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Hepatitis C/HIV-1-co-infection in Long-term Non-progressors

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ABSTRACT (I)

Background: There has been described that LTNP HIV-1-infected patients have better *in vitro* responses against Hepatitis C virus (HCV), which could lead to a better evolution of the hepatitis C. On the other hand, HCV and its treatment (interferon plus ribavirin) could influence evolution of HIV-1 infection in LTNP.

Methods: A case-control (1:2) study comparing coinfecting LTNP (n=22) vs coinfecting HAART treated normal progressors (NP) (matched by sex, age and HCV genotype) (n=44) was performed. The variables analysed were signs of hepatopathy (clinical status, AST, ALT, GGT, alkaline phosphatase, albumin, bilirubin, platelet count, liver structure and presence of splenomegaly in ultrasound examination, inflammation and fibrosis in liver biopsy), response to HCV treatment, HIV viral load (VL) and lymphocytes T subsets. A cohort of LTNP with (n=28) vs without HCV infection (n=7) was also compared to assess the influence of HCV on HIV-1 infection.

ABSTRACT (II)

Results: Liver enzymes (AST, ALT and GGT) were lower in the LTNP group than in NP ($p < 0,05$). There were no statistically significant differences between LTNP and NP in clinical signs of chronic liver disease at physical examination (60 vs 67%, $p = 0,67$), echostructure (normal in 66 vs 51,85%, $p = 0,76$) or degree of inflammation in liver biopsy $> 3/6$ in 42,8 vs 42,3%. The fibrosis score in live biopsy was lower in LTNP than NP $> 2/4$ in 14,28 vs 48,14%, $p = 0,10$). There were no differences in the response to HCV treatment between groups (57,1% vs 50% of viral sustained response). However, LTNP presented proportionally a higher drop of CD4 during HCV treatment, that was sustained after two years of discontinuing it [-229, 4, and -61 cells/mm³ HCV-treated LTNP (n=7), NP (n=44) and non-HCV-treated LTNP (n=15), respectively, $p < 0,05$]. 2/7 of the LTNP of our cohort needed HAART after HCV treatment because of immunological HIV disease progression. There were no statistically significant differences in CD4⁺/CD8⁺ T cells, and plasma HIV-1 RNA VL when LTNP HCV(+) were compared with LTNP HCV(-).

Conclusions: LTNP do not seem to have a better evolution or response to HCV treatment than NP. However, HCV treatment, but not HCV infection, could have a deleterious effect on evolution of LTNP.

BACKGROUND (I)

- Due to shared risk factors for transmission, coinfection with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) is very common¹.
- Complexes interactions exist between HIV and HCV:
 - Patients HIV-HCV-coinfecteds suffer from accelerated progression of chronic hepatitis².
 - Some studies suggest that HCV infection may also negatively influence the course of HIV disease³⁻⁵.
- Little is known about HIV-HCV coinfection performance in coinfecteds Long-term Non-progressors (LTNP).

BACKGROUND (II)

- There has been described that LTNP HIV-1-infected patients have better in vitro responses against Hepatitis C virus (HCV)^{6,7}.
- These responses could lead to a better evolution of the hepatitis C in LTNP patients.
- Otherwise, HCV and its treatment (interferon plus ribavirin) could influence evolution of HIV-1 infection in LTNP patients.

SUBJECTS AND METHODS (I)

STUDY DESIGN AND SUBJECTS: In order to evaluate the interaction between HCV-HIV-co-infection in LTNP patients (coinfected LTNP), three different strategies were performed:

- To evaluate if being LTNP determine a better hepatitis C evolution in coinfecting HIV patients, a retrospective case-control (1:2) study comparing coinfecting LTNP (n=22) and coinfecting normal progressors (NP) (n=44) was made. Patients were matched by sex, age and HCV genotype.

SUBJECTS AND METHODS (II)

- To evaluate differences in response to HCV treatment, co-infected LTNP (n=7) and NP (n=44) that had received HCV treatment were compared. Additional comparison with coinfecting LTNP (n=15) that did not have received HCV treatment was made.
- To evaluate if HCV infection influence LTNP evolution, a study comparing LTNP with (n=28) and without HCV infection (n=7) was also assessed.

