# Impact of the Use of Drugs and Substitution Treatments on the Antiviral Treatment of Chronic Hepatitis C: Analysis of Compliance, Virological Response and Quality of Life (CHEOBS)



Pascal Melin,¹ Jean-Philippe Lang,² Denis Ouzan,³ Michel Chousterman,⁴ Marina Varastet,⁵ Michel Rotily,⁵ Thierry Fontanges,⁶ Patrick Marcellin,ˀ Patrice Cacoub®

¹Hôpital Général, Saint Dizier, France; ²Centre Hospitalier Erstein, Erstein, Erstein, France; ¹Institut Arnaud Tzanck, Saint Laurent du Var, France; ¹Centre de l'Appareil Digestif, Bourgoin Jallieu, France; ¹Hôpital Beaujon, Clichy, France; ¹Hôpital Pitié-Salpêtrière, Paris, France

## Abstract

**Purpose:** CHEOBS is a French multicenter, prospective study that aimed to analyze the factors associated with the compliance with treatment by peginterferon alfa-2b and ribavirin in hepatitis C virus (HCV)-positive patients. The present analysis focuses on compliance with antiviral dual therapy, virologic response, and quality of life (SF-36) during treatment according to whether the patients were active drug users or under substitution treatment (ADU), ex-drug users (EDU), or non-drug users (NDU).

Methods: Between 2003 and 2006, 184 clinicians evaluated 2001 HCV-positive patients on day 0, every 3 months (M3, M6, M9, M12) during treatment, and 6 months after the end of treatment. Among these 2001 patients, 141 were excluded from the analysis (prescription of an antiviral single-agent therapy; date of the end of treatment or virologic response unavailable). The studied population included 1860 patients, as follows: 244 ADU, 578 EDU, and 1038 NDU. Good compliance was defined by >80% of the dose and duration of the antiviral dual therapy prescribed. Sustained virologic response was defined by a negative PCR ≥12 weeks after the end of treatment.

Results: The patient profile of the EDU group was between those of the ADU and NDU groups for mean age, body mass index (BMI), fibrosis stages, percentage of patients with a high level of education, a level of debt difficult to manage, high consumption of alcohol, psychiatric disorders, or chronic diseases. Most of the patients (72.2%) were naive to any antiviral treatment but were more numerous (P < 0.001) in the ADU (82.3%) group than in the EDU (73.5%) or NDU (69.1%) group. The good compliance of patients with dual therapy was similar in all three groups: NDU, 49.4%; EDU, 48.6%; ADU, 52.2% (P = 0.7). The sustained virologic response rate did not differ in the ADU, EDU, and NDU groups: 57.8%, 50.9%, and 49.3%, respectively (P = 0.13). The quality of life of patients in the ADU group was less altered on the physical and psychological levels than in patients in the other groups.

**Conclusions:** The rate of sustained virologic response was similar in the active or substitution drug users and in the ex- or non-users. Excess consumption of alcohol, a precarious socioeconomic situation, and the psychiatric diseases observed in drug users in this study did not have a negative impact on the studied factors. On the contrary, young age, recent contamination, high prevalence of genotype 3 infection, lower BMI, less severe stage of fibrosis, and good compliance with treatment seem to have balanced the negative parameters. **Note:** Abstract has been updated since submission.

- The French Consensus Conference of February 2002 recommended treating patients infected with hepatitis C virus (HCV) with stable drug use<sup>1</sup>
- Key findings from the Hepacom Study, a 12-month, multicenter, observational prospective study of treatment-naive chronic hepatitis C patients treated in the French health care system, were<sup>2</sup>:
- Only one-third of patients with access to health care initiated antiviral treatment — Access to treatment was more difficult among these patient populations:
- Women HIV-coinfected patients
- Drug users receiving substitution therapy
- Data from Hepacom revealed that health care access was still limited for drug users, suggesting that further study of this patient population was needed

