 doi:10.1111/j.1365-2893.2009.01223.x

Role of treatment for depressive symptoms in relieving the impact of fatigue in HIV–HCV co-infected patients: ANRS Co13 Hepavih, France, 2006–2008

L. Michel,[1,2,3] V. Villes,[4,5,6] F. Dabis,[7] B. Spire,[4,5,6] M. Winnock,[7] M.-A. Loko,[7] I. Poizot-Martin,[8] M. A. Valantin,[9,10] P. Bonnard,[11] D. Salmon-Céron,[2,12] M. P. Carrieri[4,5,6] and the ANRS Co13 HEPAVIH Study Group* [1]*INSERM U669, Paris, France;* [2]*Université Paris-Sud et Université Paris Descartes, UMR-S0669, Paris, France;* [3]*AP-HP, Hôpital Emile Roux, Centre de Traitement des Addictions, Limeil-Brévannes, France;* [4]*INSERM, U912 (SE4S), Marseille, France;* [5]*Université Aix Marseille, IRD, UMR-912, Marseille, France;* [6]*ORS PACA, Observatoire Régional de la Santé Provence Alpes Côte d'Azur, Marseille, France;* [7]*INSERM U897, ISPED, Université Victor Segalen, Bordeaux, France;* [8]*CHU Sainte Marguerite, Marseille, France;* [9]*CHU de la Pitié Salpétrière, Paris, France;* [10]*INSERM U943, Université Pierre et Marie Curie, Paris, France;* [11]*Hôpital Tenon, Paris, France and* [12]*Hôpital Cochin Port-Royal, Paris, France*

Received June 2009; accepted for publication September 2009

SUMMARY. Fatigue is a major component of quality of life (QOL) and is associated with depression in HIV–HCV co-infected individuals. We investigated whether treating depressive symptoms (DS) could mitigate the impact of fatigue on daily functioning in co-infected patients, even those at an advanced stage of disease. The analysis was conducted on enrolment data of 328 HIV–HCV co-infected patients recruited in the French nationwide ANRS CO 13 HEPAVIH cohort. Data collection was based on medical records and self-administered questionnaires which included items on socio-behavioural data, the fatigue impact scale (FIS) in three domains (cognitive, physical and social functioning), depressive symptoms (CES-D classification) and use of treatments for depressive symptoms (TDS). After multiple adjustment for gender and unemployment, CD4 cell count <200 per mm^3 was associated with a negative impact of fatigue on the physical functioning dimension ($P = 0.002$). A higher number of symptoms causing discomfort significantly predicted a higher impact of fatigue on all three dimensions ($P < 0.001$). This was also true for patients with DS receiving TDS when compared with those with no DS but receiving TDS. A significant decreasing linear trend ($P < 0.001$) of the impact of fatigue was found across the categories 'DS/TDS', 'DS/no TDS', 'no DS/TDS' and 'no DS/no TDS'. Despite limitations related to the cross-sectional nature of this study, our results suggest that routine screening and treatment for DS can reduce the impact of fatigue on the daily functioning of HIV–HCV co-infected patients and relieve the burden of their dual infection.

Keywords: ART, depression, fatigue, hepatitis C, quality of life.

INTRODUCTION

Fatigue is one of the most frequent symptoms in patients living with hepatitis C, its prevalence ranging from 50% to 67% [1–3]. It is functionally associated with depression and is a core symptom in the diagnosis of major depressive disorders. (Diagnostic and Statistical Manual of Mental Disorders, DSM-IV) [4]. Fatigue and depression are correlated in HIV-infected patients [5–8]. Moreover, fatigue has also been found to mediate the relationship between functional limitations and depression in HIV-infected men [9] and to be independently associated with poor health-related quality of life (HRQL) in HCV-infected patients [10,11].

While in HCV-only patients there is a correlation between fatigue and depression [2], in HIV–HCV co-infected patients, such a relationship may be more complex and consequently requires more thorough investigation. In co-infected individuals, fatigue can be influenced by additional factors arising from their exposure to multiple treatments [12] as well as by the specific psychosocial characteristics of this

Abbreviations: AD, antidepressant use; AIDS, acquired immune deficiency syndrome; ART, antiretroviral therapy; DS, depressive symptoms; DSM-IV, diagnostic and statistical manual of mental disorders revision 4; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HRQL, health-related quality of life; IQR, interquartile range; OST, opioid substitution treatment; RNA, ribonucleic acid.

Correspondence: Laurent Michel, AP-HP, Hôpital Emile Roux, Centre de Traitement des Addictions, 1 avenue de Verdun, 94456 Limeil-Brévannes, France. E-mail: laurent.michel@erx.aphp.fr
*See composition in Appendix.

population, mainly composed of drug users [13]. Furthermore, although fatigue is also a major component of quality of life in this population [13,14], it is still unclear to what extent it may be more attributable to psychosocial factors and co-occurring depression than to HIV or HCV disease [13,15] and whether treating depression may reduce the impact of fatigue on patient functioning.

The aim of this study was to assess to what extent depression and treating depressive symptoms (DS) can reduce the impact of fatigue on patient functioning once HIV and HCV clinical statuses as well as other psychosocial factors are taken into account.

MATERIAL AND METHODS

Study design

In 2006, a nationwide cohort, ANRS CO 13 Hepavih, recruiting HIV–HCV co-infected individuals was initiated in 17 outpatient hospital services delivering care to HIV–HCV co-infected individuals in France. Individuals enrolled had to be HIV antibody-positive and have chronic HCV infection confirmed by Western blot and plasma RNA assays. Patients who agreed to participate signed a letter of informed consent and were provided with self-administered questionnaires collecting socio-behavioural and psychosocial data at the baseline visit and at scheduled annual visits. Clinical and biological data, such as HIV plasma viral load, CD4 cell count and liver cirrhosis status were collected from a clinical research form, completed by medical staff in clinical centres. The study was approved by the institutional review board of Hôpital Cochin (Paris).

Questionnaire

The self-administered questionnaire included items on sociodemographic characteristics, treatment history and psychosocial data, including patient perceptions concerning the impact of fatigue on their daily life and self-reported side effects.

Patient perceptions of the functional impact of fatigue were evaluated using the fatigue impact scale (FIS) [16], a psychometric instrument designed to collect self-reports about the impact of fatigue on patient cognitive, physical and psychosocial functioning over the previous month. The FIS attributes domain scores for each of these three functioning types ranging from 0 to 40, except for psychosocial functioning which ranges from 0 to 80 (the total score ranging therefore from 0 to 160). Higher scores denote a higher perceived impact of fatigue (i.e. a more negative perceived impact on daily functioning). Patient DS were assessed using the Center for Epidemiological Studies Depression Questionnaire (CES-D) [17] which enables the computation of a global depression score ranging from 0 to 60, with gender-specific cut-off values (17 for women and 23 for men). Score values above the gender-specific cut-off point were taken as indicative of depression.

