TELMISARTAN DECREASES MONOCYTE CX3CR1 EXPRESSION IN TREATED HIV

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Background

- Telmisartan is an angiotensin receptor blocker and peroxisome proliferator-activated receptor (PPAR)-γ agonist that is active in adipose tissue (AT) and has anti-inflammatory properties.

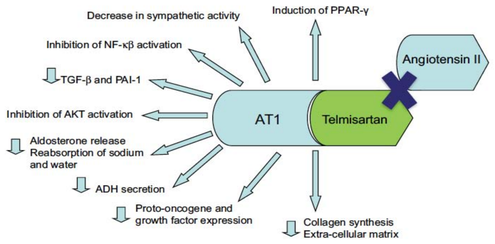

Fig. 1. Effects of telmisartan.[1]

- Fractalkine is a chemokine produced by activated or stressed cells to promote cell survival.
- Secretion of fractalkine by adipocytes and expression of its receptor, CX3CR1, on monocytes/macrophages have been implicated in AT inflammation, obesity and cardiometabolic disease.[2-5]

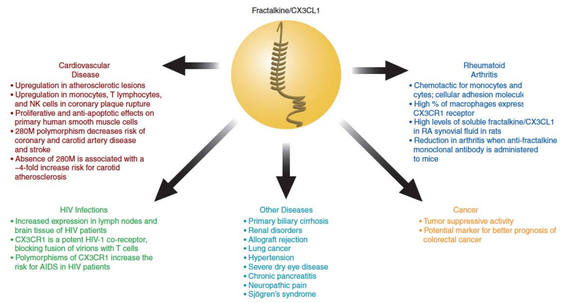

Fig 2. Fractalkine disease associaitons.[5]

- Fractalkine and CX3CR1 expression are mediated by PPAR-γ suppression and endotoxemia,[3] both sequelae of HIV.
- We hypothesized that telmisartan would improve the profile of AT immune cells and AT function in persons with HIV (PWH) on suppressive antiretroviral therapy (ART).

Methods

Study Design
- Secondary analysis from a completed, randomized (2:1)-controlled trial of PWH who received telmisartan 40mg daily for 4 weeks then 80mg daily for 44 weeks or no drug while continuing ART.[6]

Inclusion Criteria
- Age ≥18 years
- HIV-1 RNA <50 copies/mL on ART for ≥48 weeks at entry
- Maintained HIV-1 RNA <200 copies/mL at Week 48
- Had subcutaneous AT biopsy samples at Weeks 0 and 48

Analyses
- AT was obtained by excisional biopsy from the inguinal region and paraffin embedded for immunohistochemistry or digested by Liberase for cell isolation and cryopreservation. Immune cell profiling was performed via flow cytometry.
- Interleukin (IL)-6, adiponectin and insulin gene expression were determined by ELISA (IL-6) or PCR array.
- 48-week changes were compared using two-sided rank-sum, signed-rank tests and Spearman correlations (α=0.05).

References and Acknowledgements

[1]*Int J Nephrol Renovasc Dis.* 2010; 3: 33–38. [2]*Biochim Biophys Acta.* 2016 Nov;1861(11): 1614-1622. [3]*Diabetes.* 2011 May;60(5):1512-8. [4]*Brain Behav Immun*. 2014 May;38:25-35. [5]*Mol Interv*. 2010 Oct; 10(5): 263–270. [6]*J Infect Dis*. 2018 May 5;217(11):1770-1781.

