Clinical Protocol

Mycophenolate mofetil therapy for reduction of the HIV reservoir

Sponsored by:
amfAR, The Foundation for AIDS Research

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Statement of Compliance

The trial "Mycophenolate mofetil therapy for reduction of the HIV reservoir" will be conducted in compliance with the protocol, International Conference on Harmonization Good Clinical Practice (GCP) E6, the applicable regulatory requirements, including the U.S. Code of Federal Regulations applicable to clinical studies (45 CFR 46 concerning informed consent and IRB regulations), and by investigators who have completed Protection of Human Subjects Training.

Signature Page 1

Your signatures below constitute your approval of this protocol and the attachments, and provides the necessary assurances that you will conduct this trial according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and International Conference on Harmonization guidelines.

The Lead Principal Investigator(s) should sign this page. A copy of this Signature Page 1 should be filed with the holder of the Regulatory documents and a copy should be maintained at the site.

Principal Investigator:

_____
Print/Type

Signed: _____ Date: _____
Name/Title

Co-Principal Investigator:

_____
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Signature Page 2

The signature below constitutes the approval of this protocol and the attachments by the investigators, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and International Conference on Harmonization guidelines.

The Investigator(s) of Record from each participating clinical site should sign the Signature Page 2 as appropriate. This Signature Page 2 should be maintained at each site.

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol. I will comply with all requirements regarding the obligations of investigators as outlined in the Statement of Investigator which I have also signed.
I have read and understand the information in the product insert including the potential risks and side effects of the product under investigation, and will ensure that all associates, colleagues, and

employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

Investigator of Record:

_____
Print/Type

Signed: _____
Signature

Date: _____

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List of Abbreviations

AE	Adverse Event/Adverse Experience
ART	Antiretroviral Therapy
ca-DNA	Cell-associated HIV DNA
ca-RNA	Cell-associated HIV RNA
CFR	Code of Federal Regulations
CMV	Cytomegalovirus
CRF	Case Report Form
dd-PCR	Digital droplet PCR
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IND	Investigational New Drug
IEC	Independent or Institutional Ethics Committee
IMPDH	Inosine Monophosphate Dehydrogenase Activity
IRB	Institutional Review Board
IUPM	Infectious Unit Per Million
MMF	Mycophenolate Mofetil
N	Number (typically refers to participants)
NIAID	National Institute of Allergy and Infectious Diseases, NIH
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OHSR	Office for Human Subjects Research
PBMC	Peripheral Blood Mononuclear Cells
PI	Protease Inhibitor
PK	Pharmacokinetics
PO	Per os (by mouth)
QVOA	Quantitative Viral Outgrowth Assay
SAE	Serious Adverse Event/Serious Adverse Experience
scVL	Single copy plasma viral load
TAPT	Total Anti-Proliferation Test
TILDA	Tat/rev-Induced Limiting Dilution Assay
TREC	T Cell Receptor Excision Circles
VL	Viral Load
WHO	World Health Organization

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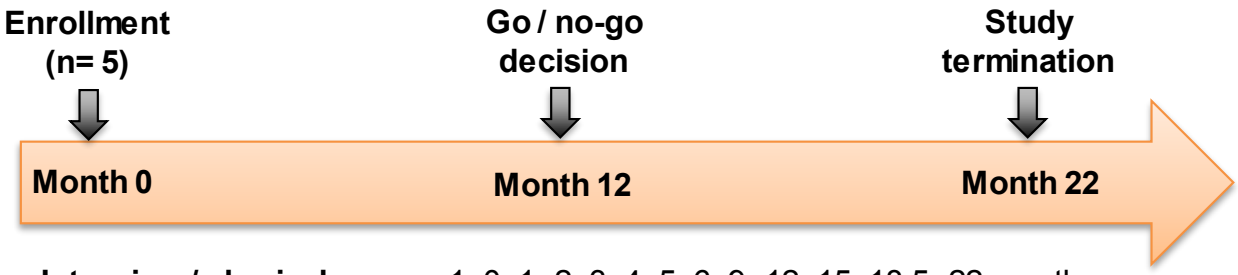
Protocol Summary

Table 1. Summary of Protocol	
Full Title	Mycophenolate mofetil therapy for reduction of the HIV reservoir
Short Title	MMF for HIV reservoir reduction
Clinical Trial Phase	Phase II study
IND Sponsor (if applicable)	Applied and confirmed "exempt" status with FDA
Conducted By	Fred Hutchinson Cancer Research Center University of Washington
Principal Investigators	Joshua T. Schiffer, MD, MSc and Florian Hladik, MD, PhD
Sample Size	Approximately 5 HIV-infected subjects
Study Population	HIV infected individuals on ≥2 years of suppressive ART who will specifically need to have demonstrated full viral suppression with at least four negative plasma viral loads with no more than one documented viral blip during this time.
Study Site	University of Washington AIDS Clinical Trials Unit (UW ACTU) at Harborview Medical Center in Seattle
Study Design	A prospective, open label trial
Study Duration	Accrual will require approximately 2 months. Each enrolled participant will be followed for 22 months
Study Agent	Mycophenolate mofetil or Myfortic©
Treatment Duration	22 months
Primary Objective	**Establish the impact of prolonged anti-proliferative therapy on the HIV reservoir.** We will test the following hypotheses*:* 1. MMF or Myfortic© therapy will lead to a progressive decrease in reservoir size over 22 months of treatment. 2. MMF or Myfortic© therapy will lead to a continual shift in HIV reservoir composition from primarily effector memory $CD4_+$ T cells (T_{em}) and central memory $CD4_+$ T cells (T_{cm}) to primarily stem cell like memory (T_{scm}) and naïve (T_n) $CD4_+$ T cells. 3. MMF or Myfortic© will eliminate detectable measures of the HIV reservoir, including by cell-associated DNA/mRNA and quantitative viral outgrowth.
Secondary Objectives	**Establish the safety of prolonged MMF or Myfortic© therapy in 5 chronically HIV-1 infected patients whose viral loads are fully suppressed by ART.**

	We will test the following hypotheses*:* 1. MMF or Myfortic© will be well-tolerated and will not decrease adherence to or antiviral efficacy of ART. 2. Peripheral $CD4_+$ T cell counts and percentages will not meaningfully decrease during treatment with MMF or Myfortic© and ART. 3. There will be no excess risk of opportunistic infections in MMF or Myfortic© treated study participants.
Endpoint	The primary endpoint of the study is HIV reservoir size at the end of drug treatment.

Figure 1: Study schema



- **Interview / physical exam:** -1, 0, 1, 2, 3, 4, 5, 6, 9, 12, 15, 18.5, 22 months
- **Safety labs:** -1, 0, 1, 2, 3 weeks, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 15, 18.5, 22, 22.5 months
- **Urine HcG (point-of-care-test for female participants):** with each safety labs
- **Anti-proliferative assays:** 0 and 1 week (inclusion testing), 1, 6, 12, 22 months
- **MPA (mycophenolic acid) serum levels:** 0, 1 week, 1, 2, 3, 6, 9, 12, 15, 18.5, 22 months
- **Peripheral blood T cell TREC levels:** 0, 1, 6, 12, 22 months
- **Blood for RNA sequencing:** 0 and 1 week, 1, 3, 6, 9, 12, 15, 18.5, 22 months
- **Plasma scVL:** 0, 1, 3, 6, 9, 12, 15, 18.5, 22 months
- **Reservoir assays (DNA ddPCR, mRNA ddPCR):** 0, 1, 2, 3, 4, 6, 9, 12, 15, 18.5, 22 months
- **Reservoir qVOA:** 0, 12, 22 months
- **Rectal biopsies for reservoir assays (optional):** 0, 12 & 22 months
- **Influenza vaccine:** 6-12 months (seasonal) with antigen assay 1 month later

