

# Increased Microbial Translocation (MT) is Associated to Lack of Early Virological Response to Pegylated Interferon + Ribavirin Treatment in HIV/HCV Coinfected Patients with Good Viro-Immunological Response to HAART

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## Introduction

HCV infection is a major cause of death among HIV-infected patients.

HIV and HCV share common transmission pathways. The simultaneous presence of HIV aggravates the prognosis of HCV infection in each stage of disease. HIV/HCV co-infected subjects seem to have an increased risk of clinical progression to liver cirrhosis.

Similarly, HIV/HCV coinfection is associated to more rapid progression to AIDS and to a significant reduction in the recovery of CD4+ count following introduction of highly active antiretroviral therapy (HAART).

The pathogenic mechanisms of the interplay between the two viruses are still unclear.

There is evidence that increased microbial translocation secondary to HIV-driven enteropathy and measured by circulating levels of lipopolysaccharide (LPS) is a cause of generalised immune activation both in HIV infection (Brenchley *et al.*, Nature Medicine. 2006) and HIV/HCV coinfection (Balagopal *et al.*, Gastroenterology. 2008).

Numerous studies on cell cultures and animal models have shown that exposure of liver tissue to high levels of LPS results in inflammation and fibrinogenesis.

We hypothesised that microbial translocation might be relevant in the response to HCV treatment in HIV/HCV coinfecting patients possibly in relation with immune hyperactivation.

## Objectives

✓To investigate a possible correlation between the stage of HCV chronic hepatitis, microbial translocation and T-cell activation.

✓To evaluate whether the levels of microbial translocation before the initiation of anti-HCV therapy are associated to liver disease and to early response to HCV therapy in HIV/HCV coinfecting patients.

## Methods

### PATIENT POPULATION (cross-sectional study)

We studied 98 HIV/HCV coinfecting patients on HAART with HIV-RNA <50 cp/mL, starting peg-IFN- $\alpha$  (180 mcg or 1.5 mcg/kg) + weight-dosed ribavirin (1000/1200 mg) subdivided in early virological responders (EVR) and non-EVR (n-EVR):

✓54 EVR: patients with HCV-RNA <15 UI/mL at month 3 of anti-HCV therapy.

✓44 non-EVR: patients with HCV-RNA >15 UI/mL at month 3 of anti-HCV therapy.

**Table 1. Stages of fibrosis (Knodel)**

Fibrosis stages	Description
F0	No fibrosis
F1, F2	Periportal fibrous expansion
F3	Bridging fibrosis, porto-portal or porto-central fibrosis
F4	Cirrhosis

## IMMUNE ASSAYS

Plasma was collected to evaluate:

✓LPS level (Limulus Amebocyte assay, Cambrex) and sCD14 level (ELISA, R&D).

PBMCs were collected to evaluate:

✓ Activation (HLA-DR+CD38+) expression by flow cytometric analysis

## STATISTICAL ANALYSIS

Comparisons between groups were made using T-test and Spearman correlation coefficient. Statistical analysis was performed using the SPSS statistical package (SPSS Inc. Chicago, Illinois, USA).

## Results

54 pts (55%) reached EVR, while 44 (45%) were non-EVR (n-EVR).