A questionnaire collected data about the occurrence of 39 treatment-related symptoms (defined here as self-reported side effects) over the previous 4 weeks and the discomfort they caused. This questionnaire, based on the Symptoms Distress Module proposed by Justice *et al.* [18], which lists symptoms known to occur during antiretroviral treatment (ART), was broadened to include questions on lipodystrophy symptoms (change in body shape, larger stomach, larger breasts, slimmer legs, slimmer arms, visible veins on the legs, hollow cheeks, slimmer buttocks, accumulation of fat in the neck).

Data about antidepressant medications were collected using a question asking the patient whether he/she was receiving antidepressants prescribed by a physician (a list of possible drugs was also provided). Although this questioning method is reliable (i.e. using a list) [19] and agreement between self-reports and prescriptions is high [20], the risk of misclassification with drugs for DS existed. For this reason, we preferred to label this variable based on self-reports as 'use of treatments for depressive symptoms' (TDS).

When comparing self-reports with data from medical records for patients for whom this information was available, the following antidepressants and treatments for DS were found: fluoxetine, venlafaxin, paroxetin, citalopram, escitalopram, mianserin, amitryptilin, olanzapin, bromazepam, alprazolam, oxazepam, diazepam and clorazepat.

Drug use was defined as reporting the use of at least one drug, including nonprescribed opioid substitution therapy or nonprescribed psychotropic drugs but excluding cannabis.

Statistical methods

Cirrhosis status was validated based on an algorithm considering liver biopsy, indirect clinical signs of cirrhosis (oesophageal varices, ascites, liver encephalopathy, digestive bleeding) as well as Fibroscan® [21] and Fibrotest® [22] results.

A combined variable classifying patients according to depressive symptoms and treatments for depressive symptoms (TDS) was constructed to evaluate whether the effectiveness of TDS could relieve the impact of fatigue on patient functioning. This variable classified patients according to the following categories: 'DS and TDS', 'DS and no TDS', 'no DS and TDS' and 'no DS and no TDS'. Patients with DS and TDS were considered as the reference category as they were likely to be those with the most severe depressive symptoms. A significant linear trend across the different categories was also tested.

A combined variable characterising individuals with severe immunodepression and liver cirrhosis was built to take into account the impact of the joint HIV–HCV co-morbidity on fatigue impact.

All analyses were performed on enrolment data. The three fatigue impact scores were used as multiple response variables in a MANOVA (multivariate analysis of variance) [23].

This analysis identifies factors associated with the three dimensions of fatigue while taking into account the inter-dimensional correlations. Variables were considered eligible for the multivariate model when their *P*-value based on *F*-test (Wilks' lambda) was lower than 0.25 for at least one dimension of the FIS. The final model was built using a backward procedure based on the least-squares method.

To obtain interpretable coefficients for the explanatory variables, three multiple linear regression models were computed, one for each dimension of fatigue, and were based on the pattern of variables identified by the MANOVA. Linear trends across the different categories of ordinal variables were also tested in these models.

Patients

Patients who were receiving HCV treatment had recovered after HCV treatment or who presented an AIDS-defining event were not included in this study to avoid any interference with fatigue. Among the 522 patients included, who were provided with the self-administered questionnaire, 328 (63%) had complete data for liver cirrhosis status, CD4, depression and fatigue.

No significant differences, except for age, were found between socio-demographic and clinical characteristics of patients with complete data (n = 328) compared with those with incomplete data (n = 194).

RESULTS

Median [IQR] age was 42 [40–46] years, men accounted for 70% of the study population, and the majority (n = 206, 64%) were HIV-infected through injecting drug use (IDU).

In this study sample, 86% of the patients had undetectable plasma HIV RNA, and median CD4 cell count per mm^3 was 444 [292–643]. Twenty-two percent of individuals had HCV genotype 2 or 3, while 78% had genotype 1 or 4.

Among the 328 patients selected for the analysis, 27% presented liver cirrhosis, and 12% had a low CD4 count (<200 per mm^3). Median [IQR] FIS scores were 9 [2–18] for cognitive impact of fatigue, 10 [4–21] for physical impact of fatigue and 17 [4–37] for social impact of fatigue.

At the enrolment visit, most patients were on ART (91%), 34 were being treated with efavirenz and 16 with nevirapine as nonnucleoside reverse transcriptase inhibitors (NNRTI). The most commonly prescribed protease inhibitors were ritonavir, atazanavir and lopinavir ± ritonavir. Forty-two patients (12.9) presented DS while receiving TDS, 89 (27.4) were classified as presenting DS and not receiving TDS, 21 (6.5%) had no DS but were receiving TDS, while 173 (53.2%) presented no DS and were not receiving TDS (Table 1).

Median [IQR] number of self-reported side effects and self-reported side effects causing discomfort were 7 [1–14] and 2 [0–8], respectively. Other characteristics of the 328 patients are presented in Table 1.

Table 1 Baseline characteristics of HIV–HCV co-infected patients of the HEPAVIH French Cohort enrolled in the analysis of fatigue (n = 328)

	n (%*) or Median [IQR]
Age (years)	42 [40–46]
Men	229 (69.8)
HIV transmission group	
Homosexual	42 (13.0)
IDU	206 (63.6)
Heterosexual	38 (11.7)
Others	38 (11.7)
Having child (or children)	104 (32.4)
Secondary school certificate	93 (30.5)
Employed	151 (47.3)
Living in a couple	147 (45.7)
Owner or tenant of their home	262 (80.4)
Comfortable housing conditions (as perceived by respondent)	264 (81.0)
Cognitive impact of fatigue†	9 [2–18]
Physical impact of fatigue†	10 [4–21]
Social impact of fatigue†	17 [4–37]
No depressive symptoms (DS) and no treatment for depressive symptoms (TDS)	173 (53.2)
No DS and TDS	21 (6.5)
DS and no TDS	89 (27.4)
DS and TDS	42 (12.9)
Drug use‡	37 (11.3)
Cannabis use§	150 (45.7)
Daily alcohol consumption¶	29 (9.0)
Number of self-reported side effects	7 [1–14]
Number of self-reported side effects causing discomfort	2 [0–8]
CD4 cell count per mm^3	444 [292–643]
Nadir CD4 per mm^3	153 [69–244]
Undetectable HIV viral load	277 (85.5)
Liver cirrhosis**	90 (27.4)
ASAT (UI/l)	50 [36–73]
ALAT (UI/l)	59 [36–88]
Receiving Efavirenz	34 (11.2)

Univariate analyses (Table 2) show that female gender, unemployment, lack of children, uncomfortable housing conditions and not living in a couple were factors significantly associated with a higher impact of fatigue on patient cognitive, physical and social functioning. While a history of drug injection receiving opioid substitution treatment (OST) and cannabis use were associated with a negative impact of fatigue on all three dimensions, cocaine use and ongoing drug use had a negative impact only on the social dimension of fatigue.