SUBJECTS AND METHODS (III)

METHODS: All patients were obtained from the HIV cohort from a single centre (Hospital Clínic of Barcelona). Analysis of data was made retrospectively based on clinical history chart revision.

Variables analysed were:

- Signs of liver disease:
 - Clinical signs at physical examination (hepatomegaly and splenomegaly).
 - Blood test data: AST, ALT, GGT, alkaline phosphatase, albumin, bilirubin, platelet count.
 - Ultrasonographic data: Liver structure and presence of splenomegaly.
 - Histological data (from liver biopsy): Inflammation and fibrosis degree.

SUBJECTS AND METHODS (IV)

- Response to HCV treatment.
- Plasma HIV-1 RNA viral load (PVL),
- Lymphocytes T subsets.

STATISTICAL ANALYSIS: A SPSS 10.0 software was used. There analysis between groups was done either with t test, ANOVA or Mann-Whitney test when necessary. To compare into groups, we used either t test or Wilcoxon test.

RESULTS (I)

INFLUENCE OF LTNP STATUS IN HEPATITIS C EVOLUTION

GENERAL AND HIV RELATED VARIABLES

- Epidemiological variables between compared groups were not different.
- LTNP group presented higher CD4 cell count, especially nadir CD4, and lower peak PVL. In the moment of analysis, as NP were under HAART, their CD4 cell count did have increased and their PVL did have reduced (**Table 1**).

RESULTS (II)

TABLE 1: Characteristics of HCV-HIV co-infected patients

	LTNP (n=22)	NP (n=44)	p
Age (years) (mean \pm SD)	41.1 \pm 5,2	40.9 \pm 4.7	0.8
Sex (men/women)	17/5	34/10	1
Injecting drug user	21	37	
Alcohol abuse	7	13	1
Duration of HIV infection (years) (mean \pm SD)	13.2 \pm 3.4	11.25 \pm 4.4	0.08
Duration of HCV infection (years) (mean \pm SD)	19.9 \pm 5.1	19.3 \pm 5.1	0.7
CD4 (cells/mm³)(mean \pm SD)	779.7 \pm 228.2	608.8 \pm 265.6	0.012
Nadir CD4 (cells/mm³)(mean \pm SD)	546.8 \pm 183.5	229.3 \pm 142.3	<0.001
Plasmatic viral load (copies RNA/mL)	3976 \pm 5221	762.6 \pm 3432	0.014
Peak viral load	10948 \pm 12596	182792 \pm 302248	<0.001

RESULTS (III)