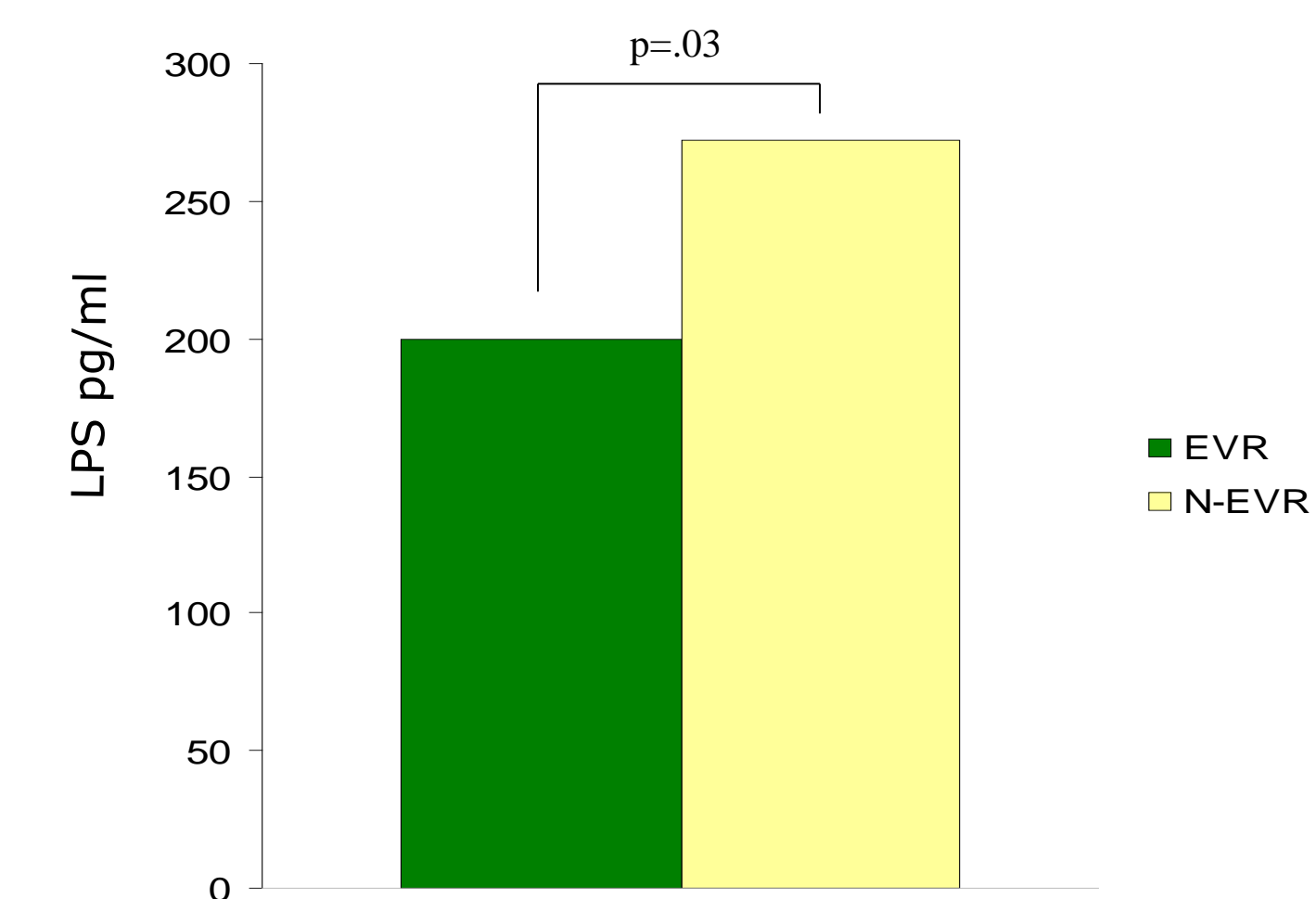
Table 2 shows clinical and immunological data according to EVR response.

Plasma sCD14 correlated with AF and with HCV genotypes 1 and 4. HCV genotypes 1-4 and AF were associated with sCD14 levels. MT parameters (plasma LPS and sCD14) were significantly more elevated in n-EVR than in EVR patients, while T-cell activation (HLA-DR and CD38) was not significant different between n-EVR and EVR patients.