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Results

Table 1: Baseline Characteristics*

	Telmisartan (N=22)	Control (N=13)	Total (N=35)
Male sex	21 (95%)	12 (92%)	33 (94%)
Age (years)	49 (40, 54)	50 (41, 52)	49 (40, 54)
Race/Ethnicity			
White Non-Hispanic	12 (55%)	5 (38%)	17 (49%)
Black Non-Hispanic	4 (18%)	7 (54%)	11 (31%)
Hispanic (regardless of race)	5 (23%)	1 (8%)	6 (17%)
More than one race	1 (5%)	0 (0%)	0 (3%)
BMI (kg/m^2)	25.2 (23.3, 29.6)	23.9 (21.4, 26.6)	25.1 (22.3, 27.9)
CD4$^+$ T cell count (cells/mm^3)	618 (383, 841)	556 (444, 821)	572 (402, 841)
HIV-1 RNA (copies/mL)			
<40	18 (82%)	10 (77%)	28 (80%)
Detectable	4 (18%)	3 (23%)	7 (20%)
Median (Min, Max)	223.5 (97, 899)	114 (55, 2340)	188 (55, 2340)
ART class			
NRTI	18 (82%)	13 (100%)	31 (89%)
NNRTI	7 (32%)	7 (54%)	14 (40%)
PI	13 (59%)	6 (46%)	19 (54%)
INSTI	10 (45%)	0 (0%)	10 (29%)

*Median (interquartile range, IQR) or percentage reported
BMI=body mass index, ART=antiretroviral therapy, NRTI=nucleoside reverse transcriptase inhibitor, NNRTI=non-nucleoside reverse transcriptase inhibitor, PI=protease inhibitor, INSTI=integrase strand transfer inhibitor

Table 2: Changes in AT Monocyte Subsets at Week 48

	Telmisartan		Control		Between-group P-value[1]
	Median (IQR)	P-value[2]	Median (IQR)	P-value[2]	
(CD14$^+$16$^-$)CX3CR1$^+$ (%)	-10.4 (-33.3, 13.6)	0.33	13.1 (-0.8, 19.1)	0.06	0.029
(CD14$^+$16$^+$)CX3CR1$^+$ (%)	-18.7 (-44.8, 22.9)	0.31	10.7 (-13.3, 26.8)	0.38	0.15
(CD14^{lo}16$^+$)CX3CR1$^+$ (%)	-15.7 (-42.7, 31.3)	0.55	11.6 (-13.0, 35.5)	0.31	0.25
(CD163$^+$)CX3CR1$^+$ (%)	-15.4 (-33.9, 13.8)	0.18	12.1 (-17.6, 17.7)	0.68	0.29
(CD14$^+$16$^-$)TLR4$^+$ (%)	-4.2 (-12.0, -0.6)	0.002	-0.0 (-5.5, 3.1)	0.68	0.036

[1]Rank sum test; [2]Signed-rank test.

Figure 3: Changes in AT Monocyte CX3CR1$^+$ at Week 48 by Study Arm

Filled boxplots represent Telmisartan and open boxplots represent control group; diamonds represent means.

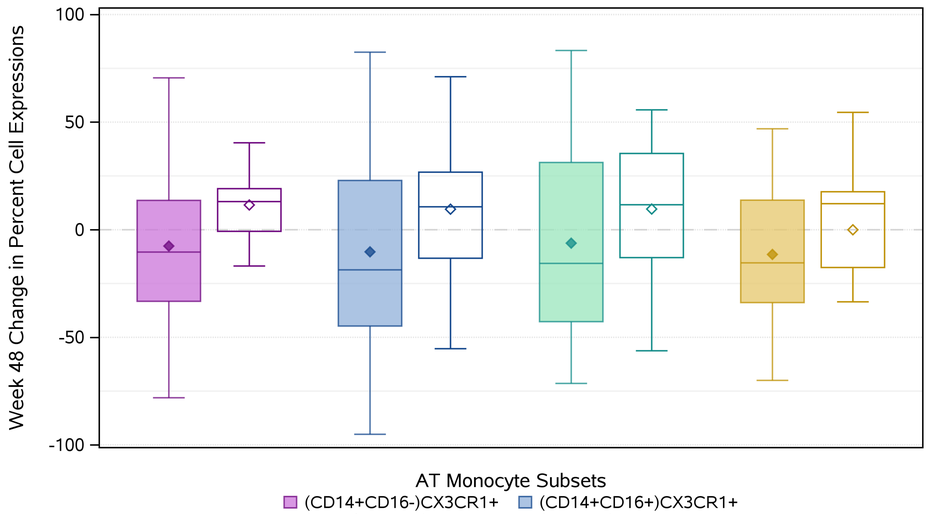
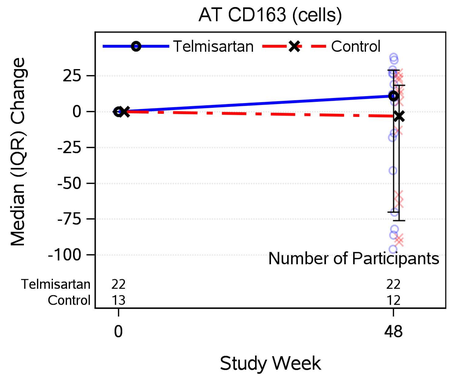


