**Mycophenolate Mofetil for Depletion of the HIV Reservoir**

Joshua T. Schiffer1,2, Claire Levy3, Sean Hughes3, Mel Padullo4, Katrina Puckett2, Eric Helgeson2, Robert D. Harrington2, Florian Haidl1,2

1Fred Hutchinson Cancer Research Center, Seattle, WA, USA, 2University of Washington, Seattle, WA, USA

### Introduction

- The HIV reservoir consists of ~10^10 latently infected cells containing replication competent virus, which persists despite decades of ART.
- A 1:20,000 to 1:50,000 larger number of cells contain non-intact, replication-competent virus.
- HIV latency ensues in a unique chromosomal location within each newly incompetent HIV DNA.
- Activating HIV using cellular proliferation rather than new viral gene expression to achieve latency resolution.

### Methods

#### Trial Design
- Randomized, double-blind, placebo-controlled trial of MMF for reduction of the HIV reservoir.
- Enrollment size 60 participants
- University of Washington, Seattle AGTU/Seattle MECC Medical Center
- One week of MTF 500 mg b.i.d. followed by MTF 250 mg b.i.d. daily for 48 or 46 weeks.
- 80% of enrolled patients 30-60 years with CD4+ T cells > 350/mm^3.
- Prevented viral side and assessment of reservoir size.
- Graft vs. host at 48 weeks based on at least a >0.25 log_10 reduction in HIV DNA.

#### Study schema

![Study schema](image)

### Participation

- Serologically and clinically confirmed HIV infection
- CD4+ T cell count > 350/mm^3
- No pregnancy / intention to become pregnant / breast feeding
- No current or previous ART for >2 years
- Documentation of anti-proliferative effect at peak MMF dose (see below)
- Exclusion of severe, unstable disease, prior diagnosis of AIDS, active infection, substance abuse, medical non-compliance, abnormal lab values
- No previous pump withdrawal, antiretroviral or prophylactic contraceptives or other anti-HIV medication.
- No pregnancy / intention to become pregnant / breast feeding

### Trial oversight

- Trial sponsor: UWACT
- The Foundation for AIDS Research
- Performance in accordance with the principles of the Declaration of Helsinki
- Approved by the University of Washington IRB

### Results

**Enrollment**
- 5 enrolled participants
- One participant self-discharged early during the trial for personal reasons.

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Week 24</th>
<th>Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Placebo</td>
<td>505</td>
<td>481</td>
</tr>
<tr>
<td>2</td>
<td>500 mg</td>
<td>714</td>
<td>700</td>
</tr>
<tr>
<td>3</td>
<td>750 mg</td>
<td>628</td>
<td>614</td>
</tr>
<tr>
<td>4</td>
<td>750 mg</td>
<td>628</td>
<td>614</td>
</tr>
</tbody>
</table>

**Results continued**

![Graph 1](image)

**Tc m**

- CD4+ T cells selected by negative selection and sorted on BD Biosciences LSRII
- Fluorescence-activated cell sorting (FACS) analysis on QuantaSoft
- gag, env
- 5'pol, 3'pol
- deltaD

**Virol**

- Plasma RNA viral load
- 72, 84, 96 weeks
- Interview / physical exam
- No persistent effect on proliferation marker expression (Ki67+) in circulating T cells
- No persistent effect on proliferation marker expression (Ki67+) in circulating CD8+ T cells

**HIV reservoir kinetics**

- Rapid turnover of effector T cells containing HIV in post-therapy.
- Latent phase, viral rebound following ART.

**Diagnostic analyses**

- MMF tolerability and toxicity
- Exploratory analyses
- MMF anti-retroviral effect

**Discussion**

- 64 weeks of MMF well tolerated and not associated with anabolic or immunologic failure on ART.
- No reduction in viral load or HIV DNA.
- No shift in the HIV reservoir towards a predominance of slowly proliferating CD4+ T cells.
- An explanation for lack of reservoir reduction and decrease in proliferation is yet to be identified.
- Subtherapeutic drug levels may explain lack of efficacy.
- MMF anti-proliferative effect achieved in 2/3 treated patients.
- Part-study showed complete effect of MMF on reservoir volume and %82 expression.
- Modulating 1020% reduction in proliferation is required to achieve reservoir reduction.
- Other possible explanations include compensatory survival mechanisms in non-proliferating CD4+ T cells, co-stimulation with thymic emigrants or drug resistance.
- Future studies with higher doses are warranted.

### References