An increasing number of self-reported side effects and of self-reported side effects causing discomfort significantly

Table 1 (Continued)

	n (%*) or Median [IQR]
ART (*n* = 304)	
IP + NRTI	207 (68.1)
IP + no NRTI	16 (5.3)
No IP + NNRTI	39 (12.8)
No IP + no NNRTI	42 [13.8]

IP, protease inhibitors; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, nonnucleoside reverse transcriptase inhibitors. *Percentage calculated on available data. †See definition in methods section. ‡Use of at least one drug (including nonprescribed substitution treatment or nonprescribed psychotropic drugs; cannabis was excluded from this computation) during the previous 4 weeks. §At least once in the previous 4 weeks. ¶During the previous 6 months. **Cirrhosis status was defined using an algorithm considering liver biopsy, indirect clinical signs of cirrhosis (oesophageal varices, ascites, liver encephalopathy, digestive bleeding) as well as Fibroscan® and Fibrotest®.

augmented the impact of fatigue on cognitive, physical and social functioning. Receiving efavirenz was negatively associated with the three dimensions of the impact of fatigue.

The combined variable 'depressive symptoms and treatments for depressive symptoms (TDS)' was significantly associated with the cognitive, physical and social dimensions of fatigue impact. When the group of patients with DS receiving TDS was considered as the reference category, a significant decreasing linear trend of the impact of fatigue on the three dimensions was found across the categories 'DS/TDS', 'DS/no TDS', 'no DS/TDS' and 'no DS/no TDS' (Fig. 1, Table 3).

Among clinical characteristics, individuals with CD4 < 200 cells/mm^3 were more likely to report a higher impact of fatigue on the three dimensions, while those with liver cirrhosis mainly experienced a negative impact of fatigue on physical functioning.

After multiple adjustments (Table 3), female gender, unemployment, receiving efavirenz and the number of self-reported symptoms causing discomfort remained associated with all three dimensions of fatigue. Patients with a lower CD4 cell per mm^3 exhibited a higher impact of fatigue on physical functioning.

In addition, individuals with DS and receiving TDS (a proxy of severe depression) presented a significant higher impact of fatigue on cognitive, physical and social functioning. Interestingly, when using a multiple linear regression for each dimension of fatigue, the significant linear relationship across the categories 'DS/TDS', 'DS/no TDS', 'no DS/TDS' and 'no DS/no TDS' was confirmed on the three dimensions ($P < 0.001$).

DISCUSSION

The present study clearly shows that the impact of fatigue on daily functioning in HIV–HCV co-infected individuals is determined by two dimensions. The first, psychosocial and demographic, is expressed by the number of discomforting side effects, employment status and gender (women). The second is clinical and is related to the severity of HIV disease, choice of ART, depression and its management.

Interestingly, patients successfully treated for their depression exhibited similar levels of fatigue impact to those with no DS and not taking TDS.

To our knowledge, this is the first time a study has clearly shown that successful treatment for depression may act on fatigue by reducing its negative impact on cognitive, physical and social functioning of HIV–HCV co-infected patients.

Previous studies have already underlined the extent to which depressed HIV-infected patients remain excluded from antidepressant medications [24].

Furthermore, HIV-infected patients with a history of depression have unfortunately been shown to face significant and lengthy delays before accessing HIV treatment [25].

Depressive symptoms have been found to be associated with HIV disease progression, even after controlling for adherence and socio-demographic characteristics [26,27]. In a US-based large cohort study, continuous ART use and lack of depression were the strongest predictors of favourable outcomes [28].

Depressive symptoms, although common in chronic hepatitis C before treatment [29], are mostly reported during treatment with interferon plus ribavirine [30–32], sometimes mixed with hypomanic symptoms [32]. These symptoms are also associated with reduced quality of life [33].

For this reason, treating depression in HIV–HCV co-infected individuals could weaken the negative impact of fatigue on quality of life [14,34] and improve both neurocognitive functions [35] and adherence to treatment for both infections [36,37].

Screening and appropriate management of DS in co-infected patients should therefore be considered as a priority in a programme of comprehensive care to minimise not only the negative repercussions of fatigue on patient functioning because of chronic hepatitis C [1,2] but also the detrimental consequences of untreated depression on patient clinical and psychosocial outcomes [27,38]. Indeed, appropriate treatment should be initiated as soon as possible when a patient meets the criteria for depression [39,40]. Although the CES-D cannot be considered a diagnostic tool for detecting depression, it is worth noting that in our study, only 32% of the patients presenting DS were receiving antidepressants. However, caution should be taken when prescribing antidepressants in patients with a history of bipolar disorder [41] or in those receiving HCV treatment and presenting manic or hypomanic symptoms [32], as the state of these patients could severely worsen with antidepressant use. In some cases, antidepressant use may fail to be effective [42] and

Table 2 Predictors of the impact of fatigue on cognitive, physical and social functioning (FIS) in HIV–HCV co-infected patients: univariate analyses using MANOVA models (HEPAVIH French Cohort enrolled in the analysis on fatigue, $n = 328$)*

