**BACKGROUND AND PREMISE:**
- Incomplete immune recovery among persons with HIV (PHIV) receiving ART is associated with excess clinical risk.
- Fibrosis (i.e., collagen deposition) within the paracortical zone of lymphatic nodes (LN) contributes to depletion of naïve and central memory T-cells and impaired immune reconstitution.
- LN collagen deposition is mediated by transforming growth factor beta (TGF-β) as a consequence of ongoing immune activation.
- We hypothesized that the angiotensin receptor blocker (ARB) losartan would inhibit fibrosis and improve T-cell recovery, given its established treatment effects in blocking TGF-β signaling.

**STUDY DESIGN:**
We pooled data from two randomized (1:1), double-blind, placebo-controlled trials (RCTs) of losartan (100mg daily):
- **LIFE-HIV:** "Losartan to Reduce Inflammation and Fibrosis Endpoints in HIV Disease", a subset of n=63 enrolled into a lymph node (LN) biopsy substudy.
- **RTF-HIV:** "Reversing Tissue Fibrosis to Improve Immune Reconstitution in HIV".

**Statistical Methods:**
- Tissue and Blood Analyses: The percent area of collagen and CD4+ T-cells in LN were quantified in the parafollicular T-cell zone, using immunohistochemistry (IHC) followed by quantitative image analysis (QIA). Figure 2 demonstrates a throromine stain of collagen (blue) within LN tissue (LEFT), followed by a corresponding image where all collagen is displayed in black and non-collagen tissue removed (RIGHT). The percent area of collagen in tissue is then estimated; corresponding methods were applied to estimate percent area of CD4+ T-cells. ELISA and electrochemiluminescence assay methods were used to measure biomarkers in blood.
- **Randomization:**
- **LIFE-HIV:**... 
- **RTF-HIV:**... 

**RESULTS:**
- **Characteristics:**
  - **Table 1:**
    - **LIFE-HIV:**... 
    - **RTF-HIV:**... 
    - **Combined:**... 

**Main Findings:**
- Analysis of lymph node (LN) tissue from n=50 with longstanding HIV disease support that LN fibrosis is associated with alterations in T-cell homeostasis, but treatment with losartan (100mg) did not improve LN CD4+ T-cells or collagen when compared to placebo, or within persons, over 12 months.

**Table 1:**
<table>
<thead>
<tr>
<th>Sample Size</th>
<th>LIFE-HIV</th>
<th>RTF-Trial</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=20</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>N=30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=50</td>
<td></td>
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</tbody>
</table>

**Table 2:**
<table>
<thead>
<tr>
<th>Clinical Factors</th>
<th>Estimate (95% CI); p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>0.19 (0.01, 0.37); 0.07</td>
</tr>
<tr>
<td>BMI kg/m²</td>
<td>0.63 (0.46, 0.83); 0.002</td>
</tr>
<tr>
<td>CD4+ count</td>
<td>0.59 (0.41, 0.81); 0.002</td>
</tr>
<tr>
<td>CD4+ and CD8+</td>
<td>0.61 (0.43, 0.83); 0.002</td>
</tr>
</tbody>
</table>

**SUMMARY OF RESULTS:**
- At baseline (Table 2), greater LN collagen was associated with less CD4+ cells (est: -3.8, p<0.001) and both greater collagen and less CD4+ cells were associated with:
  - 1. Significantly higher levels of CD4+ T-cells in blood, as well as a lower CD4:CD8 ratio.
  - 2. Lower nadir CD4+ count and longer duration of HIV diagnosis, but these associations did not reach significance.

**LIFE-HIV:**
- Losartan treatment was not associated with a significant difference in change of LN collagen or CD4+ T-cells over 12 months (center Figure).
- Nor with biomarkers of fibrosis or blood CD4+ and CD8+ counts (data not shown). Analyses within treatment groups also did not demonstrate significant changes.

**IMPLICATIONS:**
- Among older persons with longstanding HIV disease, losartan did not alter lymphatic tissue fibrosis or T-cell immune reconstitution, given the importance for restoring health among persons living with HIV.

**Table 2:**
<table>
<thead>
<tr>
<th>Plasma Biomarkers</th>
<th>Estimate (95% CI); p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α, pg/mL</td>
<td>0.68 (0.45, 0.95); 0.002</td>
</tr>
<tr>
<td>IL-6, pg/mL</td>
<td>0.67 (0.44, 0.95); 0.002</td>
</tr>
<tr>
<td>sCD163, ng/mL</td>
<td>0.68 (0.45, 0.95); 0.002</td>
</tr>
</tbody>
</table>

**CITATIONS:**

**ACKNOWLEDGEMENTS:**
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