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

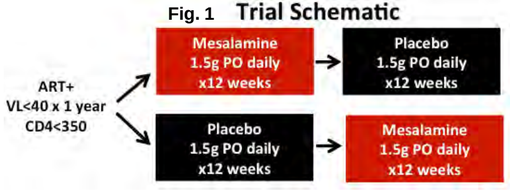
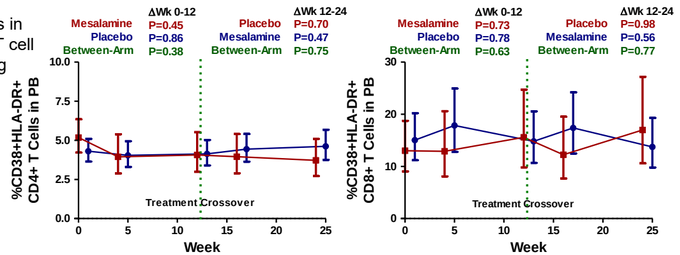


Table 1. Baseline characteristics of study participants

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

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

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.

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