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TELMISARTAN DECREASES HIV-1 RNA IN LYMPH NODES IN TREATED HIV INFECTION

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I. Introduction

- Chronic inflammation in people with HIV can lead to lymph node (LN) fibrosis and limit CD4⁺ T-cell recovery.
- Telmisartan, an angiotensin receptor blocker and PPAR-γ agonist, has anti-fibrotic and anti-inflammatory properties.
- In this completed, randomized-controlled trial of 44 adults with HIV-1 RNA <50 copies/mL on antiretroviral therapy (ART) for ≥48 weeks, telmisartan did not decrease LN fibrosis (i.e. collagen I by immunohistochemistry [IHC]) more than did ART alone.
- We hypothesized that telmisartan therapy would decrease macrophage infiltration and HIV-1 RNA⁺ cells and increase CD4⁺ T-cells in LN.

II. Methods

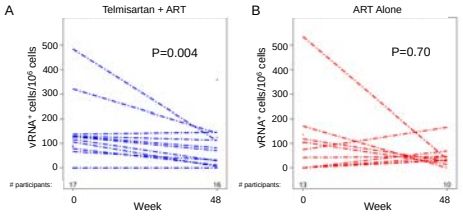
- A5317 was trial of adults with HIV-1 RNA <50 copies/mL on ART for ≥48 weeks who were randomized 2:1 to telmisartan plus ART or ART alone for 48 weeks.
- Excisional LN biopsies were obtained at entry and week 48.
- The number of LN HIV-1 RNA⁺ (vRNA⁺) cells was measured by RNAscope in the laboratory of Dr. Jacob Estes.
- The numbers of CD4⁺ T cells and CD68⁺CD163⁺ macrophages were measured by IHC and the percentage calculated based on the total number of cells (determined by hematoxylin stain based on segmentation of the nuclei).
- Forty-four participants enrolled, and 41 completed the 48-week study period. Twenty-six participants had paired LN samples for RNAScope, 28 had paired samples for CD4⁺ T cell and CD163⁺ quantification in the T cell zone, and 25 had paired samples for CD4⁺ T cell and CD163⁺ quantification in the B cell follicle.
- At the α=0.05 level, statistical testing used signed-rank tests, Spearman correlations and an extension of the rank-sum test which estimated the θ statistic (the probability of a random telmisartan arm value being less than or equal to a random control arm value).

III. Results

Table 1. Baseline characteristics.

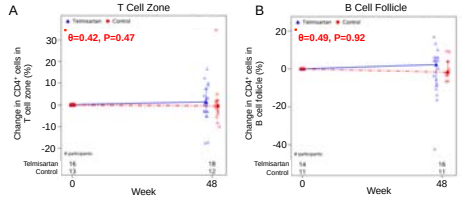
		ART + Telmisartan (N=29)	ART Alone (N=15)	Total (N=44)
Sex	Male	27 (93%)	14 (93%)	41 (93%)
	Female	2 (7%)	1 (7%)	3 (7%)
Age (years)	Median	47	50	48
	IQR	41, 51	39, 52	41, 52
Race/Ethnicity	White Non-Hispanic	16 (55%)	6 (40%)	22 (50%)
	Black Non-Hispanic	5 (17%)	8 (53%)	13 (30%)
	Hispanic (regardless of race)	7 (24%)	1 (7%)	8 (18%)
BMI (kg/m²)		25.4	23.7	25.0
		23.3, 29.8	21.4, 26.6	22.6, 28.4
CD4 count (cells/mm³)	Median	604	556	588
	IQR	438, 812	444, 906	444, 841
HIV-1 RNA (copies/ml)	<40	24 (83%)	12 (80%)	36 (82%)
	Detectable	5 (17%)	3 (20%)	8 (18%)
	Median (IQR)	188 (73, 579)	114 (55, 2340)	151 (66, 739)
Antiretrovirals	NRTI	24 (83%)	15 (100%)	39 (89%)
	NNRTI	9 (31%)	8 (53%)	17 (39%)
	PI	17 (59%)	7 (47%)	24 (55%)
	INSTI	14 (48%)	0 (0%)	14 (32%)

Figure 1. Change in HIV-1 RNA⁺ cells in lymph nodes



Baseline median (IQR) LN number of HIV-1 RNA⁺ cells/10⁶ cells (vRNA⁺ cells) was 97 (0, 130) overall: 106 (67, 130) in the ART + telmisartan arm **(A)** and 75 (0, 118) in the ART alone arm **(B)**. vRNA⁺ cells changed by -48 cells (-88, 0; P=0.004; N=13), a 45% decrease, in the telmisartan arm **(A)** and +18 cells (-91, +45; P=0.70; N=10) in the ART alone arm, with the between-arm comparison of θ=0.65, P=0.28. By morphology, vRNA⁺ cells were lymphocytes. Findings were independent of INSTI use.