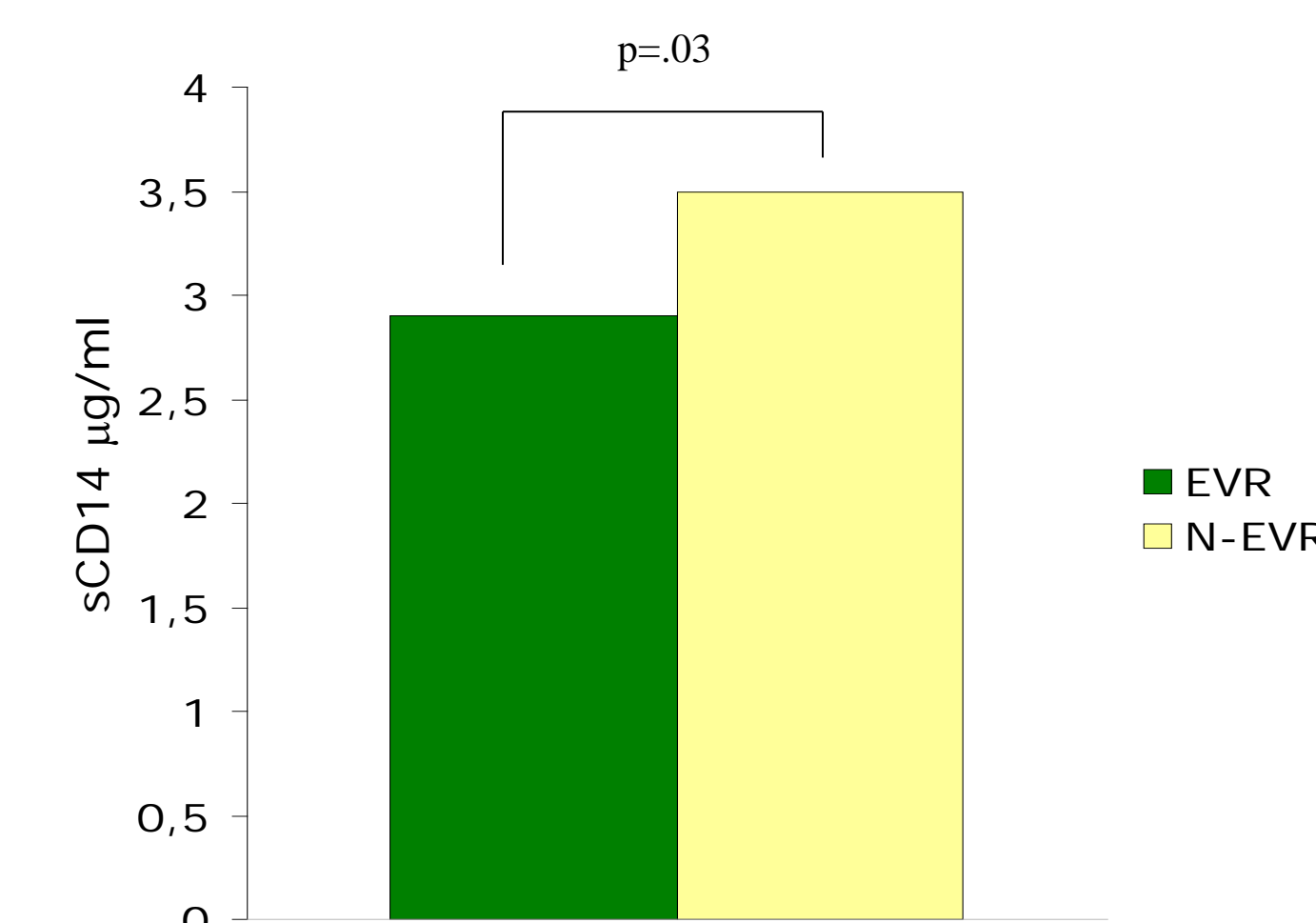
**Table 2. Patients' characteristics**

PARAMETERS	EVR (n = 54)	N-EVR (n = 44)	p
Age, years; mean (range)	43,6 (29 - 55)	43,7 (36 - 53)	0,7
CD4Nadir, cell/mm <sup>3</sup> ; mean (range)	199 (1 - 620)	155 (2 - 599)	0,12
CD4 T0, cell/mm <sup>3</sup> ; mean (range)	451 (179 - 901)	453 (62 - 1016)	0,9
HCV-RNA, Log cp/ml; mean (range)	5.2 (2.8 - 7.0)	5.8 (4.4 - 7.3)	0,02
HCV gt 2-3; n (%)	45 (83)	8 (18)	<0,001
Advanced Fibrosis; n (%)	16 (30)	27 (63)	0,01
LPS, pg/ml; mean (range)	200 (<75 - 420)	272 (<75 - 768)	0,03
sCD14, mcg/ml; mean (range)	2,9 (1,6 - 6,3)	3,5 (1,8 - 9,7)	0,03
CD8 DR+38+, %; mean (range)	42,04% (18 - 62)	42,42% (13 - 44)	0,47

