failure visit.**

Post-entry, record any acute febrile illnesses (see section 4.2.4 for definition of an acute febrile illness; see section 6.2.2 for timing of visits in case of a febrile illness).

Concomitant Medications
Post-entry, all new and discontinued concomitant medications and vaccines received must be recorded.

Study Treatment Modifications
Record all study treatment modifications, including initial doses, participant-initiated and/or protocol-mandated modifications, and inadvertent and deliberate interruptions of more than 3 days since the last visit. Record any permanent discontinuation of treatment.

6.3.5 ECG

An ECG will be performed at screening. Post-screening, an ECG will be performed to assess for new cardiac arrhythmias if the participant has a resting HR of >100 bpm, irregular HR, or complains of new palpitations. ECGs will be interpreted in real time during the study.

6.3.6 Laboratory Evaluations

At screening and study entry all laboratory values must be recorded. For post-entry assessments, record the following:

- All values for hemoglobin, creatinine, AST, ALT, and platelet counts regardless of grade;
- Abnormal laboratory findings per section 7.2.

Hematology
Hemoglobin, hematocrit, red blood cells (RBC), mean corpuscular volume (MCV), white blood cell count (WBC), differential WBC, absolute neutrophil count (ANC), and platelet count.

Liver Function Tests
Total bilirubin, AST (SGOT), ALT (SGPT), alkaline phosphatase, indirect bilirubin, and γ-glutamyl transaminase (GGT). **If sites are unable to collect the required test values at week 46, they may collect them at week 48.**

Chemistry
Fasting serum glucose, triglycerides, cholesterol (LDL, HDL, and total), electrolytes (sodium, potassium, chloride, phosphate, and bicarbonate), creatinine, blood urea nitrogen (BUN), total protein, and albumin.

These tests are only required at week 48 if they were not done at week 46. **If sites are unable to collect the required test values at week 46, they may collect them at week 48. Fasting serum glucose is not needed at the Screening visit.**

NOTE A: Metabolic Studies (free fatty acids [refer to the A5383 Laboratory Processing Chart, LPC]). Plasma free fatty acids will be assessed on fasting blood samples sent in batch through Quest labs using the Nonesterified Fatty Acids test not by the site.

NOTE B: Values for HOMA-IR will be calculated by SDAC. HOMA-IR (incorporates fasting glucose and insulin levels [insulin from stored samples]) to be calculated during data analysis, not by the site.

Pregnancy Test
A negative serum or urine pregnancy test must be obtained within 24 hours prior to study entry. For persons assigned female sex at birth and with reproductive potential: Serum or urine β-HCG. (Urine test must have a sensitivity of <25 mIU/mL). Record pregnancy and pregnancy outcome per section 8.3. Post entry, see section 8.3 for collection requirements for pregnancy.

CMV Serology
CMV IgG serology using a FDA-approved assay at any US laboratory that has a CLIA certification or its equivalent. Historical positive results can be used.

6.4 Immunologic Studies

$CD4^+/CD8^+$
Screening absolute $CD4^+/CD8^+$ count and percentages must be performed within 90 days prior to study entry (pre-treatment) at a laboratory that possesses a CLIA certification or equivalent.

For entry and post-entry evaluations, all laboratories must possess a CLIA certification or equivalent.

See section 6.3 for timing of blood draws.

6.5 Virologic Studies

Plasma HIV-1 RNA
Screening HIV-1 RNA must be performed within 90 days prior to study entry at a laboratory that possesses a CLIA certification or equivalent. Eligibility will be determined based on the screening value.

6.6 Stored Plasma/Peripheral Blood Mononuclear Cells (PBMCs)/Serum

PBMCs, plasma, and serum will be stored for future analysis. See section 6.3 for timing of blood draws. For specimen processing, storage and shipping instructions, see the A5383 LPC.

6.7 Plasma Pharmacokinetic (PK) Sampling

At each visit indicated in section 6.1, a single PK sample will be drawn and stored for future exploratory analyses. Venous PK will be performed at treatment initiation and at weeks 4, 8, 46, and 60 (as indicated in section 6.1) so these samples must be collected prior to the morning doses of letermovir and**/or** ART.

Participants should be stable on ART for at least 10 days (i.e., no ART regimen change for 10 days) prior to PK draws with confirmation of full adherence for the last four ART doses and **for Arm A** (for all post-treatment initiation visits) the last four doses of study treatment. **Similarly, for statin-treated participants, full adherence should be confirmed for the last four statin doses prior to a PK draw.** The date and time of the last four ART**, statin (if applicable),** and study treatment **doses prior to each PK blood draw should be recorded. For participants who normally take ART, statin, and/or study medication doses in the morning, o**n the day of PK sampling, blood should be drawn before the morning dose of study **treatment for participants in Arm A** and **before any** morning dose of ART **(and statin, if applicable) in both arms**. In the case where a morning dose of study treatment**,** ART**, or statin** dose is taken before the PK sample is drawn, or if any of the four preceding doses have been missed, the PK sampling should be rescheduled during the same week, if possible. If this is not possible, contact the A5383 protocol team (actg.teamA5383@fstrf.org) for guidance. These tests are only required at week 48 if they were not done at week 46.

NOTE A: Participants should not be asked to change their usual ART, statin or study medication dose timing. Nevertheless, participants who take an ART, statin, or study medication dose in the morning should delay their dose until after the blood draw on days that include PK sampling. Time of the last (most recent) ART, statin, and study treatment dose (for Arm A) should be recorded for all participants.

For specimen processing, shipping, and storage instructions, refer to the A5383 LPC. Refer to section 11.0 for the assay details.

6.8 Adherence Assessment

At the time points indicated in section 6.1, participants will complete the adherence assessment. The assessment will collect data on ART and study treatment adherence.

The adherence assessment eCRF is **to be completed in the iMedidata Patient Cloud app. In the event a site does not have a tablet, the participant experiences difficulty using a tablet, or the participant speaks Spanish, the form is** posted on the DMC Portal in the Forms Management Utility. **See the A5383 MOPS for more information.**

6.9 Genital and Oral Secretion Collection

Participants must refrain from sexual intercourse **and ejaculation** and avoid using intravaginal products for 48 hours prior to sample collection. Semen will be obtained by masturbation at the visits indicated in section 6.1. Semen collection can be performed at home as long as semen is transported to the processing lab within 2 hours of collection. Semen should be kept at room temperature until delivery to the processing lab. Cellular pellet and seminal plasma will be processed according to the procedure outlined in the A5383 Manual of Procedures (MOPS), and stored as described in the A5383 LPC.

Two **(**self-collected **or staff-collected)** vaginal swabs will be collected per section 6.1 and placed into a sterile tube as outlined in the MOPS and LPC. Participants with a vagina may elect to have vaginal swab collection via self-collection (collected at home) or by study personnel during the study visit.

NOTE: Semen and vaginal swabs are requested because it is far easier to detect CMV in these samples than in the blood. Thus, collecting these samples allows us to measure a direct effect of letermovir on CMV replication. Nevertheless, some participants may be uncomfortable providing (or unable to provide) semen or vaginal swab specimens. If a participant is uncomfortable or unable to provide these specimens, this is acceptable, but the reason for the missing specimen needs to be noted in the eCRF.

Oral secretion collection will be undertaken with a throat wash (see MOPS for instructions). Participants should not eat, **drink,** chew gum, mints or candy; brush/floss teeth; or smoke for 90 minutes before throat wash collections.

NOTE: Participants may drink water prior to throat wash collection, however, all other beverages are prohibited.

6.10 Rectal Swab Collection

Rectal swabs will be collected per section 6.1 and stored per the A5383 MOPS.

NOTE A: Rectal swabs are requested because it is far easier to detect CMV in these samples than in the blood. Thus, collecting these samples allows us to measure a direct effect of letermovir on CMV replication. Nevertheless, some participants may be uncomfortable providing (or unable to provide) rectal swab specimens. If a participant is uncomfortable or unable to provide rectal swab specimens, this is acceptable, but the reason for the missing specimen needs to be noted in the eCRF.

NOTE B: If rectal swabs cannot be performed at the Study Entry visit (0 ENT), then they should be obtained at the Treatment Initiation visit (0 IOT). Similarly, if rectal swabs cannot be performed at the week 46 visit, then they should be obtained at the week 48 visit.

6.11 Physical Function Testing

At the time points indicated in section 6.1, participants will be asked to rise 10 times from a seated position from a standard height chair that does not have wheels or arms. Time to complete 5 and 10 rises from the chair will be captured (see the A5383 MOPS for further details). Frailty will be assessed by the frailty phenotype, as previously defined by Fried et al. (2001). Frailty assessments will include 4-meter gait speed (two measures), grip strength (three measures), unintentional weight loss, exhaustion, and low activity by self-report, identical to the methods utilized in A5322/HAILO. See the A5383 MOPS for further details. These tests are only required at week 48 if they were not done at week 46.

NOTE: If the Physical Function Testing cannot be performed at the Study Entry visit (0 ENT), then they should be carried out at the Treatment Initiation visit (0 IOT).

6.12 Brief Neuropsychological (NP) Testing **and Limited Neurophysiological Evaluations**

At the time points indicated in section 6.1, participants will complete the Trail Making A & B, **WAIS-III** Digit Symbol, and HVLT-R NP tests (see the A5383 MOPS for further details). These tests are only required at week 48 if they were not done at week 46.

NOTE: If the Brief NP Testing and Limited Neurophysiological Evaluations cannot be performed at the Study Entry visit (0 ENT), then they should be carried out at the Treatment Initiation visit (0 IOT) or at the next scheduled study visit.

6.13 Questionnaires

The questionnaires are to be completed using the iMedidata Patient Cloud app on either a tablet or smartphone, except the Computerized Adaptive Testing for Mental Health (CAT-MH), which is detailed in the A5383 MOPS and can be completed on a desktop or laptop computer. If a site does not have a tablet or smartphone to use, or the participant has difficulty using a tablet or smartphone,

the site may download the questionnaires from the Forms Management Utility on the DMC Portal. For Spanish-speaking participants, these questionnaires are only available in paper format. The CAT-MH cannot be completed by paper and must be completed electronically. See the A5383 MOPs for more information about accessing the iMedidata Patient Cloud app and the CAT-MH.

Please note that, for the following assessments and questionnaires (Brief Mood Test/Depression Assessment, Brief Sleep Assessment, and Sexual and Gender Identity Questionnaire), each assessment or test is only required at the initiation of treatment visit (0 IOT) if it cannot be performed at the Entry visit (0 ENT).

Brief Mood Test/Depression Assessment
At the study visits indicated in section 6.1, participants will complete the Patient Health Questionnaire-9 (PHQ9). In addition, the CAT-MH and the General Anxiety Disorder-7 (GAD-7) scale, a brief measure of anxiety, will be administered. These tests are only required at week 48 if they were not done at week 46.

Brief Sleep Assessment
At the study visits indicated in section 6.1, participants will complete the Pittsburgh Sleep Quality Index. The assessment will include data on the duration of the sleep cycle, quality of sleep, and use of sleep medication (if applicable). These tests are only required at week 48 if they were not done at week 46.

Sexual and Gender Identity Questionnaire
At the study visits indicated in section 6.1, participants will complete a sexual and gender identity questionnaire.

Telephone, text message, or e-mail contact
Participants will be contacted via telephone, text message, or e-mail after receiving the study treatment to remind them of their upcoming study visits and to ask about study treatment adherence. Remote contact guidance is provided in the A5383 MOPS.

7.0 ADVERSE EVENTS AND STUDY MONITORING

7.1 Definition of Adverse Events

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or diagnosis that occurs in a study participant during the conduct of the study REGARDLESS of the attribution (i.e., relationship of event to medical treatment/study product/device or procedure/intervention). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.

7.2 Adverse Event Collection Requirements for this Protocol

All AEs must be recorded on the eCRFs if any of the following criteria have been met.