	Cognitive impact†			Physical impact†			Social impact†		
	B coeff [95%CI]	F	*P*-value	B coeff [95%CI]	F	*P*-value	B coeff [95%CI]	F	*P*-value
Women	**3.1 [0.7; 5.5]**	**6.53**	**0.01**	**3.1 [0.6; 5.6]**	**5.72**	**0.02**	**6.6 [1.9; 11.3]**	**7.66**	**0.006**
Age	**0.12 [−0.06; 0.31]**	**1.67**	**0.20**	0.10 [−0.10; 0.30]	1.03	0.31	0.05 [−0.31; 0.42]	0.09	0.77
IDU [HIV transmission group)	**1.4 [−0.9; 3.7]**	**1.44**	**0.23**	**1.9 [−0.6; 4.4]**	**2.32**	**0.13**	**4.5 [0.0; 9.0]**	**3.88**	**0.05**
Having child[ren)	**−4.3 [−6.6; −1.9]**	**12.73**	**$<10^{-3}$**	**−4.5 [−7.1; −2.0]**	**12.65**	**$<10^{-3}$**	**−8.4 [−13.1; −3.8]**	**12.65**	**$<10^{-3}$**
Secondary school certificate	**−1.9 [−4.4; 0.6]**	**2.20**	**0.14**	**−2.2 [−4.9; 0.4]**	**2.71**	**0.10**	**−5.2 [−10.1; −0.3]**	**4.35**	**0.04**
Employed	**−5.5 [−7.6; −3.3]**	**24.57**	**$<10^{-3}$**	**−6.1 [−8.4; −3.8]**	**27.2**	**$<10^{-3}$**	**−12.7 [−17.0; −8.5]**	**35.52**	**$<10^{-3}$**
Living in a couple	**−2.9 [−5.1; −0.6]**	**6.41**	**0.01**	**−3.4 [−5.8; −1.0]**	**7.83**	**0.005**	**−6.7 [−11.1; −2.4]**	**9.15**	**0.003**
Owner or tenant of their home	−0.6 [−3.4; 2.2]	0.19	0.66	**−2.3 [−5.3; 0.7]**	**2.34**	**0.13**	**−4.2 [−9.7; 1.2]**	**2.31**	**0.13**
Comfortable housing conditions [as perceived by respondent)	**−4.5 [−7.3; −1.8]**	**10.4**	**0.001**	**−4.1 [−7.1; −1.1]**	**7.43**	**0.007**	**−10.9 [−16.3; −5.4]**	**15.56**	**$<10^{-3}$**
No DS and no TDS	**−14.3 [−17.1; −11.4]**	**45.59**	**$<10^{-3}$**	**−14.3 [−17.5; −11.2]**	**36.39**	**$<10^{-3}$**	**−30.1 [−35.6; −24.6]**	**53.68**	**$<10^{-3}$**
No DS and TDS	**−9.5 [−13.9; −5.0]**			**−11.0 [−16.0; −6.1]**			**−20.3 [−28.9; −11.7]**		
DS and no TDS	**−4.6 [−7.7; −1.5]**			**−5.2 [−8.6; −1.7]**			**−10.2 [−16.3; −4.2]**		
DS and TDS [reference)									
Daily alcohol consumption‡	0.8 [−3.1; 4.7]	0.15	0.70	1.7 [−2.5; 5.8]	0.62	0.43	4.1 [−3.6; 11.8]	1.09	0.30
Cannabis use§	2.7 [0.5; 4.8]	5.65	0.02	2.6 [0.2; 4.9]	4.61	0.03	5.9 [1.6; 10.2]	7.24	0.008
Cocaine use§	0.6 [−3.9; 5.0]	0.06	0.81	1.3 [−3.5; 6.0]	0.27	0.60	**6.8 [−1.9; 15.5]**	**2.39**	**0.12**
Heroine use§	1.3 [−4.6; 7.2]	0.19	0.66	2.4 [−3.8; 8.7]	0.59	0.44	6.6 [−5.0; 18.2]	1.25	0.26
History of IDU	**1.4 [−1.0; 3.8]**	**1.39**	**0.24**	**2.3 [−0.2; 4.8]**	**3.16**	**0.08**	**5.2 [0.5; 9.9]**	**4.71**	**0.03**
Drug use¶	0.3 [−3.1; 3.8]	0.04	0.85	1.5 [−2.2; 5.2]	0.64	0.42	4.1 [−2.8; 10.9]	1.35	0.25
Receiving ART	0.4 [−3.5; 4.4]	0.04	0.83	−0.2 [−4.5; 4.0]	0.01	0.91	−0.8 [−8.6; 6.9]	0.05	0.83
ART ($n = 304$)									
No IP + no NNRTI	**0.6 [−2.9; 4.1]**	**1.85**	**0.14**	**0.4 [−3.4; 4.2]**	**1.71**	**0.17**	**1.4 [−5.5; 8.4]**	**2.27**	**0.08**
No IP + NNRTI	**−2.1 [−5.5; 1.4]**			**−1.6 [−5.3; 2.0]**			**−4.8 [−11.6; 1.9]**		
IP + no NRTI	**5.0 [0.3; 10.3]**			**5.6 [0.0; 11.2]**			**10.5 [0.1; 20.8]**		
IP + NRTI (reference)									
Receiving Efavirenz	**−4.4 [−8.0; −0.7]**	**5.45**	**0.02**	**−4.0 [−7.9; −0.1]**	**4.05**	**0.05**	**−9.6 [−16.8; −2.4]**	**6.81**	**0.01**
Receiving OST	**3.8 [1.0; 6.6]**	**7.30**	**0.007**	**5.9 [2.9; 8.8]**	**15.61**	**$<10^{-3}$**	**10.4 [4.9; 16.0]**	**13.67**	**$<10^{-3}$**
Number of self-reported side effects	**0.61 [0.48; 0.74]**	**84.96**	**$<10^{-3}$**	**0.71 [0.58; 0.85]**	**106.43**	**$<10^{-3}$**	**1.30 [1.05; 1.55]**	**102.45**	**$<10^{-3}$**
Number of self-reported side effects causing discomfort	**0.92 [0.77; 1.08]**	**133.44**	**$<10^{-3}$**	**1.04 [0.88; 1.21]**	**158.52**	**$<10^{-3}$**	**1.76 [4.45; 2.08]**	**121.48**	**$<10^{-3}$**
Liver cirrhosis	1.1 [−1.4; 3.5]	0.74	0.39	**1.8 [−0.8; 4.5]**	**1.87**	**0.17**	1.2 [−3.7; 6.1]	0.23	0.63
CD4 < 200 per mm^3	2.0 [−1.4; 5.4]	1.32	0.25	**4.2 [0.6; 7.8]**	**5.28**	**0.02**	**4.3 [−2.4; 11.0]**	**1.58**	**0.21**
Nadir CD4 per mm^3	−0.004 [−0.011; 0.004]	0.98	0.32	**−0.006 [−0.014; 0.001]**	**2.76**	**0.10**	−0.006 [−0.020; 0.008]	0.70	0.40

Table 2 (Continued)

	Cognitive impact†			Physical impact†			Social impact†		
	B coeff [95%CI]	F	*P*-value	B coeff [95%CI]	F	*P*-value	B coeff [95%CI]	F	*P*-value
Detectable HIV viral load	0.8 [−2.3; 4.0]	0.26	0.61	**2.5 [−0.8; 5.9]**	**2.19**	**0.14**	2.8 [−3.4; 9.1]	0.80	0.37
HCV genotype 1 or 4	**1.9 [−0.8; 4.6]**	**1.97**	**0.16**	**2.3 [−0.6; 5.2]**	**2.50**	**0.12**	**4.4 [−0.9; 9.7]**	**2.70**	**0.10**
ASAT (UI/l)	−0.006 [−0.029; 0.017]	0.27	0.60	−0.007 [−0.032; 0.017]	0.35	0.56	−0.023 [−0.068; 0.023]	0.98	0.32
ALAT (UI/l)	−0.008 [−0.024; 0.008]	0.90	0.35	**−0.014 [−0.031; 0.003]**	**2.51**	**0.11**	**−0.028 [−0.059; 0.004]**	**2.98**	**0.09**
Diabetic patient	**3.3 [−2.1; 8.8]**	**1.46**	**0.23**	**4.2 [−1.6; 10.0]**	**2.02**	**0.16**	6.1 [−4.7; 16.8]	1.23	0.27