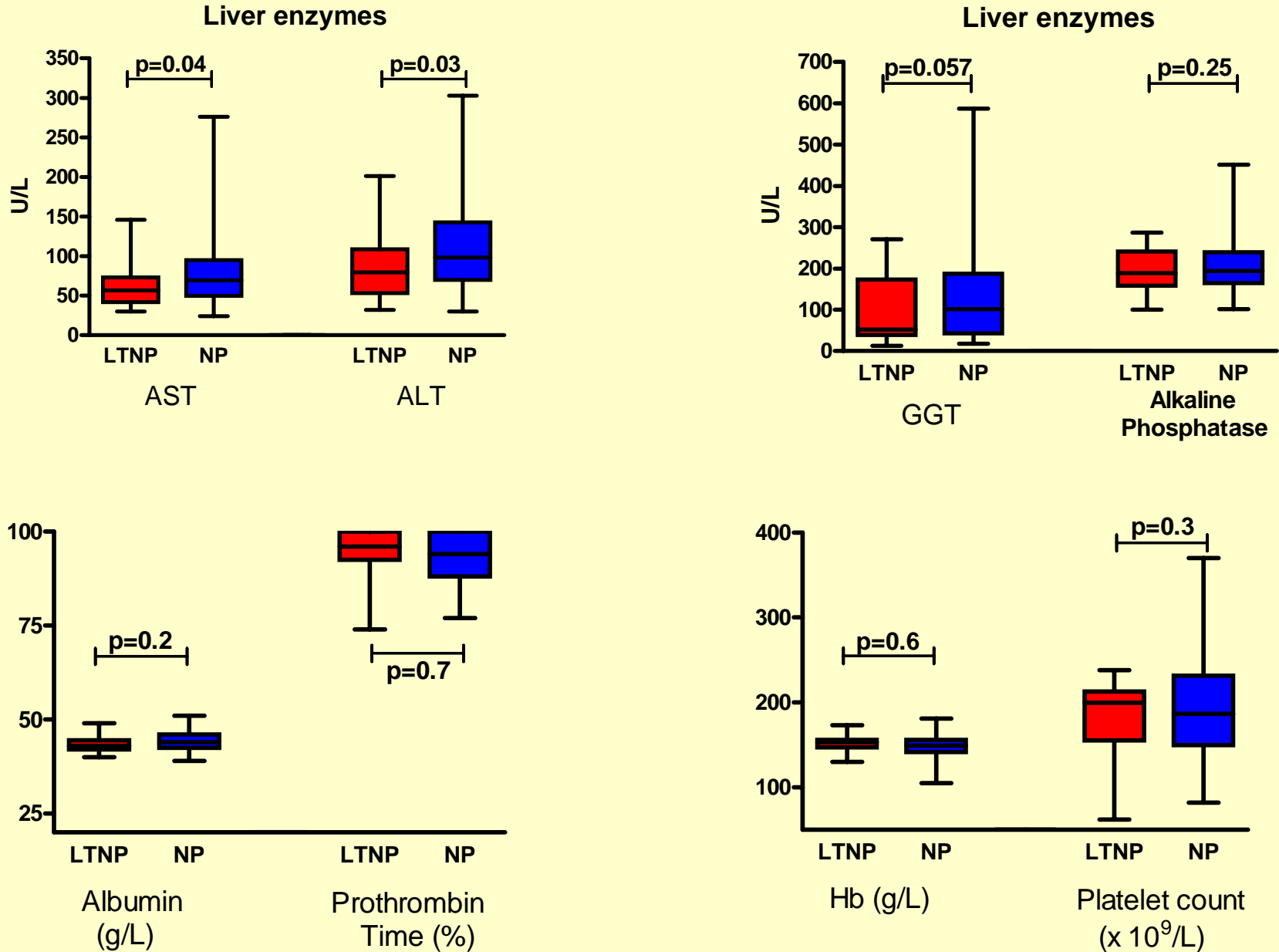
CLINICAL VARIABLES

- There were not clinical decompensations due to liver cirrhosis in any group.
- There were not statistical differences between clinical signs of hepatic disease at physical examination (60% vs 67%, $p=0.67$).

BLOOD TEST VARIABLES

- LTNP presented significantly lower alteration in liver enzymes. There were not differences in other biochemical or hematological data (**Figure 1**).

