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Telmisartan Does Not Improve Lymph Node or Fat Fibrosis in Treated HIV Infection

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I. Introduction

- Chronic HIV infection is characterized by persistent inflammation and immune activation that can lead to tissue injury and fibrosis.
- Lymph node (LN) fibrosis may limit CD4$^+$ T-cell recovery.
- LN and adipose tissue (AT) fibrosis may contribute to systemic inflammation and comorbidities.
- Telmisartan is an angiotensin receptor blocker and PPAR-γ agonist with anti-inflammatory and anti-fibrotic properties.
- We hypothesized that telmisartan would decrease LN or AT fibrosis in HIV-1-infected adults on suppressive antiretroviral therapy (ART).

II. Methods

Study Design: Randomized controlled trial enrolling 44 adults (≥18 years old) who were HIV-1-infected and had HIV-1 RNA <50 copies/mL on ART for ≥48 weeks.

Intervention: Randomized 2:1 to received telmisartan 40mg daily for 4 weeks then 80mg daily for 44 weeks or no drug while continuing ART.

Primary endpoints: Changes in % collagen I deposition by immunohistochemistry (IHC) in inguinal LN and subcutaneous lower abdominal AT after 48 weeks. IHC was performed and interpreted by a blinded central reader.

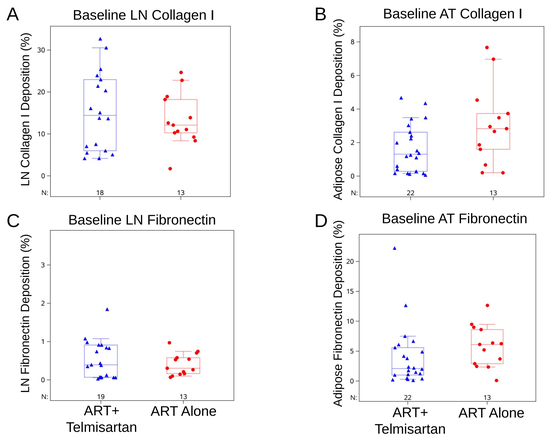
Statistical analysis: Thirty-nine participants provided 90% power to detect a 4% between-group difference in collagen I deposition. Forty-four participants enrolled, 41 completed the 48-week study period, and 34 and 30 participants had paired LN and AT specimens, respectively, of sufficient quality for analysis. Statistical testing used signed-rank tests, rank-sum tests 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.

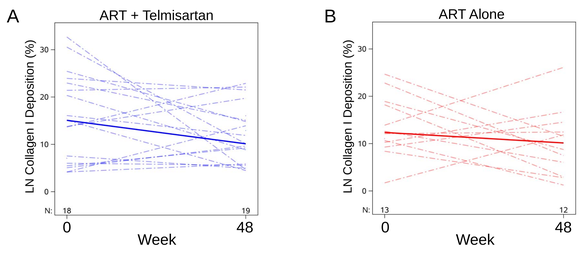
		ART + Telmisartan (N=29)	ART Alone (N=15)	Total (N=44)
Sex	Male	27 (93%)	14 (93%)	41 (93%)
	Female	2 (7%)	1 (7%)	3 (7%)
Age (years)	Median	47	50	48
	IQR	41, 51	39, 52	41, 52
Race/Ethnicity	White Non-Hispanic	16 (55%)	6 (40%)	22 (50%)
	Black Non-Hispanic	5 (17%)	8 (53%)	13 (30%)
	Hispanic (regardless of race)	7 (24%)	1 (7%)	8 (18%)
BMI (mg/kg^2)		25.4	23.7	25.0
		23.3, 29.8	21.4, 26.6	22.6, 28.4
CD4 count (cells/mm^3)	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%)
Duration of ART (years)	Median	11	11	11
	IQR	11, 11	11, 12	11, 11

