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**Impaired anger control as an underappreciated side effect of treatments for chronic
HCV infection in HIV-HCV coinfecting patients**

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Impaired anger control as an underappreciated side effect of treatments for chronic HCV infection in HIV-HCV coinfecting patients

Abstract

OBJECTIVE: To study the specific impact of treatments for chronic hepatitis C virus (HCV) infection on anger expression and control in adult patients coinfecting with HIV and HCV receiving antiretroviral therapy.

DESIGN: In 2005, a cross-sectional survey, collecting both clinical and sociobehavioral data, was conducted in two French clinical centers among adult patients coinfecting with HIV and HCV.

METHODS: Participants were asked to answer anonymously a self-administered questionnaire aimed at obtaining sociodemographic, clinical and behavioral characteristics including self-reported treatments' side effects, quality of life (WHOQOL-HIV BREF), and irritability and anger (STAXI-2). Clinical characteristics were obtained from medical records.

RESULTS: Among the 139 patients who were receiving antiretroviral therapy at the time of survey and who had complete self-reported data, 24 were being treated for their HCV infection, using either pegylated interferon (pegIFN) and ribavirin (RBV) or pegIFN alone. Control of anger was significantly lower among treated patients than among untreated ones (STAXI-2 anger control-out dimension median scores of 18.5 *versus* 23 respectively, $P = 0.02$). Sociodemographic and clinical characteristics did not differ significantly between these 2 groups. Control of angry feelings was significantly correlated with psychological and social relationship dimensions of quality of life.

CONCLUSION: Treatment of HCV-HIV co-infected patients may require closer monitoring for anger control issues and adjustment of treatment as appropriate.

Keywords:

Anger, HIV/HCV coinfection, Interferon, Ribavirin, Quality of life

Impaired anger control as an underappreciated side effect of treatment(s) for chronic HCV infection in HIV-HCV coinfecting patients

Introduction

With the dramatic improvement in treating many fatal complications of HIV infection, liver disease as a consequence of viral hepatitis C has emerged as a major cause of morbidity and mortality (2, 3). As an estimated 15- 30% of HIV infected patients are also infected with hepatitis C virus (HCV) (4, 5), HIV-HCV coinfection has become a critical issue because of the interactions between the two viruses (6, 7) which worsen the clinical course of HCV infection (8, 9). Besides, in patients already being treated with antiretrovirals, HCV infection constitutes an additional burden associated with disabling symptoms, such as fatigue, which impair their quality of life (QOL) (10). Pegylated interferon alpha (PegIFN) therapy in combination with ribavirin (RBV) is the most efficient treatment for HCV infection (11). While anxiety and depression have been extensively described as common side effects of interferon therapy, data on the occurrence and management of other neuropsychiatric disorders such as anger remain scarce (12-15). However, anger has been identified as an independent predictor of progression to AIDS (16) and its prevalence in older HIV-infected patients has been reported (17). In this context, we aimed at investigating the specific impact of treatment for HCV infection on anger expression and control in adult HIV-HCV coinfecting patients receiving antiretroviral therapy.

Patients and methods

In 2005, a cross-sectional survey was conducted among 223 coinfecting patients being followed-up in two clinical centers located in the south of France (Nice, Marseilles). Participation in the survey was proposed to all adult HIV-infected patients who were co-

infected with HCV virus, as documented by a positive HCV RNA detection test. Patients who agreed to participate were presented a self-administered questionnaire which included items on clinical status and history, sociodemographic characteristics and behavioral data, as well as self-reported side effects of antiretrovirals and QOL (WHO QOL-HIV BREF scale (18)). This scale assesses six dimensions of QOL: physical QOL (bodily pain, sleep, tiredness), psychological QOL (satisfaction with cognitive capacity, self-esteem, self-image, positive and negative feelings), environmental QOL (satisfaction with physical security, home, accessibility and quality of health care, information, transport, pollution, noise, spare-time activities), level of independence QOL (mobility, employment), QOL concerning social relationship aspects (interpersonal relationships, social support, sexual activity, social integration in relation to seropositivity) and spirituality. Patients' irritability and anger were evaluated using the French adaptation of the 57-item State-Trait Anger Expression Inventory-2 (STAXI-2) of Spielberger (19), which aims at exploring the different facets of anger simultaneously. This psychometric instrument measures the intensity of anger as an emotional state (State Anger, associated score ranging from 15 to 60) and the disposition to experiencing angry feelings as a personality trait (Trait Anger, associated score ranging from 10 to 40). It also contains a subscale evaluating anger expression and control. According to Spielberger's in-depth analyses concerning the factorial structure of the instrument, this subscale can be divided into four distinct dimensions: expressing anger towards other people or objects in the environment (Anger Expression-Out), holding in angry feelings (Anger Expression-In), controlling angry feelings by preventing the expression of anger towards other people or objects in the environment (Anger Control-Out), and controlling angry feelings by calming down or cooling off (Anger Control-In). Because of the correlations between Anger Expression-In and Anger Expression-Out on one part, and between Anger Control-In and Anger Control-Out on the other part, subscale scoring can be done either separately for each

dimension (scores range: 8 to 32), or using a global anger expression and control score. Higher scores denote more anger.