FIGURE 1: Blood test data

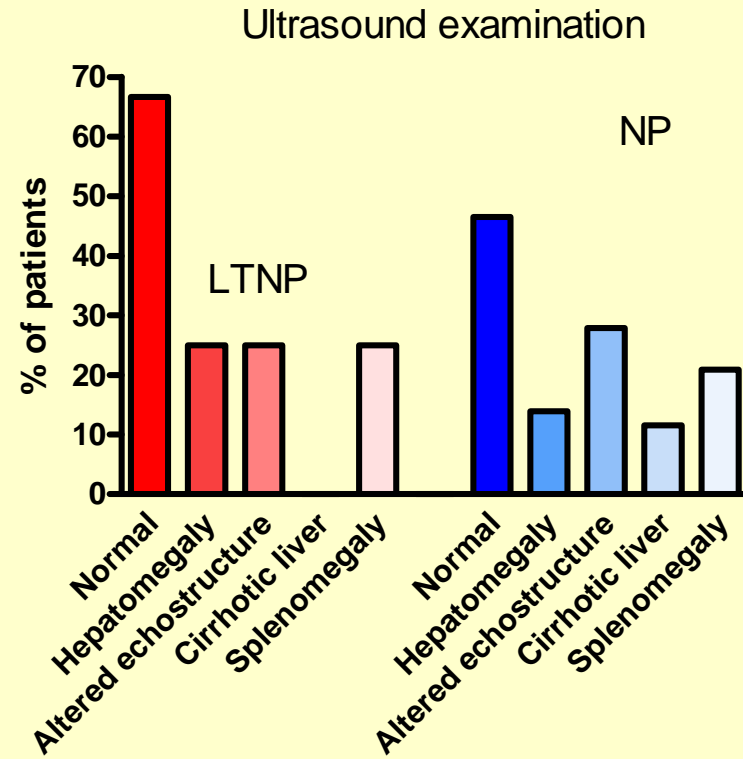
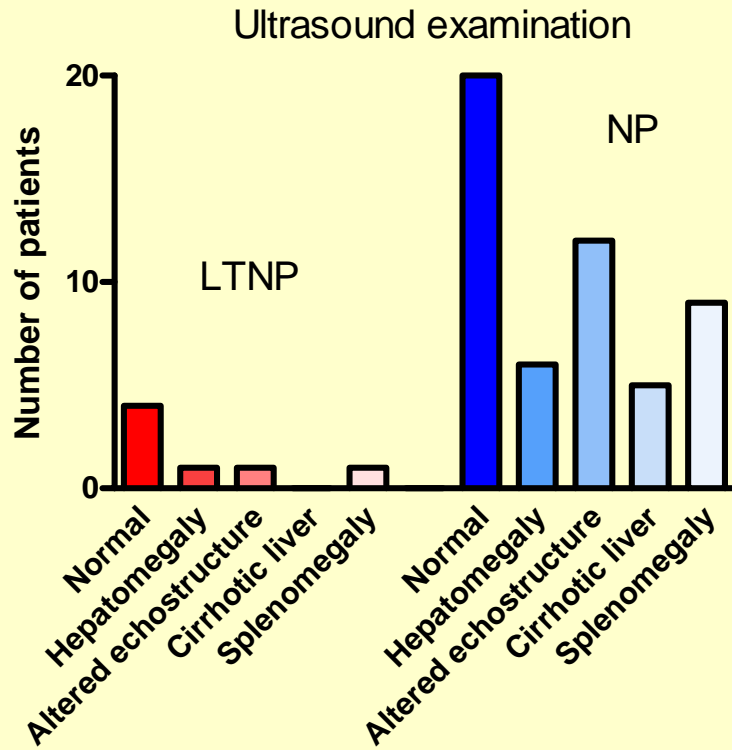


RESULTS (IV)

ULTRASONOGRAPHIC VARIABLES

- Ultrasonographic liver study could be recovered from 6/22 LTNP and 43/44 LTNP.
- There were not significant differences between liver evaluation by ultrasounds, although NP presented a higher number of cirrhotic livers and echostructure alteration ($p=1$, 0.41 and 1 for cirrhotic liver, abnormal ultrasound and presence of splenomegaly respectively) (**Figure 2**).