Table 2. Schedule of study visits and blood draws

ACTU-2100 MMF Study Schedule of Events
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		MMF 500mg QD LEAD-IN / STEP 1	MMF 500mg BID LEAD-IN / STEP 2a				IF NO ANTI-PROLIFERATIVE EFFECT, MMF 750mg BID LEAD-IN / STEP 2b			
	Eligibility	Entry	week 1	week 2 T	week 2 P	Phone call to stop MMF in case of lacking efficacy by anti-proliferation test	week 3	week 4 T	week 4 P	Phone call to stop MMF in case of lacking efficacy by anti-proliferation test
TEST/ TIMING	**-1**	**0**	**0.25**	**0.5**	**0.5**		**0.75**	**Mo. 1**	**Mo. 1**	
2018 Flu Vaccine month 6~12										
Flu vaccine response evaluation										
Rectal Biopsies **OPTIONAL** (to Hladik Lab)		**BIOP**								
Complete Interview/Complete PE	X									
Limited Interview/Limited PE		X	X	X				X		
Limited Interview only (no PE)							X			
Discussion of MMF side effects	X	X								
Obtaining consent	X									
MMF Drug 500mg MMF for the first week, then go up to 2x500mg for the second week		**Dispense x1 week**	**Dispense x2 weeks**				**Dispense x2 wks or x5 wks**			
Urine PG---all visits with safety labs	0	0	0	0				0		
PT/PTT (**Pre-BIOP** safety) blue	4.5									
CBC & Diff Lavender Hemogard Tube)	3	3	3	3				3		
Comp Panel (3.5mL SST)	3.5	3.5	3.5	3.5				3.5		
CD4/CD8 (Lavender Top Tube)	4	4	4	4				4		
MMF Levels (at HMC) (3.5mL SST)		3.5		3.5	3.5			3.5	3.5	
HCABX & HBSAGX (only-as needed) (5mL SST)	5									
TB IGRA (only-as needed) (3 Quantiferon-TB Gold Tubes 1 mL each	3									
Low Level VL Assay (10mL EDTA)		0						20		
QVOA		100								
Anti-Proliferation Assay (3.5mL SST)		7		3.5	3.5			3.5	3.5	
8.5mL Yellow ACD tubes for Anti Proliferation Assays, FACS for Ki67, TREC level PCR, Cell-associated DNA and mRNA ddPCR, PBMC and plasma banking		**85**		**8.5**	**8.5**			**102**	**8.5**	
2.5 mL PAXgene Blood RNA Tube for Hladik Lab		**5**		**5**				**2.5**		
MLs	**23**	**211**	**10.5**	**31**	**15.5**			**142**	**15.5**	
Rolling volumes/8 weeks (max 450mL)		234.0	244.5	275.5	291.0		291	433.0	448.5	
TEAspoons	*4.7*	*42.8*	*2.1*	*6.3*	*3.1*		*0.0*	*28.8*	*3.1*	
TABLEspoons	*1.6*	*14.3*	*0.7*	*2.1*	*1.0*		*0.0*	*9.6*	*1.0*	
	Eligibility	Entry	week 1	week 2 T	week 2 P		week 3	week 4 T	week 4 P	

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IF ANTI-PROLIFERATIVE EFFECT, MMF 500mg BID STEP 3 (ENROLLMENT)																
IF ANTI-PROLIFERATIVE EFFECT, MMF 750mg BID STEP 3 (ENROLLMENT), OTHERWISE D/C VISIT AT WEEK 5																
week 5	week 6	week 8	week 10	wk 12 T	wk 12 P	week 16	week 20	wk 24 T	wk 24 P	week 28	week 32	week 36	week 40	week 44	wk 48 T	wk 48 P
Mo. 1.25	Mo. 1.5	Mo. 2	Mo. 2.5	Mo. 3	Mo. 3	Mo. 4	Mo. 5	Mo. 6	Mo. 6	Mo. 7	Mo. 8	Mo. 9	Mo. 10	Mo. 11	Mo. 12	Mo. 12
								~		~	~	VAC	~	~	~	
													20			
															BIOP	
		X		X		X	X	X				X			X	
	X		X							X	X		X	X		
R		R		R		R	R	R		R	R	R	R	R	R	
	0	0	0	0		0	0	0		0	0	0	0	0	0	
	3	3	3	3		3	3	3		3	3	3	3	3	3	
	3.5	3.5	3.5	3.5		3.5	3.5	3.5		3.5	3.5	3.5	3.5	3.5	3.5	
		4		4				4				4			4	
		3.5		3.5	3.5			3.5	3.5			3.5			3.5	3.5
				20				20				20			0	
															100	
				3.5	3.5			3.5	3.5			3.5			3.5	3.5
				170	8.5			170	8.5			212.5			119	8.5
				5				5				5			5	
	6.5	14	6.5	212.5	15.5	6.5	6.5	212.5	15.5	6.5	6.5	255	26.5	6.5	241.5	15.5
425.5	432.0	446.0	231.0	397.0	412.5	255.0	241.0	225.5	241.0	241.0	241.0	268.0	288.0	288.0	274.5	290.0
0.0	*1.3*	*2.8*	*1.3*	*43.1*	*3.1*	*1.3*	*1.3*	*43.1*	*3.1*	*1.3*	*1.3*	*51.7*	*5.4*	*1.3*	*49.0*	*3.1*
0.0	*0.4*	*0.9*	*0.4*	*14.4*	*1.0*	*0.4*	*0.4*	*14.4*	*1.0*	*0.4*	*0.4*	*17.2*	*1.8*	*0.4*	*16.3*	*1.0*
week 5	week 6	week 8	week 10	week 12	week 12	week 16	week 20	week 24	week 24	week 28	week 32	week 36	week 40	week 44	week 48	week 48

week 60	wk 74 T	wk 74 P	wk 88 T	wk 88 P	week 90		
Mo. 15	Mo. 18.5	Mo. 18.5	Mo. 22	Mo. 22	Mo. 22.5	ConVF	PreDC
			BIOP				
X	X		X				X
R	R						
0	0		0		0		0
3	3		3		3		3
3.5	3.5		3.5		3.5		3.5
4	4		4		4		4
3.5	3.5	3.5	3.5	3.5	3.5		
20	20		0			20	20
			100				
3.5	3.5	3.5	3.5	3.5			
212.5	212.5	8.5	119	8.5			
5	5		5				
255	255	15.5	241.5	15.5	14	20	30.5
255.0	255.0	270.5	241.5	257.0	271.0		
51.7	*51.7*	*3.1*	*49.0*	*3.1*	*2.8*	*4.1*	*6.2*
17.2	*17.2*	*1.0*	*16.3*	*1.0*	*0.9*	*1.4*	*2.1*
week 60	week 74	week 74	week 88	week 88	week 90		

The bottom row in red indicates rolling blood volumes over 8 weeks prior to and including each blood draw and should not be higher than a total of 450 mL as per University of Washington policy.

1.0 INTRODUCTION

1.1 Background

The use of antiretroviral therapy (ART) in HIV-infected patients is a shining success in medicine. These medications allow millions of patients to survive for decades, whereas untreated infection is often fatal within ten years. Widespread implementation of ART has also decreased HIV transmission because aviremic infected persons have little to no transmission potential.[1] Nevertheless, there is still an urgent need for an HIV cure that would eliminate all of the virus from the body. Complete HIV eradication, or at least a functional cure in which too little HIV remains for the virus to reactivate over the lifespan of the infected person, would allow infected persons to permanently stop taking anti-viral therapy. An immediate benefit of cure would be avoidance of possible ART-associated toxicities and drug interactions.[1,2] A definitive cure of HIV would reduce the stigma felt by many infected persons.[3] Finally, the transformation of HIV care provision from a chronic model whereby ART is given over decades to a cure therapy given over a few years, would save the United States healthcare system massive healthcare expenditures.

Strategies currently under consideration for HIV cure are contingent upon first controlling the virus with ART. Therefore, in keeping with current treatment guidelines, the usefulness of a cure intervention will depend upon the engagement and retention of infected persons in clinical care.[4] An optimistic assumption is that publicity associated with development of a safe and effective cure may drive more infected persons to seek early HIV testing and management. Widespread implementation of HIV cure would then decrease both HIV prevalence and incidence.[4] The scalability of each HIV cure approach will depend on its effectiveness, but also on its tolerability and affordability. Notably, many current HIV cure ideas involve treatments that are not yet widely used in the clinic.[5] “Off the shelf” medications that require no further research and development expenditure, and have well established toxicity profiles, are therefore attractive potential options for HIV cure.