Figure 4: No Change in Overall AT Monocyte Number with Telmisartan

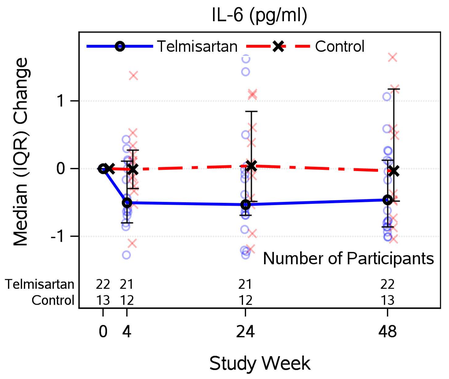


Telmisartan: +11 cells* median 48-week change, p=0.81
Control: -3 cells* median 48-week change, p=0.31

Between-group p=0.36

*Cell numbers counted as average number of cells over 40 visual fields at 400x magnification on immunohistochemistry

Figure 5: Reduced Circulating IL-6 with Telmisartan



Telmisartan: -0.5 pg/mL median 48-week change, p=0.06
Control: -0.03 pg/mL median 48-week change, p=0.46

Between-group p*=0.07

*Equally-weighted across all post-baseline time points

Figure 6: Correlation Between CD14$^+$16$^-$ CX3CR1$^+$ and Insulin Gene Expression

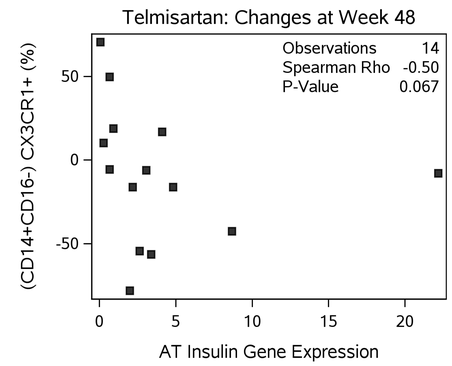
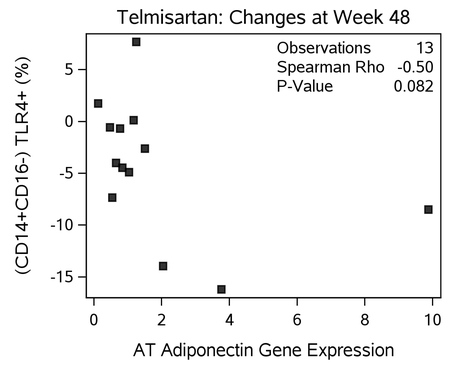


Figure 7: Correlation Between CD14$^+$16$^-$ TLR4$^+$ and Adiponectin Gene Expression



Summary & Conclusions

In this cohort of PWH on suppressive ART who were randomized to receive telmisartan or no additional drug (control) for 48 weeks:

- **Telmisartan reduced CX3CR1 and TLR4 expression on AT monocytes, suggesting reduced AT inflammation.**
- **Continued ART alone did not result in reduced AT inflammation.**
- **Changes in AT monocyte CX3CR1 and TLR4 expression correlated with improved measures of AT function.**
- **Given the role of CX3CR1 in AT inflammation, obesity and CVD, telmisartan has the potential to modulate CVD risk in PWH.**

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