FIGURE 2: Ultrasonographic data

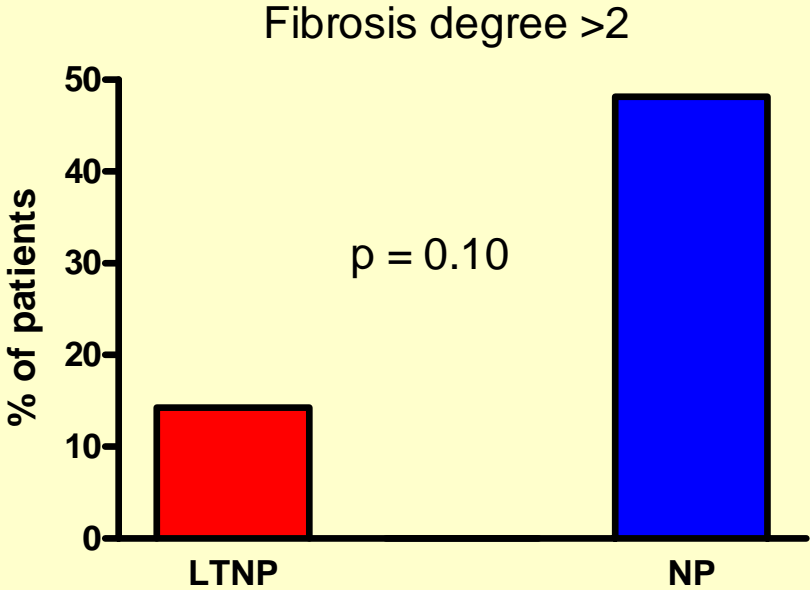
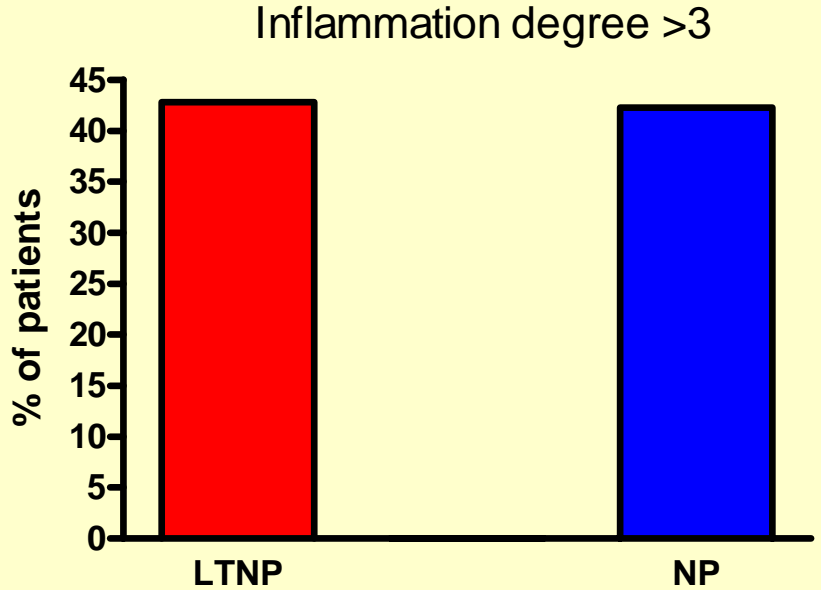
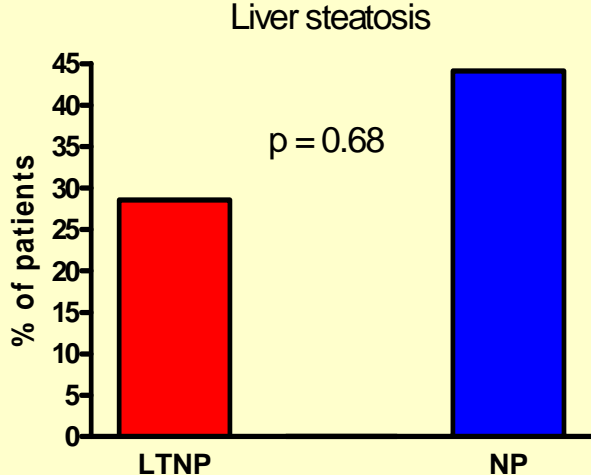
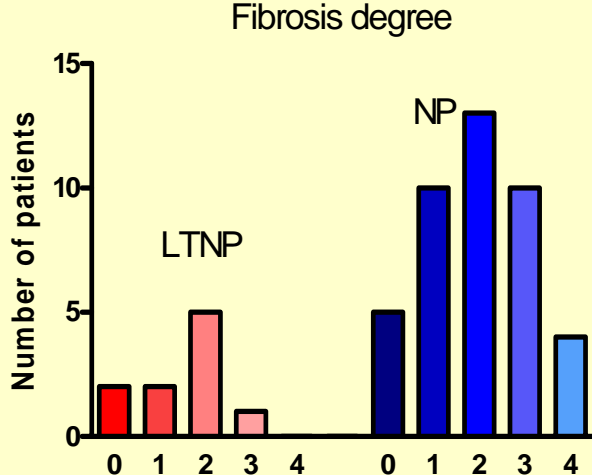
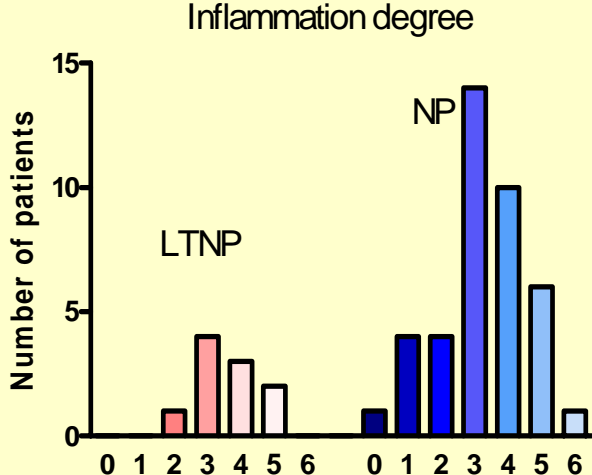


RESULTS (V)

HISTOLOGICAL VARIABLES

- Liver histology (obtained by biopsy) was available from 10/22 LTNP and 42/44 NP.
- Although the fibrosis score was lower in LTNP (14.28 vs 48.14% had $>2/4$ fibrosis score), differences were not significant ($p=0.10$) (**Figure 3**).
- There were not statistical differences neither in the inflammation degree nor in the presence of steatosis (**Figure 3**).