- All Grade ≥3 AEs

- All AEs that led to a change in study treatment/intervention regardless of grade
- All AEs meeting SAE definition or EAE reporting requirement
- All Grade ≥2 cardiac arrhythmias (i.e., atrial fibrillation, atrial flutter, etc.)
- Any Grade **≥1** SARS-CoV-2 **or monkeypox** infection **or AE related to these infections** (including any **related signs or symptoms Grade ≥**1)
  - **NOTE: Any positive SARS-CoV-2 PCR or antigen test result must be recorded on the appropriate eCRF regardless of grade and/or presence of associated symptoms. If more than one test is obtained in a given infection episode, the first and last positive test result should be recorded on the eCRF.**
- **Any acute febrile illness (>101°F)**

NOTE: SAEs or events meeting EAE reporting requirements should also be entered into the DAIDS Adverse Experience Reporting System (DAERS), an Internet-based reporting system. The DAIDS regulatory support center (RSC) will report events to Merck as appropriate.

All AEs that are reported must have their severity graded. To grade AEs, sites must refer to the DAIDS AE Grading Table, corrected Version 2.1, July 2017, which can be found on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

Serious Adverse Events (SAEs)
An SAE is defined as any untoward medical occurrence that:
- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above.

7.3 Expedited Adverse Event (EAE) Reporting to DAIDS

7.3.1 Expedited Reporting of Adverse Events to DAIDS

Requirements, definitions and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids.

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted using the DAIDS

EAE Form. This form is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting.

For questions about DAERS, please contact NIAID CRMS Support at CRMSSupport@niaid.nih.gov. Please note that site queries may also be sent from within the DAERS application itself.

For questions about expedited reporting, please contact the DAIDS RSC Safety Office at DAIDSRSCSafetyOffice@tech-res.com.

7.3.2 Reporting Requirements for this Study

- The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study.
- The study agent for which expedited reporting is required is letermovir.
- In addition to the SAE reporting category identified above, DAIDS will provide Merck and Company, Inc., with expedited SAE reporting of the following:
  - Cancers with no other event (regardless of association), fetal losses (regardless of association) and Immune Reconstitution Inflammatory Syndrome (IRIS) events which meet seriousness criteria (regardless of association).
  - Any overdoses of Study Product.
  - Abnormal pregnancy outcomes
- Pregnancies (without abnormal outcomes or other SAE) will be reported to Merck and Company by DAIDS on a quarterly basis.

7.3.3 Grading Severity of Events

The DAIDS AE Grading Table, corrected Version 2.1, July 2017, must be used and is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

7.3.4 Expedited AE Reporting Period

- The expedited AE reporting period for this study is as per the EAE manual.
- After the protocol-defined EAE reporting period, unless otherwise noted, only suspected, unexpected serious adverse reactions (SUSARs) as defined in Version 2.0 of the DAIDS EAE Manual, will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

7.4 Study Monitoring

The protocol team will monitor the conduct and safety of the study via regular summaries of accrual, study discontinuation, sample and data completeness, and adverse events pooled over treatment arms, as appropriate.

The DAIDS Clinical Representative will review and assess select EAE reports for potential impact on the study participant safety and protocol conduct as per DAIDS policies, guidance documents, and SOPs as applicable.

The study will undergo interim review at least annually by an ACTG-appointed Study Monitoring Committee (SMC), although the SMC may elect to deviate from this timeline. In the event that enrollment for the first 40 participants takes longer than 6 months, a separate SMC meeting will be held 6 months after the first participant is enrolled. SMC reviews would then continue every 6-12 months after this point. The SMC will review accrual, baseline characteristics, conduct of the study (including premature study and premature study treatment discontinuations), AEs by study treatment arm, $CD4^+$ T cell counts and HIV-1 RNA levels/suppression, and plasma CMV DNA levels (and if applicable, letermovir resistance results) over time by study treatment arm, and data/sample availability. The SMC may decide to monitor the study more frequently to review and assess whether or not the goal of enrolling at least one third (30 participants in each arm) individuals assigned female sex at birth not on testosterone or individuals assigned male sex at birth on feminizing sex hormones, is met. Further, the SMC may choose to closely monitor that at least one half (45 participants) in each arm have $CD4^+$ T cell counts <350 cells/mm^3. The SMC may recommend protocol revisions if there is significant difficulty in meeting the enrollment goals for these strata. Study enrollment will be halted if ≥3 study participants in the letermovir arm experience confirmed loss of HIV-1 virologic suppression.

Plasma will be sent from the central repository in batches throughout the study for assessment of CMV DNA levels in a designated laboratory at least every 6 months. The first shipment will happen in time for results to be considered by the SMC at the time of the futility analysis. The DMC will be notified of all detectable plasma CMV DNA levels (at any level) at any visit after treatment initiation. If the participant is in the letermovir arm, the DMC will reflexively request that an aliquot of plasma from the visit be sent from the central specimen bank (i.e., BRI) for letermovir resistance testing (which will be conducted in batch every 6 months). The first interim review for tolerability will occur at the time of futility analysis. We expect this to occur at approximately 9 months after the enrollment of the first study participant, once the 40^{th} enrolled participant has reached 8 weeks on study, plasma samples have been tested for an initial protocol-specified assessment of immunologic futility, and data have been analyzed. Enrollment will pause after the 40^{th} participant has started study treatment and until (and if) the SMC deems the intervention not to be futile, but enrolled participants will be allowed to continue on study (i.e., beyond week 8) while the interim analysis is being conducted. An interim review should also be convened if, at any time, CMV DNA levels are detectable in plasma in 12 or more participants while taking study medications (Arm A only), letermovir resistance is detected in plasma specimens in two participants (Arm A only), new Grade ≥2 atrial fibrillation or atrial flutter of any grade is identified in four participants, a participant experiences a Grade 4 AE related to study treatment, or 3 or more participants in the letermovir arm experience HIV-1 virologic failure or any concern is identified by the DAIDS clinical representative, the study chairs, or study statisticians in consultation with the team. See section 10.0 for statistical and other considerations related to interim monitoring.

Consideration for modification of the study would be solely at the discretion of the SMC.

Detailed plans for study monitoring will be outlined in a Study Progress Data and Safety Monitoring Plan (SPDSMP) developed by the Statistical and Data Management Center (SDMC) prior to enrollment of the first participant.

8.0 CLINICAL MANAGEMENT ISSUES

8.1 Toxicity

Only toxicities related to study treatments provided through the study will be considered in this section.

The general guidelines presented in this section apply to toxicities that are not specifically addressed in section 8.2.

Grade 1 or 2
Participants who develop Grade 1 or 2 AE or toxicity felt to be related to study treatment may continue study treatment at the discretion of the site investigator with close follow-up. If a participant chooses to discontinue study treatment, the site should notify the CMC within 72 hours. Participants will have premature study treatment discontinuation evaluations performed as noted in section 6.1. These participants will remain on study, off study treatment and have all evaluations performed per section 6.1 through completion of the study.

Grade 1 or 2 symptoms including menopausal symptoms such as hot flashes, vaginal dryness, and flushing will not obligate study treatment discontinuation. Similarly, nausea, vomiting, and diarrhea responsive to supportive measures such as antiemetics will not obligate study treatment discontinuation.

Grade 3
Participants who develop a Grade 3 AE or toxicity thought by the site investigator to be related to study treatment should have study treatment withheld and the site should consult with the CMC. The participant should be reevaluated weekly until the AE returns to Grade ≤2, at which time study treatment may be reintroduced at the discretion of the site investigator in consultation with the CMC.

If the same Grade 3 AE or toxicity recurs within 4 weeks after reintroduction of study treatment, study treatment must be permanently discontinued if the site investigator considers the AE or toxicity related to study treatment. The CMC should be notified within 72 hours. However, if the same Grade 3 AE or toxicity recurs after 4 weeks, the management scheme outlined above may be repeated.

Participants experiencing a Grade 3 AE or toxicity requiring permanent discontinuation of study treatment should be followed weekly until the AE resolves. Participants will have premature study treatment discontinuation evaluations performed as noted per sections

6.1 and 6.2.5. These participants will remain on study, off study treatment and have all evaluations performed per section 6.1 through completion of the study.

Grade 4
Participants with Grade 4 asymptomatic laboratory abnormalities may continue study treatment if the site investigator has compelling evidence that the toxicity is NOT related to study treatment.

Participants who develop a Grade 4 symptomatic AE or toxicity will have study treatment permanently discontinued. The CMC should be notified within 72 hours.

Participants experiencing a Grade 4 AE or toxicity requiring permanent discontinuation of study treatment should be followed weekly until the AE or toxicity resolves or returns to baseline. Participants will have premature study treatment discontinuation evaluations performed as noted in sections 6.1 and 6.2.6. These participants will remain on study, off study treatment and have all evaluations performed per section 6.1.

8.2 Other Conditions (Specific Management of Toxicities Related to Study-Provided Drugs)

Detectable plasma CMV DNA levels
Plasma CMV DNA levels may uncommonly be detectable in ART-suppressed HIV-infected individuals, and in this setting are usually not suggestive of the presence of classically defined CMV end-organ disease (e.g., retinitis, colitis, etc.). Thus, no clinical management action is needed for detectable plasma CMV DNA levels unless there are symptoms suggestive of CMV end-organ disease, which would be extremely rare in the proposed study population. There is also no need for a repeat visit to confirm a detectable CMV DNA level in plasma.

Per section 7.4, the DMC will be notified of all detectable plasma CMV DNA levels (at any level) at any visit after treatment initiation. If the participant is in the letermovir arm, the DMC will reflexively request that an aliquot of plasma from the visit be sent from the central repository for letermovir resistance testing. If letermovir resistance is detected, the site investigator, participant, and SMC will be notified and study treatment will be discontinued.

Participants will have premature study treatment discontinuation evaluations performed as noted in section 6.1. These participants will remain on study, off study treatment and have all evaluations performed per section 6.1.

New onset atrial fibrillation or flutter
If a participant is found to develop new onset atrial fibrillation or flutter during the treatment phase of the study, study treatment will be discontinued and the participant will be referred to a local cardiologist for management. The study team cardiologists can also assist with ECG interpretation as well as counseling teams on appropriate management on a case-by-case basis.

8.3 Pregnancy

Pregnancy and pregnancy outcome will be recorded on the eCRFs. Pregnancies that occur on study should be reported prospectively to The Antiretroviral Pregnancy Registry. More information is available at www.apregistry.com. Telephone: 800-258-4263; Fax: 800-800-1052.

Pregnancy Outcomes and Reporting
If a participant has completed the study or chooses to discontinue from the study before the end of the pregnancy, then site staff should request permission to contact them regarding pregnancy outcomes at the end of pregnancy. If the information is obtained, pregnancy outcomes will be submitted on an eCRF at the end of the pregnancy.

Pregnant participants will discontinue study treatment and any remaining study visits, however, study discontinuation evaluations will be completed and will continue to be followed as part of the study. At the end of the pregnancy, outcome and adverse events for the participant and infant will be recorded on the outcome eCRF. See section 7.3.2 for additional reporting requirements for abnormal pregnancy outcomes.

8.4 SARS-CoV-2/COVID-19 Infection

Participants with suspected or confirmed SARS-CoV-2 infection should be referred for appropriate testing and/or treatment. Sites should contact the A5383 CMC (actg.CMCa5383@fstrf.org) regarding completion of screening.

NOTE: Self-reported, positive home tests (PCR or antigen test) dates can be used to document a confirmed SARS-CoV-2/COVID-19 infection.

9.0 CRITERIA FOR DISCONTINUATION

9.1 Permanent and Premature Treatment Discontinuation

- Failure by the participant to complete the Treatment Initiation visit (and for Arm A, those who do not start letermovir).
- Drug-related toxicity (see sections 8.1 and 8.2).
- Requirement for prohibited medications (see section 5.4.2).
- Pregnancy (given conflicting data on teratogenicity in animal models, incident pregnancy during study will trigger discontinuation of study drug).
- Request by participant to terminate treatment.
- Clinical reasons believed life-threatening by the physician, even if not addressed in section 8.1 of the protocol.
- Presence of letermovir resistance in plasma CMV isolates of participant in the letermovir arm.

9.2 Premature Study Discontinuation

- Failure by the participant to attend two consecutive clinic visits.
- **Pregnancy.**

- Request by the participant to withdraw.
- Request of the primary care provider if she or he thinks the study is no longer in the best interest of the participant.
- At the discretion of the ACTG, IRB/EC, FDA**,** NIAID, Office for Human Research Protections (OHRP), other government agencies as part of their duties, investigator, or industry supporter.