The major barrier to HIV eradication is the HIV reservoir. The reservoir consists predominately of memory CD4+ T cells, which harbor non-replicating HIV DNA that is integrated into chromosomal DNA. Complete elimination of these cells, or at least inactivation of the “silent” HIV within these cells, is required for cure. The total reservoir typically consists of approximately 1-10 million CD4+ T cells.[6-8] On a per cell basis, the rate of reactivation of HIV is extraordinarily low. Yet, antiretroviral treatment interruption (**ATI**) studies demonstrate that HIV will reactivate approximately once per week.[9,10] Thus, to achieve a lifetime remission from HIV reactivation off ART, the vast majority of the reservoir must be eliminated.

Two groups estimated that a one-year remission off ART would require a 100- to 1000-fold reduction in the number of latently infected cells.[10,11] Given the low number of cells that would remain after such an intervention, a major challenge is to achieve reliable and rapid measurement of the HIV reservoir. Total cell-associated HIV DNA is a sensitive method to estimate reservoir size,[12-15] but is misleading because most HIV DNA is not replication competent. The gold standard quantitative viral outgrowth assay (**QVOA**) is specific for replication competent HIV but is laborious, slow and requires a large number of CD4+ T cells, making it less feasible for repeat monitoring.[16] Much of the reservoir exists within deep tissues such as lymphatic tissue in the gastrointestinal tract (**GALT**) and lymph nodes: this adds to the challenge of quantitating latently HIV infected cells.

Numerous technologies are being evaluated to eradicate the HIV reservoir. A majority of potential interventions are in preclinical development. Examples include gene therapy delivery of HIV DNA editing enzymes, chimeric antigen T cell therapy (CAR T cells), therapeutic vaccines, delivery of HIV

antibodies or anti-HIV synthetic peptides, and transplantation of HIV resistant cells.[5] Several latency-reversing agents (**LRAs**) are being actively tested in human study participants.[17] LRAs are designed to reactivate HIV from its latent form with the hope of inducing two downstream effects. First, cells with replicating HIV will lyse due to HIV replication while ART prevents infectious spread to new cells. Second, presentation of HIV peptides on the cell surface will induce a cytolytic immune response that may be augmented by other interventions such as a vaccine or CAR T cells. Unfortunately, demonstration of a reservoir reduction following clinical LRA therapy is so far lacking.[17]

1.2 Study rationale

Our research group designed a mathematical model with the initial goal of identifying the most important barriers to eradication of the reservoir. This analysis led to the conclusion that anti-proliferative therapy provided over a sustained period of time is potentially a far more potent approach than one time use of LRAs.[18]

Based on extensive existing phylogenetic data, we first assumed that after suppressive ART of >1 year, ongoing HIV replication does not contribute to persistence of the HIV reservoir.[19-26] We demonstrated that even in the context of partially effective ART, the survival of the latent reservoir can be decoupled from active viral replication. The latent pool of cells can then be characterized with an exponential clearance equation, which is analogous to the compound interest formula in finance and characterizes the slow clearance of the HIV reservoir over many decades. Two papers estimate the reservoir clearance half-life to be 44 months,[6,7] which means that it would take over 60 years for the reservoir to be cleared with ART alone.

On suppressive ART, the latent reservoir clearance rate consists of the sum of three latent cell processes: proliferation, death and reactivation to active viral replication. Importantly, observed per cell proliferation rates are several orders of magnitude higher than reactivation rates.[27] We identified in the literature that cells composing the reservoir, including effector memory (**T_{EM}**), central memory (**T_{CM}**), naïve (**T_N**) and stem cell like (**T_{SCM}**) memory $CD4_+$ T cells, proliferate at rates similar to comparable cells without HIV integration.[26,28-30] For example, a T_{CM} cell divides roughly once every 2 months.[31] On the other hand, ATI studies suggest that a single HIV-infected cell within the reservoir will reactivate at a rate of approximately once every 265 years.[10] Thus, because the viral reactivation rate is negligible and the net clearance rate of the latent reservoir approaches zero,[6,7] the proliferation and death rates must be approximately in equilibrium.

Using our model, we demonstrate that a small but prolonged decrease in HIV reservoir clearance rate would have a greater impact on decreasing the size of the reservoir than a single larger decrease in reservoir size, as would occur with a single dose of effective LRA treatment. This result is analogous to compound interest whereby small changes are amplified when applied over a long duration. Our model predicts that decades of ART would be needed after a 10-fold one-time reduction in the reservoir to achieve cure. Yet, a continuous 10-fold reduction in clearance rate would induce a functional cure in under five years.

We next examined the theoretical effects of continuous alterations of the component rates that determine the overall clearance rate. If we assume a medical intervention that has a continuous effect on HIV reactivation, this intervention would need to induce a 100-fold increase in the basal reactivation rate for three years in order to approach a functional cure. On the other hand, just a 3-fold decrease in the proliferation of reservoir cells extended over three years of treatment may be enough for a functional cure. Therefore, continuous anti-proliferative therapy would be the most efficient method to induce a cure.

Several pieces of data are consistent with the predictions of our mathematical model. Chapuis *et al* treated six study participants with MMF for 20 weeks.[32] Half of these patients demonstrated a substantial reduction in reservoir size measured by QVOA, ranging from 1 to 2 orders of magnitude. In addition, treated patients had a decrease in T cell proliferation as measured by Ki67 staining. Garcia *et al* treated nine chronically infected and ART-suppressed study participants with low-dose MMF for 17 weeks in addition to their ART.[33] The authors noted that serum obtained 12 hours post dosing demonstrated a pronounced anti-proliferative effect (>60% inhibition) on T cells *in vitro* in 6 of the 9 subjects on MMF. These 6 patients had a notable median 6-12 week delay in viral rebound and a lowering of viral load set point following ATI, compared to the untreated controls as well as to the three study participants on MMF whose serum did not have strong anti-proliferative activity. A delay of this magnitude is consistent with an approximately 10-fold decrease in reservoir size,[34] which aligns with predictions from our model. Our model further suggests that had participants taken ART and MMF for three years as we propose, then long-term remission would have been possible.

While MMF has been used in HIV+ patients receiving organ and blood transplants, findings under these conditions indicate multiple confounders in transplantation settings,[35-38] rendering them unsuitable to evaluate the effect of MMF.

1.3 Study drug

Mycophenolate mofetil (MMF) is a prodrug of mycophenolic acid, which inhibits an enzyme required for proliferation of lymphocytes, including B and T cells. MMF is used to prevent organ rejection following lung, liver, heart and kidney organ transplantation. Moreover, MMF is commonly used as a steroid-sparing agent for autoimmune diseases.

MMF safety in HIV-infected patients has been established in over 300 HIV+ solid organ transplant recipients and other clinical settings.[39-59] Fewer than 10% of treated participants developed nausea. Renal toxicity, cytopenia, opportunistic infections or decrease in peripheral CD4+ T cell counts were not noted.[39-45,49] Of note, we will use 500mg twice daily in our study, which is lower than the 2-3g/day to prevent organ rejection. We will increase to 750 mg twice daily if an adequate anti-proliferative effect is not noted on a lower dose.

Myfortic© is an enteric coated version of the MMF which is associated with less nausea, vomiting and diarrhea. Myfortic© will be used for participants who have refractory nausea, vomiting and / or diarrhea on MMF, and who wish to remain in the study.

2.0 STUDY HYPOTHESES AND OBJECTIVES

2.1 Hypotheses

2.1a MMF or Myfortic© will be well tolerated and will not decrease adherence to or antiviral efficacy of ART.

2.1b Peripheral CD4+ T-cell counts and percentages will not meaningfully decrease during treatment with MMF or Myfortic© and ART.

2.1c There will be no excess risk of opportunistic infections in MMF or Myfortic© treated study participants.