DS, depressive symptoms; TDS, treatment for depressive symptoms; OST, opioid substitution treatment. *A multiple linear regression was also used to separately model each scale as outcome to obtain the coefficients and 95% CI reported in the table. †Variables eligible for multivariate model are either in bold ($P < 0.25$) or highlighted in grey ($P < 0.05$). ‡During the previous 6 months. ‡At least once in the previous 4 weeks. §Use of at least one drug (including nonprescribed substitution treatment or nonprescribed psychotropic drugs; cannabis was excluded from this computation) during the previous 4 weeks

Fig. 1 Boxplots of fatigue impact on cognitive, physical and social functioning (FIS) according to depressive symptoms (DS) and treatment for depressive symptoms (TDS) in HIV–HCV co-infected patients (HEPAVIH French Cohort Study, $n = 328$ individuals).

may need to be complemented with more comprehensive psychiatric therapy. The choice of antidepressant is vital. Antidepressants which are neither inducers, inhibitors or metabolised by the hepatic cytochrome P450 iso-enzyme group are preferable. It is also important to underline that

Table 3 Predictors of the impact of fatigue on cognitive, physical and social functioning (FIS) in HIV–HCV co-infected patients: multivariate MANOVA models (HEPAVIH French Cohort enrolled in the analysis on fatigue, $n = 328$)[#]

	Cognitive Impact*			Physical Impact*			Social Impact*		
	Adjusted B coeff [95%CI]	F	*P*-value	Adjusted B coeff [95%CI]	F	*P*-value	Adjusted B coeff [95%CI]	F	*P*-value
Women	**2.0 [0.2; 3.9]**	**4.54**	**0.03**	**2.3 [0.3; 4.3]**	**5.11**	**0.03**	**4.9 [1.3; 8.5]**	**7.23**	**0.008**
Employed	−1.4 [−3.2; 0.4]	2.30	0.13	**−2.0 [−3.9; −0.2]**	**4.56**	**0.03**	**−4.5 [−7.9; −1.1]**	**6.85**	**0.009**
No depressive symptoms (DS) and no treatment for depressive symptoms (TDS)	**−11.4 [−14.2; −8.6]**	**28.88**	**$<10^{-3}$**	**−10.3 [−13.2; −7.4]**	**20.25**	**$<10^{-3}$**	**−24.7 [−29.9; −19.4]**	**37.27**	**$<10^{-3}$**
No DS and TDS	**−7.5 [−11.7; −3.3]**			**−8.1 [−12.5; −3.7]**			**−17.3 [−25.2; −9.4]**		
DS and no TDS	**−4.0 [−6.9; −1.1]**			**−4.1 [−7.1; −1.0]**			**−8.8 [−14.4; −3.3]**		
DS and TDS (reference)									
CD4 < 200 per mm^3	1.6 [−1.0; 4.2]	1.51	0.22	**4.4 [1.6; 7.1]**	**9.85**	**0.002**	4.2 [−0.8; 9.1]	2.77	0.10
Number of self-reported side effects causing discomfort	**0.71 [0.55; 0.86][$]**	**80.99**	**$<10^{-3}$**	**0.84 [0.68; 1.00][$]**	**104.03**	**$<10^{-3}$**	**1.24 [0.95; 1.53][†]**	**69.33**	**$<10^{-3}$**
Receiving Efavirenz	**−3.3 [−0.6; −6.0]**	**5.83**	**0.02**	**−3.3 [−6.1; −0.5]**	**5.37**	**0.02**	**−7.5 [−12.5; −2.4]**	**8.40**	**0.004**

[#]A multiple linear regression was also used to separately model each scale as outcome to obtain the coefficients and 95% CI reported in the table. *Variables highlighted in bold ($P < 0.05$) [†]Per one side effect increase

starting HCV treatment in individuals who are also HIV -infected can further improve DS and quality of life [43].

The number of self-reported side effects causing discomfort significantly contributes to an increased impact of fatigue on all dimensions of patient's functioning. Previous research has already demonstrated that in HIV-infected individuals, the number of self-reported side effects is a major determinant of nonadherence to treatment [44–46], is more frequently reported in individuals HIV-infected via IDU [47] and is also associated with suicidal ideation [48]. As our study sample was mainly composed of individuals with a history of drug use, the association between the three dimensions of fatigue and the number of self-reported side effects causing discomfort underlines the need for appropriate counselling and individualised strategies to manage perceived side effects [12]. It has already been shown that HIV–HCV co-infected patients tend to refuse starting HCV treatment more often than those who are monoinfected [49] probably because of the apprehension regarding the toxicity burden of an additional therapy and associated fatigue. They also tend to discontinue HCV therapy more frequently than HCV-monoinfected patients [49].

The associations found between ongoing drug use, OST, history of injection and fatigue in univariate analyses may be related to the fact that fatigue or sedation from illicit opiate use are common side effects of opioids and opioid substitution therapies. This is especially true at their initiation or when excessive doses are used [50–52]. This sedative effect could be caused by the anticholinergic activity of opioids [51]. Fatigue may also result from opioid-induced inhibition of adrenal androgen [53] and/or the action of opioids on sleep architecture [54], possibly related to depression [55]. Interactions between substitution therapies and certain antiretroviral agents (most often after antiretroviral cessation or switching) or interferon alpha may also play a role by increasing plasma levels of methadone [56,57]. Closer monitoring of methadone use in co-infected patients, especially during treatment adjustments may thus be necessary to improve perceived physical fatigue.

The present study also shows for the first time to what extent immune suppression – expressed by the number of CD4 cell per mm^3 – can deteriorate all dimensions of patient functioning through fatigue. In many studies, fatigue is more frequently associated with psychosocial factors than with clinical condition, level of immunosuppression or ART [6,13,58]. Moreover, the association with undetectable plasma HIV RNA and decreased impact of fatigue in univariate analyses also strengthens this conclusion.

The burden of the severity of HIV on fatigue impact also suggests that in clinical practice, the initiation of HCV treatment in co-infected patients should be considered as soon as possible and certainly before progression to AIDS or end-stage chronic hepatitis. Nevertheless, even in patients with advanced fibrosis or cirrhosis, a sustained viral response after anti-HCV treatment is associated with an improved quality of life [59].