10.0 STATISTICAL CONSIDERATIONS

10.1 General Design Issues

A5383 is a phase II, randomized, open-label, controlled, multicenter trial being conducted at US sites to evaluate the tolerability and anti-inflammatory efficacy of letermovir 480 mg once daily for 48 weeks in adults with HIV-1 and CMV with ART-mediated suppression. Participants will be randomized 1:1 to receive either letermovir (Arm A) or no anti-CMV treatment (Arm B). Participants will be on study for 60 weeks (48 weeks on study treatment with 12 weeks of post study treatment follow-up). The total sample size will be 180 participants (90 in Arm A, 90 in Arm B).

10.2 Outcome Measures

Primary and secondary outcome measures listed below will be addressed in the study's primary Statistical Analysis Plan (SAP), which will define the content of the Primary Analysis Report. This report will form the basis for the primary study manuscript and results reporting to ClinicalTrials.gov. Outcomes of interest for secondary and exploratory objectives intended for subsequent publications are listed under "Other Outcome Measures."

10.2.1 Primary Outcome Measures

Change from baseline to week 46/48 in sTNFRII.

10.2.2 Secondary Outcome Measures

10.2.2.1 Occurrence of Grade ≥3 AE or confirmed HIV-1 virologic failure after initiation of study treatment.

10.2.2.2 Mucosal and plasma CMV DNA levels at weeks 8, 46, 48, 52, and 60.

10.2.2.3 Change from baseline to weeks 8, 46/48, 52, and 60 in sCD163.

10.2.2.4 Change from baseline to weeks 8, 52, and 60 in sTNFRII.

10.2.3 Other Outcome Measures

10.2.3.1 Change from baseline to weeks 8, 46/48, 52 and 60 in inflammatory and coagulation markers (sCD14, IL-6, hsCRP, and D-Dimer).

10.2.3.2 Change from baseline to weeks 8, 48, 52, and 60 in cellular monocyte activation markers.

10.2.3.3 Change from baseline to week 48 in CMV IgG titer.

10.2.3.4 Change from baseline to week 48 in CMV-specific T-cells.

10.2.3.5 Change from baseline to weeks 8, 46/48, 52, and 60 in microbial translocation markers (B-D-Glucan, I-FABP, LBP, and zonulin).

10.2.3.6 Change from baseline to weeks 8, 46/48, 52, and 60 in multiplex-bead-array assay output.

10.2.3.7 Change from baseline to weeks 8, 46/48, 52, and 60 in markers of the coagulation cascade (suPAR, plasmin-alpha2-antiplasmin complex [PAP] and prothrombin fragment 1+2 [F1+2]).

10.2.3.8 Change from baseline to weeks 8, 46/48, 52, and 60 in soluble markers of endothelial activation (sICAM-1, sVCAM-1, sTF, E-selectin and P-selectin).

10.2.3.9 Change from baseline to weeks 8, 48, 52, and 60 in $CD4^+/CD8^+$ ratio.

10.2.3.10 Change from baseline to weeks 8, 48, 52, and 60 in $CD8^+CD38^+$HLA-DR+ T cells.

10.2.3.11 Change from baseline to weeks 8, 48, 52, and 60 in $CD8^+$CD28-$CD57^+$ T cells.

10.2.3.12 Change from baseline to weeks 46 and 60 in HOMA-IR and plasma levels of free fatty acids.

10.2.3.13 Change from baseline to weeks 46 and 60 in frailty score.

10.2.3.14 Change from baseline to weeks 46 and 60 in gait speed time.

10.2.3.15 Change from baseline to weeks 46 and 60 in grip strength.

10.2.3.16 Change from baseline to weeks 46 and 60 in continuous chair rise time.

10.2.3.17 Change from baseline to weeks 46 and 60 in VACS index score (as calculated here: https://vacs.med.yale.edu/calculator/IC).

10.2.3.18 Change from baseline to weeks 8 and 48 in single copy assay of HIV-1 RNA and cell-associated HIV-1 RNA and total HIV DNA.

10.2.3.19 Change from baseline to week 48 in the clonality of the HIV reservoir.

10.2.3.20 Change in plasma levels of commonly used ART drugs (tenofovir, integrase inhibitors) **and statins** during letermovir use.

10.2.3.21 Change from baseline in plasma proteomics signature at week 48

10.2.3.22 Change from baseline to weeks 46 and 60 in neurocognitive functioning (Trail Making A & B, Digit Symbol, and HVLT-R (HAILO Battery).

10.2.3.23 Change from baseline to weeks 46 and 60 in PHQ9.

10.2.3.24 Change from baseline to weeks 46 and 60 in Pittsburgh Sleep Quality Index.

10.2.3.25 Change from baseline to weeks 46/48 and 60 in plasma NFL.

10.2.3.26 Occurrence of letermovir resistance mutations after initiation of letermovir.

10.2.3.27 **Fold-change in seasonal influenza vaccine-specific IgG titers from last available pre-vaccine time point to the first available time point 4-12 weeks post-vaccination for flu vaccinations occurring after the initiation of treatment visit (0 IOT).**

10.3 Randomization and Stratification

After eligibility is confirmed and entry (pre-treatment) evaluations have been performed, participants will be randomized at a 1:1 ratio (letermovir: no treatment) using permuted blocks without institutional balancing with stratification by sex at birth and hormonal status (female sex assigned at birth without use of testosterone and male sex assigned at birth with use of feminizing sex hormones versus others) and screening $CD4^+$ T-cell count (<350 vs. ≥350 cells/mm^3). Our goal is to enroll half of all participants in each arm to the <350 cells/mm^3 stratum and one third of all participants in each arm to the stratum defined by female sex assigned at birth without use of testosterone or male sex assigned at birth with use of feminizing sex hormones. Given feasibility concerns, we will not require that sex stratification be balanced within each $CD4^+$ T cell count stratum.

10.4 Sample Size and Accrual

It is anticipated that it will take up to 2 years to accrue 180 participants that receive study treatment. This timeline is estimated based on the following recruitment process: Approximately 3 months for the futility analysis phase; 5-6 months before futility analysis is complete; 12 months to recruit the remaining 140 participants. Participants not initiating study treatment will be replaced to reach the target of 180 and will not be included in the analysis. Participants who received at least one dose of study treatment will not be replaced. The sample size for A5383 was determined based on the primary endpoint of sTNFRII.

Immunologic primary outcome

The primary objective of this study is to compare sTNFRII change over 48 weeks of treatment in participants randomized to letermovir compared to no treatment. The sample size calculations are based on the primary hypothesis testing Ho: $\mu_{letermovir} = \mu_{no\ treatment}$ targeting 90% power in the comparison of changes in $\log_{10}$-transformed sTNFRII between letermovir and no treatment.

Our assumed standard deviation (SD) of the change in sTNFRII from treatment initiation to week 48 was estimated from prior ACTG projects where the SD of the change in sTNFRII levels ranged from 0.11 to 0.21 $\log_{10}$ pg/mL when just a single measure was used at each time point. In ACTG A5325 averaging two sTNFRII values at both baseline and follow-up lead to a 15%-30% reduction in the change SD compared to using one value at each time point. Assuming a change SD of 0.15 $\log_{10}$ pg/mL and allowing for some reduction due to averaging at baseline and follow-up, we arrived at an SD estimate of 0.123. Using this SD of change to week 48 and a Type I error rate of 5%, an expected drop-out/missing data rate of up to 15% in each arm, we will have 90% power to detect an effect size as small as 0.065 $\log_{10}$ pg/mL in the sTNFRII level change from baseline to week 48 between groups if we enroll 90 participants in each arm (assuming an average of two measures at baseline and week 48).

Per NWCS 329, each $\log_{10}$ pg/mL increase in sTNFRII levels was associated with a 50.4-fold increased odds of MI/stroke (using year 1 biomarker assessment), which corresponds to a 22.5% decreased odds of a non-AIDS event for each 0.065 $\log_{10}$ pg/mL decrease in sTNFRII, a clinically relevant effect size we would want to be powered to detect.

The following table summarizes the calculation of the sample sizes corresponding to the detection of various effect sizes under various assumed standard deviations, with the effect size, standard deviation, and adjusted sample size selected for this study shown in *italics*.

Table 10.4-1: Sample Size Calculations

Effect size in $\log_{10}$ sTNFRII (difference between letermovir and no treatment)	Std Dev of Δ Baseline to Week 48	Total Sample size (90% power, alpha=0.05)	Adjusted Sample Size (15% inflation)
0.050	0.100	86*2=172	102*2=204
	0.123	129*2=258	152*2=310
	0.150	191*2=382	225*2=450
0.065	0.100	51*2=102	60*2=120
	0.123	*77*2=154*	*90*2=180*
	0.150	113*2=226	133*2=266
0.080	0.100	34*2=68	40*2=80
	0.123	51*2=102	60*2=120
	0.150	75*2=150	89*2=178

While this study is not fully powered to differential treatment effects by sex and gender-affirming hormone status, those analyses are of interest. It is also important to understand treatment effects among transgender and gender non-binary participants. Similar to the above, we will not have sufficient power to detect treatment effects for each group, so we will conduct exploratory analyses between groups (cis-men, trans-men, cis-women, trans-women, gender non-binary of female sex assigned at birth and gender non-binary of male sex assigned at birth).

If one third of enrolled participants are female sex assigned at birth without use of testosterone or male sex assigned at birth with use of feminizing sex hormones, we expect 25 evaluable participants in this stratum per arm. This provides 80% power to detect a 0.099 $\log_{10}$ pg/mL difference and 90% power to detect a 0.115 $\log_{10}$ pg/mL difference.

Assuming a mean change of 0 $\log_{10}$ pg/mL for all participants in the no anti-CMV treatment arm and an overall treatment effect of 0.065 $\log_{10}$ pg/mL, we have approximately 42% power to detect a sex*treatment interaction effect of 0.075 $\log_{10}$ pg/mL (0.04 $\log_{10}$ pg/mL in those assigned male sex at birth and not on feminizing sex hormones or female sex at birth on masculinizing hormones and 0.115 $\log_{10}$ pg/mL in those assigned female sex at birth and not on masculinizing hormones or male sex at birth and on feminizing hormones).

<u>Tolerability secondary outcome</u>

A secondary objective is to assess the tolerability of letermovir. With a study sample size of 180 participants, 90 participants will receive no anti-CMV treatment and 90 will receive letermovir.

The 90 participants receiving letermovir will provide 90% probability of observing a Grade ≥3 AE that would occur in 2.6% or more of participants receiving letermovir.

With 90 letermovir and 90 untreated participants and assuming a Grade ≥3 AE in 2% of the untreated participants, there will be 80% power to detect a difference between the arms if 11% or more of the letermovir participants have a Grade ≥3 AE. If the proportion with an AE in the no anti-CMV treatment arm is 5% there will be 80% power to detect a difference of 13% (5% vs.18%). These calculations are based on a one-sided 5% alpha Fisher's exact test.

CMV shedding secondary outcome:
One main secondary objective is to determine if letermovir influences the mucosal shedding of CMV DNA during treated HIV infection. We hypothesize that letermovir will significantly reduce the frequency of mucosal shedding compared to untreated participants. Based on our preliminary data in participants receiving ART with suppressed plasma HIV-1 RNA, we expect 50% mucosal CMV shedding at any one time of sampling. After letermovir administration, we expect that <10% of participants will still be shedding CMV in their mucosal secretions at weeks 8, 46, and 48 compared to 50% of participants receiving no anti-CMV treatment. Since CMV shedding fluctuates over time, repeated observations at study entry (pre-treatment) and week 0 as well as at weeks 46 and 48 will provide a more stable estimate of the degree of shedding at baseline before starting the intervention and at the end of treatment.

The binary mucosal shedding outcome will reflect the presence or absence of any detectable oral, rectal, and genital CMV shedding. With 77 evaluable participants per arm, a two-sided 5% type I error, and three repeated measurements (weeks 8, 46, and 48) assumed to have a compound symmetry covariance structure with a within participant correlation of 0.60, we will have 80% power to detect a difference of at least 19% (50% shedding in no anti-CMV treatment vs. 31% shedding in letermovir) and 90% power to detect a difference of at least 22% (50% vs. 28%). These power calculations were conducted in PASS Version 15.0.4 with the "Tests for Two Proportions in a Repeated Measures Design" procedure.