2.1d MMF or Myfortic© therapy will lead to a progressive decrease in reservoir size over 22 months of treatment.

2.1e MMF or Myfortic© therapy will lead to a continual shift in HIV reservoir composition from primarily effector memory $CD4_+$ T-cells (T_{em}) and central memory $CD4_+$ T-cells (T_{cm}), to primarily stem cell like memory (T_{scm}) and naïve (T_n) $CD4_+$ T-cells.

2.1f MMF or Myfortic© will eliminate detectable measures of the HIV reservoir, including cell-associated DNA/mRNA, and quantitative viral outgrowth.

2.1g MMF or Myfortic© will not decrease the humoral immune response to routine annual influenza vaccination.

2.2 Primary Outcomes

2.2a Change in cell-associated HIV DNA (ca-DNA) reservoir size as measured by multiplexed digital droplet PCR in study participants on versus off MMF or Myfortic© (historical controls).

2.2b Change in HIV replication by single copy viral load (scVL) in study participants on versus off MMF or Myfortic© (historical controls).

2.3c Change of viral reactivation by cell-associated HIV mRNA in study participants on versus off MMF or Myfortic© (historical controls).

2.3d Change of the inducible HIV reservoir size by quantitative viral outgrowth assay (QVOA) in study participants on versus off MMF or Myfortic© (historical controls).

2.3d Change of the cellular composition of the HIV DNA reservoir in study participants on versus off MMF or Myfortic© (historical controls).

2.3 Secondary Outcomes

2.3a $CD4_+$ T cell numbers that recently emigrated from the thymus

2.3b Blood $CD4_+$ T cell count

2.3c Complete blood cell count, comprehensive metabolic panel

2.3d Incidence of opportunistic infection

2.3e Antibody response to annual influenza vaccination

3.0 STUDY DESIGN

This is an open-label, randomized Phase II trial to determine whether MMF given over 22 months meaningfully decreases the size of the HIV reservoir.

At the University of Washington in Seattle, we will enroll 5 study participants who have been on ≥2 years of suppressive ART. Study participants will be followed closely for at least 22 months with safety labs and serial measurements of the HIV reservoir (specifically, cell-associated HIV DNA and mRNA (**ca-DNA & ca-RNA**), quantitative viral outgrowth assay (**QVOA**), and single copy plasma viral

load (**scVL**)). A “go/no-go” decision will occur after 12 months based on pre-defined thresholds of reduction in the HIV reservoir measured with ca-DNA.

All participants will be offered enrollment in a sub-study in which an anoscopy with rectum biopsies is performed on 3 occasions to assess the reservoir in the gastrointestinal lymphatic tissue (**GALT**

We will vaccinate study participants with the annual influenza vaccine and analyze their humoral response to this vaccine approximately one month later with a routine blood draw done in conjunction with a safety labs blood draw.

We hypothesize that low doses of MMF will be well tolerated among healthy HIV-infected study participants who have fully ART-suppressed HIV. We hypothesize that the incidence of opportunistic infections will not exceed that of comparable larger cohorts of HIV-treated patients. Of note, certain opportunistic infections such as herpes zoster or HSV-2 recurrence continue to occur despite suppressive ART, while pneumocystis pneumonia, CMV end organ disease, cryptococcus and many other opportunistic infections are much less common in this context. Therefore, in the event of an infection, we will confer with the data safety management (DSM) panel to discuss whether this event is directly attributable to MMF. Finally, we hypothesize that peripheral blood $CD4_+$ and $CD8_+$ T cell counts will remain unchanged throughout MMF therapy, and that HIV replication will remain controlled on ART with addition of MMF.

We hypothesize at least a 0.25-log reduction in cell-associated HIV DNA at one-year intervals in study participants who have a demonstrated anti-proliferative response to MMF treatment. We hypothesize that cell-associated HIV DNA will undergo a shift from predominant residence in T_{CM} and T_{EM} to predominant residence in T_N and T_{SCM}. In regards to our sub-study, we predict that reservoir depletion will occur with equivalent rates in blood and GALT.

4.0 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria

a. Confirmed HIV infection, by two different positive antibody tests and/or detectable plasma HIV RNA on two different dates

b. ≥18 and ≤65 years of age

c. Continuous ART during the last two years, with current ART preferably including an integrase inhibitor

d. HIV RNA <40 copies / mL on four occasions during continuous ART of ≥ 2 years with no more than one blip of <1000 HIV RNA copies / mL

e. $CD4_+$ T cell count > 350/mm_3 within the past 365 days

f. Karnofsky score ≥80

g. Plan to reside in area 2 years

h. Consents to study

i. “Step 1” lead-in phase: Tolerability of MMF during one week dose escalation of 500 mg once daily (or Myfortic© 360 mg once daily)

j. "Step 2a" lead-in phase: Demonstrated tolerability and anti-proliferative effect (>= 80% anti-proliferative effect) of one week of MMF 500 mg twice daily (or Myfortic© 360 mg twice daily)

k. "Step 2b" lead-in phase (only if necessary based on inadequate anti-proliferative effect on 500 mg bid): Demonstrated tolerability and anti-proliferative effect (>= 80% anti-proliferative effect) of one week of MMF 750 mg twice daily (or Myfortic© 540 mg twice daily)

4.2 Exclusion Criteria

a. Active malignancy including skin cancer, myelodysplastic syndrome, or myeloproliferative disease within 24 weeks prior to study entry

b. Prior organ or bone marrow transplantation

c. Diagnosed autoimmune disease

d. Medical need for ongoing treatment with an immunosuppressive drug

e. Diagnosis of AIDS (defined as any AIDS-defining opportunistic infection or cancer, or a history of blood $CD4_+$ T cell count < 200/μL)

f. Active opportunistic infection

g. Using disallowed medications (see 4.3)

h. Vomiting or diarrhea which prohibits consistent use of study drugs

i. Pregnant, intention to become pregnant, or breastfeeding

j. Woman of child bearing age who are NOT using two forms of birth control OR practicing complete abstinence

k. Excessive ingestion of ethanol, determined by an AUDIT score of >8

l. Substance abuse

m. History of medical non-compliance

n. Quantiferon TB positive

o. The following laboratory values (<30 days before enrollment):

- Hemoglobin < 8.5 mg/dL
- Absolute neutrophil count < 1000 cells/mm_3
- ALT > 2 x upper limit of normal
- Platelet count ≤ 100,000/uL
- Creatinine clearance < 60 mL/min

4.3 Disallowed Medications

a. Proton pump inhibitors

b. Rifampin
c. Cholestyramine
d. Colestipol
e. Estrogen or progestin contraceptive
f. Cyclosporine, tacrolimus or pimecrolimus
g. Fingolimod
h. Leflunomide
i. Magnesium salts
j. Metronidazole (oral)
k. Monoclonal antibodies
l. Tofacitinib
m. Systemic corticosteroids

4.4 Eligibility and Enrollment

Protocol enrollment is available to all interested qualified individuals willing to adhere to the study. Written informed consent for study participation must be obtained before any study-related procedures are performed. Participant enrollment evaluation follows the Schedule of Evaluations (Table 2 and Section 12.0).

4.5 Sub-Study Procedures

Co-enrollment into observational studies is allowed if blood volumes permit. Co-enrollment into other interventional studies will be considered by the study team on a case-by-case basis, and will depend upon blood volumes, whether participation is likely to interfere with completion of this study or the outcome of this study.