The association found between receiving Efavirenz and a lower impact of fatigue on the different dimensions of patient functioning is in theory not consistent with results from clinical trials where efavirenz has been found to be associated with higher levels of depression and fatigue [60,61]. On the other hand, it is consistent with the current French prescription practices where Efavirenz is prescribed to those patients who are less likely to discontinue it [62], for example patients with no history of major depression. Among nonnucleoside reverse transcriptase inhibitors (NRTI) drugs, nevirapine was also tested but it was not associated with the outcome. Protease inhibitors without nucleoside reverse transcriptase inhibitors were weakly associated with a higher impact of fatigue but only in the univariate analysis (Table 2).

HIV and HCV infections have already been shown to have a higher impact on fatigue correlates and dimensions in women than in men [2,8]. This is consistent with our results which show that women are more vulnerable to the impact of fatigue in daily life.

One of the limitations of our study is its cross-sectional nature which only allowed us to detect associations and not causal relationships. In particular, no information was available concerning when or on what basis treatments for DS were introduced.

Although the CES-D cannot be considered a diagnostic tool for major depression and other scales could potentially provide improved screening power [63], it remains an appropriate tool for detecting DS with gender-specific cut-off values [17].

Finally, it is worthwhile mentioning that as access to care for HIV-infected individuals in France is free, the sample enrolled in this study is likely to be highly representative of the general population of French HIV–HCV infected individuals currently in care in this country.

CONCLUSION

Our study clearly indicates that treating DS may play a major role in reducing fatigue impact. This impact is higher in women and is related to social status, HIV immunosuppression, ART choice and perceived toxicity. Consequently, individualised interventions to limit the impact of fatigue should be seriously considered for both women and individuals with severe immunosuppression before and during HCV treatment. Early initiation of anti-HCV treatment, routine assessment and combined management of fatigue, depression and discomforting side effects can potentially improve the quality of life of co-infected patients and relieve the burden of their dual infection.

ACKNOWLEDGEMENTS

This study was sponsored and funded by the French National Agency for Research on Aids and Viral Hepatitis (ANRS), with the participation of Abbott France, Glaxosmithkline,

Roche and Schering Plough and INSERM's 'Programme cohortes TGIR'. We thank all health care providers and patients who participated in the cohort's implementation and follow-up. Special thanks to Sandrine Couffin-Cadierques, Laurence Allain and Marcia Trumeau for encouraging the ANRS CO 13 HEPAVIH project. The authors would like to thank Jude Sweeney for the English revision and editing of the manuscript.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1 Foster GR, Goldin RD, Thomas HC. Chronic hepatitis C virus infection causes a significant reduction in quality of life in the absence of cirrhosis. *Hepatology* 1998; 27(1): 209–212.
2 Poynard T, Cacoub P, Ratziu V *et al.* Fatigue in patients with chronic hepatitis C. *J Viral Hepat* 2002; 9(4): 295–303.
3 Bonkovsky HL, Woolley JM. Reduction of health-related quality of life in chronic hepatitis C and improvement with interferon therapy.The Consensus Interferon Study Group. *Hepatology* 1999; 29(1): 264–270.
4 APA. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). 4th edn. Washington, DC: APA, 1994.
5 Barroso J, Lynn MR. Psychometric properties of the HIV-Related Fatigue Scale. *J Assoc Nurses AIDS Care* 2002; 13(1): 66–75.
6 Henderson M, Safa F, Easterbrook P, Hotopf M. Fatigue among HIV-infected patients in the era of highly active antiretroviral therapy. *HIV Med* 2005; 6(5): 347–352.
7 Breitbart W, McDonald MV, Rosenfeld B, Monkman ND, Passik S. Fatigue in ambulatory AIDS patients. *J Pain Symptom Manage* 1998; 15(3): 159–167.
8 Voss JG. Predictors and Correlates of Fatigue in HIV/AIDS. *J Pain Symptom Manage* 2005; 29(2): 173–184.
9 Ferrando S, Evans S, Goggin K, Sewell M, Fishman B, Rabkin J. Fatigue in HIV illness: relationship to depression, physical limitations, and disability. *Psychosom Med* 1998; 60(6): 759–764.
10 Gutteling JJ, de Man RA, van der Plas SM, Schalm SW, Busschbach JJ, Darlington AS. Determinants of quality of life in chronic liver patients. *Aliment Pharmacol Ther* 2006; 11: 1629–1635.
11 Kallman J, O'Neil MM, Larive B, Boparai N, Calabrese L, Younossi ZM. Fatigue and health-related quality of life (HRQL) in chronic hepatitis C virus infection. *Dig Dis Sci* 2007; 52(10): 2531–2539.
12 Marcellin F, Preau M, Dellamonica P *et al.* Adding HCV treatment to HIV treatment in HIV-HCV coinfected patients: the impact on the different dimensions of fatigue and self-reported side effects. *J Pain Symptom Manage* 2007; 34(4): 413–421.
13 Braitstein P, Montessori V, Chan K *et al.* Quality of life, depression and fatigue among persons co-infected with HIV and hepatitis C: outcomes from a population-based cohort. *AIDS Care* 2005; 17(4): 505–515.
14 Marcellin F, Preau M, Ravaux I, Dellamonica P, Spire B, Carrieri MP. Self-reported fatigue and depressive symptoms as main indicators of the quality of life (QOL) of patients living with HIV and Hepatitis C: implications for clinical management and future research. *HIV Clin Trials* 2007; 8(5): 320–327.
15 Thein H, Maruff P, Krahn M *et al.* Cognitive function, mood and health-related quality of life in hepatitis C virus (HCV)-monoinfected and HIV/HCV-coinfected individuals commencing HCV treatment. *HIV Med* 2007; 8(3): 192–202.
16 Fisk JD, Ritvo PG, Ross L, Haase DA, Marrie TJ, Schlech WF. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. *Clin Infect Dis* 1994; 18 (Suppl. 1): S79–S83.
17 Fuhrer R, Rouillon F. La version française de l'échelle CES-D. Description and translation of the autoevaluation scale (in French). *Psychiatrie et Psychobiologie* 1989; 4: 163–166.
18 Justice AC, Holmes W, Gifford AL *et al.* Development and validation of a self-completed HIV symptom index. *J Clin Epidemiol* 2001; 54 (Suppl. 1): S77–S90.
19 Gama H, Correia S, Lunet N. Questionnaire design and the recall of pharmacological treatments: a systematic review. *Pharmacoepidemiol Drug Saf* 2009; 18(3): 175–187.
20 Cotterchio M, Kreiger N, Darlington G, Steingart A. Comparison of self-reported and physician-reported antidepressant medication use. *Ann Epidemiol* 1999; 9(5): 283–289.
21 Sandrin L, Fourquet B, Hasquenoph JM *et al.* Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. *Ultrasound Med Biol* 2003; 29(12): 1705–1713.
22 Imbert-Bismut F, Ratziu V, Pieroni L, Charlotte F, Benhamou Y, Poynard T. Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. *Lancet* 2001; 357(9262): 1069–1075.
23 Nelder JA, Wedderburn RWM. Generalized linear models. *J Roy Stat Soc* 1972; 135: 370–384.
24 Katz MH, Douglas JM Jr, Bolan GA *et al.* Depression and use of mental health services among HIV-infected men. *AIDS Care* 1996; 8(4): 433–442.
25 Fairfield KM, Libman H, Davis RB, Eisenberg DM. Delays in protease inhibitor use in clinical practice. *J Gen Intern Med* 1999; 14(7): 395–401.
26 Bouhnik AD, Preau M, Vincent E *et al.* Depression and clinical progression in HIV-infected drug users treated with highly active antiretroviral therapy. *Antivir Ther* 2005; 10(1): 53–61.
27 Villes V, Spire B, Lewden C *et al.* The effect of depressive symptoms at ART initiation on HIV clinical progression and mortality: implications in clinical practice. *Antivir Ther* 2007; 12(7): 1067–1074.
28 Anastos K, Schneider MF, Gange SJ *et al.* The association of race, sociodemographic, and behavioral characteristics with response to highly active antiretroviral therapy in women. *J Acquir Immune Defic Syndr* 2005; 39(5): 537–544.
29 Kraus MR, Schafer A, Faller H, Csef H, Scheurlen M. Psychiatric symptoms in patients with chronic hepatitis C receiving interferon alfa-2b therapy. *J Clin Psychiatry* 2003; 64(6): 708–714.