Accrual
Once all sites are registered and letermovir becomes available, we expect each site to enroll an average of two participants per month. We expect the first 40 participants to be enrolled within 3 months once all sites are registered. After the first 40 participants have started therapy, enrollment will pause until these first 40 participants reach week 8, at which time a futility analysis will be performed, to ensure that there is some early evidence for an effect on systemic immune activation (sTNFRII and sCD163 in plasma). Assuming that after reviewing these data, the SMC determines that the intervention is not futile, the study will then reopen enrollment and recruit the remaining 140 participants to achieve the enrollment target of 180. With a planned 16 sites participating, at one participant per month, we expect this second phase of enrollment to be completed, more or less, in 12 months.

10.5 Data and Safety Monitoring

10.5.1 Interim Monitoring Guidelines

Scheduled interim reviews are outlined in section 7.4.

Interim Week 8 Futility Analysis

The purpose of the interim futility analysis is to use early observed data to assess if a fully accrued trial is unlikely to attain statistically significant results. While futility analyses typically use observed data for a protocol's primary outcome (for this study, change from baseline to week 48 in sTNFRII), the study team wished to look at an earlier time point since it would take over one year to obtain week 48 sTNFRII data on any subset of participants. Therefore it was decided that the futility analysis will be based on changes in sTNFRII from baseline to week 8 rather than week 48. In addition, a second futility analysis will examine change from baseline to week 8 in sCD163 in order to assess a different potential pathway for a letermovir effect.

Because the team wants the futility analysis to be completed before opening the substudy, which involves invasive procedures, it was decided that enrollment would pause after the first 40 participants start treatment. At this point the futility analysis will be conducted. Using the observed data on the first 40 participants, the estimated mean and 95% confidence interval (CI) within each arm and the difference between arms will be provided for each futility outcome. In addition, the observed data on the first 40 participants will be combined with simulated, unobserved data for the remaining 140 future participants. This simulation will be repeated thousands of times in order to assess conditional power and generate predicted interval plots (PIPS). The future data will be simulated under a range of plausible scenarios, including but not limited to: the effect midway between the null and the currently observed effect; the effect midway between the observed effect and the expected effect; and the expected effect. From these simulations, summary statistics of the final treatment effect and 95% CI will be provided.

While there is no standard threshold for stopping a clinical trial for futility, typical thresholds are conditional power <20% or <30%. Because our futility outcomes use 8 week changes and the team expects approximately 50% of the expected Week 48 effect to be observed at this earlier time point, we feel that each should be assessed at <20% under a range of plausible scenarios. Consideration should be given to stopping the trial early if BOTH the sCD163 and sTNFRII outcomes are determined to be futile. Our hope is to minimize the chances of stopping the trial early for futility if the reduced effect is in fact observed at week 8.

The following table summarizes conditional power under a range of observed and future data scenarios for sTNFRII and assumes an SD of 0.123 $\log_{10}$ pg/mL.

Table 10.5.1-1: Conditional Power for sTNFRII

Mean difference observed in first 40 participants (log_{10} pg/mL)	Mean difference simulated for remaining 140 participants (log_{10} pg/mL)	Conditional power[1]
0	0	1.3%
	0.008125	3.1%
	0.01625	6.7%
	0.024375	12.8%
	0.0325	21.9%
0.008125	0.008125	3.9%
	0.0203125	11.2%
	0.0325	25.1%
0.01625	0.01625	9.8%
	0.024375	17.6%
	0.0325	28.4%
0.024375	0.0121875	8.5%
	0.024375	20.4%
	0.028413	25.8%
	0.0325	32.0%
0.0325	0.01625	13.8%
	0.024375	23.4%
	0.0325	35.8%

[1] PASS Sample Size Software, Conditional Power of Two-Sample T-Tests, NCSS.com

Using the observed data, a supplemental logistic regression will also be done to estimate the odds of achieving the reduced week 8 sTNFRII reduction of 0.0325 log_{10} pg/mL. For this model, each participant will have a single outcome measure (week 8 sTNFRII change of ≤-0.0325 log_{10} pg/mL vs. >-0.0325 log_{10} pg/mL). The intent of this supplementary dichotomous outcome is to explore whether the average treatment effect is preferentially driven by a small subset of individuals. Participant-level changes will also be provided to the SMC as well as stratified analyses exploring whether there are baseline factors that appear to predict treatment effects, including CD4 count (<350 vs. ≥350) and above versus below the median sTNFRII level at baseline.

The following table summarizes conditional power under a range of observed and future data scenarios for sCD163. In the valganciclovir trial, the mean treatment effect at week 8 for sCD163 was 0.046 log_{10} ng/mL. As with our projections for sTNFRII, given a possible smaller contribution of asymptomatic CMV replication to immune activation in those with higher $CD4^+$ counts, we expect the week 8 effect in the letermovir trial (where half will have $CD4^+$>350) to be approximately half of the effect observed in the valganciclovir trial, but that continued treatment through week 48 will continue to decrease levels by a similar amount. Accordingly, the projections below assume a SD of 0.085 log_{10} ng/mL

(the standard deviation of the change observed in the valganciclovir trial) and that 50% of the hypothesized 48 week effect at week 8 will be 0.023 log_{10} µg/mL.

Table 10.5.1-2: Conditional Power for sCD163

Mean difference observed in first 40 participants (log_{10}ug/mL)	Mean difference simulated for remaining 140 participants (log_{10}ug/mL)	Conditional power[1]
0	0	1.3%
	0.00575	3.2%
	0.0115	6.9%
	0.01725	13.3%
	0.023	23.0%
0.00575	0.00575	4.0%
	0.014375	11.7%
	0.023	26.3%
0.0115	0.0115	10.2%
	0.01725	18.4%
	0.023	29.8%
0.01725	0.08625	8.8%
	0.01725	21.3%
	0.020125	27.1%
	0.0325	33.6%
0.023	0.0115	14.4%
	0.01725	24.5%
	0.023	37.5%

[1] PASS Sample Size Software, Conditional Power of Two-Sample T-Tests, NCSS.com

Using the observed data, a supplemental logistic regression will be done to estimate the odds of achieving the reduced week 8 sCD163 reduction of 0.023 log_{10} µg/mL. For this model, each participant will have a single outcome measure (8 week sCD163 change of ≤-0.0325 log_{10} µg/mL vs. >-0.0325 log_{10} µg/mL). The intent of this supplementary dichotomous outcome is to explore whether the average treatment effect is preferentially driven by a small subset of individuals. Participant-level changes will also be provided to the SMC as well as stratified analyses exploring whether there are baseline factors that appear to predict treatment effects, including CD4 count (<350 vs. ≥350) and above versus below the median sCD163 level at baseline.

If the intervention is found to be futile in the overall population for both sTNFRII and sCD163 outcomes, we believe that it is still important to examine the subset of participants with $CD4^+$<350 in the futility analysis. It is plausible that asymptomatic CMV replication will be a much greater driver of immune activation in individuals with lower $CD4^+$ counts. Furthermore, those with $CD4^+$<350 are at

much greater risk of end organ disease than those who restore $CD4^+$ counts >500 (~35% to 2-fold increased risk for MI/Stroke in CNICS and HOPS cohorts respectively, and approximately a 2-fold increased risk of T2DM events in the Vancouver cohort). Thus, if an intervention might work for the $CD4^+$<350 subgroup, we would still want to develop it for the $CD4^+$ <350 population even if it did not work for those with higher $CD4^+$ counts. Our goal is to enroll at least half of participants in each arm with $CD4^+$<350 even in the futility analysis phase, so there should be at least 10 participants in each arm within the $CD4^+$<350 stratum. If there appears to be a trend toward benefit in this subpopulation, the SMC may consider recommending a re-design of the trial restricted to the $CD4^+$<350 subset.

10.6 Analyses

10.6.1 Efficacy Analyses

All statistical tests will be two-sided with a nominal alpha level of 0.05. Because this is a phase II study and all potential biologic activities of the intervention are of interest, analyses will be as-treated, and limited to participants who 1) have baseline and week 48 sTNFRII measurements, 2) remain on study product through week 48 with self-reported adherence >50%, 3) do not have a confirmed virologic failure (as defined per section 6.2.4 at or prior to week 48, and 5) did not receive vaccines or have concurrent acute illness within 1 week of treatment initiation and week 48 assessments (as defined per section 6.3.4).

NOTE: Participants experiencing inflammatory conditions at the time of a visit are instructed to wait 7 days before measurements are obtained. Measurements obtained while inflammatory conditions are present will not be included in the analysis. The presence and resolution of an inflammatory condition is based on participant symptoms (i.e., fever, chills, swelling, redness) and at the judgement of the study clinician.

A supplemental intent-to-treat primary sTNFRII analysis and secondary CMV shedding analysis will also be performed and will include all randomized participants. No adjustment for multiple testing will be performed.

10.6.1.1 Primary sTNFRII Analysis

To reduce intra-participant variability, two blood draws will be performed at study entry (pre-treatment), treatment initiation, and at weeks 46 and 48. The measurements will be the average of two sTNFRII results. If repeat measurements are not available at either of these time points, a single measurement will be used rather than the average.

Changes in sTNFRII from baseline to week 48 will be compared between the letermovir arm and the no anti-CMV treatment arm by

simple linear regression. For this model each participant will have a single outcome measure of sTNFRII change from baseline to week 48. The covariates will be study arm with screening $CD4^+$ cell count and sex plus hormonal therapy (the stratification factors).

A supplemental logistic regression will be done to estimate the odds of achieving the targeted sTNFRII reduction of 0.065 $\log_{10}$ pg/mL which, as previously stated, has been associated with a clinically relevant 22.5% reduction in CAD events. For this model, each participant will have a single outcome measure (48 week sTNFRII change of ≤ -0.065 $\log_{10}$ pg/mL vs > -0.065 $\log_{10}$ pg/mL). The covariates will be study arm with screening $CD4^+$ cell count and sex plus hormonal therapy (the stratification factors).

Six supplemental linear regression analyses will be performed. The first will perform the primary analysis using a modified intent-to-treat population (mITT) consisting of all participants who have been exposed to letermovir or no anti-CMV treatment. The remaining **five** will use the PP population and will assess differential letermovir effects by 1) baseline sTNFRII tertile, 2) CD4 strata, and 3) sex and hormonal therapy strata by additionally adjusting for these main effects and the study arm by main effect interaction, 4) presence versus absence of mucosal CMV shedding at baseline**, and 5) baseline use of an allowed statin.**

10.6.1.2 Secondary CMV Shedding Analysis

CMV DNA shedding at weeks 8, 46, and 48 will be compared between treatment arms using a generalized estimating equations (GEE) model with a binary outcome and a compound symmetry covariance structure (other correlation structures will be considered if appropriate).

10.6.1.3 Additional Secondary and Other Analyses

The remaining continuous outcome measures will be analyzed by simple linear regression similar to the primary sTNFRII analysis. (Other outcome measures will not have the supplemental regression analyses performed).

10.6.1.4 Tolerability Analyses

All statistical tests will be one-sided with a nominal alpha level of 0.05 and will include all participants who initiated study treatment. The proportion of participants with an AE in each arm will be compared with Fisher’s exact test and the highest AE grade per participant will be compared across arms with the Wilcoxon rank sum test.

11.0 PHARMACOLOGY PLAN

Pharmacology Rationale

Letermovir, an anti-CMV drug approved for CMV prophylaxis in seropositive alloHSCT individuals (Merck Sharp & Dohme Corp 2019), has not been previously studied in individuals with HIV, including assessment of potential for ART drug-letermovir interactions. Further, in this study, letermovir is being explored for several novel indications, for which it is important to establish PK/PD relationships: how differences in letermovir PK confer clinical or biomarker responses (PD).

Letermovir is eliminated primarily via fecal excretion (93% overall recovery, with 70% unchanged) and is subject to minimal metabolism by UGT1A1, UGT1A3, and potentially CYP3A (34). *In vitro,* letermovir is a time-dependent CYP3A inhibitor, a CYP2C8 inhibitor, and a CYP2B6, CYP2C9, CYP2C19 and time-dependent CYP3A4 inducer. It is an *in vitro* substrate for the organic anion transporter polypeptides 1B1 and 1B3 (OATP1B1/3) and P-glycoprotein (P-gp). Letermovir is an inhibitor of BCRP, bile salt export pump (BSEP), multi-drug resistance protein 2 (MRP2), organic anion transporter 3 (OAT3), P-gp, and OATP1B1/3 *in vitro*. Clinical *in vivo* CYP interactions have been observed, including reduced voriconazole exposure likely due to CYP2C9 and CYP2C19 induction by letermovir, and increased midazolam exposure via CYP3A inhibition by letermovir.