Figure 1. Baseline collagen and fibronectin deposition in LN and adipose tissue



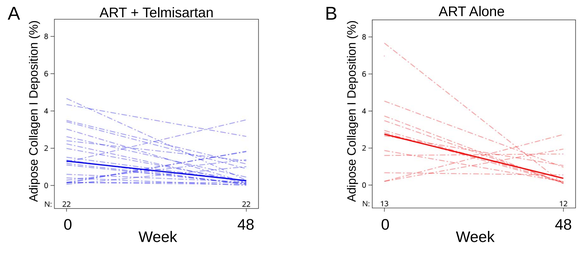
A) Baseline median (IQR) lymph node (LN) area with collagen I deposition was 13.7% (7.5, 21.4) overall: 14.4% (6.0, 23.0) in the ART + telmisartan group and 12.1% (10.3, 18.2) in the ART alone group. **B)** Baseline adipose tissue (AT) collagen I deposition was 1.9% (0.4, 3.4) overall: 1.3% (0.3, 2.6) in the ART + telmisartan group and 2.8% (1.6, 3.7) in the ART alone group. **C)** Baseline LN fibronectin deposition was 0.39% (0.11, 0.78) overall: 0.39% (0.07, 0.91) in the ART + telmisartan group and 0.30% (0.16, 0.58) in the ART alone group. **D)** Baseline AT fibronectin deposition was 3.7% (1.2, 6.4) overall: 2.1% (1.0, 5.6) in the ART + telmisartan group and 6.1% (2.9, 8.6) in the ART alone group.

Figure 2. Change in % collagen I in LN over 48 weeks



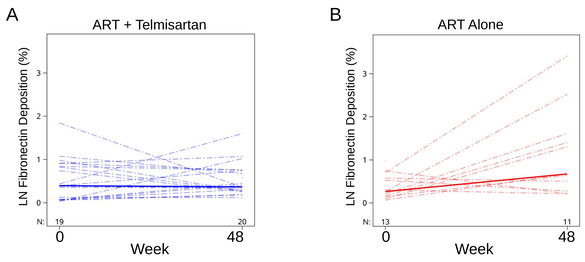
LN collagen I deposition changed over 48 weeks by -2.6% (-10.6, 4.6; P=0.08 by signed-rank test) overall: **A)** -2.4% (-10.6, 3.4; P=0.24) in the ART + telmisartan group and **B)** -6.1% (-11.7, 5.8; P=0.23) in the ART alone group. The difference between groups was not statistically significant: θ=0.50 (0.26, 0.73; P=0.97).

Figure 3. Change in % collagen I in adipose tissue over 48 weeks



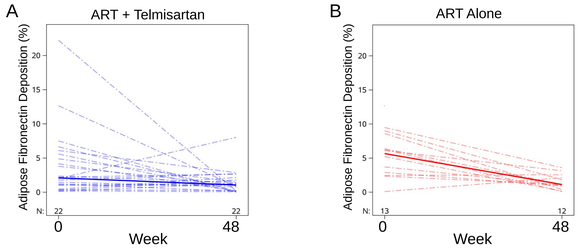
Adipose tissue collagen I deposition changed significantly over 48 weeks by -1.3% (-2.5, -0.01; P=0.001 by signed-rank test) overall: **A)** -1.1% (-2.1, -0.01; P=0.02) in the ART + telmisartan group and **B)** -2.2% (-3.5, -0.02; P=0.03) in the ART alone group. The difference between groups was not statistically significant: θ=0.37 (0.14, 0.60; P=0.27).

Figure 4. Change in % fibronectin in LN over 48 weeks



LN fibronectin deposition changed over 48 weeks by 0.12% (-0.16, 0.61, P=0.16 by signed-rank test) overall: **A)** 0.01% (-0.40, 0.35, P=0.95) in the ART + telmisartan group and **B)** 0.61% (-0.09, 1.40, P=0.054) in the ART alone group. The difference between groups was not statistically significant: θ=0.72 (0.49, 0.94, P=0.057).

Figure 5. Change in % fibronectin in adipose tissue over 48 weeks



Adipose tissue fibronectin deposition changed significantly over 48 weeks by -2.4% (-5.5, 0.1; P<0.001 by signed-rank test) overall: **A)** -0.8% (-4.0, 0.5; P=0.05) in the ART + telmisartan group and **B)** -4.0% (-6.0, -1.6; P=0.005) in the ART alone group. The difference between groups was not statistically significant: θ=0.36 (0.16, 0.56; P=0.17).

IV. Conclusions

- **In HIV-1-infected adults on suppressive ART, angiotensin receptor blockade and PPAR-γ agonism with telmisartan for 48 weeks did not improve LN or AT fibrosis more than continued ART alone.**
- **Notably, AT collagen I and fibronectin decreased significantly over 48 weeks, with a non-significant decrease in LN collagen I, in HIV-1-infected adults taking ART.**
- **Among HIV-1-infected adults on ART with high CD4 counts, LN collagen I deposition is consistent with published findings of untreated HIV-1-infected adults.**
- **This trial is the first longitudinal study of LN and AT fibrosis in treated HIV infection and will inform design of future studies with tissue endpoints.**
- **Analyses of tissue HIV expression and circulating and tissue-level inflammatory and fibrotic signatures are ongoing.**

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