- This analysis from the CHEOBS study compared the efficacy, tolerability, compliance, and effect on quality of life of pegylated interferon (PEG-IFN) alfa-2b (PegIntron®; Schering-Plough) + ribavirin (RBV) in 3 groups of patients with chronic hepatitis C
- Non-drug users (NDU)
- Ex-drug users (EDU)
- Active drug users or users undergoing substitution treatment (ADU)

# **Patients and Methods**

### **Patients**

- Patients aged 18 and older who had chronic hepatitis C and initiated treatment with PEG-IFN alfa-2b (1.5 µg/kg/wk) alone or in combination with RBV (800-1200 mg/d, depending on body weight) were eligible
- Patients were treatment naive or were nonresponders or relapsers to previous anti-HCV therapy

#### **Study Design**

- The CHEOBS study was a prospective, multicenter, observational study conducted between 2003 and 2006
- Patients were enrolled from 184 centers in France that specialize in the management of hepatitis C

#### Questionnaires

- Both the investigator and the patient completed questionnaires at baseline, approximately every 3 months during treatment, and 6 months after treatment cessation
- The investigator questionnaire collected the following information:
- Patient sociodemographic data
- History of HCV infection
- History of psychoactive drug use
- Hepatitis C therapy received before inclusion in the CHEOBS study
- Planned hepatitis C treatment
- Treatment modifications
- Virologic status of the patient 6 months after treatment cessation

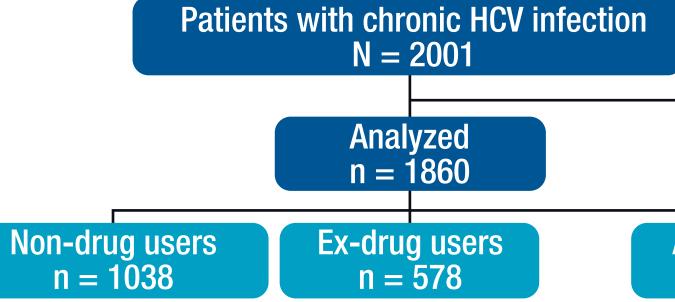
— Therapeutic education provided to the patient

- Patient self-questionnaires collected the following information:
- Quality-of-life assessment (SF-36 form)
- Compliance with PEG-IFN alfa-2b + RBV treatment

# Results

- This analysis includes 1860 patients who were classified as NDU, EDU, and ADU (including patients undergoing substitution therapy) (Figure 1)
- Of the 244 ADU, 72 patients were receiving methadone therapy and 137 were receiving buprenorphine

Figure 1. Patient flow diagram. HCV = hepatitis C virus.



Excluded: n = 141- Monotherapy (n = 37) - Date of cessation of combination therapy unknown (n = 79) - Virologic response unknown (n = 25)

Active drug users or substituted patients

n = 244

- Patient sociodemographics, comorbidities, and risk factors are shown in Table 1
- Hepatitis C disease characteristics for enrolled patients are shown in Table 2

#### **Table 1. Baseline Characteristics of Patients**

	NDU	EDU	ADU	D
	n = 1038	n = 578	n = 244	Р
Sociodemographics	n/n (%)	n/n (%)	n/n (%)	
Men	512/1035 (49)	428/578 (74)	198/243 (82)	<0.001
Age, y, mean ± SD	51.7 ± 12.6	41.7 ± 6.3	$37.5 \pm 6.2$	<0.001
BMI, kg/m², mean ± SD	25.3 ± 4.5	23.6 ± 4.2	$23.2 \pm 3.7$	<0.001
<b>Employment status</b>				<0.001
Professional activity	575/1035 (56)	385/578 (67)	138/244 (57)	
Unemployed	70/1035 (7)	114/578 (20)	88/244 (36)	
Other	390/1035 (38)	79/578 (14)	18/244 (7)	
Education level				<0.001
Low	570/1023 (56)	337/569 (59)	182/242 (75)	
High	453/1023 (44)	232/569 (41)	60/242 (25)	
Indebtedness				<0.001
Difficult to manage	30/832 (4)	42/471 (9)	28/206 (14)	
None or easy to manage	802/832 (96)	429/471 (91)	178/206 (86)	
Comorbidities				
Psychiatric history				
Depression	183/1036 (18)	175/578 (30)	95/242 (39)	<0.001
Suicide attempt	31/1032 (3)	48/577 (8)	45/241 (19)	<0.001
Hospitalization for mental illness	46/1031 (5)	63/575 (11)	47/242 (19)	<0.001
Psychiatric illnesses	168/1023 (16)	138/576 (24)	97/240 (40)	<0.001
Other chronic illnesses	366/1020 (36)	95/571 (17)	30/239 (13)	<0.001
Risk factors				
Alcohol consumption, >20 g/d	23/169 (14)	44/187 (24)	34/93 (37)	<0.001
Tobacco consumption	218/1021 (21)	424/569 (75)	217/242 (90)	<0.001