Given its relatively recent approval (2017), few clinical interaction studies have been performed post-approval. While there is no direct evidence supporting a UGT-mediated interaction with letermovir, this is a commonly shared pathway with many ARTs, including frequently utilized integrase inhibitors. Thus there is a need for clinical confirmation of the absence of drug-drug interactions with this class of ARTs.

Dolutegravir, a UGT1A1/3, CYP3A, CYP1A9, BCRP, and P-gp substrate, has been a common subject of drug-drug interaction studies [ViiV Healthcare Company. Dovato-dolutegravir sodium and lamivudine tablet, film coated Research Triangle Park, NC2019 [updated April 8, 2019; cited 2019 June 4, 2019]. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=68e45422-43ed-4cfb-9356-fae88d14a53a]. Due to a low IC_{90}, some were not deemed clinically significant [Cottrell et al., 2013; Song et al., 2011], while rifampin, a UGT1A1 and CYP3A inducer, exhibited a clinically significantly lower than expected dolutegravir exposure warranting dose adjustment [Dooley et al., 2013]. Further, a study of isoniazid-rifapentine coadministration with dolutegravir was stopped due to serious toxicities related to endogenous cytokine release [Brooks et al., 2018]. While the underlying mechanism is not known, hypotheses have implicated metabolic pathways. Other integrase inhibitors and ARTs, including elvitegravir [Gilead Sciences Inc. Stribild-elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate tablet, film coated, Foster City, CA, 2019 (updated January 28, 2019, cited June 4, 2019)], tenofovir [Gilead Sciences Inc. Viread-tenofovir disoproxil fumarate tablet, coated Foster City, CA, 2019 (updated April 29, 2019; cited 2019 June 4, 2019)] [Barcelo et al., 2016], raltegravir [Merck Sharp & Dohme Corp. Isentress-raltegravir tablet, film coated Whitehouse Station, NJ, 2019 (updated

March 4, 2019; cited 2019 June 4, 2019)] [Kassahun et al., 2007], abacavir [Soars et al., 2004], and emtricitabine [Gilead Sciences Inc. Emtriva-emtricitabine capsule Foster City, CA, 2019 (updated December 14, 2018; cited 2019, June 4, 2019)] are UGT substrates, and many are substrates or inhibitors of common transporters [Custodio et al., 2014; Zembruski et al., 2011].

Cobicistat, used to boost elvitegravir exposure, is a substrate and strong inhibitor of CYP3A, which may potentiate CYP3A-mediated interactions when given with letermovir, also an *in vivo* moderate CYP3A inhibitor [Merck Sharp & Dohme Corp. Prevymis-letermovir tablet, film coated (package insert); Whitehouse Station, NJ, 2019 (updated March 5, 2019; cited June 4, 2019)]. Protease inhibitors may also be impacted by or impact letermovir PK: atazanavir is a strong CYP3A inhibitor/substrate and UGT1A inhibitor, darunavir is a CYP3A substrate [Janssen Products LP. Prezita-darunavir tablet, film coated. Titusville, NJ, 2019 (updated June 6, 2019; cited June 7, 2019)], and ritonavir is a CYP3A inhibitor and substrate [AbbVie Inc. Norvir-ritonavir tablet, film coated; N. Chicago, IL, 2018 (updated November 19, 2018; cited June 7, 2019)].

Complex transporter-mediated interactions may also exist and impact letermovir exposure and other drugs. A study of cyclosporine, tacrolimus, and sirolimus in healthy participants demonstrated increased exposure for cyclosporine, tacrolimus, and sirolimus (AUC 1.7-, 2.4, 3.4-fold respectively), and additionally cyclosporine increased letermovir AUC by 2.1-fold. Cyclosporine is an *in vitro* inhibitor of OATP1B1/3, P-gp, and BCRP, all potential contributors to increased letermovir exposure [McCrea et al., 2019].

By collecting blood plasma for PK levels of letermovi**r,** commonly utilized ARV drugs, **and statins,** future exploratory analyses can be performed to assess potential for clinically significant metabolic and transporter-mediated interactions and the need for further intensive PK interaction studies. Further, these samples can be utilized in future exploratory analyses linking PK exposure to outcomes of interests for use in dose optimization and characterization of potential drivers of PK and PD variability. These analyses may inform letermovir dosing in future studies and foster further hypothesis generation.

11.1 Pharmacology Objectives

To obtain samples to be used for future exploratory analyses to:

11.1.1 Assess PK interactions between letermovir and ART **and allowed statins**.

11.1.2 To establish the PK/Pharmacodynamic (PD) relationship between letermovir **and statin** exposure and study endpoints (e.g., change in sTNFRII levels).

11.2 Pharmacology Study Design

Plasma samples will be collected at the treatment initiation visit (week 0), and at the post-treatment initiation visits at weeks 4, 8, 46, and 60 for ART and letermovir

quantification. All samples will be stored for future batched analysis of ART**, statins,** and letermovir following study completion.

12.0 DATA COLLECTION AND MONITORING

12.1 Records to Be Kept

Electronic case report form (eCRF) screens will be made available to sites for data entry. Participants must not be identified by name on any data submitted to the DMC. Participants will be identified by the participant identification number (PID) and study identification number (SID) provided by the ACTG DMC upon randomization.

12.2 Role of Data Management

12.2.1 Instructions concerning entering study data on eCRFs will be provided by the ACTG DMC. Each CRS is responsible for keying the data in a timely fashion.

12.2.2 It is the responsibility of the ACTG DMC to assure the quality of computerized data for each ACTG study. This role extends from protocol development to generation of the final study databases.

12.3 Clinical Site Monitoring and Record Availability

12.3.1 Monitoring visits may be conducted on-site or remotely. Remote visits may include remote source document verification using methods specified for this purpose by NIAID. Remote monitoring visits may be performed in place of, or in addition to onsite visits to ensure the safety of study participants and data integrity [FDA Guidance Document, 2021]. The site **must** make available study documents for site monitors to review utilizing a secure platform that is HIPAA and 21 CFR Part 11 compliant. **The Data Management Center will configure Medidata Remote Source Review (RSR) and make it available to all sites. We encourage Sites to use the DMC provided Medidata RSR platform but other** potential platform options include: Veeva SiteVault, site-controlled SharePoint or cloud-based portal, **and** direct access to Electronic Medical Record (EMR), and Medidata Rave Imaging Solution. Other secure platforms that are 21 CFR Part 11 compliant may be utilized, as allowed by the DAIDS Office of Clinical Site Oversight (OCSO).
FDA. FDA Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards, March 2020, Updated on January 27, 2021. Accessed at: https://www.fda.gov/media/136238/download

12.3.2 The site investigator will make study documents (e.g., consent forms, drug distribution forms, eCRFs) and pertinent hospital or clinic records readily available for inspection by the ACTG, IRB/EC, the site monitors, FDA, the

NIAID, the OHRP, the industry supporter or designee, other local, US, and international regulatory entities for confirmation of the study data.

13.0 PARTICIPANTS

13.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the Informed Consent Form and any subsequent modifications will be reviewed and approved by the IRB or EC responsible for oversight of the study. A signed consent form will be obtained from the participant (or legal guardian, or person with power of attorney for participants who cannot consent for themselves). The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant, or legal guardian, and this fact will be documented in the participant's record.

13.2 Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain participant confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the ACTG, IRB/EC, FDA, NIAID, OHRP, other local, US, and international regulatory entities as part of their duties, or the industry supporter or designee.

13.3 Study Discontinuation

The study may be discontinued at any time by the ACTG, IRB/EC, FDA, NIAID, OHRP, other country-specific government agencies as part of their duties to ensure that research participants are protected, or the industry supporter.

14.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by ACTG policies. Any presentation, abstract, or manuscript will be made available for review by the industry supporter prior to submission.

15.0 BIOHAZARD CONTAINMENT

As the transmission of HIV 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 blood and shipping and handling of all specimens for this study, as currently recommended by the CDC and the National Institutes of Health.

All dangerous goods and materials, including diagnostic specimens and infectious substances, must be transported using packaging mandated by CFR 42 Part 72. Please refer to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations.

16.0 REFERENCES

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INFORMED CONSENT FORM
AND
AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION

Sponsor / Study Title:

The National Institute of Allergy and Infectious Diseases (NIAID) / "Randomized, Controlled Trial to Evaluate the Anti-inflammatory Efficacy of Letermovir (Prevymis) in Adults with Human Immunodeficiency Virus (HIV)-1 and Asymptomatic Cytomegalovirus (CMV) Who Are on Suppressive ART and Its Effect on Chronic Inflammation, HIV Persistence, and Other Clinical Outcomes (ELICIT)"

Protocol Number:	**A5383**
Principal Investigator:(Study Doctor)	**«PiFullName»**
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SUMMARY

PURPOSE

This is a research study and your participation in this study is voluntary. The purpose of this study is to evaluate whether letermovir (Prevymis), taken as two 240 mg tablets (480 mg total) or one 480 mg tablet once daily for 48 weeks, reduces inflammation (described below) in adults with human immunodeficiency virus (HIV-1) who also have cytomegalovirus (CMV) without any symptoms and who have been on effective anti-HIV medication for at least one year. Reducing inflammation might in turn help prevent some longer-term consequences of HIV, like heart disease and diabetes. This study will also look at whether you experience any side effects to the study drug.

STUDY TREATMENT

Letermovir, provided as two pills (each at a dose of 240 mg) or one pill (at a dose of 480 mg) given by mouth once a day, is approved by the US Food and Drug Administration (FDA) to prevent CMV disease in patients who have undergone allogeneic stem cell transplant. There are two groups in this study. You will have a 50/50 chance of going into each of the two groups. Participants in one group will get letermovir and participants in the other group will get no anti-CMV treatment.

NUMBER OF PARTICIPANTS

There will be a total of 180 participants, divided into 2 study treatment groups. Ninety (90) participants will receive the active study treatment (letermovir) and 90 participants will receive no anti-CMV treatment.

LENGTH OF STUDY

The study will last for about 1 year and 2 months (about 11 months on either letermovir or no anti-CMV treatment and then about another 3 months of follow-up). You will be on letermovir or no anti-CMV treatment for 48 weeks. After the first 40 participants have started study treatment (either letermovir or no anti-CMV treatment) and reached their 8-week study visit, we will stop enrollment for a while and do an initial analysis to make sure that letermovir is having some effect before enrolling the remaining participants. If no effect is seen at that point, we will consider stopping the study.

REQUIRED ACTIVITIES

Blood collections

At some clinic visits, some blood will be collected from a vein in your arm.

Special procedures

At several of the clinic visits, throat washes, rectal swabs, and genital secretion (semen or vaginal swab) will be collected**, because it is far easier to detect CMV in these samples than in blood. You do not have to provide genital secretions or rectal swabs if you feel uncomfortable in doing so or are not able to provide them.** Physical function assessments will also be done. Neuropsychological tests will also be performed during clinic visits. All participants will have an electrocardiogram (ECG) performed at the initial screening visit.

RISKS

The following are possible:

- Common letermovir side effects
  - Nausea
  - Diarrhea
  - Vomiting
  - Swelling in the arms and legs
  - Cough
  - Headache
  - Tiredness
  - Stomach (abdominal) pain
- Possible letermovir side effects that are uncommon but potentially serious:
  - Fast heart rate or pulse
  - Atrial fibrillation, a condition of the heart that can cause a fast heart rate and increase the risk of stroke

- Possible interactions between letermovir and antiretroviral therapy (ART) or other medications
- Developing letermovir-resistant CMV
- Allergic reactions such as rash or hives
- Risks associated with blood draws
  - Pain and bruising at the site of blood draw
  - Infection
  - Hypotension (lowering of blood pressure)
  - Feeling lightheaded or fainting
- Mild discomfort during vaginal swab collection
- Mild discomfort, coughing or a tingling feeling, or slight stinging during throat wash
- You may have mild discomfort when the rectal swab is performed, particularly if you are already suffering from sores or hemorrhoids. If you are already having pain in the rectal area, be sure to let the study team know.

BENEFITS — No direct health benefits should be expected from participating in this study. Information learned from this study may help others who have HIV and CMV.