5.0 STUDY TREATMENT

5.1 Drug Regimen, Administration and Duration

- Both MMF and Myfortic© should be taken on an empty stomach, 1 hour before or 2 hours after food intake
- Entry / “Step 1” lead-in period:
  - Mycophenolate mofetil (MMF) 500 mg or Myfortic© 360 mg daily for one week as the “Step 1” lead-in phase
- Week 1 visit / “Step 2a” lead-in period:
  - Tolerability check
  - Start MMF 500 mg or Myfortic© 360 mg twice daily for 2 weeks as the “Step 2a” lead-in phase

- Week 2 visit:
  - Tolerability check
  - Anti-proliferative testing
- Week 3 visit:
  - If week 2 test shows a desired anti-proliferative effect (>=80% reduction in T cell proliferation one-hour post dosing): continue study at MMF 500 mg or Myfortic© 360 mg twice daily for 22 months ("Step 3" enrollment)
  - If week 2 test does not show a desired anti-proliferative effect (<80% reduction in T cell proliferation one-hour post dosing): dose escalation to MMF 750 mg or Myfortic© 540 mg twice daily for 2 weeks ("Step 2b" lead-in phase)
- Week 4 visit (only if dose escalation to MMF 750 mg or Myfortic© 540 mg twice daily occurred at week 3 visit):
  - Tolerability check
  - Anti-proliferative testing
- Week 5 visit (if dose escalation to MMF 750 mg or Myfortic© 540 mg twice daily occurred at week 3)
  - If week 4 test shows a desired anti-proliferative effect (>=80% reduction in T cell proliferation one-hour post dosing): continue study at MMF 750 mg or Myfortic© 540 mg twice daily for 22 months ("Step 3" enrollment)
  - If week 4 test does not show a desired anti-proliferative effect (<80% reduction in T cell proliferation one-hour post dosing): discharge from study

5.2 Drug Formulation

MMF tablets, 250 mg, 500 mg
Myfortic© tablets, 180 mg, 360mg

5.3 Drug Supply

- Drugs will be procured locally in Seattle and stored by the AIDS Clinical Trial Unit pharmacy at Harborview Medical Center. Only drugs approved by the US Food and Drug Administration (FDA) will be used.

6.0 PARTICIPANT MANAGEMENT

6.1 Procedures

Participants in this study will take 500 mg MMF once per day for one week as a lead in to limit drug-related side effects. Provided they are tolerating the drug at lower dose, they will then initiate 500 mg MMF twice a day for 22 months in addition to their regular anti-HIV treatment. MMF will be switched to Myfortic© in the event of poorly tolerated nausea, vomiting or diarrhea and participant agreement to remain in the study. As described above, dose escalation to 750 mg MMF twice daily is possible in the event of an inadequate anti-proliferative effect. Participants will visit the clinic and provide samples (blood and optional rectal biopsies) several times during the course of the study. If feeling nausea or vomiting, participants will be offered ondansetron 4mg oral tablets. The specific procedures for the study visits are outlined below.

Eligibility Visit (approximately 2 hours)

During this visit, we will do the following:

1) Provide participants with general information about the 2 West Clinic
2) Ask participants to sign the Study Consent Form, the Release of Medical Information Form, and HIPAA Authorization Form
3) Document that participants have HIV by medical records and also determine if participants have a medical condition that would preclude them from entering the study. In the event that documentation is unavailable, we will ask participants to allow us to do these tests after counseling and obtaining their verbal consent
4) Take a medical and medication history
5) Assess substance use history, including alcohol, and sexual risk behavior
6) Perform a general clinical exam (including vital signs: weight, height, blood pressure, pulse and temperature)
7) Obtain a urine specimen for pregnancy testing in female participants
8) Draw about 5 teaspoons of blood for routine blood tests (blood cell counts and signs of anemia, kidney or liver dysfunction)
9) Perform blood testing for hepatitis B and C if results are not already available from within 12 months prior to eligibility visit.

Entry Visit (approximately 1 hour) / Step 1 Lead-in

If the information obtained at the eligibility visit indicates that a participant is eligible to participate in the study, we will ask them to come to the clinic for an entry visit. The purpose of this visit will be to enroll the participant in the study and obtain additional blood samples. We will ask all participants to take MMF for one week following this visit.

During this visit, we will do the following:

1) Draw 211 mL (43 teaspoons) of blood
2) Perform follow up urine pregnancy testing in female participants
3) Provide the study drug (MMF 500 mg daily) and instructions on how to use it.
4) Schedule follow-up visits
5) Answer any questions
6) Focused physical exam as needed

One-Week Visit (approximately 30 minutes) / Step 2a Lead-in

Six days after enrolling in the study, we will ask participants to make a follow-up visit to discuss tolerability of the drug. Participants will be seen in the morning of day 7. If they are tolerating the dose, then their dose will be increased to MMF 500 mg twice daily.

At this visit, we will:

1) Draw a combined total of 10.5 mL of blood (about 2 teaspoons).

2) Ask the participant how they are tolerating the study medication
3) Answer any questions
4) Focused physical exam as needed

Two-Week Visit (approximately 30 minutes)

Thirteen days after enrolling in the study, we will ask participants to make a follow-up visit to measure anti-proliferative effect at trough and peak MMF levels. Participants will be seen in the morning of day 14, approximately 12 hours after the last evening MMF dose. We will draw a small blood sample, then administer the morning MMF dose, ask the participant to wait for 60 minutes, and then take another small sample. We will use the first sample to assess the anti-proliferative effect at trough MMF levels, and the second sample to assess the anti-proliferative effect at peak MMF levels. At this visit, we will:

5) Draw a combined total of 46.5 mL of blood (about 9 teaspoons) on 2 occasions separated by 1 hour.
6) Ask the participant how they are tolerating the study medication
7) Answer any questions
8) Focused physical exam as needed

Three-Week Visit (approximately 30 minutes)

The purpose of this visit is to determine how the participant is responding to the study drug. Based on the results of the peak MMF time point studies done in the lab, we will determine whether the participant is eligible to continue participating in the study at the current dose for 22 months (Step 3 / Enrollment) or might require a dose escalation (Step 2b / lead-in).

If a participant does not have the desired anti-proliferative effect to MMF 500 mg twice daily at the two-week visit, we will administer MMF 750 mg po twice daily (Step 2b / lead-in): this will occur at the three-week visit because it takes approximately one week for the anti-proliferative assay to be performed.

No blood will be drawn at the three-week visit.

Four-Week Visit (approximately 30 minutes)

For participants on 500 mg bid and those who required dose escalation to 750 mg bid, we will recheck for an anti-proliferative effect at a week 4 visit. Participants will be seen in the morning, approximately 12 hours after the last evening MMF dose. We will draw a small blood sample, then administer the morning MMF dose, ask the participant to wait for 60 minutes, and then take another small sample. We will use the first sample to assess the anti-proliferative effect at trough MMF levels, and the second sample to assess the anti-proliferative effect at peak MMF levels. At this visit, we will:

1) Draw a combined total of 157.5 mL of blood (about 11 teaspoons) on 2 occasions separated by 1 hour.
2) Ask the participant how they are tolerating the study medication

3) Answer any questions
4) Focused physical exam as needed

Five-Week Visit (approximately 30 minutes): only for participants receiving 750 mg po bid

The purpose of this visit is to determine how participants who required escalation to 750 mg bid are responding to the study drug. Based on the results of the peak MMF time point studies done in the lab on the week 4 visit, we will determine whether the participant is eligible to continue participating in the study at the current dose for 22 months (Step 3 / Enrollment).

If participants do not have the desired anti-proliferative effect to MMF 750 mg twice daily, they will be discharged from the study at the week 5 visit.

No blood will be drawn at the week 5 visit.

Treatment Modification

If a participant develops nausea or diarrhea anytime during the first week on MMF 500 mg daily, we will offer the participant a change from MMF 500 mg daily to Myfortic© 360 mg daily. Myfortic© is an enteric coated version of MMF which is associated with less nausea and diarrhea in certain patients. If the participant tolerates the first week of Myfortic© 360 mg daily, then we will switch to Myfortic© 360 mg twice daily during the second week. If this is tolerated, then we will test for an anti-proliferative effect per protocol.

In the case of refractory nausea or diarrhea after week one, participants will be offered a change from MMF 500 mg twice daily to Myfortic© 360 mg twice daily. If a study participant is on MMF 750 mg twice daily, then we will switch to Myfortic© 540 mg twice daily. Participants will always have the option of withdrawing their participation from the trial rather than switching to Myfortic©.