### Table 2. Hepatitis C Disease Characteristics and Etiology

<sup>a</sup>Or equivalent.

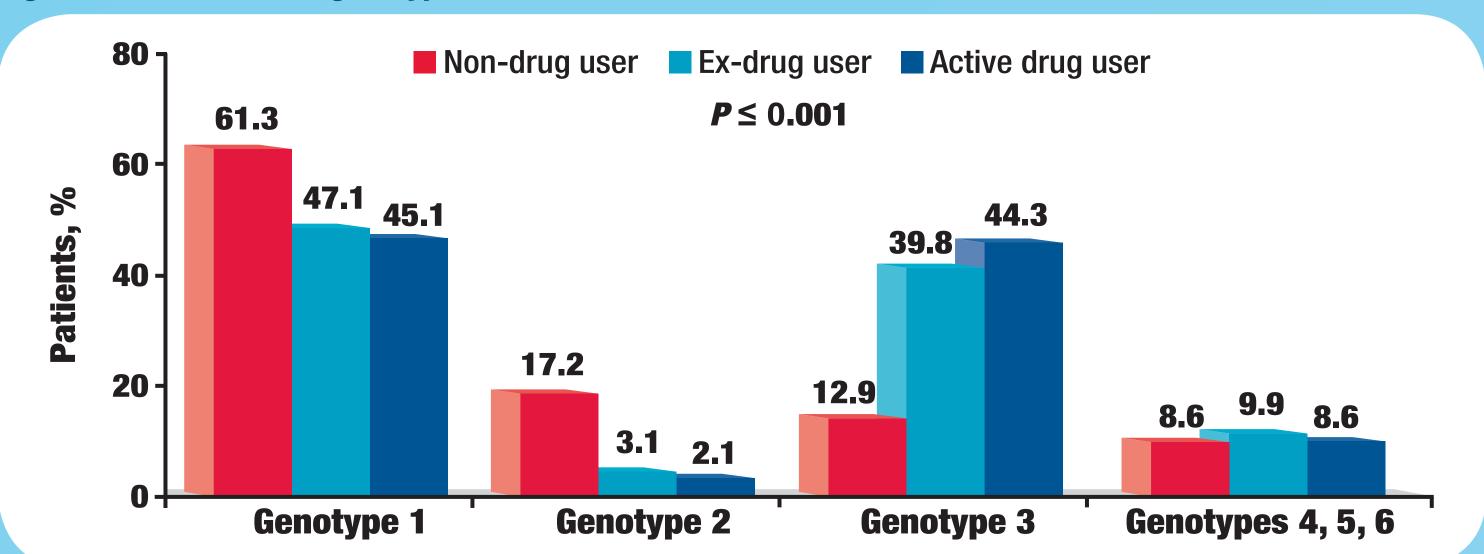
NDU       EDU       ADU $n = 1038$ $n = 578$ $n = 244$	P		
	n = 578	n = 244	
n/n (%)	n/n (%)	n/n (%)	
474/1019 (47)	19/578 (3)	3/244 (1)	<0.001
12/1019 (1)	546/578 (95)	234/244 (96)	<0.001
542/1019 (53)	28/578 (5)	9/244 (4)	<0.001
$23.5 \pm 9.7$	19.8 ± 7.6	15.0 ± 7.0	<0.001
			0.175
440/770 (57)	240/430 (56)	116/182 (64)	
330/770 (43)	190/430 (44)	66/182 (36)	
10/1034 (1)	38/578 (7)	15/242 (6)	0.001
6/1025 (1)	10/575 (2)	8/241 (3)	0.003
			0.040
408/891 (46)	241/489 (49)	74/192 (39)	
483/891 (54)	248/489 (51)	118/192 (62)	
			0.025
301/895 (34)	174/492 (35)	74/193 (38)	
439/895 (49)	250/492 (51)	103/193 (53)	
155/895 (17)	68/492 (14)	16/193 (8)	
	n/n (%) 474/1019 (47) 12/1019 (1) 542/1019 (53) 23.5 ± 9.7  440/770 (57) 330/770 (43) 10/1034 (1) 6/1025 (1)  408/891 (46) 483/891 (54)  301/895 (34) 439/895 (49)	n = 1038 n/n (%) 19/578 (3) 12/1019 (1) 546/578 (95) 542/1019 (53) 28/578 (5) 23.5 ± 9.7 19.8 ± 7.6  440/770 (57) 240/430 (56) 330/770 (43) 190/430 (44) 10/1034 (1) 38/578 (7) 6/1025 (1) 10/575 (2)  408/891 (46) 241/489 (49) 483/891 (54) 248/489 (51)  301/895 (34) 174/492 (35) 439/895 (49) 250/492 (51)	n = 1038       n = 578       n = 244         n/n (%)       n/n (%)       n/n (%)         474/1019 (47)       19/578 (3)       3/244 (1)         12/1019 (1)       546/578 (95)       234/244 (96)         542/1019 (53)       28/578 (5)       9/244 (4)         23.5 ± 9.7       19.8 ± 7.6       15.0 ± 7.0         440/770 (57)       240/430 (56)       116/182 (64)         330/770 (43)       190/430 (44)       66/182 (36)         10/1034 (1)       38/578 (7)       15/242 (6)         6/1025 (1)       10/575 (2)       8/241 (3)         408/891 (46)       241/489 (49)       74/192 (39)         483/891 (54)       248/489 (51)       118/192 (62)         301/895 (34)       174/492 (35)       74/193 (38)         439/895 (49)       250/492 (51)       103/193 (53)