OTHER CHOICES — Instead of being in this study, you have the choice of treatment for asymptomatic CMV infection with:

- Treatment with other experimental drugs for asymptomatic CMV infection, (if you qualify), or
- No treatment – which is the current standard of care for asymptomatic CMV infection

INTRODUCTION

You are being asked to take part in this research study because you have HIV (the virus that causes AIDS). This study is sponsored by the National Institutes of Health (NIH). The study doctor in charge of this study at this site is listed on page one of this consent form. Before you decide if you want to be a part of this study, we want you to know about the study.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign and date this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

CMV is a very common virus that infects the majority of adults and over 90% of people with HIV. Most healthy people (those without HIV and with an intact immune system) that have CMV have

no symptoms at all but carry the virus in the body for their entire life. A large part of the body's immune defenses is actually devoted to keeping CMV from replicating (making copies of itself). When the immune system is very weak, such as during advanced AIDS (for example, a CD4 count less than 50), CMV can escape the control of the immune system, replicate at high levels, and cause symptoms (such as eye problems like retinitis or gut problems like colitis). While such high levels of CMV replication typically don't occur anymore once the immune system gets stronger on HIV medications, it is possible that the immune system may not recover to 100% strength during anti-HIV treatment, allowing very low-level CMV replication to occur in the body. These low levels of CMV replication may not be enough to cause retinitis or colitis, but they may be enough to cause low-level inflammation (a reaction of the body to injury or infection) in the blood vessels and the fat tissue, possibly increasing the chance of heart disease or diabetes, conditions that appear to be increased in people with HIV.

The investigators of this study think that treating low-level CMV might reduce inflammation in people with HIV who are otherwise doing well on anti-HIV medications, and reduce their risk for heart disease, diabetes, and other aging-related complications. The study is designed to specifically address this hypothesis.

Letermovir (Prevymis), is FDA approved to prevent severe CMV disease in adults who carry CMV without any symptoms and who are receiving special cells from another person. This is also known as allogenic stem cell transplantation and is usually used to treat a blood cancer. Letermovir is not approved for others with CMV, including those with HIV. Because letermovir has been shown to reduce CMV disease in these people who have a weakened immune system, it is proposed that it may also reduce the amount of CMV and inflammation in people with HIV. The use of Letermovir (Prevymis) in this study is investigational because it is the first time that letermovir is being used in individuals living with HIV.

The purpose of this study is to see if letermovir is safe and effective when given to people who have both well-controlled HIV infection and asymptomatic CMV infection. This study will also gather data on the effectiveness of letermovir to reduce inflammation when compared to no anti-CMV treatment. In addition, the study will collect information on whether you experience any side effects from the study drug. The effects of letermovir in reducing the amount of CMV virus and inflammation in people living with HIV are still unknown.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

Information Collected at Screening

If you decide to take part in this study, you will have a screening visit to determine if you qualify for the study.

There is some information that we collect on everyone who is screened for an ACTG study. As part of your screening visit, some demographic (such as, age, sex/gender, race), clinical (such as, disease condition, diagnosis, use of sex hormones), and laboratory (such as, $CD4^+$ cell count, viral load) information will be collected from you. We also collect information on whether you use (or have used) illicit intravenous (IV) drugs.

We will collect this information even if you are found to be not eligible to receive the study drug. This information is collected so that ACTG researchers can determine whether there are patterns and/or common reasons why people do not join a study.

Screening

At the screening visit, you will be asked for your medical and medication history, you will have a physical exam, have your blood drawn, have a pregnancy test (if appropriate), have short neuropsychological testing, and receive a test for the health of your heart known as an electrocardiogram (ECG). The screening visit should take between 60-90 minutes to complete. If, during your screening visit, study staff suspect or confirm that you have a SARS-CoV-2 infection, you will be referred to an appropriate testing and/or treatment center.

Study Entry (Pre-Study Treatment) and Study Treatment Initiation Visits

The schedule of visits and study procedures are explained in Appendix I. **While some of the visits may occur remotely (please see Appendix I), most** will occur in person. **Study visits take place** at 4, 8, 16, 24, 32, 40, 46, 48, 52, and 60 weeks after you enter the study. Each of these visits will take between 30 and 60 minutes.

Following the screening visit, if you qualify for the study, you will have a brief physical exam, blood draw, pregnancy test (if appropriate), rectal swab, and provide oral and genital fluid samples (saliva, semen or vaginal swab). You will also complete questionnaires that ask about your sleep behavior (at the Study Treatment Initiation visit, and at weeks 46, 48, and 60 only), mood, sex and gender identity, and overall well-being. A type of blood draw called Plasma Pharmacokinetic (PK) sampling will also be collected at the Study Treatment Initiation visit. Pharmacokinetic samples allow researchers to determine how the body handles (absorbs, metabolizes and eliminates) the study treatment over time.

Semen, vaginal, and rectal swabs are requested because it is much easier to detect CMV in these samples than in the blood. Thus, providing these samples allows us to better measure the direct effect that letermovir has on CMV. Nevertheless, we understand that you may be uncomfortable providing (or unable to provide) semen, vaginal, or rectal swab samples. You can still participate in the study if you do not wish to provide these samples.

If you qualify for the study, you will be randomized to receive either the study treatment (letermovir) or no anti-CMV treatment. Randomized means that your assignment will be random, like rolling dice or flipping a coin to land on heads or tails. In this study, you will have a 50/50 chance of receiving study treatment versus no anti-CMV treatment. You will receive the study treatment or no anti-CMV treatment for 48 weeks and will continue to take your usual HIV medication. HIV medication will not be provided to you through the study.

Please note that you must continue your medication(s) for HIV while enrolled in this study, and your HIV must remain well-controlled (undetectable – meaning under 50 viral copies/ml, depending on the assay used) in order for you to continue to receive the study drug in this study.

There are a number of medications that should not be taken while you are participating in this study. Please inform your study doctor about any new prescriptions, other medications**, or herbal remedies** you are considering before you start taking them, so that the study doctor can advise whether they are safe to take while on this study.

Please also note that you are encouraged to use condoms and/or other barrier methods during the study to prevent HIV and other disease transmission, and for at least 90 days after your last dose of study **drug**. You must also use effective contraception during this study if you or your partner is able to become pregnant. **Sperm donation and egg donation should also be avoided during this period.**

Follow-up Visits

You will have follow-up visits **remotely or** in person **(see Appendix I)** at weeks 4, 8, 16, 24, 32, 40, 46, 48, 52, and 60. Most of these visits will take between 30 and 60 minutes. You will be asked how you are feeling, how you are sleeping, what medications you are taking, and whether you are taking your study treatment and HIV medications. Between 5 and 120 mL (1 teaspoon to 8 tablespoons) of blood may be collected at any one visit. At some of these visits, you may have rectal swabs collected and/or provide oral and genital fluid samples (saliva, semen, or vaginal swab). Saliva will be collected by a throat wash (in other words, you will gargle water and spit it into a cup). A Plasma PK sample will also be collected at some of the follow-up visits. A Plasma PK refers to a pharmacokinetic test that is done to measure the amount of study drug in your blood. An ECG will only be performed during follow-up visits if you have an abnormal heart rate, rhythm, and/or palpitations. You will also be asked about your sleep patterns and behaviors during some of the visits. A few visits will be shorter, allowing you to pick up refills of your study treatment, undergo a physical examination, and answer some questions about how well you are taking your study treatment and HIV medications. You will be required to fast (nothing to eat or drink except for water) at least 8 hours before all blood draws – except before any visits to recheck HIV levels after prior tests show the amount of HIV in your blood may have increased to a high enough level to suggest that HIV is not well controlled in your body (virologic failure).

Remote Follow-up Visits

Sometimes, the study staff may need to conduct a scheduled visit remotely (for example, by telephone, or via telehealth). This could happen for any of the reasons listed below

- If you are not feeling well
- If someone living with you is not feeling well
- Local conditions or guidelines prevent you from being able to travel to the clinic
- The site is temporarily unable to conduct non-essential visits in the clinic (for example, because of a problem at the facility or because of a public health emergency)
- At the discretion of the A5383 study team

Regardless of the reason, the site study staff will attempt to contact you and obtain as much of the required information from you as is possible. Study drug supplies might be delivered to your home, if needed. **Typically, visits would not be conducted remotely if you needed to travel to the clinic to refill study drug or had any new side effects or health problems that require medical attention.**

Follow-up Visits (weeks 8, 46 and 48)
If you are enrolled during the first phase of the study before the planned interim analysis (first 40 participants in the overall study), and if the week 8 visit is scheduled to take place at a time when it is not possible to conduct an in-person visit, the site may postpone your scheduled week 8 visit for up to **6** weeks so that you can safely attend the visit in person.

If both your week 46 and 48 visits are scheduled to take place at a time when it is not possible to conduct an in-person visit, the site may postpone you**r** scheduled week 48 visit for up to **6** weeks so that you can safely attend the visit in person. If such a postponement is necessary, you would be asked to continue taking study **drug** during that period (for up to **6** weeks) so that you are still taking study **drug** at the time of the final "on treatment" study visit (for example, up to 5**4** total weeks of study **drug** instead of the originally planned 48 weeks). The **study** staff will try to conduct your week 48 visit in person. If the week 48 visit is delayed, the weeks 52 and 60 visits will also be delayed (in other **words**, the off-treatment phase of the study would still be 12 weeks).

Telephone, E-mail, or Text Message Contact
After receiving the study treatment, you will be contacted by telephone, text message, or e-mail between visits to remind you of study visits and to track your adherence to the study treatment.

MAY I CHOOSE THE TYPES OF RESEARCH THAT MY SAMPLES AND INFORMATION ARE USED FOR?

Some of your blood and genital fluid samples will be stored and used for testing of the body's immune (protective) response, swelling (inflammation), and the presence of both CMV and HIV that is required for this study.

Identifiers will be removed from your samples and from any private information that has been collected about you. This means that no one looking at the labels or at other information will be able to know that the samples or information came from you.

The tests described in this consent are required by this study. **However, if you are not able to or do not choose to provide genital secretions or rectal swabs, then you do not have to provide them**.

Optional use of samples in other studies
When samples are no longer needed for this study, the ACTG may want to use them in other studies and share them with other researchers. These samples are called "extra samples". The ACTG will only allow your extra samples to be used in other studies if you agree to this. If you have any questions, please ask.

Identifiers will be removed from your samples and from any private information that has been collected about you. This means that no one looking at the labels or at other information will be able to know that the samples or information came from you.

Extra samples are stored in a secure central place called a repository. Your samples will be stored in the ACTG repository in the United States.

There is no limit on how long your extra samples will be stored.
When a researcher wants to use your samples and information, their research plan must be approved by the ACTG. Also, the researcher's institutional review board (IRB) will review their plan. IRBs protect the rights and well-being of people in research. If the research plan is approved, the ACTG will send your samples to the researcher's location. This means that researchers who are not part of the study team may use your samples without asking you again for your consent. The researcher is not likely to ever know who you are. You will not be paid for your samples.

You may withdraw your consent for research on your extra samples at any time and the specimens will be discarded. You may decide whether or not you will permit the use of your stored samples for other studies in the consent signature page below.

COMMERCIAL PROFIT

Your biospecimens collected during this study will never be used for commercial profit.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

A total of 180 people will take part in this study.

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study for about 14 months (1 year and 2 months).

WHY WOULD THE STUDY DOCTOR OR SPONSOR TAKE ME OFF THIS STUDY EARLY?

The study doctor or sponsor may need to take you off the study early without your permission if:
- If you are unable to attend the Study Treatment Initiation visit
- If you are unable to attend two consecutive study visits
- The study is stopped or cancelled
- Per the request of your primary care provider if they think the study is no longer in your best interest
- A Safety Monitoring Committee (SMC) recommends that the study be stopped early (A SMC is an outside group of experts who monitor the study.)
- **You become pregnant**

The study doctor may also need to take you off the study treatment without your permission if:
- Continuing the study treatment may be harmful to you
- You need a treatment that you may not take while on the study

- You become pregnant
- You are not able to take the study treatment as required by the study

If you must stop taking the study treatment before the study is over, the study doctor may ask you to continue to be part of the study and return for some study visits and procedures.

