# Mesalamine to Reduce Immunologic Activation during HIV Infection: A Randomized Controlled Trial

**Introduction**

*Gut epithelial barrier defects during HIV may promote systemic microbial translocation and persistent immune activation.*

HIV infection is associated with induction of indoleamine-2,3-dioxygenase (IDO) in the gut leading to catabolism of tryptophan to kynurenine, a metabolite toxic to Th1 and NK cells, cells primarily important in the maintenance of epithelial integrity and decreased HIV.

- Thirds of patients with advanced HIV disease exhibit sarcoidosis markers consistent with inflammatory bowel disease (IBD) or eosinophils to Saccharomyces cerevisiae (ASCIA), outer membrane to porin C of E. coli (OMP-C), bacterial flagellin (CDW-B), and pANCA.

We hypothesized that mesalamine, a mucosally active anti-inflammatory agent capable of decreasing microbial translocation in IBD, might decrease microbial translocation in treated HIV infection, leading to decreases in microbial translocation and immune activation.

-Apisro is a once-daily delayed- and extended-release oral formulation (375 mg, 4 tablets daily) of mesalamine designed to release in the ileum and colon (Salix Pharmaceuticals).

**Objective**

1. **Primary outcome:** Week 12 change in the percent of activated CD8+ T-lymphocytes (HLA-DR+).
2. **Secondary outcomes:** Change in immunologic markers and viral load in gut and blood, markers of inflammation and microvascular function (flow-mediated dilation [FMD] and hyperemic velocity).

**Methods**

- Double-blind placebo-controlled randomized trial (12 weeks placebo and 12 weeks mesalamine (Apriso); trial registered at ClinicalTrials.gov (NCT01010102).

Four subjects screened and 33 subjects enrolled (18 to begin on placebo, 15 to begin on mesalamine).

There were 2 deaths (unrelated to study intervention) and 4 dropouts (underlying cirrhosis, drug relapse, inability to commit, n=2).

**Results**

**Table 1. Baseline characteristics of study participants**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=15)</th>
<th>Mesalamine (n=18)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>40.6 (21.3)</td>
<td>42.0 (21.3)</td>
<td>0.70</td>
</tr>
<tr>
<td>Male gender, %</td>
<td>10 (66.7)</td>
<td>16 (88.9)</td>
<td>0.26</td>
</tr>
<tr>
<td>Mean CD4 count, cells/µl</td>
<td>217 (90 to 500)</td>
<td>29 (14 to 90)</td>
<td>0.04</td>
</tr>
<tr>
<td>CD4 count, % decrement</td>
<td>-2.0 to -8.0</td>
<td>-2.0 to -8.5</td>
<td>0.44</td>
</tr>
<tr>
<td>Duration of ART regimen, months</td>
<td>12.1 (9.0 to 15.0)</td>
<td>10.9 (7.0 to 15.0)</td>
<td>0.77</td>
</tr>
<tr>
<td>HLA-DR expression, %</td>
<td>0.7 (1.0 to 4.0)</td>
<td>0.3 (0.0 to 0.5)</td>
<td>0.63</td>
</tr>
<tr>
<td>HIV RNA level, copies/ml</td>
<td>9.0 (8.0 to 10.0)</td>
<td>9.0 (8.0 to 10.0)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

**Table 2. Changes in immunologic, virologic, and cardiovascular parameters during FIRST 12 weeks of study**

<table>
<thead>
<tr>
<th>Timepoints</th>
<th>Placebo</th>
<th>Mesalamine</th>
<th>Between-Arm</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 0</td>
<td>0.7%</td>
<td>0.6%</td>
<td>-0.1%</td>
<td>0.36</td>
</tr>
<tr>
<td>Week 12</td>
<td>2.1%</td>
<td>2.1%</td>
<td>0.0%</td>
<td>0.68</td>
</tr>
<tr>
<td>Week 24</td>
<td>1.6%</td>
<td>1.6%</td>
<td>0.0%</td>
<td>0.40</td>
</tr>
</tbody>
</table>

**Table 3. Changes in immunologic, virologic, and cardiovascular parameters during 12 weeks after treatment crossover**

<table>
<thead>
<tr>
<th>Timepoints</th>
<th>Placebo</th>
<th>Mesalamine</th>
<th>Between-Arm</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 0</td>
<td>0.7%</td>
<td>0.7%</td>
<td>-0.0%</td>
<td>0.72</td>
</tr>
<tr>
<td>Week 12</td>
<td>2.1%</td>
<td>2.1%</td>
<td>0.0%</td>
<td>0.68</td>
</tr>
<tr>
<td>Week 24</td>
<td>1.6%</td>
<td>1.6%</td>
<td>0.0%</td>
<td>0.40</td>
</tr>
</tbody>
</table>

**Summary/Conclusions**

- Strong evidence to support the use of mesalamine, a malarial preparation designed to release in the colon, significantly affects either systemic or colonic immune activation levels in HIV-infected individuals with incomplete CD4+ cell recovery on suppressive ART.

- Alternative strategies to decrease microbial translocation and systemic immune activation are needed.

Acknowledgements: We thank SCOPe and UCSC GCRC staff and the participants.

Funding: Supported by the California HIV/AIDS Research Program IDEA award, Salix Pharmaceuticals, and an NHLBI Research Award on HIV Pathogenesis, with support from NIH and the National Foundation for AIDS Research (NFAIDR) and the AIDS Research Enterprises (DARE).

**Figure 1. Trial Schematic**

**Figure 2. Changes in CD4 and CD8 T cell activation during mesalamine.**

**Figure 3. Changes in immunologic, virologic, and cardiovascular parameters during FIRST 12 weeks of study.**

**Figure 4. Changes in immunologic, virologic, and cardiovascular parameters during 12 weeks after treatment crossover.**

---

**Figure 5. Mean CD4+ and CD8+ T Cell Counts.**

**Figure 6. Changes in CD4+ T Cell Counts.**

**Figure 7. Changes in CD8+ T Cell Counts.**

**Figure 8. Changes in CD4:CD8 T Cell Ratio.**

**Figure 9. Changes in CD4+ T Cell Counts.**

**Figure 10. Changes in CD8+ T Cell Counts.**

**Figure 11. Changes in CD4:CD8 T Cell Ratio.**

**Figure 12. Changes in CD4+ T Cell Counts.**

**Figure 13. Changes in CD8+ T Cell Counts.**

**Figure 14. Changes in CD4:CD8 T Cell Ratio.**

---

**Contact:** Ma Somsouk, MD, MA
1001 Polmar Ave., #3012
Novato, CA 94945
ma.somsouk@ucsf.edu

---

**AIDS Research Institute**

---

**Institution:** University of California, San Francisco; CA; Leidos Biomedical Research, Inc., Frederick National Laboratory, Frederick, MD