ADU = active drug user or user undergoing substitution treatment; BMI = body mass index; EDU = ex-drug user; NDU = non-drug user.

 Among NDU, most patients had genotype 1 or 2 infection Figure 2. Distribution of genotypes.

— The proportions of patients with genotype 3 infection were higher among EDU and ADU than among NDU

• The distribution of genotypes was significantly different across the 3 patient groups ( $P \le 0.001$ ; Figure 2)



### **Treatment Dosing, Duration, and Adherence**

- There was significant heterogeneity across the patient groups in terms of duration of treatment and dosing of PEG-IFN alfa-2b ( $P \le 0.001$ ; Table 3)
- Mean duration of therapy was longer in NDU than in EDU or ADU
- Mean PEG-IFN alfa-2b doses were higher in ADU than in NDU or EDU

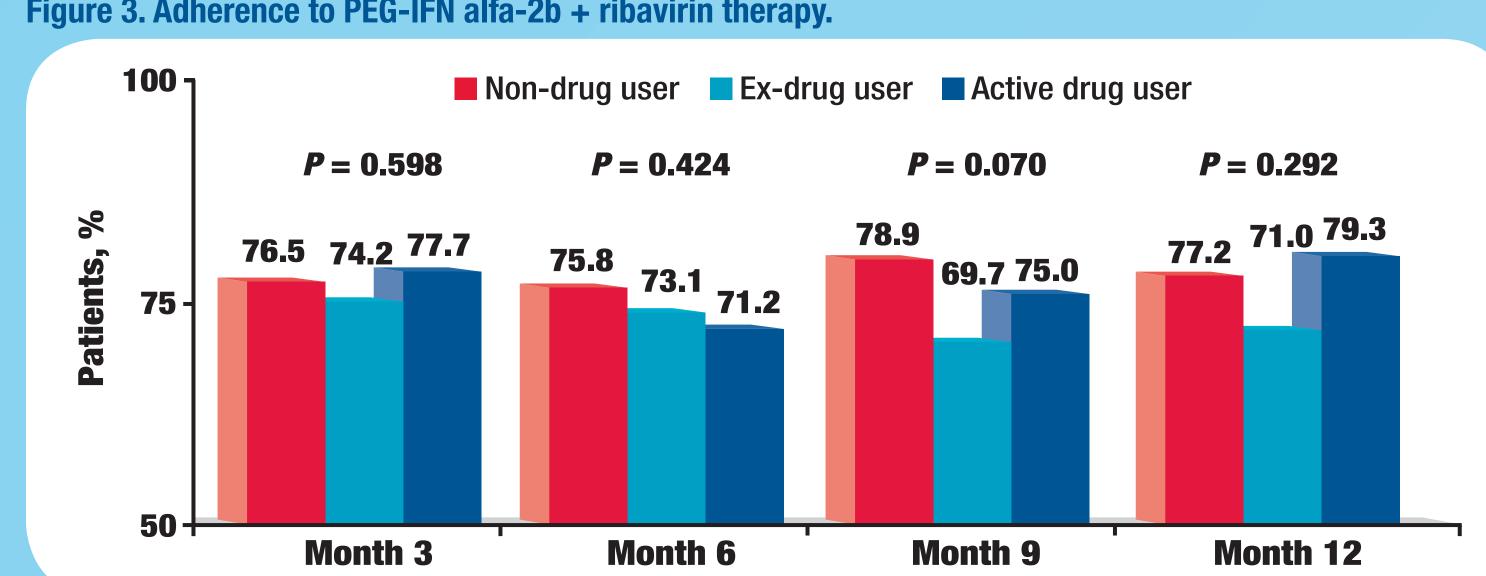
#### **Table 3. Investigator-Reported Dose and Duration**

NDU n = 1038	EDU n = 578	ADU n = 244	P
315/1038 (30)	169/578 (29)	79/244 (32)	0.653