IF I HAVE TO PERMANENTLY STOP TAKING STUDY-PROVIDED LETERMOVIR (PREVYMIS), OR ONCE I LEAVE THE STUDY, HOW WOULD LETERMOVIR BE PROVIDED?

During the study:

- If you must permanently stop taking study-provided letermovir before your study participation is over, the study staff will discuss other options that may be of benefit to you.

After the study:

- After you have completed your study participation, the study will not be able to continue to provide you with the letermovir you might have received on the study. If continuing to take this or similar drugs/agents would be of benefit to you, the study staff will discuss how you may be able to obtain them.

WHAT ARE THE RISKS OF THE STUDY?

There are risks to taking part in any research study.

The study treatment used in this study may have side effects, some of which are listed below. In a research study, all of the risks or side effects may not be known before you start the study. You need to tell your study doctor or a member of the study team immediately if you experience any health problems.

Please note that these lists do not include all the side effects seen with this study drug. These lists include the more serious or common side effects with a known or possible relationship to the study drug. If you have questions concerning the additional side effects, please ask the medical staff at your site.

There is a risk of serious and/or life-threatening side effects when non-study medications and/or vaccines are taken or given with the study treatment. For your safety, you must tell the study doctor or nurse about all non-study medications and/or vaccines you are taking or given before you start the study and also while you are on the study. You are encouraged to receive standard vaccinations including influenza vaccination (in other words, flu vaccine) and COVID-19 vaccination, while you are on the study, but these vaccinations should occur at least 14 days before you start any study visits or right after the study visits. Also, you must tell the study doctor or nurse before enrolling in any other clinical trials (studies) while on this study.

Everyone participating in this research study will be monitored (watched carefully, through frequent visits and other contact between visits) for side effects. You will be monitored during the administration of study treatment to keep track of your blood counts and organ function, particularly your kidney and liver function. Side effects that you might experience may go away after you stop taking the study treatment. You will be monitored closely for any of the severe, life-threatening side effects listed below. Some of these side effects may be permanent. Appropriate medical care will be provided, if necessary, including additional treatment, hospitalization and/or surgery.

Commonly reported but mild side effects of letermovir (seen in about 5% more people when compared to people getting no anti-CMV treatment):

- Nausea
- Diarrhea
- Vomiting
- Swelling in the arms and legs
- Cough
- Headache
- Tiredness
- Stomach (abdominal) pain

These mild side effects do not generally last more than a few days and usually do not require treatment, but you may be given non-prescription medication to help relieve the symptoms.

Less common, but potentially severe side effects of letermovir:

- Tachycardia (fast heart rate or pulse)
- Atrial fibrillation, a condition of the heart that can cause a fast heart rate and increase the risk of stroke.

Studies of letermovir in male rats have shown that there were reduced or abnormal sperm counts in rats that received high doses of letermovir. Therefore, if you are a study participant with testicles, your sperm count may be affected. For this reason, all study participants who produce sperm must do the following during the **study** treatment period and for at least 90 days after the last dose of study treatment:

- Use contraception
- Refrain from donating sperm

As with all drugs, you could have an allergic reaction such as a rash or hives. Allergic reactions can be dangerous; if you develop an allergic reaction, you will be given medication (similar to Benadryl) to counter the reaction.

Risks of Letermovir resistance

There is a potential risk that the CMV in your body might become resistant to letermovir. This would only potentially cause harm if you eventually needed to use letermovir to prevent or treat a severe CMV disease in the future. Since severe CMV disease primarily only occurs when the immune system is very weak (as with untreated and/or advanced AIDS or after a bone marrow or organ transplant), it is unlikely that you would need letermovir treatment in the future. It is

also unclear whether developing letermovir resistance while receiving the study treatment would result in continued CMV resistance to letermovir in the body after the study is completed. While letermovir resistance tests might be performed on samples obtained in this study, you will only receive research results that are important to your immediate health and those that require the need for medical treatment.

Risk of not being able to suppress HIV viral load while on study drug
While we do not anticipate significant interactions between letermovir and the anti-HIV drugs in your regimen, with any new medication there is always the possibility that there could be interactions with other medications that you are taking that we do not expect, making them less effective. We will monitor your HIV viral load in the study, and if your HIV viral load increases (and is confirmed with a second blood draw) while taking the study drug, we will stop the study drug but your participation in the trial will continue. If that were to happen, we would also perform an HIV drug resistance test to see if HIV has become resistant to one or more drugs in your regimen and share those results with you and your doctor. While it is unlikely that you will develop new HIV drug resistance, if it were to happen, it might require a change in your HIV drug regimen to suppress your HIV viral load again.

Risks Associated With Collection of Genital Secretion (Semen or Vaginal Swabs)
- There are no known physical risks associated with semen collection by masturbation.
- You may experience mild discomfort related to the insertion of the vaginal swab.

Risks Associated With Collection of Oral Secretions using Throat Washes
- You may experience mild discomfort during this procedure.
- Occasionally there can be coughing or a tingling feeling, or slight stinging.

Risks of Rectal Swab
You may have mild discomfort when the swab is performed, particularly if you are already suffering from sores or hemorrhoids. If you are already having pain in the rectal area, be sure to let the study team know.

Risks Associated with Blood Draw
Blood draws may cause pain and bruising, and rarely, infection at the site of the blood draw. There is also a risk of anemia (low red blood cell count) or hypotension (low blood pressure). Sometimes, having blood drawn will cause people to feel lightheaded or even to faint.

Risks Associated with Electrocardiogram (ECG)
An ECG traces the electrical activity of the heart. You may have mild irritation, slight redness, or itching at the sites on your skin where the recording patches are placed.

Risks Associated with Questionnaires
The questionnaires used in this study may be upsetting. You do not need to answer any questions that you are not comfortable with.

If you are having suicidal thoughts or feel in crisis, call the study doctor at the telephone number listed on the first page of this form. You can also call or text the National Suicide

& Crisis Lifeline at 9-8-8 or 1-800-273-TALK (8255). The Lifeline numbers are answered 24 hours a day every day of the year by a skilled, trained counselor. You can also present to a healthcare provider, your local emergency room, or call 9-1-1 to be connected to local emergency services.

Unknown Risks

You might have side effects or discomforts that are not listed in this form. Some side effects may not be known yet. New ones could happen to you. Tell the study doctor or study staff right away if you have any problems.

ARE THERE RISKS RELATED TO PREGNANCY?

It is not known whether this study treatment might hurt an unborn child. For study participants who are able to become pregnant, the study treatment may involve risks to you (or to the embryo or fetus, if you become pregnant), which are currently unforeseen. There does not seem to be risk to an unborn child if your partner becomes pregnant. While participating in this research study, including the 48 weeks of study treatment and the subsequent 12 weeks of follow-up off study treatment, you should not become pregnant and should not nurse a baby. You may be provided counseling about preventing pregnancy. Let your study doctor know immediately if you become pregnant. Your primary doctor should also be told if this happens. If you are pregnant, you may not take part in this study. If you are nursing a baby and do not want to stop, you cannot take part in this study. If you can become pregnant, a urine or blood pregnancy test will be obtained before you receive the study treatment. If you think you may be pregnant at any time during the study, tell your study staff right away. The study staff will talk to you about your choices. **In addition, you should avoid donating sperm or eggs while you are participating in the study.**

If you can become pregnant and are participating in sexual activity that could lead to pregnancy, you must use reliable birth control that you can discuss with the study staff. At least one of the following methods MUST be used while you are in the study:

- Condoms with or without a spermicide
- Diaphragm or cervical cap with spermicide
- Intrauterine device (IUD)
- Hormone-based contraceptive

If you become pregnant while on study, the study staff would like to obtain information from you about the outcome of the pregnancy (even if it is after your participation in the study ends). If you are taking anti-HIV drugs when you become pregnant, your pregnancy will be reported to an international database that collects information about pregnancies in participants who were assigned female sex at birth and of reproductive potential taking anti-HIV drugs. This report will not use your name or other information that could be used to identify you.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

No direct health benefits should be expected from participating in this study. Information learned from this study may help others who have HIV.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

Instead of being in this study you have the choice of:

- Treatment with prescription drugs available to you
- Treatment with experimental drugs, if you qualify
- No preventive treatment for CMV infection, which is the current standard of care for asymptomatic CMV infection

Please talk to your study doctor about these and other choices available to you. Your study doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

We will do everything we can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have gotten a Certificate of Confidentiality from the US Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your participation. Also, any publication of this study will not use your name or identify you personally. Having a Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study. Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities.

Your records may be reviewed by the US Food and Drug Administration (FDA), the ACTG, the US Office for Human Research Protections (OHRP), or other local, US, and international regulatory entities as part of their duties (insert name of site) Advarra institutional review board (IRB) (a committee that protects the rights and safety of participants in research), National Institutes of Health (NIH), other local, US, and international regulatory entities, study staff, study monitors, the drug company supporting this study, and its designees. This means that absolute confidentiality cannot be guaranteed.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. **L**aw. This **Web site** will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

WHAT ARE THE COSTS TO ME?

The study will pay for all research-related tests and assessments and for the study drug, letermovir (Prevymis). Taking part in this study may lead to added costs to you and your insurance company. In some cases, it is possible that your insurance company will not pay for these costs because you are taking part in a research study.

Anti-HIV medicines and birth control will not be provided by the study, and will be your responsibility to obtain, as advised by your treating physician and subject to coverage through your health insurance.

WILL I RECEIVE ANY PAYMENT?

Compensation

You may be reimbursed for your time and travel expenses as part of your participation in this study. You will be paid up to a total of $xx.xx if you complete this study. You will be paid for the visits you complete according to the following schedule:

- $xx.xx for Visits xxx.
- $xx.xx for Visits xxx.
- $xx.xx for Visits xxx.

If you do not complete the study, for any reason, you will be paid for each study visit you do complete.

You will be paid _____ *["after each visit," "annually," "bi-weekly," etc.]*

If you have any questions regarding your compensation for participation, please contact the study staff.

[OR]

You will not receive any monetary compensation for your participation in this study.

WHAT HAPPENS IF I AM INJURED?

If you are injured as a result of being in this study, you will be given immediate treatment for your injuries. The cost for this treatment will be charged to you or your insurance company.

[Sites: Please modify (if necessary) and insert one of these two statements, as appropriate to your site. If your site is required to carry CTI, this must be indicated in the informed consent.]

- There is no program for compensation through the US National Institutes of Health, but this site has clinical trials insurance. This insurance will allow the site to provide you with monetary compensation if you suffer harm as a result of participating in this research study.

OR

- There is no program for compensation either through this institution or the NIH.

You will not be giving up any of your legal rights by signing and dating this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. Your decision will not have any impact on your participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which you are otherwise entitled.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHOM TO CONTACT ABOUT THIS STUDY

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the study doctor at the telephone number listed on the first page of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research participants. If you have any questions about your rights as a research participant, and/or concerns or complaints regarding this research study, contact:

- By **mail**:
  Study Subject Adviser
  Advarra IRB
  6100 Merriweather Dr., Suite 600
  Columbia, MD 21044
- Or call **toll free**: 877-992-4724
- Or by **email**: adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: Pro00048976.

SIGNATURE PAGE

Please choose the response that matches what you want by putting your initials in the space provided. Please ask the staff any questions that you have before you indicate your selection.

Research without Human Genetic Testing

If you agree, your extra samples may be stored (with usual protection of your identity) and used for ACTG-approved HIV-related research that does not include human genetic testing. Genetic testing is a type of medical test that identifies specific characteristics of your genes. Your body, like all living things, is made up of cells. Cells contain deoxyribonucleic acid, also known as "DNA". DNA is like a string of information put together in a certain order. Parts of the string make up "genes". Genes contain instructions on how to make your body work and fight disease. Differences or changes in DNA explain some of the physical differences among people. These differences partly explain why some people get diseases like cancer or diabetes while others do not. Genetic testing looks at the differences in people's DNA. This testing also looks at how differences affect health and the body's response to disease and study treatment

____ (initials) I understand, and I agree to this storage and possible use of my samples.

OR

____ (initials) I understand, but I do not agree to this storage and possible use of my samples.

Research with Human Genetic Testing

The ACTG has a study (A5128) that collects samples and requires consent for genetic testing: A5128, Plan for Obtaining Informed Consent to use Stored Human Biological Materials (HBM) for Currently Unspecified Analyses.

Your extra samples from A5383 will not be used for human genetic testing unless you sign a separate consent form for study A5128.