FIGURE 3: Histological data



RESULTS (VI)

RESPONSE TO TREATMENT

- There were no differences in the response to HCV treatment between groups (**Figure 4**).
- After HCV treatment all patients presented a CD4 drop. This drop was higher in LTNP, and differently from NP, did not recovered after two years of follow-up (**Figure 5**).
- After two years of follow-up co-infected LTNP HCV treated presented lower CD4 count than untreated co-infected LTNP (**Figure 5**).
- 2/7 LTNP needed to start HAART due to immunological impairment.

**FIGURE 4: Sustained viral response
(6 months) after HCV treatment**

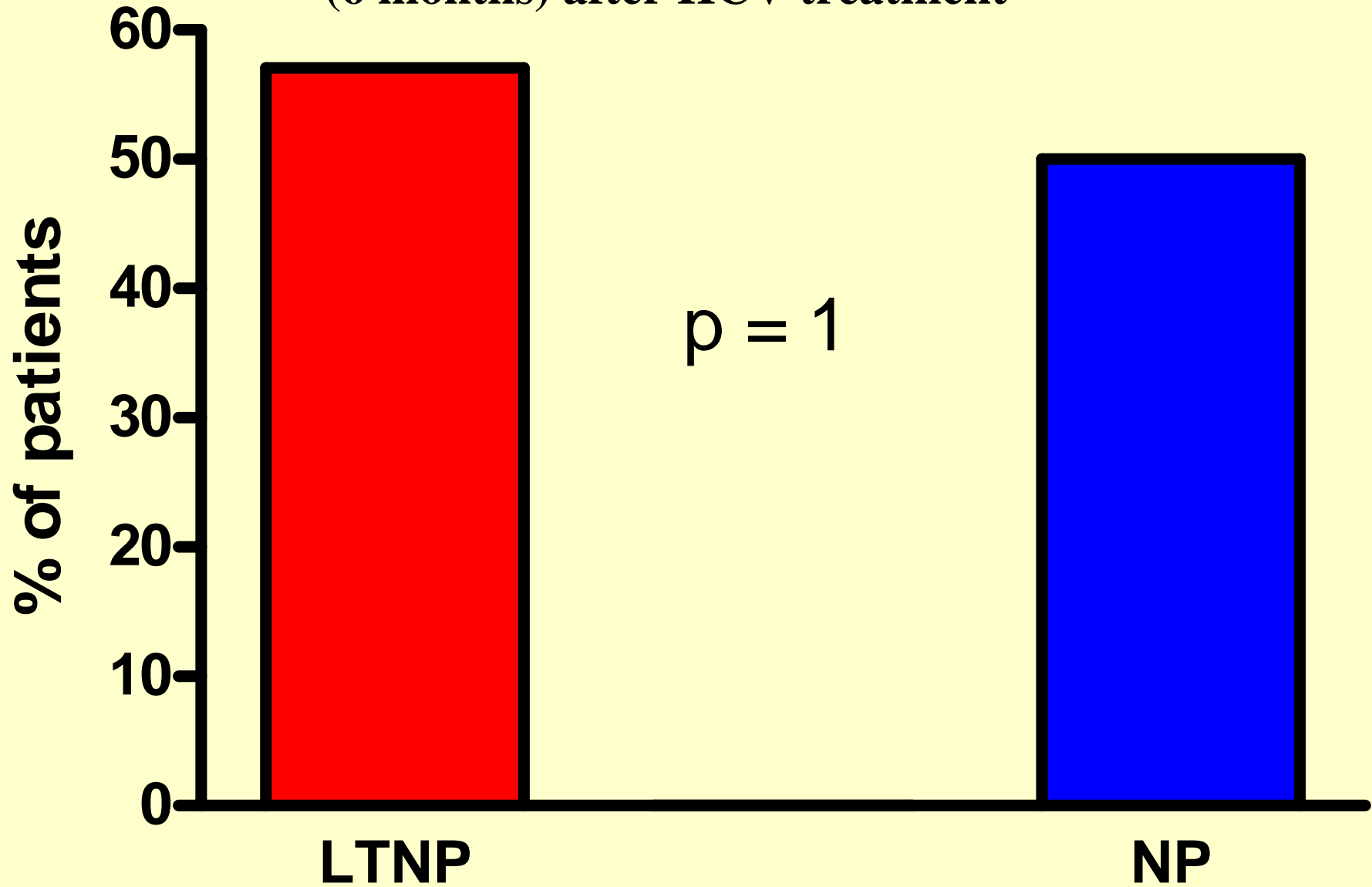
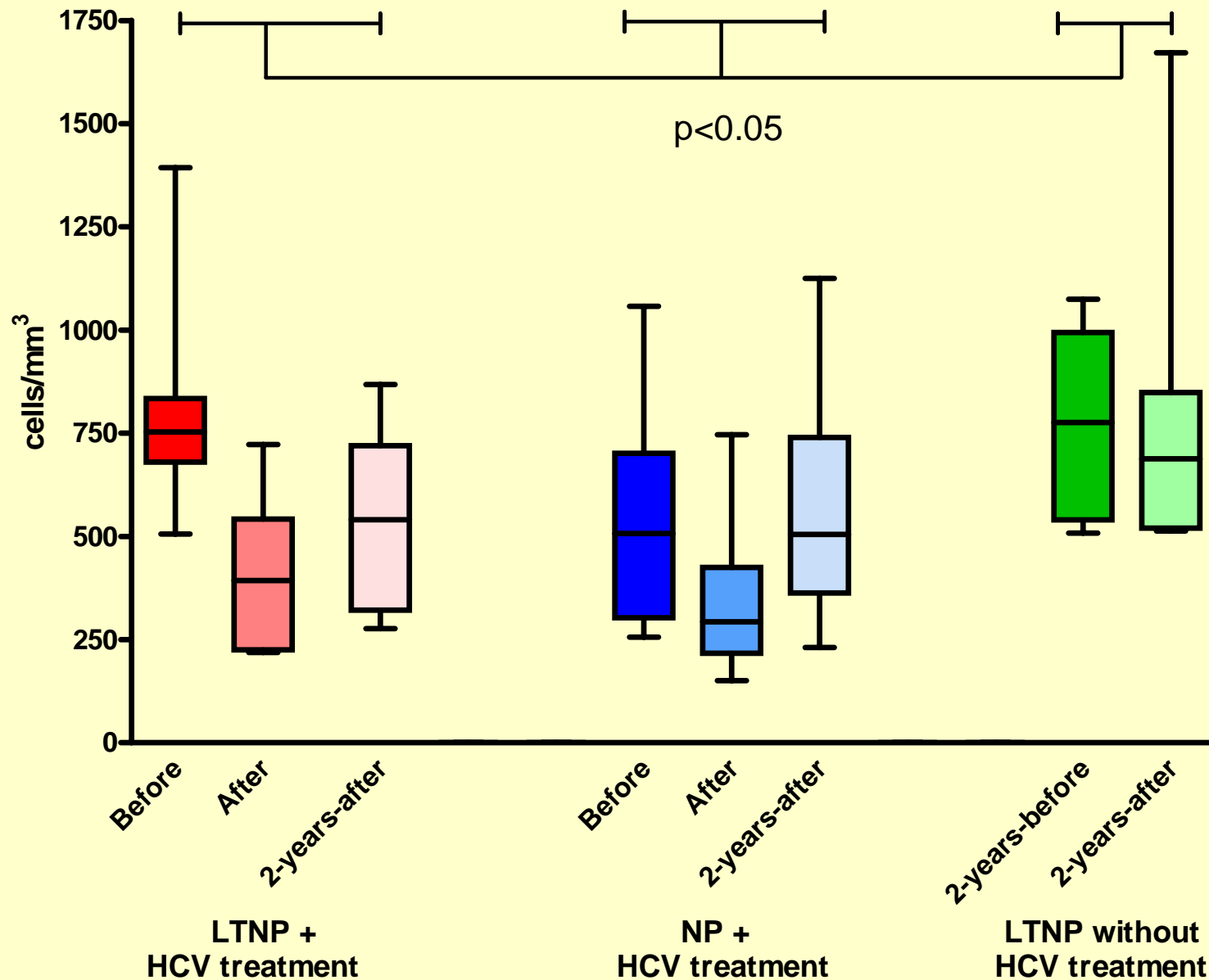