604/1038 (58)	325/578 (56)	160/244 (66)	0.041
1.32 ± 0.29	$1.35 \pm 0.27$	$1.40 \pm 0.21$	0.001
890 ± 182	905 ± 155	904 ± 148	0.287
$1.3 \pm 0.32$	$1.33 \pm 0.3$	$1.40 \pm 0.23$	<0.001
879 ± 204	897 ± 171	896 ± 163	0.285
	$37.4 \pm 17.6$ $315/1038 (30)$ $604/1038 (58)$ $1.32 \pm 0.29$ $890 \pm 182$ $1.3 \pm 0.32$	$37.4 \pm 17.6$ $35.0 \pm 16.2$ $315/1038$ (30) $169/578$ (29) $604/1038$ (58) $325/578$ (56) $1.32 \pm 0.29$ $1.35 \pm 0.27$ $890 \pm 182$ $905 \pm 155$ $1.3 \pm 0.32$ $1.33 \pm 0.3$	n = 1038n = 578n = 244 $37.4 \pm 17.6$ $35.0 \pm 16.2$ $33.0 \pm 16.6$ $315/1038$ (30) $169/578$ (29) $79/244$ (32) $604/1038$ (58) $325/578$ (56) $160/244$ (66) $1.32 \pm 0.29$ $1.35 \pm 0.27$ $1.40 \pm 0.21$ $890 \pm 182$ $905 \pm 155$ $904 \pm 148$ $1.3 \pm 0.32$ $1.33 \pm 0.3$ $1.40 \pm 0.23$

ADU = active drug user or user undergoing substitution treatment; EDU = ex-drug user; NDU = non-drug user. <sup>a</sup><40 weeks genotype 1 (G1), G4, G5, and G6 infection; <20 weeks for G2 and G3 infection.