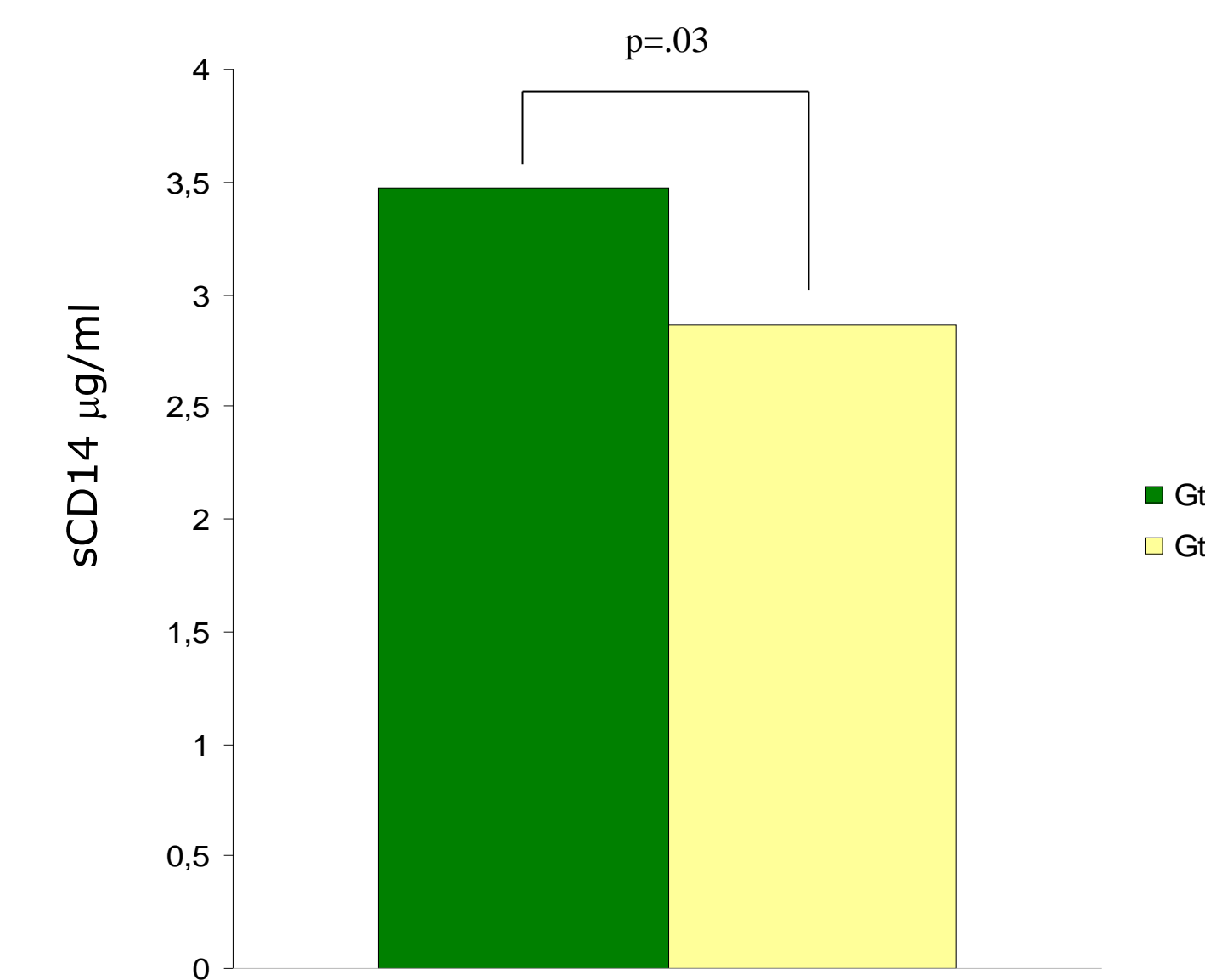
**Figure 1. Patients with an early virological response to anti HCV treatment display lower plasma levels of LPS than patients with no response.**