30 Raison CL, Borisov AS, Broadwell SD *et al.* Depression during pegylated interferon-alpha plus ribavirin therapy: prevalence and prediction. *J Clin Psychiatry* 2005; 66(1): 41–48.
31 Gohier B, Goeb JL, Rannou-Dubas K, Fouchard I, Cales P, Garre JB. Hepatitis C, alpha interferon, anxiety and depression disorders: a prospective study of 71 patients. *World J Biol Psychiatry* 2003; 4(3): 115–118.
32 Constant A, Castera L, Dantzer R *et al.* Mood alterations during interferon-alfa therapy in patients with chronic hepatitis C: evidence for an overlap between manic/hypomanic and depressive symptoms. *J Clin Psychiatry* 2005; 66(8): 1050–1057.
33 Castera L, Constant A, Bernard PH, de Ledinghen V, Couzigou P. Lifestyle changes and beliefs regarding disease severity in patients with chronic hepatitis C. *J Viral Hepat* 2006; 13(7): 482–488.
34 Fleming CA, Christiansen D, Nunes D *et al.* Health-related quality of life of patients with HIV disease: impact of hepatitis C coinfection. *Clin Infect Dis* 2004; 4: 572–578.
35 Clifford DB, Evans SR, Yang Y, Gulick RM. The neuropsychological and neurological impact of hepatitis C virus co-infection in HIV-infected subjects. *AIDS* 2005; 19 (Suppl. 3): S64–S71.
36 Klein MB, Cooper C, Brouillette MJ *et al.* CTN-194 (PICCO): design of a trial of citalopram for the prevention of depression and its consequences in HIV-Hepatitis C co-infected individuals initiating pegylated interferon/ribavirin therapy. *Contemp Clin Trials* 2008; 29(4): 617–630.
37 Starace F, Ammassari A, Trotta MP *et al.* Depression is a risk factor for suboptimal adherence to highly active antiretroviral therapy. *J Acquir Immune Defic Syndr* 2002; 31 (Suppl. 3): S136–S139.
38 Himelhoch S, Medoff DR. Efficacy of antidepressant medication among HIV-positive individuals with depression: a systematic review and meta-analysis. *AIDS Patient Care STDS.* 2005; 19(12): 813–822.
39 Mauss S. Treatment of viral hepatitis in HIV-coinfected patients-adverse events and their management. *J Hepatol* 2006; 44 (Suppl. 1): S114–S118.
40 Pence BW, Miller WC, Whetten K, Eron JJ, Gaynes BN. Prevalence of DSM-IV-defined mood, anxiety, and substance use disorders in an HIV clinic in the Southeastern United States. *J Acquir Immune Defic Syndr* 2006; 42(3): 298–306.
41 Henry C, Demotes-Mainard J. Avoiding drug-induced switching in patients with bipolar depression. *Drug Saf* 2003; 26(5): 337–351.
42 Cook JA, Grey D, Burke-Miller J *et al.* Effects of treated and untreated depressive symptoms on highly active antiretroviral therapy use in a US multi-site cohort of HIV-positive women. *AIDS Care* 2006; 18(2): 93–100.
43 Fumaz CR, Munoz-Moreno JA, Ballesteros AL *et al.* Influence of the type of pegylated interferon on the onset of depressive and neuropsychiatric symptoms in HIV-HCV coinfected patients. *AIDS Care* 2007; 19(1): 138–145.
44 Duran S, Spire B, Raffi F *et al.* Self-reported symptoms after initiation of a protease inhibitor in HIV-infected patients and their impact on adherence to HAART. *HIV Clin Trials* 2001; 2(1): 38–45.
45 Protopopescu C, Marcellin F, Spire B *et al.* Health-related quality of life in HIV-1-infected patients on HAART: a five-years longitudinal analysis accounting for dropout in the APROCO-COPILOTE cohort (ANRS CO-8). *Qual Life Res* 2007; 16(4): 577–591.
46 Ammassari A, Murri R, Pezzotti P *et al.* Self-Reported Symptoms and Medication Side Effects Influence Adherence to Highly Active Antiretroviral Therapy in Persons With HIV Infection. *J Acquir Immune Defic Syndr* 2001; 28(5): 445–449.
47 Carrieri MP, Villes V, Raffi F *et al.* Self-reported side-effects of anti-retroviral treatment among IDUs: a 7-year longitudinal study (APROCO-COPILOTE COHORT ANRS CO-8). *Int J Drug Policy* 2007; 18(4): 288–295.
48 Carrico AW, Johnson MO, Morin SF *et al.* Correlates of suicidal ideation among HIV-positive persons. *AIDS* 2007; 21(9): 1199–1203.
49 Zehnter E. Treatment of Chronic Hepatitis C With Peginterferon alfa-2a (PEG) and Ribavirin (RBV) in Patients With HIV Coinfection in the Real-Life Setting in Germany. Boston: AASLD meeting, 2007; 37(1): 95–100.
50 Shaiova L. The management of opioid-related sedation. *Curr Pain Headache Rep* 2005; 9(4): 239–242.
51 Benyamin R, Trescot AM, Datta S *et al.* Opioid complications and side effects. *Pain Physician* 2008; 11 (Suppl. 2): S105–S120.
52 Ridge G, Gossop M, Lintzeris N, Witton J, Strang J. Factors associated with the prescribing of buprenorphine or methadone for treatment of opiate dependence. *J Subst Abuse Treat* 2008; 37(1): 95–100.
53 Daniell HW. DHEAS deficiency during consumption of sustained-action prescribed opioids: evidence for opioid-induced inhibition of adrenal androgen production. *J Pain* 2006; 7(12): 901–907.
54 Dimsdale JE, Norman D, DeJardin D, Wallace MS. The effect of opioids on sleep architecture. *J Clin Sleep Med* 2007; 3(1): 33–36.
55 Wang D, Teichtahl H, Goodman C, Drummer O, Grunstein RR, Kronborg I. Subjective daytime sleepiness and daytime function in patients on stable methadone maintenance treatment: possible mechanisms. *J Clin Sleep Med* 2008; 6: 557–562.
56 Bruce RD, Altice FL, Gourevitch MN, Friedland GH. Pharmacokinetic drug interactions between opioid agonist therapy and antiretroviral medications: implications and management for clinical practice. *J Acquir Immune Defic Syndr* 2006; 5: 563–572.
57 Gupta SK, Sellers E, Somoza E, Angles L, Kolz K, Cutler DL. The effect of multiple doses of peginterferon alfa-2b on the steady-state pharmacokinetics of methadone in patients with chronic hepatitis C undergoing methadone maintenance therapy. *J Clin Pharmacol* 2007; 47(5): 604–612.
58 Sullivan PS, Dworkin MS. Prevalence and correlates of fatigue among persons with HIV infection. *J Pain Symptom Manage* 2003; 25(4): 329–333.
59 Bonkovsky HL, Snow KK, Malet PF *et al.* Health-related quality of life in patients with chronic hepatitis C and advanced fibrosis. *J Hepatol* 2007; 46(3): 420–431.