 Adherence (>80% of the recommended dose of PEG-IFN alfa-2b and RBV for >80% of the recommended duration [according to genotype]) to therapy was similar in all patient groups (Figure 3)

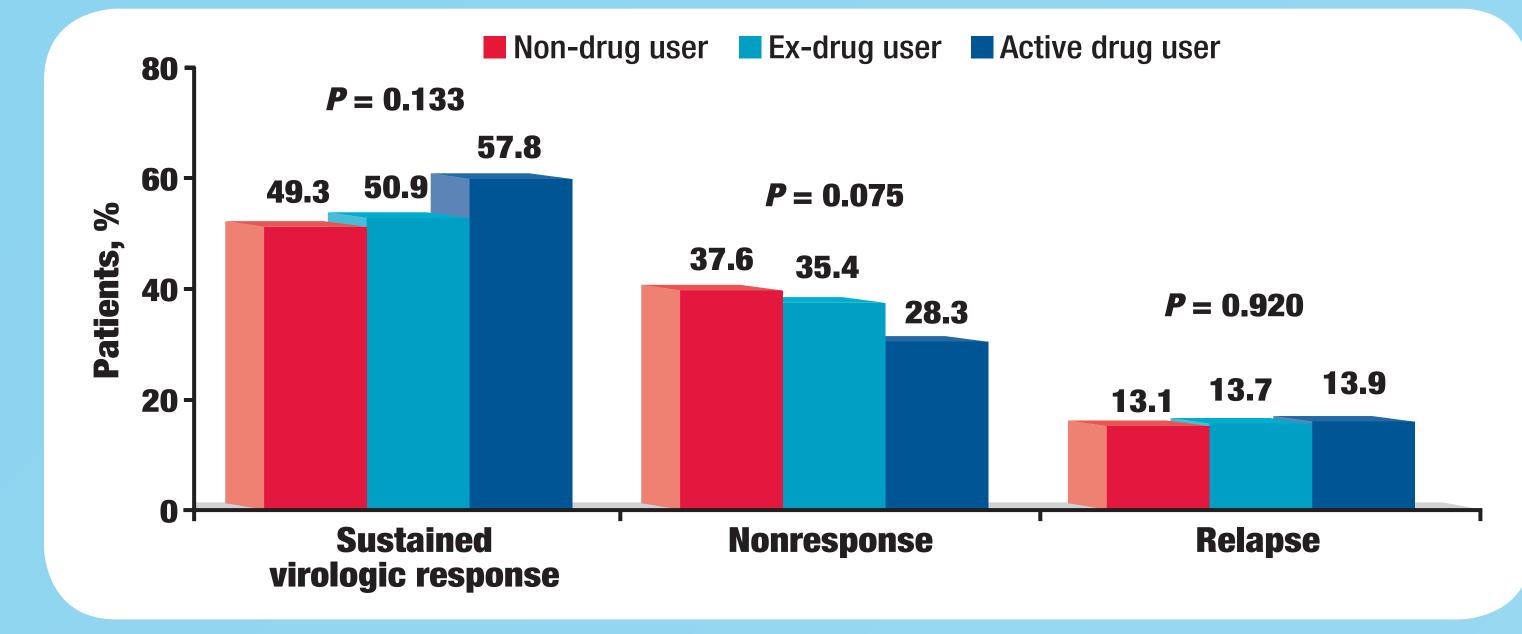
#### Figure 3. Adherence to PEG-IFN alfa-2b + ribavirin therapy.