Your **study** site staff might ask you if you would like to participate in the A5128 study. If you would like to participate, you will sign and date a separate consent form.

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below and date the form.

_____	_____
Participant's Name (print)	Participant's Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff's Signature and Date

AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION

If you decide to be in this study, the study doctor and study staff will use and share health data about you to conduct the study. Health data may include:

- **Your name.**
- **Address.**
- **Phone number.**
- **Date of birth.**
- **Medical history.**
- **Information from your study visits, including all test results.**

Health data may come from your study records or from existing records kept by your regular doctor or other health care workers.

For this study, the study staff may share health data about you with authorized users. Authorized users may include:

- **Representatives of The National Institute of Allergy and Infectious Diseases (NIAID) or the industry sponsor Merck & Co., Inc.**
- **Representatives of Advarra IRB (an Institutional Review Board that reviews this study).**
- **The Food and Drug Administration (FDA) and other US federal and state agencies.**
- **Government agencies to whom certain diseases (like HIV, hepatitis, and STDs) must be reported.**
- **Governmental agencies of other countries.**
- **Outside individuals and companies, such as laboratories and data storage companies, that work with the researchers and sponsor and need to access your information to conduct this study.**
- **Other research doctors and medical centers participating in this study, if applicable.**
- **A data safety monitoring board which oversees this study, if applicable.**

Your health data will be used to conduct and oversee the research, including for instance:

- **To see if the study drugs work and are safe.**
- **To compare the study drugs to other drugs.**
- **For other research activities related to the study drugs.**

Once your health data has been shared with authorized users, it may no longer be protected by federal privacy law and could possibly be used or disclosed in ways other than those listed here.

Your permission to use and share health data about you will end in 50 years unless you revoke it (take it back) sooner.

You may revoke (take back) your permission to use and share health data about you at any time by writing to the study doctor at the address listed on the first page of this form.

If you do this, you will not be able to stay in this study. No new health data that identifies you will be gathered after your written request is received. However, health data about you that has already been gathered may still be used and given to others as described in this form.

Your right to access your health data in the study records will be suspended during the study to keep from changing the study results. When the study is over, you can access your study health data.

If you decide not to sign and date this form, you will not be able to take part in the study.

STATEMENT OF AUTHORIZATION

I have read this form and its contents were explained. My questions have been answered. I voluntarily agree to allow study staff to collect, use and share my health data as specified in this form. I will receive a signed and dated copy of this form for my records. I am not giving up any of my legal rights by signing and dating this form.

_____
Printed Name of Participant

_____ _____
Signature of Participant **Date**

APPENDIX I: A5383 DESCRIPTION OF STUDY VISITS AND EVALUATIONS

I. Study Visit Schedule

The study site staff can answer any questions you have about individual study visits, how long they will last, or about the tests that will occur. The table below can be used as a quick reference for you, along with the explanations that follow.

Table 1: Expected Study Visit Schedule

Evaluation or Procedure	Screening[1]	Study Entry	Study Treatment Initiation (Week)	Post-**Study** Treatment Initiation Evaluations (Weeks)										
			0	4	8	16	24	32	40	46	48	52	60	Extra Visits[2]
Consent & contact information collected	✓													
HIV status confirmed	✓													
Questions about your health and medications you are taking	✓	✓												
Physical examination	✓	✓	✓	✓	✓		✓			✓	✓	✓	✓	✓
Electrocardiogram (ECG)	✓	needed only if an abnormal heart rate/rhythm is found												
Blood collected	✓	✓	✓	✓	✓		✓			✓	✓	✓	✓	✓
Plasma Pharmacokinetic (PK) sampling			✓	✓	✓					✓	✓[4]		✓	
Pregnancy test	✓	✓	✓	when pregnancy is suspected										
Study treatment adherence assessment			✓	✓	✓	✓	✓	✓	✓	✓	✓			
Collection of genital and oral secretions		✓	✓		✓					✓	✓	✓	✓	✓

Evaluation or Procedure	Screening[1]	Study Entry	Study Treatment Initiation (Week)	Post-**Study** Treatment Initiation Evaluations (Weeks)										
			0	4	8	16	24	32	40	46	48	52	60	Extra Visits[2]
Rectal swab collection		✓[3]			✓					✓	✓[4]		✓	
Physical Function/Frailty testing		✓[3]								✓	✓[4]		✓	
Brief **thinking/memory** testing		✓[3]								✓	✓[4]		✓	
Brief mood questionnaires		✓[3]			✓					✓	✓[4]	✓	✓	
Brief sleep assessment		✓[3]								✓	✓[4]		✓	
Sexual & Gender Identity Questionnaire		✓[3]												
Telephone, text message, or e-mail contact	between visits as needed													
Additional clinical assessments (as needed)						✓[5]		✓[5]	✓[5]					
Remote data collection	Possible[6]													

1 Screening: After you have read and signed the consent form, you will have several tests done to make sure that you meet the requirements for joining the study. If it appears or is confirmed that you might have SARS-CoV-2 infection, the **study** site staff will refer to you for appropriate testing and/or treatment.

2 Extra Visits: You will be required to attend a short number of extra study visits if the amount of HIV in your blood has increased to a high enough level that shows the HIV is not well-controlled in your body (virologic failure). If this is the case, you will remain in the study but stop study treatment (letermovir), complete a premature study discontinuation visit, and complete all remaining study visits. **These visits will also be used to document any reasons (other than virologic failure) that may explain why you are leaving the study early.**

3 **This evaluation will be completed at the Study Treatment Initiation (week 0) visit if it was not completed at the Study Entry visit.**

4 Th**is** evaluation will be completed on the week 48 visit if **it was** not completed during the week 46 visit.

[5] **Additional clinical assessments: You may be required to complete additional clinical assessments (which might be remote), to collect information on any adverse effects you are experiencing, changes in medications, or changes in study treatment. These additional visits will happen at weeks 16, 32, and 40.**

[6] Remote data collection: You may be required to take part in remote data collection throughout the study period.

II. Explanation of Evaluations/Procedures

Below are descriptions of the evaluations. You will be told the results of all tests performed with the exception of tests to look at the levels of study drug in your body and for future ACTG-approved testing.

Consent and contact information collected
After you read the consent and have had a chance to ask questions about the study, you will sign the consent form if you want to continue and join the study.

HIV status checked
If there is no record available, an HIV-1 test will be done. If an HIV-1 test has to be done, you may have to sign a separate consent form before this is done. You will be told the results of the HIV-1 test as soon as it is available.

Questions about your health and medications you are taking
Study staff will ask you questions about your medical and medication history.

Physical examination
You will have a physical exam. Your weight will be recorded at each visit; however, your height will only be recorded at the Study Entry visit. You will have a complete physical exam at the screening visit and a brief physical exam at the other visits.

Electrocardiogram (ECG)
All participants will have an ECG collected at the initial screening visit. An ECG will be performed to monitor the health of your heart. After you have entered the study, an ECG is only needed if you have an abnormal heart rate, rhythm, and/or palpitations.

Blood collected
Blood will be collected from a vein in your arm at some visits for research tests including liver function tests, your HIV viral load (a measure of the amount of HIV in your blood), your $CD4^+$ T-cell count (a measure of the strength of your immune system, the system that helps your body fight infections), and CMV serology (a measure of how much CMV antibodies are in your body). Antibodies are proteins made in the body in response to a foreign substance. In this case, the foreign substance is CMV. Other routine lab tests such as hematology and chemistry will also be carried out. You will also have some blood stored at most visits. Liver function tests check the levels of certain enzymes and proteins in your blood. Levels that are higher or lower than normal can indicate liver problems.

Plasma Pharmacokinetic (PK) sampling
Blood will be collected for PK testing from a vein in your arm at some visits. These blood samples will allow researchers to determine how the body absorbs the study treatment or other medications over time.

Pregnancy test
If you are able to become pregnant and you are engaging in sexual activity that can lead to pregnancy, you will be asked to give a small urine or blood sample (about 5 mL or 1 teaspoon) for a pregnancy test.

Study treatment adherence assessment
After you have started taking the study treatment, you will be asked questions about how well you remember to take the study treatment and how well you are taking your anti-HIV treatment medications. This information will be collected at all study visits up to week 48.

Collection of genital secretions
You will be asked to refrain from sexual activity and, if applicable, to avoid using intravaginal products 48 hours prior to the genital sample collection.

- Semen-producing participants: You will be asked to provide self-collected seminal sample by masturbation within 2 hours prior to the study visits. Semen collection can be performed at home as long your sample can be transported to the study clinic within 2 hours of collection at room temperature. These samples will be used for future testing.
- Participants with a vagina: You will be asked to provide vaginal swabs during the study visits; you may choose whether to self-collect your vaginal swab or have study personnel obtain the sample. These samples will be used for future testing.

Collection of genital secretions is requested because it is far easier to detect CMV in these samples than in the blood. Thus, collecting these samples allows us to better measure the direct effect that letermovir has on CMV. Nevertheless, if you are uncomfortable with providing (or unable to provide) semen or vaginal swab samples, you can chose not to provide these samples and still participate in the study.

Collection of oral secretions
Your saliva will be collected with a throat wash and the sample will be used for future testing. You should not eat, chew gum, mints or candy; brush/floss teeth; or smoke for 90 minutes before throat wash collections.

Rectal swab collection
The rectal swab is collected to study the different kind of bacteria in your stool (poop). A swab will gently be inserted approximately 2 cm into the anal canal and moved side-to-side before being removed. These samples will be stored and will be tested after the study is over.

Collection of rectal secretions is requested because it is far easier to detect CMV in these samples than in the blood. Thus, collecting these samples allows us to better measure the direct effect that letermovir has on CMV. Nevertheless, if you are uncomfortable with providing (or unable to provide) rectal swab samples, you can chose not to provide these samples and still participate in the study.

Physical Function/Frailty Testing
We will assess your physical function with tests that mimic activities that you might do during the day. These include measuring the time it takes you to rise from a chair, walk across the room, and squeeze with your hand. The tests will take approximately 10 minutes.

Brief **thinking/memory** testing
You will have some tests that are used to diagnose a brain disorder or disease. The testing will evaluate different brain processes including attention, visual search/scanning, and the ability to make and change plans. This type of testing will also look at your verbal learning and memory.

Brief mood questionnaires (mood test/depression assessment)
You will complete brief mood questionnaires that are used to screen, diagnose, monitor, and measure the presence and/or severity of depression and anxiety. **Three different questionnaires will be used to collect this information. One is called the Patient Health Questionnaire-9 (PHQ-9) which asks questions about depression. A second questionnaire you will complete is called the Generalized Anxiety Disorder-7 (GAD-7) questionnaire which asks about anxiety. A third** questionnaire you will complete **is** referred to as the Computerized Adaptive Testing for Mental Health (CAT-MH). The CAT-MH is a cloud-based data capture system. You will enter your responses into a tablet device and your data will be processed via a HIPAA compliant and secure Amazon Web Services platform. In order to ensure that your data remains confidential and to protect your privacy, a random number will be assigned to identify you. Only **study** site staff will maintain secure records linking you to your random number. The company that makes the CAT-MH iPad Application will send us the results of your questionnaires. The company will only be able to identify you by the random number generated for you. To protect your privacy, the company will not be able to link your information back to you.

Brief sleep assessment
You will have a short sleep assessment to measure your sleep patterns. The assessment will include information on how long you sleep, the quality of sleep, and any use of sleep medication.

Sexual and Gender Identity Questionnaire
You will complete a brief questionnaire about your sexual orientation and gender identity.

Telephone, e-mail, or text message contact
After receiving the study treatment, you will be contacted by telephone, text message, or e-mail between visits to remind you of study visits and medication adherence.

Additional clinical assessments (as needed)
During your participation in the study, you may be required to complete additional study visits to take part in additional clinical assessments. At the additional clinical assessment visits, information will be collected on any adverse effects you are experiencing, any changes to medications you are taking, or any changes in the study treatment. These assessments may take place remotely.

Remote data collection

During your participation in the study, if you are not able to attend in-person visits (for example, because you are not feeling well, if someone living with you is not feeling well, if local conditions or guidelines prevent you from being able to travel to the clinic, if the site is temporarily unavailable, or at the discretion of the A5383 study team), the study staff may need to conduct a scheduled visit with you remotely (for example, by telephone or via telehealth).