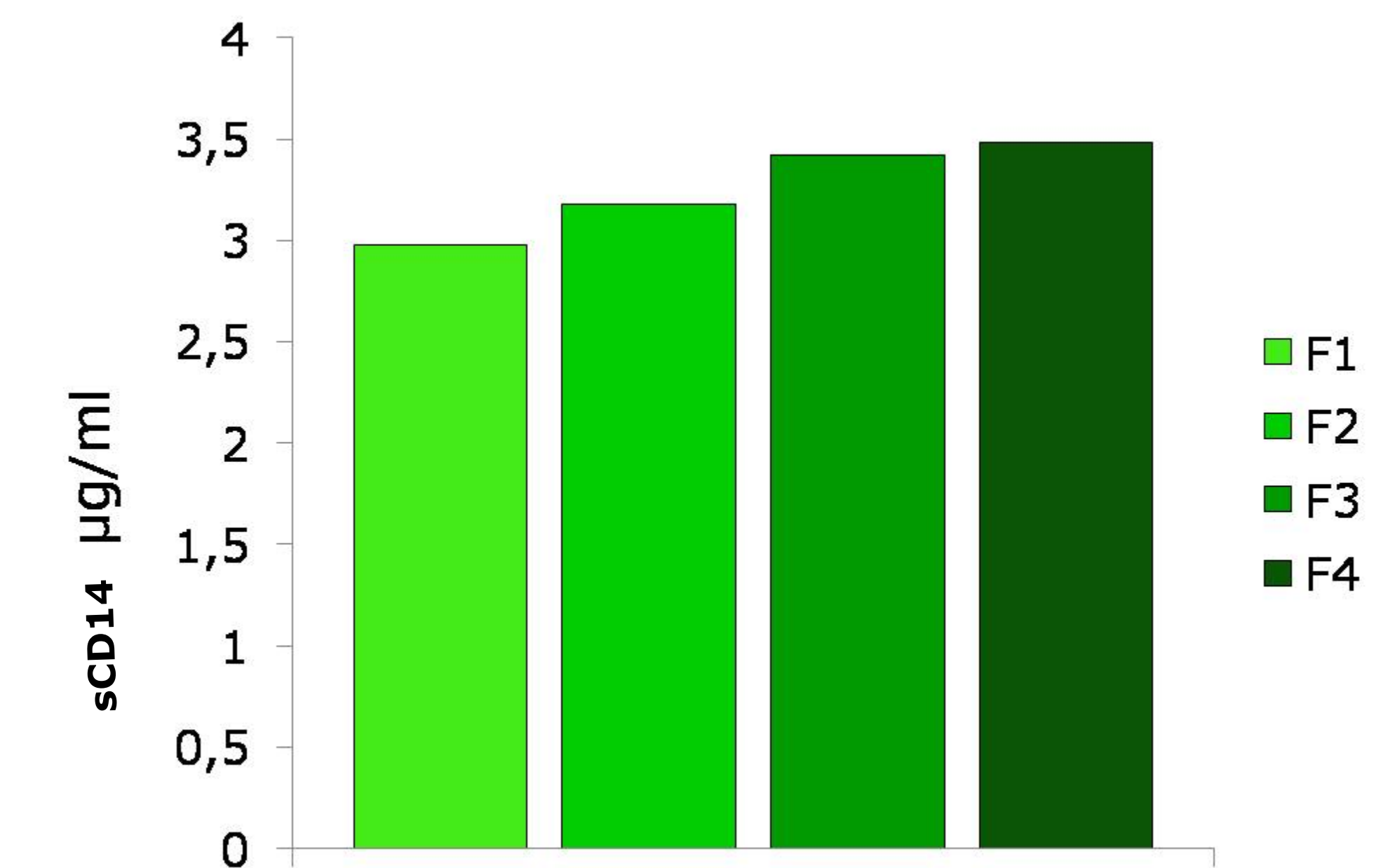
**Figure 2. Patients with an early virological response to anti HCV treatment display lower plasma levels of sCD14 than patients with no response.**



