Poster # **341**

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

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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) activity in the gut leading to catabolism of tryptophan to kynurenine, a metabolite toxic to Th17 T helper cells, cells principally important in the maintenance of epithelial integrity and decreased during HIV.

•Two-thirds of patients with advanced HIV disease exhibit serologic markers consistent with inflammatory bowel disease (IBD) (e.g., antibodies to Saccharyomyces cerevesiae (ASCA), outer membrane to porin C of E. Coli (Omp-C), bacterial flagellin (CBir1), and pANCA.

•We hypothesized that mesalamine, a mucosally active anti-inflammatory agent shown to decrease mucosal inflammation in IBD, might decrease mucosal inflammation in treated HIV infection, leading to decreases in microbial translocation and systemic immune activation.

•Apriso 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, Inc.).

Objective

•1˚ outcome: Week 12 change in the percent of activated (CD38+ HLA-DR+) CD8+ T cells from baseline.

•2˚ outcomes: Changes in other immunologic markers and viral load in blood and gut, markers of macro and microvascular function (flow-mediated dilatation [FMD] and hyperemic velocity).

Methods

•Double-blind placebo-controlled randomized crossover trial (12 weeks placebo and 12 weeks mesalamine (Apriso)); trial registered at ClinicalTrials.gov (NCT01090102).

•41 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 drop outs (underlying cirrhosis, drug relapse, inability to commit (n=2)).

Fig. 1 Trial Schematic

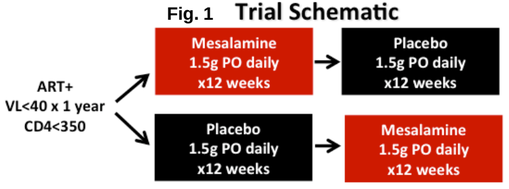
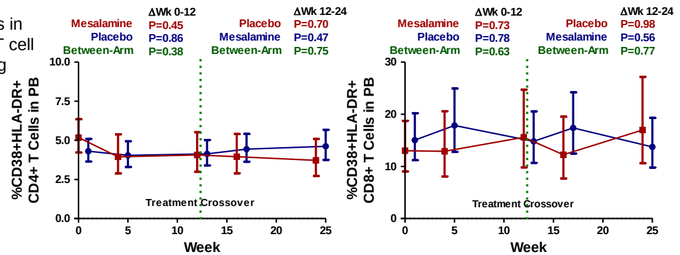


Table 1. Baseline characteristics of study participants

Characteristic	Placebo Median (IQR) N=18	Mesalamine Median (IQR) N=15
Age, years	60 (49 to 62)	53 (49 to 62)
Male gender, No. (%)	18 (100)	15 (100)
Nadir CD4 count, cells/mm^3	21 (7 to 50)	39 (14 to 90)
CD4+ T cell count, cells/mm^3	242 (205 to 293)	249 (135 to 269)
Duration of ART regimen, months	23 (18 to 34)	31 (17 to 41)
Hepatitis B or C positive, No. (%)	3 (17)	3 (20)

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



Summary/Conclusions

•We found no strong evidence that administration of a mesalamine preparation designed to release in the colonic mucosa significantly affects either systemic or colonic immune activation levels in HIV-infected individuals with incomplete CD4+ T cell recovery on suppressive ART.

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

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

	Placebo (n=18)			Mesalamine (n=15)			Between-Arm
	Baseline Median (%)	Mean $\log_{10}$ Δ from Wk 0-12 (95% CI)	P Value	Baseline Median (%)	Mean $\log_{10}$ Δ from Wk 0-12 (95% CI)	P Value	P Value
PERIPHERAL BLOOD							
Immunology							
CD8+ T Cells (38+/DR+)	13.4	-0.01 (-0.10 to 0.07)	0.78	12.2	0.03 (-0.14 to 0.20)	0.73	0.63
CD4+ T Cells (38+/DR+)	3.74	-0.006 (-0.07 to 0.06)	0.86	4.97	-0.05 (-0.17 to 0.07)	0.45	0.38
sCD14 (ng/ml)	1,730	-0.13 (-0.22 to -0.03)	0.010	1,787	-0.02 (-0.09 to 0.06)	0.65	0.14
IL-6 (pg/ml)	1.37	0.15 (-0.01 to 0.32)	0.067	2.05	-0.07 (-0.24 to 0.09)	0.40	0.07
D-dimer (ng/ml)	336	-0.04 (-0.22 to 0.14)	0.67	673	-0.20 (-0.43 to 0.04)	0.096	0.27
K:T ratio (nM/uM)	43	0.005 (-0.03 to 0.04)	0.81	41	0.01 (-0.04 to 0.06)	0.69	0.87
Virology							
HIV RNA single copy assay (copy/ml)	0.6	-0.17 (-0.40 to 0.07)	0.16	2.1	-0.01 (-0.33 to 0.13)	0.39	0.68
Cardiovascular							
FMD Diameter	4.82	-0.002 (-0.01 to 0.004)	0.51	4.33	-0.002 (-0.009 to 0.005)	0.56	0.99
FMD 60	2.62	-0.004 (-0.06 to 0.05)	0.87	5.19	-0.04 (-0.02 to 0.10)	0.22	0.27
FMD 1VTI	71.3	0.003 (-0.09 to 0.09)	0.95	81.8	-0.02 (-0.10 to 0.06)	0.60	0.73
RECTAL MUCOSA[a]							
Immunology							
CD8+ T Cells (38+/DR+)	19.2	0.01 (-0.08 to 0.10)	0.82	17.6	-0.01 (-0.11 to 0.09)	0.83	0.80
CD4+ T Cells (38+/DR+)	8.7	0.05 (-0.11 to 0.21)	0.57	12.6	0.06 (-0.14 to 0.25)	0.32	0.86
Virology							
HIV RNA[b] (per 10^6 cells)	21.0	0.37 (-0.39 to 1.13)	0.34	15.4	-0.19 (-1.15 to 0.77)	0.70	0.33
HIV DNA[b] (per 10^6 cells)	52.3	-0.01 (-0.58 to 0.55)	0.97	29.9	0.31 (-0.43 to 1.06)	0.41	0.47