#### Virologic Response

• Virologic response rates assessed at least 12 weeks after completion of therapy were not significantly different among patient groups (Figure 4)

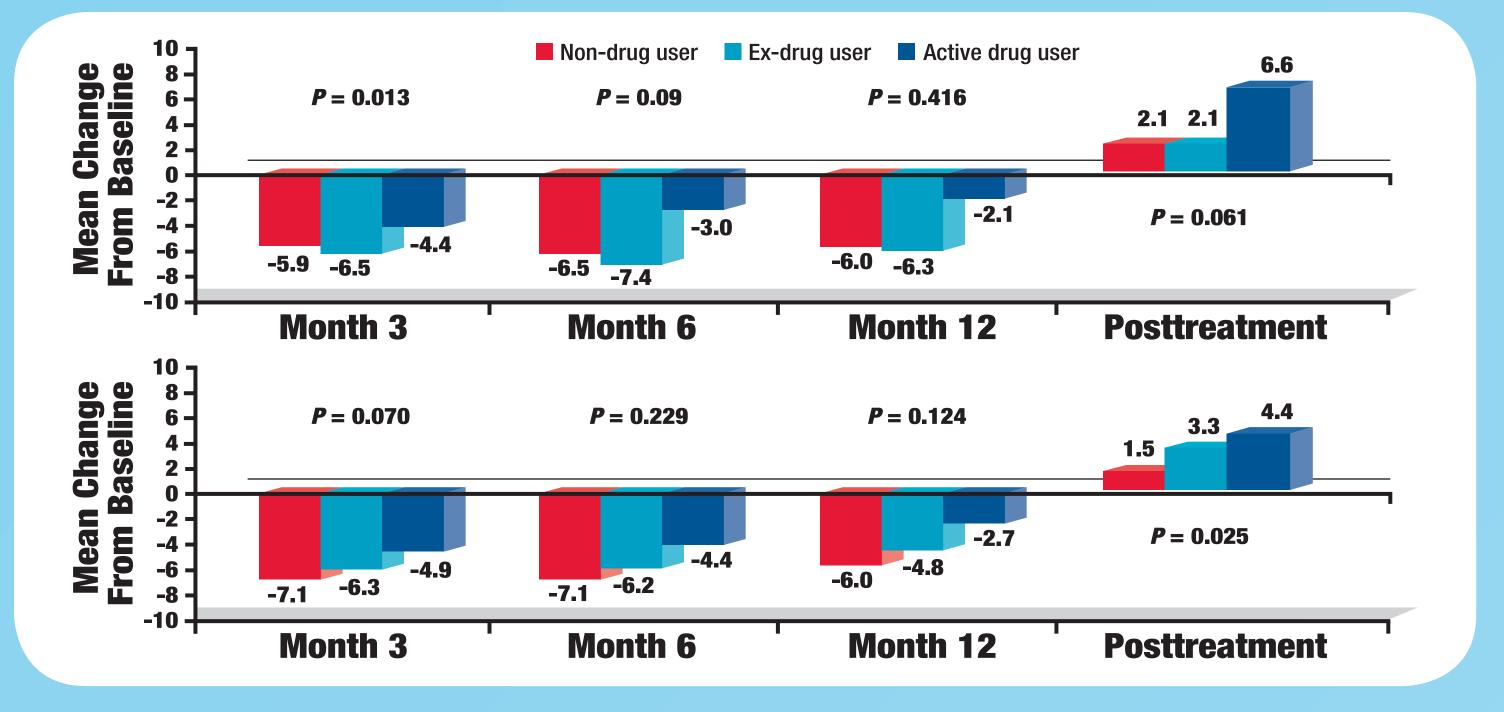
#### Figure 4. Virologic response rates at 12 weeks after end of treatment.