FIGURE 5: CD4 count evolution after HCV treatment



RESULTS (VII)

INFLUENCE OF HCV IN LTNP EVOLUTION

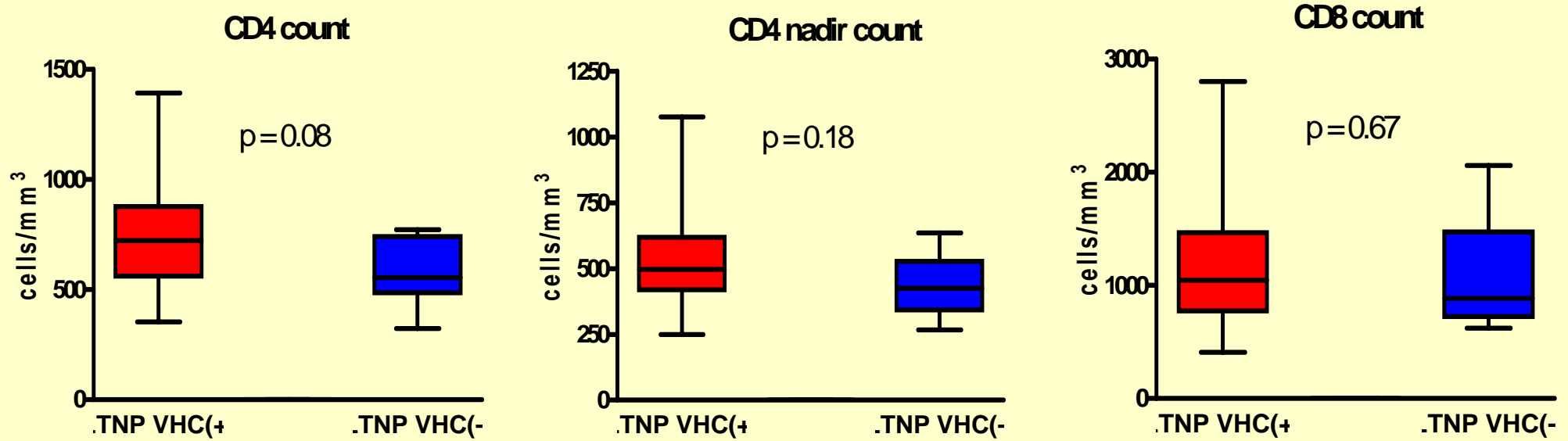
- 28 co-infected LTNP and 7 HIV-mono-infected LTNP were compared. Characteristics are exposed in **Table 3**.
- Co-infected LTNP were, differently from mono-infected, mostly injecting drug users, with a longer HIV evolution (**Table 3**).
- There were not statistically significant differences either in CD4, CD4 nadir or CD8 T cell count (**Figure 6**).

RESULTS (VIII)

TABLE 3: Characteristics of LTNP patients

	HIV-HCV-co-infected (n=28)	HIV-mono-infected (n=7)	p
Age (years) (mean \pm SD)	42.5 \pm 7.3	40.7 \pm 8.2	0.6
Sex (men/women)	20/8	5/2	1
Years since 1st HIV serology	13.7 \pm 3.8	11 \pm 1.8	0.013
HIV risk factor			
Injecting drug user	25	1	<0.001
CD4 (cells/mm³)(mean \pm SD)	758.7 \pm 245.7	579 \pm 154.1	0.08
Nadir CD4 (cells/mm³)(mean \pm SD)	526 \pm 178.8	444.28 \pm 124.51	0.18

FIGURE 6: CD4/CD8 count in mono- and co-infected LTNP



CONCLUSIONS

- LTNP do not seem to have a better evolution or response to HCV treatment than NP.
- However, HCV treatment, but not HCV infection, could have a deleterious effect on evolution of LTNP.

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