FMD, flow-mediated dilation; K:T, kynurenine:tryptophan; VTI, velocity time integral

[a] There were 15 and 11 consented to mucosal biopsies in the placebo arm and mesalamine arm, respectively, but one in each arm did not contribute a second time point.

[b] Total HIV RNA and DNA level from whole GALT biopsies were based on cell equivalents normalized by GAPDH and TERT copy number, respectively.

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

	Placebo → Mesalamine (n=17)			Mesalamine → Placebo (n=12)			Between-Arm
	Wk 12 Median (%)	Mean $\log_{10}$ Δ from Wk 12-24 (95% CI)	P Value	Wk 12 Median (%)	Mean $\log_{10}$ Δ from Wk 12-24 (95% CI)	P Value	P Value
PERIPHERAL BLOOD							
Immunology							
CD8+ T Cells (38+/DR+)	13.9	-0.03 (-0.15 to 0.08)	0.56	13.7	0.003 (-0.19 to 0.19)	0.98	0.77
CD4+ T Cells (38+/DR+)	4.3	0.02 (-0.04 to 0.09)	0.47	4.7	0.01 (-0.06 to 0.09)	0.70	0.75
sCD14 (ng/ml)	1,505	0.08 (-0.06 to 0.21)	0.26	1,855	-0.03 (-0.10 to 0.04)	0.45	0.28
IL-6 (pg/ml)	1.27	-0.04 (-0.20 to 0.12)	0.66	1.86	0.025 (-0.08 to 0.13)	0.64	0.74
D-dimer (ng/ml)	409	0.04 (-0.12 to 0.19)	0.64	459	-0.08 (-0.24 to 0.09)	0.17	0.30
K:T ratio (nM/uM)	44	0.008 (-0.04 to 0.06)	0.34	43	0.01 (-0.03 to 0.06)	0.52	0.74
Virology							
HIV RNA single copy assay (copy/ml)	0.7	-0.11 (-0.34 to -0.12)	0.36	1.7	0.04 (-0.21 to 0.28)	0.78	0.43
Cardiovascular							
FMD Diameter	4.77	-0.001 (-0.007 to 0.004)	0.64	4.38	-0.005 (-0.01 to 0.002)	0.18	0.41
FMD 60	4.41	-0.02 (-0.11 to 0.07)	0.68	6.33	-0.79 (-0.17 to 0.008)	0.08	0.45
FMD 1VTI	71.3	0.012 (-0.09 to 0.11)	0.81	77.2	0.17 (0.11 to 0.23)	<0.01	0.09
RECTAL MUCOSA							
Immunology							
CD8+ T Cells (38+/DR+)	24.7	0.02 (-0.09 to 0.14)	0.66	21.8	0.03 (-.08 to 0.14)	0.83	0.91
CD4+ T Cells (38+/DR+)	8.7	0.05 (-0.14 to 0.23)	0.57	12.1	-0.15 (-0.39 to 0.09)	0.21	0.86
Virology							
HIV RNA (per 10^6 cells)	22.2	0.18 (-0.80 to 1.16)	0.72	40.6	0.10 (-1.20 to 1.39)	0.88	0.91
HIV DNA (per 10^6 cells)	49.2	-0.14 (-0.51 to 0.24)	0.47	55.7	-0.10 (-0.33 to 0.14)	0.41	0.92

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