#### **Quality of Life**

Changes in quality-of-life scores throughout treatment are shown in Figure 5

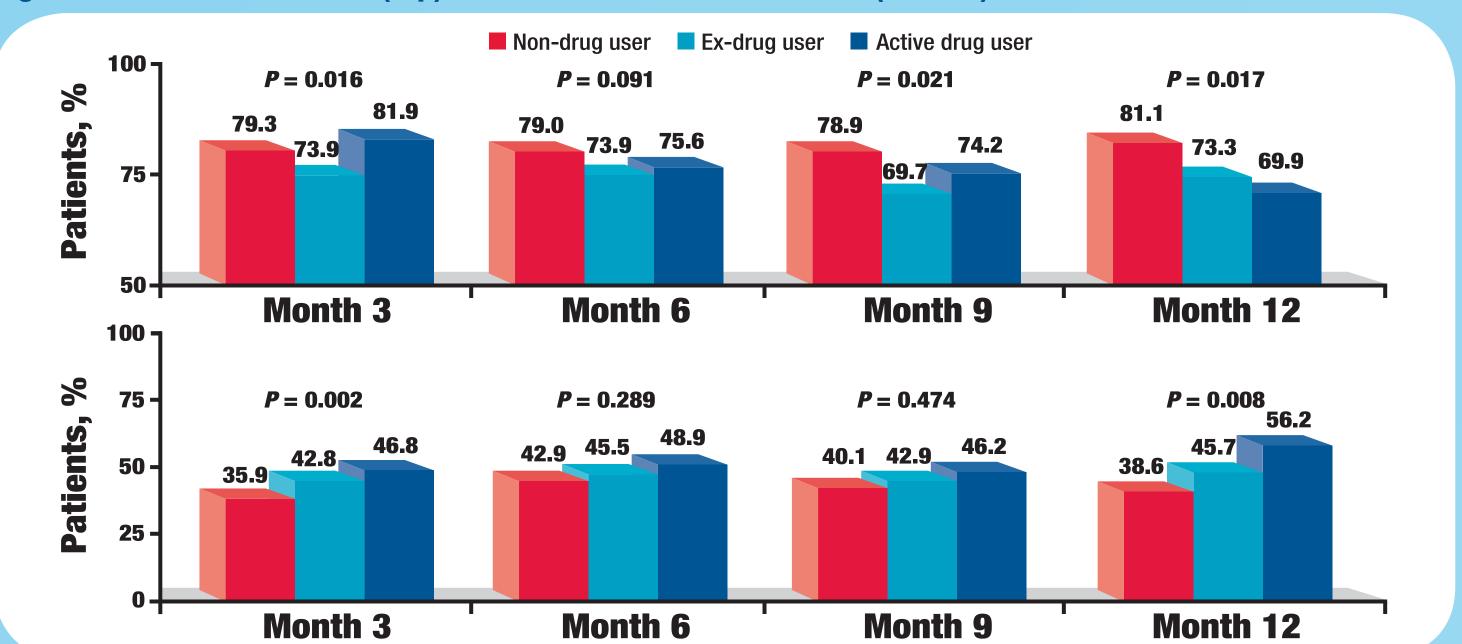
Figure 5. Quality of life (SF-36 form): mental (top) and physical (bottom) composite scores.



#### **Adverse Events**

- The incidence of adverse events is shown in Figure 6
- Mental adverse events were more common among ADU at month 3 and month 12 than among EDU and NDU

Figure 6. All adverse events (top) and all mental adverse events (bottom).



# Summary

- In this study, there was a predominance of genotype 3 infection among EDU and ADU
- Adherence to therapy and virologic response rates were similar in ADU, EDU, and NDU
- Mental adverse events were more frequent among ADU; however, combination therapy had a less negative impact on quality of life in these patients than in EDU or NDU

# Conclusions

- In this analysis, active drug use was frequently associated with excessive alcohol intake, vulnerable socioeconomic situation, and psychiatric illness
- However, active drug use did not have a negative impact on
- Adherence to PEG-IFN alfa-2b + RBV combination therapy
- Rate of premature discontinuation — Sustained virologic response rate
- It is possible that a predominance of favorable characteristics, such as young age, recent HCV infection, high prevalence of genotype 3 infection, low body mass index, and less advanced stage of fibrosis counterbalanced the potentially negative impact of the unfavorable parameters associated with active drug use

# References

1. Consensus Conference: Treatment of Hepatitis C; February 27-28, 2002; Paris, France. http://www.anaes.fr. Accessed October 6, 2008. 2. Agostini H et al. Gastroenterol Clin Biol. 2007;31:1074-1080.

#### Disclosures

P. Melin, J.-P. Lang, D. Ouzan, M. Chousterman, M. Rotily, T. Fontanges, P. Marcellin, and P. Cacoub are consultants for Schering-Plough France. M. Varastet has nothing to disclose.

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