Follow-up Visits (approximately 30 minutes)

Over the course of the study, we will ask participants to come in 19 more times **(Table 2)**. Starting at entry, for the first month, we will ask them to come in weekly, then every other week for two months, then every month for the rest of the first 12 months, then at month 15, month 18½, and a final visit at 22 months. The purpose of these visits is to obtain samples to measure how the drug is affecting the HIV reservoir and to check safety labs.

We will check to see if the amount of HIV infected cells is decreasing after one year and after two years. If not, then we will ask the participant to stop participating in the study as we wish to see an effect of the drug at that point in time.

Influenza vaccination will occur at one follow-up visit unless study participants have already received this vaccine in the community.

During these visits, we will do the following:

1) Draw between 6.5 and 255 mL of blood depending on visit **(Table 2)**.
2) Draw 2 sets of blood separated by an hour to obtain peak and trough drug levels (weeks, 12, 24, 48, 74 & 88).
3) Perform follow up urine pregnancy testing in female participants (point-of-care-test in the clinic)
4) Ask how the participant is tolerating the study medication
5) Answer any questions
6) Discuss continuation in the study
7) Perform a focused physical exam as needed

Optional Rectal Biopsy Visit (up to 2 hours)

We will give all participants the option of providing rectal biopsy samples once before starting the study medication, once at 12 months, and once at 22 months. Volunteers will be asked to have a bowel movement at home or in the clinic before the procedure. No other preparation is required. An anoscope will be inserted, and small amounts of rectal tissue from up to six locations will be biopsied. Medications e.g Lidocaine cream may be offered to participants to provide comfort prior to the rectal biopsy procedure. To reduce the risks of the procedure, we will ask the participants not to have anal sex for 5 days afterwards. Before undergoing the first procedure, participants will have their prothrombin time (PT), partial thromboplastin time (PTT) and platelet counts evaluated.
Storage of Data and Leftover Samples for Use in Future Research

Participants will be asked for permission to keep data and any remaining samples for possible use in future research studies. Residual samples will be stored indefinitely at the University of WA and/or Fred Hutch. Before conducting additional research unrelated to the original research questions, the UW HSD will review the request.

Specimens may be shared with other investigators at the UW, Fred Hutch or other institutions. The samples may not be sold or used directly for production of any commercial product. Tests may include genetic research. Each sample will be encoded (labeled) *only* with a barcode and a unique tracking number to protect participant's confidentiality.
There are no benefits to participants in the collection, storage, and subsequent research use of samples. Reports about future research done with a participant's samples will not be kept in their health records. A participant's decision can change at any time up to the point the samples are released for research use by notifying the study doctors in writing. However, if a participant consents to future use and some of their sample has already been used for research purposes, the information from that research may still be used. Participants may also withdraw their permission by asking the researchers to anonymize their samples.

6. 2 Toxicity

The participants will undergo standardized clinical evaluations at each visit. The evaluations will include an interim medical history, symptom-directed exam, assessment of concomitant medications, and collection of data on adverse events. Women of childbearing potential will undergo urine pregnancy tests at eligibility, enrollment and at each safety visit. Since MMF is FDA pregnancy category D, women involved in activity that could result in pregnancy will be required to use two forms of contraception. If women become pregnant during the study and are on a study medication, they will

discontinue the medication immediately, and have no additional anoscopies if enrolled in the sub-study. Women will be asked, but will not be required, to allow the study staff to contact them after delivery to get information about their pregnancy outcome. Pregnant participants will be linked to care appropriate for pregnant women with HIV infection.

Participants will be closely monitored in a standardized fashion for potential toxicities and adverse events. Safety labs, including complete blood count, comprehensive metabolic panel, plasma HIV RNA concentrations and CD4 T cell counts will be monitored frequently as indicated in **Figure 1** and **Table 2**.

The Division of AIDS Table for Grading the Severity of Adult Adverse Events (DAIDS AE Grading Table), Version 1.0, dated December 2004, Clarification August 2009, will be used for screening eligibility and for grading toxicities and is available at http://rsc.tech-res.com/safetyandpharmacovigilance. Alternate explanations for clinical or laboratory abnormalities that may at first appear to be related to the study agent must be explored.

Management of adverse experiences will be according to the best clinical practice and the judgment of the site investigator. Participants with Grade 3 and 4 laboratory abnormalities will be asked to return to the clinic to have the test that is abnormal repeated, preferably within 72 hours. Laboratory norms will be the institutional values of the lab performing the tests. Abnormal clinical and laboratory findings will be followed until resolution to < Grade 2 or baseline.

- Grade 1 – Continue study drug; routine monitoring.

  Grade 2 – Continue study drug; monitor closely with more frequent visits when clinically indicated.

  Grade 3 – Continue study drug while awaiting confirmatory results unless the clinician believes that remaining on study drug would be unsafe. In this case, proceed as below.

- Confirmed Grade 3 events – Study drug should be discontinued until resolution to ≤ Grade 2, unless the site investigator has compelling evidence that the toxicity is definitely NOT related to study drug. The event must be discussed with Drs. Schiffer and Harrington and then must be reviewed weekly until the toxicity resolves to ≤ Grade 2. If the event is possibly, probably, or definitely related to study drug but resolves to ≤ Grade 2 in less than 7 days, study drug can be restarted. If the toxicity worsens over the next 7 days or does not resolve to ≤ Grade 2 within 14 days, the study drug must be permanently discontinued. If the toxicity recurs or evolves to ≥ Grade 3, the study regimen must be permanently discontinued.

- Grade 4 (even before confirming) – The study drug must be discontinued unless the site investigator has compelling evidence that the event is not due to study drug. Drs. Schiffer and Harrington, and the DSM panel, must be promptly notified of all Grade 4 events. Study drug will be permanently discontinued in the event of an adverse event ≥ Grade 4 that is possibly, probably, or definitely related to study drug. Subjects experiencing adverse events requiring permanent discontinuation of drugs should be followed at least weekly until resolution of the adverse event to ≤ Grade 2 or until stabilized and no longer in need of such frequent monitoring, as determined by the site investigator.

6.3 Reporting Requirements

Grade 2 events should be recorded on CRFs at each visit and will be assessed for relationship to study drug.

Grade 3 or 4 events

- Subjects should have abnormal laboratory tests repeated as soon as possible, preferably within 72 hours (to determine if the result was spurious).
- Dr. Harrington and Dr. Schiffer must be notified of confirmed ≥ Grade 3 adverse events within 24 hours, if they are possibly, probably or definitely related to the study.
- The sponsor (American Foundation for AIDS Research or amfAR) will be notified of ≥ Grade 3 adverse events within one week, if they are possibly, probably or definitely related to the study.

6.4 Criteria for Treatment and Individual Study Participant Discontinuation

- The subject requires treatment with disallowed medications
- Pregnancy
- Nausea, vomiting or diarrhea refractory to anti-emetic medications
- Drug toxicity that requires permanent study drug discontinuation as defined in Section 6.2.
- If a participant does not plan to continue with the study
- Go / no-go criterion at month 12: participants must have at least a 0.25 log reduction from baseline at 12 months to continue on MMF. If this criterion is not met, participants will continue to be followed off study drug.
- Subject stops their antiretroviral therapy regimen for greater than 2 weeks
- The subject refuses further treatment and/or follow-up evaluations and decides to discontinue participation in the study
- The investigator determines that further participation would be detrimental to the subject's health or well-being
- The subject experiences virologic failure. Virologic failure will be managed according to local guidelines. In this study, virologic failure is defined as plasma HIV RNA ≥ 1,000 copies/mL (confirmed by repeating the assay on 2nd aliquot of the same specimen). If a participant has a viral load between 500-1000 HIV RNA copies, then we will call the participants for an immediate recheck of their viral load as soon as possible and will continue to do so, until this value normalizes or meets criteria for virologic failure. Of note, viral load may be checked by the participant's primary care provider outside of the study: these values will be available to the study PI and the criteria for virologic failure will be the same.
- The subject fails to comply with the study requirements so as to cause harm to him/herself or seriously interfere with the validity of the study results

6.5 Criteria for Study Discontinuation

- The study is cancelled at the discretion of the IRB, DSMB and / or study PIs. This decision will be based on several possible factors including mild-moderate adverse effects in multiple participants, a severe adverse reaction in a single participant, and / or lack of 1-year efficacy in all participants.