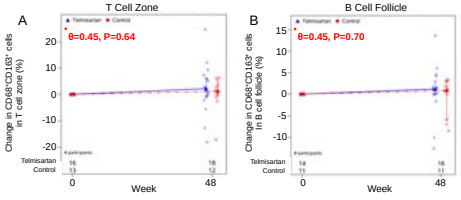
Figure 2. Change in percent (%) CD4 in lymph nodes over 48 weeks



A) % CD4⁺ T cells in T cell zone (TCZ) were 59.06% (55.67, 64.76) overall: 56.46% (53.19, 66.96) in telmisartan + ART group and 60.75% (59.06, 64.76) in the ART alone group. % CD4⁺ T cells in TCZ changed over 48 weeks by +0.30% (-3.41, +4.13; P=0.85) overall: +1.23% (-2.98, +7.40; P=0.58; N=18) in the ART + telmisartan group and -0.54% (-4.48, +1.86; P=0.68; N=12) in the ART alone group. The difference between groups was not statistically significant.

B) % CD4⁺ T cells in B cell follicle (BCF) were 27.82% (21.47, 34.58) overall: 29.30% (20.43, 34.84) in telmisartan + ART group and 24.94% (21.47, 34.58) in the ART alone group. % CD4⁺ T cells in BCF changed over 48 weeks by -0.13% (-6.40, +6.16; P=0.98) overall: +2.36% (-9.21, +6.16; P=0.90; N=16) in the ART + telmisartan group and -1.71% (-3.66, +3.87; P=0.97; N=11) in the ART alone group. The difference between groups was not statistically significant.

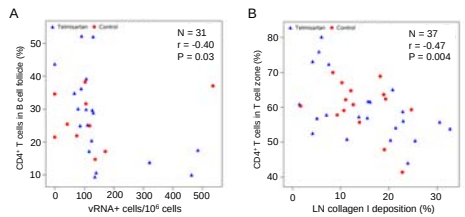
Figure 3. Change in percent (%) macrophages in lymph nodes over 48 weeks



A) % CD68⁺CD163⁺ cells (macrophages) in TCZ were 15.02% (11.60, 16.82) overall: 15.06% (10.80, 18.57) in telmisartan + ART group and 14.96% (11.74, 16.82) in the ART alone group. % macrophages in TCZ changed over 48 weeks by +1.49% (-0.88, +5.32; P=0.07) overall: +2.13% (-0.88, +6.09; P=0.17) in the ART + telmisartan group and +1.14% (-0.59, +4.33; P=0.27) in the ART alone group. The difference between groups was not statistically significant.

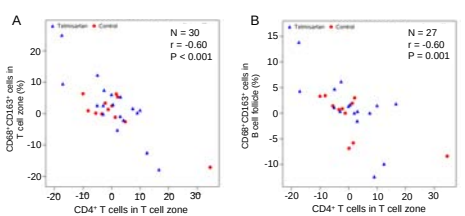
B) % macrophages in BCF were 4.17% (2.15, 6.04) overall: 3.56% (2.15, 5.98) in telmisartan + ART group and 4.24% (1.83, 10.20) in the ART alone group. % macrophages in BCF changed over 48 weeks by +1.12% (-0.04, +2.96; P=0.22) overall: +1.22% (-0.00, +3.03; P=0.16; N=18) in the ART + telmisartan group and +0.83% (-5.83, +2.96; P=0.90; N=12) in the ART alone group. The difference between groups was not statistically significant.

Figure 4. Association of collagen I, vRNA⁺ cells and CD4⁺ T cells at Week 0



A) The number of vRNA⁺ cells correlated inversely with % CD4⁺ T cells in BCF (r = - 0.40, P=0.03) but not in the TCZ (r = 0.03, P=0.85). The number of vRNA⁺ cells correlated inversely with % macrophages in TCZ (r = - 0.35, P=0.04) and BCF (r = -0.40, P=0.03). There was no association between number of vRNA⁺ cells and % collagen I. **B)** % collagen I correlated inversely with % CD4⁺ T cells in TCZ (r = -0.47, P=0.004) but not BCZ (r = 0.12, P=0.51).

Figure 5. Correlations between changes in CD4⁺ T cells and macrophages



Changes in CD4⁺ T Cells in TCZ are correlated inversely with changes in macrophages over 48 weeks in **A)** TCZ (r = -0.60, P<0.001) and **B)** BCZ (r = -0.60, P=0.001). Changes in CD4⁺ T Cells in TCZ are correlated directly with changes in CD4⁺ T cells in BCZ (r = 0.41, P=0.04), and changes in macrophages in TCZ are correlated directly with changes in macrophages in BCZ (r = 0.53, P=0.004). There were no correlations of changes in CD4⁺ T cells with changes in vRNA⁺ cells.

IV. Conclusions

- **In people with HIV-1 on suppressive ART, angiotensin receptor blockade and PPAR-γ agonism with telmisartan for 48 weeks decreased LN vRNA⁺ cells by 45%.**
- **At Week 0, people with less LN fibrosis and fewer vRNA⁺ cells had more LN CD4⁺ T cells.**
- **Decreases in LN macrophages were accompanied by better LN CD4⁺ T cell representation without a change in LN vRNA+ cells.**
- **We hypothesize that macrophages contribute to LN fibrosis and thereby limit CD4⁺ T cell recovery.**
- **Further characterization in LN of these macrophages, lymphocytes and the reservoir will clarify their interactions and the mechanism by which telmisartan may decrease the number of LN vRNA⁺ cells.**

References

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Acknowledgements

1. We would like to thank the participants and staff who participated in ACTG A5317.

2. This work was supported by NIH grants U01 AI68636, 5P30 AI028697, 5P30 AG028748-01, K24 AI56933 to JSC and K23 AI110532 to JEL.