

Lipopolysaccharide (LPS) changes in plasma of HIV-1 infected subjects during repeated treatment interruptions

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BACKGROUND

Recent data have shown that the microbial translocation consequent to the impairment of gastrointestinal barrier plays an important role in the generalized immune activation that is typical of HIV disease¹⁻². The degree of microbial translocation can be assessed by measuring plasma levels of bacterial byproducts such as lipopolysaccharide (LPS) and it has been associated to HIV progression.

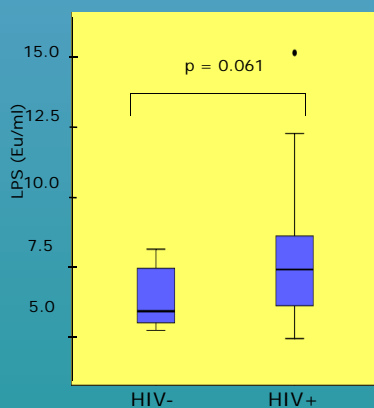
In fact, increased LPS levels have been found in HIV infected subjects respect to HIV uninfected^{1,3}. During HAART a decrease of plasma LPS levels has been observed and is inversely correlated to restoration of CD4 cells and lowering of immune activation³. Nevertheless, LPS levels in HAART treated patients did not normalize, remaining enhanced if compared to normal values.

The aim of the present study was to assess if repeated treatment interruptions in HAART-treated subjects with < 400 copies/ml of HIV-1 RNA produce significant changes in the amount of circulating LPS.

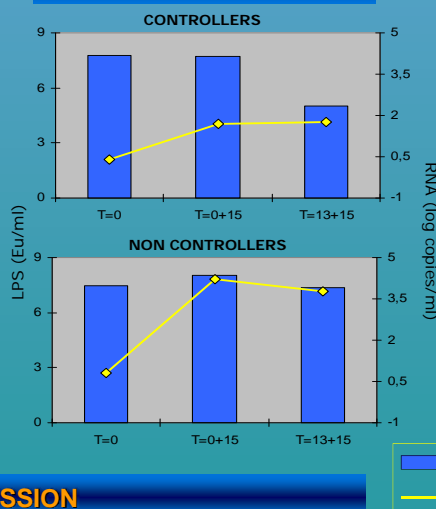
RESULTS

Fifty-one subjects were studied, 12 C and 39 NC. Compared with 10 healthy donors, at T0 they had a trend to higher LPS levels (median 7.45 and 5.97 EU/ml respectively, $p = 0.061$). C and NC were comparable for all parameters, including LPS. At T0+15, NC had higher values of HIV-1 RNA ($p < 0.001$) and CD8 ($p = 0.023$), but not of LPS. At T13+15 (4th TI), C and NC still differed for HIV-1 RNA ($p < 0.001$ and CD8 $p = 0.005$), but no change had occurred in LPS plasma levels in both groups. However, plasma LPS and HIV-1 RNA values were strongly correlated ($p < 0.001$, $R^2=0.532$).

comparison between LPS levels in HIV+ and HIV- individual



LPS and RNA levels during TI



DISCUSSION

In our study differences in LPS levels were observed between HIV infected, HAART-treated population and healthy subjects, although not significant. Several short HAART interruptions did not increase LPS plasma levels, despite the different degree of viral replication in C and NC. These data confirm and expand other Authors' observations⁵. However, the observed correlation between plasma HIV-1 RNA and LPS values at the fourth interruption indirectly suggest that viral rebound is associated to a certain degree of immune activation.

MATERIALS AND METHODS

Patients : we studied 51 subjects, on HAART for at least 1 year and with viral load < 400 copies/ml, enrolled in the intermittent arm of a randomized clinical trial (ISS-PART)⁴, comparing intermittent and continuous HAART for 24 months. Patients in the intermittent arm underwent 5 treatment interruptions (TI) lasting 1, 1, 2, 2, and 3 months, each one separated by 3 months "on HAART". For the purpose of this study, patients were retrospectively divided in two groups (Non Controllers, NC, or controllers, C) according to HIV-1 RNA levels > or ≤ 400 copies/ml during the first TI.

LPS: Plasma LPS was quantified using a commercial kit (Cambrex Bioscience, Walkersville, Maryland, USA) at study entry (T0), 2 weeks after first TI (T0 + 15) and 2 weeks after the 4th TI at month 13 (T13 + 15).

HIV-1 RNA below 50 copies/ml At baseline, plasma HIV-1 RNA below 50 copies/ml was quantified by an ultra-ultra sensitive method based on a modified Amplicor HIV-1 Monitor test version 1.5 (Roche Molecular Systems), with a limit of detection of 2.5 copies/ml.

Characteristics of study patients

	C n = 14	NC n = 37	P value
Age (years)	38 (26-62)	36 (28-71)	434
Sex (% of males)	57.1	73.0	0.322
HIV-RNA before HAART (log copies/ml)	4.2 (3.0 - 5.1)	4.7 (1.9 - 5.9)	0.047
Months of HAART	21 (15 - 41)	23 (12 - 57)	0.580

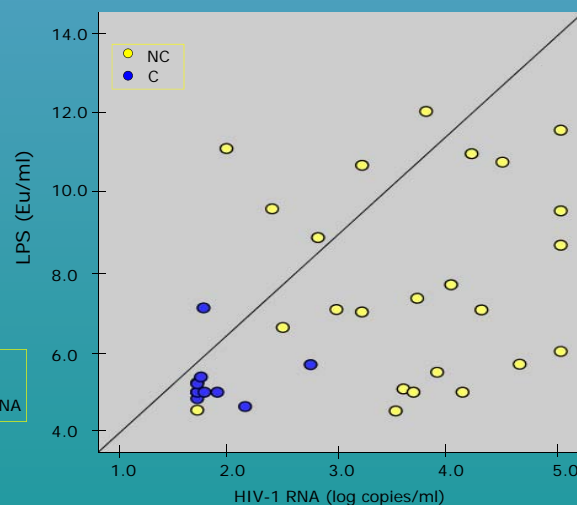
HAART regimen

	C n = 14	NC n = 37	P value
PI based	2 (14.3%)	14 (37.8%)	0.200
NNRTI based	11 (78.6%)	19 (51.4%)	
3 NRTI	1 (7.1%)	4 (10.8%)	

Viroimmunological status at time 0

	C n = 14	NC n = 37	P value
HIV-1 patients with < 2.5 copies/ml (n)	7 (58.6%)	12 (31.3%)	0.171
HIV-1 RNA (log copies/ml)	2.5 (2.5 - 100)	6.4 (2.5 - 200)	0.748
CD4 cell count (cell/ μ l)	717 (397 - 1276)	720 (370-1365)	0.147
CD8 cell count (cell/ μ l)	697 (486 - 1108)	859 (176-1467)	0.166
LPS (Eu/ml)	7.7 (5.0 - 10.8)	7.4 (5.0 - 15.2)	0.413

Correlation between viral load and LPS levels at T = 13 + 15



REFERENCES

1. Brenchley JM, et al. *Nat Med* 2006; **12**: 1365-71.
2. Brenchley JM, Douek DC. *Mucosal Immunol* 2008; **1**: 23-30.
3. Jiang W, et al. *J Infect Dis*. 2009; **199**: 1177-85
4. Palmisano L, et al. *J Acquir Immune Defic Syndr* 2007; **46**: 39-47.
5. Pappasavvas E et al. *AIDS* 2009; **23**: 369-75.