6.6 Protocol for Study Discontinuation

Participants who withdraw from the study based on criteria described in sections 6.4 and 6.5 will be asked to return for a clinic visit for laboratory and safety tests. This procedure will continue until normalization of test results.

6.7 Replacement of Study Subjects

- All participants are strongly encouraged to attend all study visit dates, however if a participant misses an appointment they will be contacted until they can re-schedule the appointment or request being discharged from the study. If a participant misses 3 consecutive visits, they will be considered "lost-to-follow-up".
- Replacement of participants. Considerable effort will be invested in maintaining participants in the study. New enrollee replaces a participant when a participant:
    - discontinues during the first six months of the study
    - is lost to follow-up during the first three months of the study
    - is unable to tolerate either MMF or Myfortic© during the lead-in phase of the study (Steps 1, 2a & 2b)
    - does not develop an adequate anti-proliferative effect on MMF or Myfortic© during the lead-in phase (Steps 2a & 2b)

7.0 EXPEDITED ADVERSE EVENT REPORTING

Requirements, definitions and methods for expedited reporting of Adverse Events are outlined in Version 2.0 of the NIH DAIDS EAE Manual, which is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/.

Since this is not an NIH-sponsored trial, ≥ Grade 3 adverse events will be reported to the sponsor, the American Foundation for AIDS Research (amfAR), within one week, if they are possibly, probably or definitely related to the study.

8.0 STATISTICAL CONSIDERATIONS

8.1 General Design Issues

This study intends to evaluate the effects of the FDA-approved drug, mycophenolate mofetil to determine if it diminishes the size of the HIV reservoir in participants on chronic ART. The study is a single-site, prospective, open label, and observational trial. We aim to enroll 5 participants on MMF 500 mg twice daily. Inclusion criteria are described above. In addition, we will screen each participant to ensure that they have a pharmacologic anti-proliferative response to MMF. The drug intervention

will last a maximum of 22 months with possibility for study extension in participants tolerating drug who demonstrate continued reservoir reduction at 22 months but still have a detectable reservoir. Participants will be followed closely with serial safety lab measurements and clinical visits to ensure drug tolerability and safety. In addition, we will ensure that HIV viral load remains suppressed. Moreover, participants will have serial measurements of their HIV DNA reservoir using various assays. In order to remain enrolled in the MMF treatment arm of the study, participants will be required to show sequential 0.25 log reductions in the HIV reservoir at month 12. We will also include a sub-study in which participants undergo an anoscopy to measure the HIV reservoir in tissue rather than blood.

8.2 Statistical outcomes

8.2.1 Main statistical outcome

- Change in cell-associated HIV DNA (ca-DNA) reservoir size as measured by multiplexed digital droplet PCR in study participants on versus off MMF (historical controls).

8.2.2 Secondary statistical outcomes

- Change in HIV replication by single copy viral load (scVL) in study participants on versus off MMF (historical controls).
- Change of viral reactivation by cell-associated HIV mRNA in study participants on versus off MMF (historical controls).
- Change of the inducible HIV reservoir size by quantitative viral outgrowth assay (QVOA) in study participants on versus off MMF (historical controls).
- Change of the cellular composition of the HIV DNA reservoir in study participants on versus off MMF (historical controls).
- $CD4_+$ T cell numbers that recently emigrated from the thymus
- Blood $CD4_+$ T cell count
- Complete blood cell count, comprehensive metabolic panel
- Incidence of opportunistic infection
- Antibody response to annual influenza vaccination

8.2.3 Rationales of using the main and secondary statistical outcomes for the study

The primary and secondary outcomes were chosen to test our hypotheses that MMF plus ART will reduce the size of the HIV latent reservoir more rapidly than ART alone. Various reservoir assays are used for the secondary outcomes to highlight the fact that each assay has limitations in terms of sensitivity and specificity, as well as blood volume required for the assay. Safety labs and clinical measures such as $CD4_+$ T cell count and HIV plasma RNA are included as secondary outcomes to allow us to assess the safety of the addition of MMF to ART.

8.3 Randomization

We will enroll 5 study participants who have been on ≥ 2 years of suppressive ART. There is no control group in this Phase II study and no randomization.

8.4 Sample Size and Accrual

8.4.1 Sample size calculation for the primary endpoint of reservoir reduction

Adequate power is not a prerequisite for this study given that any intervention that substantially reduces the reservoir in even a small number of patients would be a major step forward for the HIV cure field, and that funding is not available to support a control group. Nevertheless, our proposed study design is adequately powered to demonstrate statistical significance if MMF performs in accordance with predictions from our mathematical model. The rate of reservoir reduction on suppressive ART (no MMF) in a study by Siliciano et al was 0.0068 $\log_{10}$ infectious units per million (IUPM) resting $CD4_+$ T cells per month (95% CI for the mean rate: 0.0026 - 0.0110; standard deviation: 0.017; annualized standard deviation 0.2).[6] Similarly, Crooks described a rate of reservoir reduction on ART of 0.0072 $\log_{10}$ IUPM per month (95% CI for the mean rate: 0.0031 - 0.0108).[7] An annual decrease in $\log_{10}$ IUPM on ART alone would average 12*0.0068 = 0.082, or a 17% reduction.

8.5 Data Safety and Monitoring Plan

A Data Safety and Monitoring (DSM) panel has been formed and includes two experts in HIV clinical care (Dr. Nina Kim, MD, MSC: Associate Professor UW Department of Medicine and Dr. Shireesha Dhanireddy, MD: Associate Professor UW Department of Medicine), an expert in the clinical use of MMF (Dr. Brenda Sandmaier, MD: Professor UW Department of Medicine and Member FHCRC Clinical Research Division) and a biostatistician with considerable experience with HIV trials (Dr. Jim Hughes PhD, Professor UW Department of Biostatistics).The DSMB will focus on the safety and tolerance of all interventions, including use of MMF, phlebotomy, anoscopies, collection of rectal biopsies, and any events that may be related to participation in the study. DSMB meetings will generally be conducted by face-to-face meeting or a combination of face-to-face meeting and teleconference, consisting of an open session and a closed session. The first DSMB meeting will be an organizational meeting to review the protocol and monitoring plan; this will occur before the enrollment of the first subject. The second meeting will occur after five participants have completed week 8, and then at six months, 12 months and 22 months after study initiation. Upon completion or termination of the study, the DSMB will hold a final meeting. A summary of each review will be sent to the amFAR Program Officer if they do not participate in a DSMB meeting. The IRB will also be sent a summary of the main decision of the DSMB (e.g. to continue the study, modify, or stop the study).

In addition to the real-time Adverse Event review and the DSMB review, the PI Dr. Joshua Schiffer and co-investigator Dr. Robert Harrington will review accrual, visit completeness, data completeness, any study-related events less serious than Adverse Events, any Protocol Deviations and any “Other Problems” monthly and as appropriate, discuss any issues with the laboratory PI, Dr. Florian Hladik, and the full study team at the monthly protocol team meetings. If the amFAR Medical Officer requests cumulative summary reports of AEs, they will be made available.

The DSMB will periodically (as described above) review accumulating safety data by treatment group. Prior to each meeting, the statistician will provide the DSMB members with a confidential report of safety data by study arm. Reports will show interval as well as cumulative data. Reports will show

the data by coded treatment group; however, upon request of the DSMB, the protocol statistician will provide the Board with the actual treatment group data.

Based upon the reports, the DSMB will determine whether to recommend that the study be continued, modified, or stopped for safety reasons.