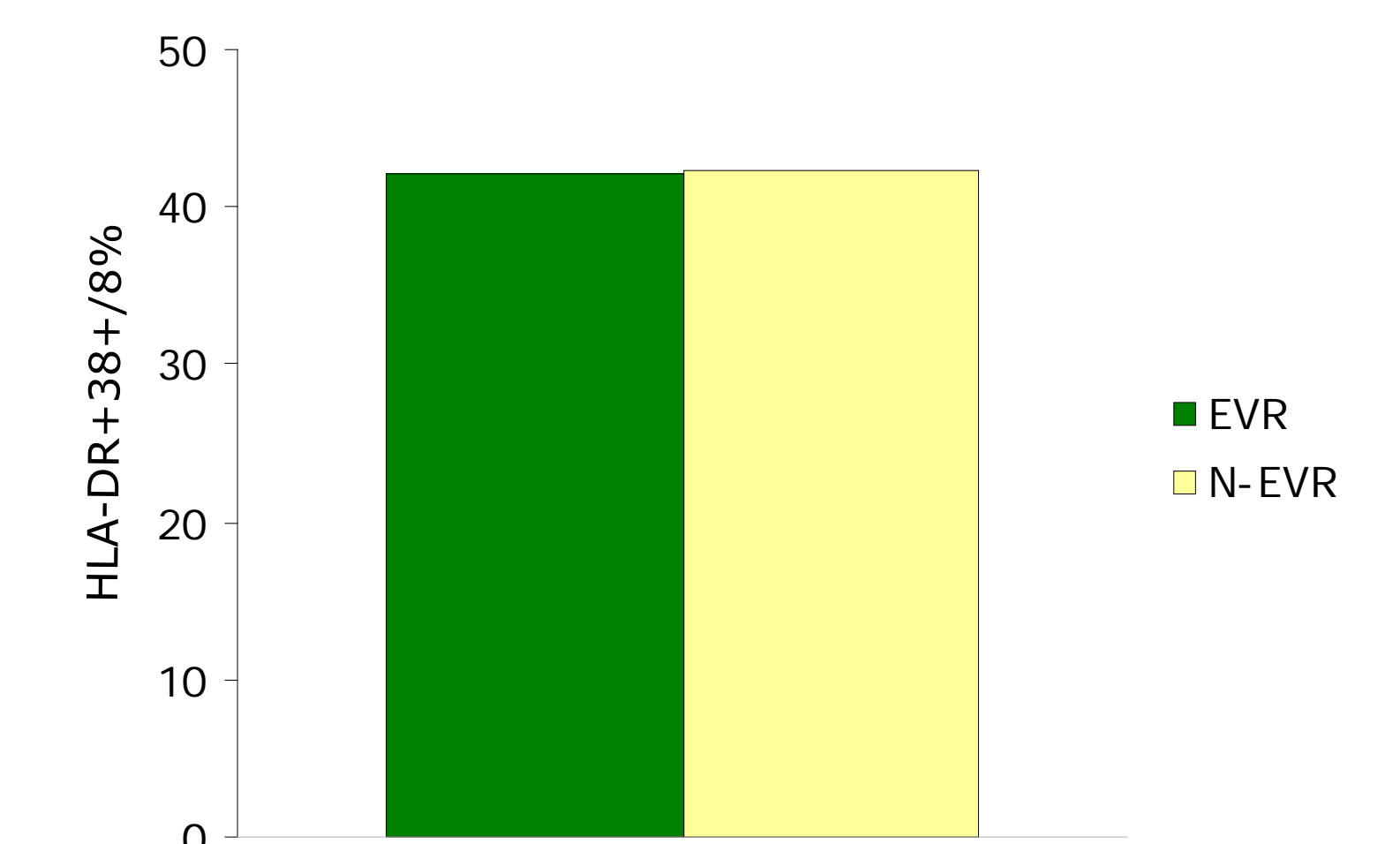
**Figure 3. Plasma sCD14 correlated with HCV genotypes 1 and 4**



**Figure 4. Plasma sCD14 correlated with Advanced fibrosis (AF).**



**Figure 5. No differences in CD8+ T lymphocyte activation are shown between patients with and without early virological response to anti HCV treatment.**



## Conclusions

- HIV/HCV coinfecting patients lacking early response to HCV therapy display heightened levels of microbial translocation.
- Parameters of microbial translocation are associated to negative clinical and virological prognostic markers of HCV disease.
- By supporting HIV-related microbial translocation as a pathway of accelerated liver disease, our data also allow to speculate for microbial translocation as adjunctive early biomarker of HCV disease progression and treatment outcome.