BACKGROUND
Persistent inflammation and immune activation are associated with end-organ diseases in treatment-suppressed HIV patients. The objective of this clinical trial was to investigate the effect of switching to raltegravir and/or adding losartan on the inflammatory/immune-activation mediators in treated HIV patients.

METHODS

48 chronic HIV patients successfully treated with 2 NRTI and 1 NNRTI or PI during at least 48w were randomized to four groups (n=12): 2 NRTI + EVF, 2 NRTI + EVF + losartan, 2 NRTI + raltegravir and 2 NRTI + raltegravir + losartan for 48 weeks (study was conducted in 2 phases) (Figure 1)

Markers of T CD4 and CD8 lymphocytes activation (HLADR+8) and senescence (CD28-CD57+), monocyte activation (CD14+, CD16+) and inflammation (hsCRP, TNF-alpha, D-dimer and IL-6) were determined at baseline and at w48 and compared between groups. IBM SPSS Statistics 20.0 was used for data analysis. We used ANOVA and the Kruskal-Wallis test with Bonferroni correction when comparisons were performed in the four groups. For comparisons between two groups we used T-test or U-Mann-Whitney when distribution of the variable was not normal.

RESULTS

After 48 weeks of intervention, a decrease in activation markers in CD4 T cells (CD38+ HLADR+, p= 0.09) and senescence markers in CD8 T cells (CD8 CD28-CD57+, p= 0.02) and an increase in the CD4/CD8 ratio (p= 0.03) was observed in patients who switched to raltegravir or to raltegravir + losartan arms (Table 3 and Figure 2). No other differences between the four arms in T lymphocytes or monocyte subsets were observed (table 3).

A sub-study splitting the cohort in two subgroups (raltegravir arms III and IV) vs no raltegravir arms (arms I and II) was performed. As compared with patients who did not switched to raltegravir, patients in the raltegravir groups showed a significant decrease in all activation and senescence populations in the T lymphocyte subsets and an increase in the CD4/CD8 ratio (a median of 0.03 vs 0.35, p=0.002, respectively. No changes in the monocyte subpopulation was observed between these two groups (table 4).

A decrease in hsCRP, IL-6, TNF-alpha and D-dimer, was observed in all the cohort with no changes between groups. Markers of microbial translocation were performed in phase I of the study with no changes after 48 weeks between arm I and II (data not shown).

CONCLUSIONS

Angiotensin receptor antagonist losartan did not have any impact on markers of inflammation, T cell activation, senescence or monocyte differentiation in HIV infected patients on cART. Conversely, raltegravir decreased activated and senescent T lymphocyte subpopulations and increased CD4/CD8 ratio in already treated HIV patients after 48 weeks compared with other triple therapy regimens, although no changes in monocyte subpopulations or markers of inflammation were observed.

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>T cells</th>
<th>CD8</th>
<th>CD4</th>
<th>CD14</th>
<th>CD16</th>
<th>CD57</th>
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Table 2. Baseline T lymphocytes and monocytes subpopulations and CD4/CD8 ratio

<table>
<thead>
<tr>
<th>Group</th>
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<th>CD8 CD57</th>
<th>CD8 CD28+ CD57+</th>
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Table 3. Delta value w48-baseline between 4 groups. T lymphocytes and monocytes subpopulations and CD4/CD8 ratio

<table>
<thead>
<tr>
<th>Group</th>
<th>CD4/CD8</th>
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<th>CD8 CD57</th>
<th>CD8 CD28+ CD57+</th>
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<tbody>
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Table 4. Delta value w48-baseline between raltegravir and no raltegravir groups. T lymphocytes and monocytes subpopulations and CD4/CD8 ratio

<table>
<thead>
<tr>
<th>Group</th>
<th>CD4/CD8</th>
<th>CD8 CD28</th>
<th>CD8 CD57</th>
<th>CD8 CD28+ CD57+</th>
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<tbody>
<tr>
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Figure 2. Differences in CD4/CD8 ratio w48-baseline between the four arms

Reference:
Berta Torres1, Alberto C Guardo2, Amanda Fabra2, Lorna Leal2, Cristina Rovira1, Carmen Hurtado2, Manel E Bargalló2, Constanza Lucero1, Irene Fernández1, Flor Etcherveny1, Josep M Gatell3, Montserrat Planà2 and Felipe García1

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