Study modification rules:

- If there are any bowel perforations from rectal biopsies, no further rectal biopsies will be performed for the study.
- If enrollment is delayed by more than 2 months after the study has enrolled its first participant because of failure to identify eligible subjects, the cumulative reasons for failure to qualify for the study will be reviewed, and changes may be made to eligibility criteria if the changes would not put participants at risk. An example of such a change would be to decrease the $CD4_+$ T cell criteria for enrollment to fewer than 350 cells/mm_3.
- If enrollment is delayed by more than 3 months after the study has started its first participant on MMF because too few subjects meet the pre-defined anti-proliferative activity of MMF by *in vitro* proliferation test after one week of initial MMF therapy, the MMF dose may be increased following a subsequent IRB approved protocol change. It is expected that this dose increase will lead to more subjects fulfilling the anti-proliferation efficacy criteria. This and any further dose increase will be discussed with the DSMB, the IRB and the amFAR program officer before implementing.

Study stopping rules:

- The study will be stopped if two participants have a confirmed > Grade 4 adverse events probably or definitely due to the study drug ingested at the prescribed amount.
- The study will be stopped if > 2 participants have confirmed Grade 3 adverse events probably or definitely due to the study drug ingested at the prescribed amount.

8.6 Analyses

Aim one anticipated results: We hypothesize at least 0.25 log reductions in the HIV reservoir at month 12 in study participants who have a demonstrated anti-proliferative response to MMF treatment. We hypothesize that cell-associated HIV DNA will undergo a shift from predominantly residing in T_{CM} and T_{EM} to predominantly residing in T_N and T_{SCM}. Further, we predict that reservoir depletion will occur with equivalent rates in blood, and GALT.

We will compute the change in reservoir volume in two ways. First, descriptively, we will use individual linear regressions to compute a slope in log viral load (**VL**) for each participant using time as the only covariate; and then we will describe the mean and standard deviation of that slope. Secondly, we will use linear mixed effects models, as others have done,[60,61] to estimate an average slope using all the data at once, and a random intercept and slope per person. Estimation of a fixed effect for the interaction of time with treatment arm will help us determine whether the reservoir decreases more quickly with ART+MMF than with ART only in historical controls. We will assess the changing composition of the reservoir using similar models and include the proportion of cells that are naive (T_N) as the outcome in a generalized linear mixed model with a log link. An interaction of time by treatment arm will determine whether rate of change in composition differs by arm.

Aim two anticipated results. We hypothesize that low doses of MMF will be well tolerated among healthy HIV-infected study participants who have fully ART-suppressed HIV. We hypothesize that the incidence of opportunistic infections will not exceed that of comparable larger cohorts of HIV-treated patients. Of note, certain opportunistic infections such as herpes zoster or HSV-2 recurrence continue to occur despite suppressive ART, while pneumocystis pneumonia, CMV end organ disease, cryptococcus and many other opportunistic infections are much less common in this context. Therefore, in the event of an infection, we will confer with the DSM panel to discuss whether any event is directly attributable to MMF. Additionally, we hypothesize that peripheral blood $CD4_+$ and $CD8_+$ T cell counts will remain unchanged throughout MMF therapy, and that HIV replication will remain well controlled on ART with the addition of MMF.

9.0 HUMAN SUBJECTS

Participant will be 5 adults and children ≥ 18 and ≤65 years of age. Participants will have received ART for at least 2 years with demonstration of full viral suppression during this time, documented by at least four negative plasma viral loads and no more than one plasma viral blip during this time. They will also have a current $CD4_+$ T cell count of ≥ 350/μl. The participants will receive 500mg MMF twice daily in addition to their ART regimen. The planned MMF treatment duration is 22 months, but efficacy Go/no-Go algorithms at the end of month 12 may lead to earlier termination of MMF treatment in some or all study participants.

All study participants must plan to reside in the Seattle area for the duration of the study. We anticipate pre-screening 30 potential study participants by medical charts to identify 15 who will be approached by study staff to schedule an in-person eligibility visit; the first 5 available study candidates will enter the anti-proliferation test phase receiving MMF for one week. We conservatively estimate that 1 of these 5 individuals will fail to document adequate T cell anti-proliferation and not be enrolled in this study. We will continue to screen and test until we enroll 5 participants with a verified in vivo anti-proliferative effect of MMF, who will then continue to take MMF for 22 months. Participants who discontinue MMF treatment due to inadequate efficacy in reducing the latent HIV reservoir at the 12 month Go/no-Go decision point, or due to treatment related side effects, will not be replaced.

Potential Risks include:

(1) Stress and anxiety could result from study participation. These will be minimized by careful explanation of study procedures, and maintenance of an open, supportive attitude by study personnel.

(2) Potential risks from participation in this study include those related to blood draws. All personnel responsible for blood drawing will be experienced phlebotomists who will follow standard procedures. Blood draws can be uncomfortable and cause bruising. Some temporary anemia could occur from study phlebotomy. A record of all study phlebotomies and blood volume drawn will be maintained for each participant, and total blood collection for clinical care and the study will be monitored and IRB limits for study purposes will not be exceeded. Specifically, individual blood draws will never be more than 270 mL and total volumes of blood drawn over an eight-week period will never be more than 450 mL.

(3) Insertion of an anoscope may be uncomfortable. Rectal biopsies usually do not hurt. However, it is possible subjects could feel some brief pain or discomfort. In rare cases, these biopsies may

cause a significant amount of bleeding or, rarely, an infection at the site that was sampled. In extremely rare circumstances, rectal biopsies can result in rectal perforation. Lidocaine cream may cause local numbness, redness, swelling or irritation. Extremely rare side effects include irregular heartbeat, shortness of breath and seizure. Precautions will be taken by the experienced study gastroenterologist at the time the biopsies are obtained to prevent perforation and to prevent or minimize bleeding and infection. In addition, as a further precaution, participants will be asked not to have anal sex for 5 days after the biopsies to help prevent any possible increase in risk of infection or bleeding.

(4) Answering questions about smoking, alcohol use, and sexual behaviors may make subjects feel uncomfortable.

(5) There are also potential risks related to confidentiality. All participating staff and faculty at the site will maintain the confidentiality of study subjects, and study materials that could expose identity will be kept in locked cabinets or in password-protected files, accessible only to the study personnel at the research clinic conducting the study with a need to know.

(6) Reports of MMF adverse reactions are based on dosages of 2-3 grams daily (rather than 1g daily in this study). A detailed description of all adverse effects and precautions is contained in the CellCept® Product Monograph, which is included in the Appendix to the Clinical Protocol. (Of note, we will be using the generic version of MMF and not CellCept.)

The principal adverse reactions associated with the oral administration of MMF include diarrhea, leukopenia, sepsis, and nausea and vomiting. There also is evidence of a higher frequency of certain types of infections, e.g., cytomegalovirus viremia, JC virus-associated progressive multifocal leukoencephalopathy (PML) and polyomavirus-associated nephropathy (PVAN). Patients receiving MMF alone or as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin. These risks appear to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent.

There are also a small number of patients who received solid organ transplants and experienced reversible falls in their red cell or white cell counts while receiving MMF. Additionally, cases of Pure Red Cell Aplasia (PRCA) have been reported in some patients receiving MMF. PRCA is a condition in which the bone marrow stops producing red blood cells. In some instances, PRCA can be reversed by reducing or stopping MMF.

MMF has embryo-fetal toxicity, causing fetal harm when administered to a pregnant female. Use of MMF during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations, especially external ear and other facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, esophagus, kidney and nervous system.

There will be adequate protection against risks including IRB approval at the study site, written informed consent, rapid reporting of adverse events and data safety monitoring as above.

(8) Use of ondansetron is occasionally associated with diarrhea, headache, fever, lightheadedness, dizziness, weakness, fatigue, constipation, rash, blurred vision, urinary retention, and muscle spasm.

(9) The most common adverse reactions (≥20%) for Myfortic© include anemia, leukopenia, constipation, nausea, diarrhea, vomiting, dyspepsia, urinary tract infection, CMV infection,

insomnia. Rare more severe complications include pure red cell aplasia and Progressive multifocal leukoencephalopathy (PML).

10.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by NIH policies.

11.0 BIOHAZARD CONTAINMENT

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and tissues, 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 Centers for Disease Control and Prevention and the National Institutes of Health.

12.0 SCHEDULE OF EVALUATIONS

See Table 2.

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