Effect of Switching to Raltegravir and/or Adding Losartan on HIV Immune Activation

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BACKGROUND

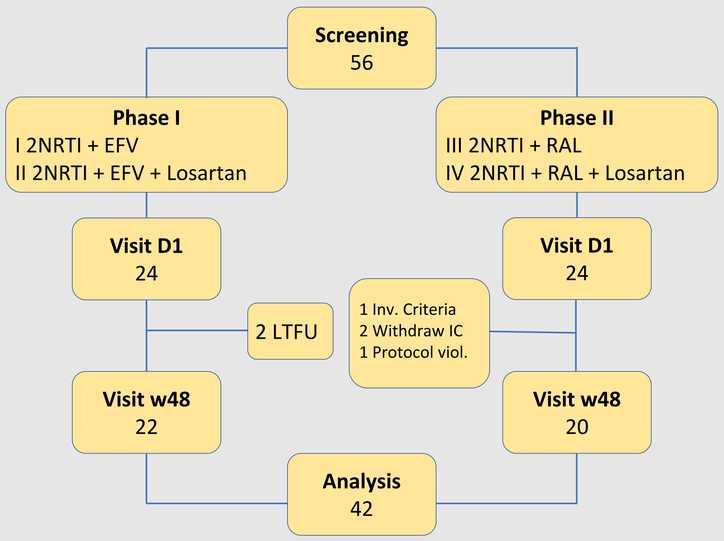
Persistent inflammation and immune activation are associated with end-organ diseases in treatment-suppressed HIV patients.The objective of this clinical trial was to investigate the effect of switching to raltegravir and/or adding losartan on the inflammatory/immune-activation mediators in treated HIV 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=48): 2NRTI + EFV, 2NRTI + EFV + losartan, 2NRTI + raltegravir and 2NRTI + raltegravir + losartan for 48 weeks (study was conducted in 2 phases) **Figure 1**

Markers of T CD4 and CD8 lymphocytes activation (HLADR+38+) 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 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.

Figure 1. Patients disposition. D1: day one; w48: week 48**;** NRTI: nucleoside reverse transcriptase inhibitors; EFV: efavirenz; RAL: raltegravir 400 mg BID.



RESULTS

Figure 2. Differences in CD4/CD8 ratio w48-baseline between the four arms

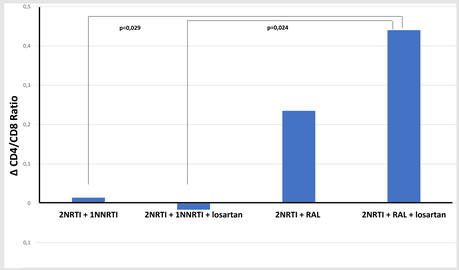


Table 1. Baseline characteristics

	All cohort Median (IQR)	2 NRTI + Efavirenz	2 NRTI + Efavirenz + losartan	2 NRTI + Raltegravir	2 NRTI + Raltegravir + Losartan	p
Age	41,1 (33,1-48,7)	40,2 (32,6-47,7)	42,6 (35-49,2)	42,9 (41,9-51,2)	34,7 (31,6-47,8)	0,2
Time since diagnosis (years)	7,8 (4,8-10,9)	6,9 (5,2-16,2)	12,3 (6,2-14,9)	8,3 (3-9,8)	5,78 (2,9-9)	0,18
Time on treatment (years)	4,9 (2,9-9,8)	4,6 (3,4-11,1)	9,3 (2,6-13,7)	8,1 (3-9)	3,8 (1,5-7,4)	0,4
CD4 nadir	307 (221-390)	344 (252-390)	310 (254-350)	199 (20-243)	411 (189-489)	**0,03**
CD4 baseline	723 (571-927)	866 (572-1069)	724 (639-960)	690 (422-849)	677 (495-769)	0,3
BMI (height/weight²)	24,7 (22-26,7)	24,8 (23,1-26,4)	25,2 (24,4-27,9)	24,9 (21,8-29,3)	22,2 (20,6-25,7)	0,27
SAP (mmHg)	120 (114-132)	120 (112-125)	120 (116-125)	129 (114-144)	119 (113-125)	0,4
DAP (mmHg)	70 (66-81)	70 (60-70)	71 (68-84)	84 (73-88)	71,5 (64-79)	**0,008**
Cholesterol (mg/dl)	173 (152-204)	168 (151-199)	191 (161-238)	181 (165-203)	155 (140-184)	0,27
LDL (mg/dl)	108 (92-124)	100 (92-159)	112 (79-145)	113 (101-125)	97 (85-116)	0,64
HDL (mg/dl)	40 (33-55)	46 (31-52)	35 (33-46)	35 (32-48)	44 (33-51)	0,8
Triglycerides (mg/dl)	106 (81-156)	84 (74-162)	123 (91-165)	134 (97-183)	87 (54-101)	**0,04**