60 Rihs TA, Begley K, Smith DE *et al.* Efavirenz and chronic neuropsychiatric symptoms: a cross-sectional case control study. *HIV Med* 2006; 7(8): 544–548.
61 Ward DJ, Curtin JM. Switch from efavirenz to nevirapine associated with resolution of efavirenz-related neuropsychiatric adverse events and improvement in lipid profiles. *AIDS Patient Care STDS.* 2006; 20(8): 542–548.
62 Spire B, Carrieri P, Garzot MA, L'Henaff M, Obadia Y. Factors associated with efavirenz discontinuation in a large community-based sample of patients. *AIDS Care* 2004; 16(5): 558–564.
63 Golub ET, Latka M, Hagan H *et al.* Screening for depressive symptoms among HCV-infected injection drug users: examination of the utility of the CES-D and the beck depression inventory. *J Urban Health* 2004; 81(2): 278–290.

APPENDIX

The ANRS CO13 HEPAVIH study group:

Scientific Committee

D. Salmon, F. Dabis, M. Winnock, M.A. Loko, P. Sogni, Y. Benhamou, P. Trimoulet, J. Izopet, V. Paradis, B. Spire, P. Carrieri, C. Katlama, G. Pialoux, I. Poizot-Martin, B. Marchou, E. Rosenthal, A. Bicart See, M. Bentata, A. Gervais, C. Lascoux-Combe, C. Goujard, K. Lacombe, C. Duvivier, D. Vittecoq, D. Neau, P. Morlat, F. BaniSadr, L. Meyer, F. Boufassa, S. Dominguez, B. Autran, A.M. Roque, C. Solas, H. Fontaine, G. Chêne, D. Costagliola, L. Allain and a member from patients' associations.

Principal investigators: D. Salmon, F. Dabis
Methodology: F. Dabis, M. Winnock
Hepatology: Y. Benhamou, P. Sogni
Virology: J. Izopet, P. Trimoulet
Social sciences : B. Spire, M.P. Carrieri, Marion Mora
Project Coordination: M. Winnock, M.A. Loko

Clinical Centres (ward / participating physicians)

CHU Cochin (Médecine Interne et Maladies Infectieuses/ D. Salmon, G. Spiridon, F. Almasi, O. Eldbouni; Hépatogastroentérologie/ P. Sogni); CHU Pitié Salpétrière (Maladies Infectieuses et Tropicales/C. Katlama, MA. Valantin, S. Dominguez; Hépatogastroentérologie/Y. Benhamou); CHU Sainte Marguerite, Marseille (Hématologie et VIH/J.A. Gastaut, I. Poizot-Martin, O. Zaegel); CHU Tenon (Maladies Infectieuses et Tropicales/G. Pialoux, P. Bonnard, F. Bani-sadr);CHU Purpan Toulouse (Maladies Infectieuses et Tropicales/B. Marchou; Hépatogastroentérologie/ K. Barange, S. Metivier); CHU Archet, Nice (Médecine Interne/ E. Rosenthal; Infectiologie/ C. Pradier); CHU Avicenne, Paris (Médecine Interne – Unité VIH/A. Krivitzky, M. Bentata); Hôpital Joseph Ducuing, Toulouse (Médecine Interne/M. Uzan, A. Bicart-See, D. Garipuy); CHU Bichat – Claude Bernard, Paris (Maladies Infectieuses/P. Yéni, A. Gervais); CHU Saint Louis (Médecine Interne/D. Séréni, C. Lascoux Combes); CHU Saint Antoine (Maladies Infectieuses et Tropicales/P.M. Girard, K. Lacombe); CHU Bicêtre (Médecine Interne/J.F. Delfraissy, C. Goujard); CHU Paul Brousse (Maladies Infectieuses/D. Vittecoq); CHU Necker (Maladies Infectieuses et Tropicales/O. Lortholary, C. Duvivier, S. Boucly), Aquitaine cohort (D.Neau, P. Morlat, I. Raymond, I. Louis)

Data collection, management and statistical analyses

D. Beniken, A. Ivanova, A. Fooladi, M. Azar, P Honoré, S. Breau, L. Serini, M. Mole, M. Malet, C. Bolliot, J. Delaune, A. Maignan, S. Gillet, L. Dequae Merchadou, E. Pambrun, A. Frosch, J. Cohen, V. Villes, P. Kurkdji, MA. Loko, M. Winnock