Table 2. Baseline T lymphocytes and monocytes subpopulations and CD4/CD8 ratio

	All cohort Median (IQR)	2 NRTI + Efavirenz	2 NRTI + Efavirenz + losartan	2 NRTI + Raltegravir	2 NRTI + Raltegravir + Losartan	p
CD4 CD38+ HLADR+ (%)	2,4 (1,5-4,1)	2,3 (1,4-5,5)	4,0 (2,6-4,4)	1,8 (1-2,5)	2,2 (1,6-3)	**0,02**
CD8 CD38+ HLADR+ (%)	9,1 (5,9-15,6)	9,6 (4,6-16)	14,6 (10,3-21,6)	6,8 (5,5-10,1)	8,8 (5-14,4)	**0,03**
CD4 CD28- CD57+ (%)	2,1 (0,6-6,6)	2,1 (1,4-7)	3,2 (0,8-8,1)	1,9 (0,6-8,8)	0,8 (0,4-3,7)	0,5
CD8 CD28- CD57+ (%)	29,6 (20,7-39,7)	25,3 (13,5-35,5)	26,4 (18,5-41)	36,1 (28,1-39,3)	30,7 (19-42,3)	0,4
0CD14+ CD16- (%)	57,7 (51,8-62,1)	58,4 (52,3-61)	57,4 (39,2-59,8)	61,6 (55,4-64,1)	56,9 (51,6-64,4)	0,4
CD14+ CD16+ (%)	3,8 (2,2-7,1)	2,7 (2-3,9)	4,2 (1,42-6,4)	4,4 (2,1-11,3)	4 (3,3-10,2)	0,3
CD4/CD8	0,9 (0,6-1,2)	1,8 (0,6-1,5)	1 (0,7-1,2)	0,7 (0,5-1,1)	0,9 (0,7-1,1)	0,5

Table 3. Delta value w48-baseline between 4 groups. T lymphocytes and monocytes subpopulations and CD4/CD8 ratio.

	All cohort Median (IQR)	2 NRTI + Efavirenz	2 NRTI + Efavirenz + losartan	2 NRTI + Raltegravir	2 NRTI + Raltegravir + Losartan	p
Δ CD4 CD38+ HLADR+ (%) Median (IQR)	-0,06 (-0,9-1,28)	0,5 (0-1,6)	1,1 (-0,8-14,6)	-0,3 (-0,8- -0,1)	-0,4 (-1,7-1,1)	0,09
Δ CD8 CD38+ HLADR+ (%)	-0,8 (-3-2,7)	1,7 (-0,7-5,9)	0,9 (-0,6-8,5)	-1,4 (-3,6- -0,9)	-3 (-8,2-3,9)	0,15
Δ CD4 CD28- CD57+ (%)	0,04 (-1,2-0,9)	0,3 (-0,9-3)	0,2 (-0,7-3,4)	-0,4 (-3,8-0,1)	0,1 (-2,2-0,4)	0,23
Δ CD8 CD28- CD57+ (%)	-0,9 (-8,7-6,3)	3,9 (1-10,4)	2,5 (-3,2-9,7)	-7 (-13,3- -4,5)	-3 (-15,6- -0,5)	**0,02**
Δ CD14+ CD16- (%)	5,1 (-3,9-11,8)	7,6 (-0,2-17,2)	-0,6 (-9,5-30)	-1,1 (-12- 11,4)	7,1 (1,2-12,3)	0,66
Δ CD14+ CD16+ (%)	-0,5 (-3,1-0,7)	-0,06 (-1,9-0,8)	-0,7 (-2,6-0,9)	0,1 (-4,5-0,9)	-1,0 (-6,2-0,6)	0,42
Δ CD4/CD8	0,2 (-0,06-0,4)	-0,03 (-0,2- 0,3)	0,04 (-0,2- 0,3)	0,36 (-0,0 – 0,5)	0,37 (0,8-0,6)	**0,01**

Table 4. Delta value w48-baseline between raltegravir and no raltegravir groups. T lymphocytes and monocytes subpopulations and CD4/CD8 ratio.

	Raltegravir groups	No raltegravir groups	p
Δ CD4 HLADR+ CD38+ (%)	-0,3 (-1,3-0,05)	0,48 (-0,6-8,4)	**0,03**
Δ CD4 CD28- CD57+	-0,3 (-2,9-0,3)	0,26 (-0,8-3,1)	**0,04**
Δ CD8 HLADR+ CD38+	-1,6 (-7- -0,03)	1,3 (-1,8-6,3)	**0,02**
Δ CD8 CD28- CD57+	-6,1 (-13,05-0,9)	3,8 (-0,6-9,8)	**0,002**
Δ CD14++ CD16-	4,2 (-3,4-11,6)	5,7 (-5,8-17,8)	0,9
Δ CD14+ CD16+	-0,6 (-4,5-0,8)	-0,3 (-2,2-0,6)	0,3
Δ CD4/CD8	0,35 (0,11-0,53)	0,03 (-1,87-0,28)	**0,002**

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= 0.01) 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 substudy 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 senescent 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.

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