Statistical methods

Characteristics of patients being treated for their HCV infection and those who were not were compared using the Wilcoxon rank-sum test (continuous variables) and Fisher's exact test (categorical variables). Correlations between STAXI-2 and QOL dimensions were explored using Pearson's correlation coefficient. Significance level was fixed at $\alpha=0.05$. Analyses were performed using SAS ® software version 9.1 for Windows (SAS Institute, Cary, NC, USA)

Results

A total of 223 patients agreed to participate in the survey, of whom 152 (68.2%) answered the self-administered questionnaire (respondents). Reasons most frequently given for non-response were lack of interest, desire or time. Respondents were not significantly different from non-respondents in terms of age, sex, HIV clinical status (HIV viral load, CDC stage C), and fibrosis stage¹ (results not shown). In order to isolate the specific effect of HCV treatment on patients' irritability and anger, we focused our analysis on patients already being treated for HIV infection at the time of the survey, as they constituted the majority of respondents (n=139, 91.4%). Characteristics of these patients are presented in Table 1. Most of them were men (64.0%), mean age (standard deviation) was 42.9 (5.4) years and mean time since HCV diagnosis was 10.9 (5.4) years. Seventy-three percent of patients had contracted HCV infection from IV drug abuse. Forty-eight patients were diagnosed with a fibrosis score

¹ data on fibrosis stage (biopsy results or FibroTest™ score) were available for half of the patients

exceeding F2 (METAVIR) and were therefore treated according to the existing recommendations for HCV treatment. Twenty-four patients were being treated for HCV infection at the time of survey, mainly using a combination therapy of pegIFN and RBV (n=21 patients) and, to a lesser extent, using pegIFN alone (n=3 patients). There was no significant difference between patients being treated for HCV and those who were not with respect to all considered socio-demographic and clinical characteristics, including CES-D global depression score (Table 1). Only one treated patient reported regular alcohol consumption during the previous six months (*vs* 27 untreated patients, $P=0.05$). Patients being treated presented significantly lower STAXI-2 scores for Anger Control-Out than those who were not, with median [interquartile range] scores of respectively 18.5 [17.5; 23] and 23 [18; 26] ($P = 0.02$) (Table 2). Anger Control-Out was positively correlated with three domains of QOL (psychological QOL: $r = 0.42$, $P < 0.0001$; social relationships QOL: $r = 0.26$, $P = 0.01$; environmental QOL: $r = 0.25$, $P = 0.01$).

Discussion

The data presented here suggest that anger control out is associated with pegIFN HCV treatment among patients co-infected with HIV. This result is consistent with literature on anger among HCV mono-infected patients (13, 17, 20), and provides further information about the association between IFN therapy and neuropsychiatric disorders, as many other studies have focused only on depression. Besides, it underlines the necessity to take into account anger as a characteristic, which can have several implications on the management of HIV and HCV. Indeed, anger has already been shown to be associated with non adherence (21) and depressive symptoms (20) in the context of HCV infection and has also been shown to impact independently on HIV clinical progression (16). Our study identified an association between anger control-out and psychological and environmental aspects of QOL as well as

social relationships. It can therefore be hypothesized that lack of anger control impairs patients' interactions with their close relations or occupational companions and also with their healthcare providers- interactions which have been shown to be of crucial importance in HIV-infected patients' QOL (22). All of these considerations underline the important role of anger among psychological disorders and difficulties of coinfecting patients and highlight the necessity of adequate management of this problem.

It is interesting to note that no difference was detected in our study in terms of depression score between those patients being treated and those not being treated for HCV infection. As HIV-infected drug users are more likely to present depressive symptoms (23), this result could be attributed to the fact that many of the study's patients may already have presented a depressive symptomatology, as more than 70% of them were HIV-infected through IDU.

In addition, our results show that anger control is the main characteristic of anger related to QOL and treatment. Again, this may be due to the high prevalence of patients infected through IDU in the study population. Indeed, a previous study indicated that drug users have a high risk of anger (related) hostility symptoms, are more likely to express anger towards other people or objects in the environment, and have less control over their angry feelings (24). Besides, a cross sectional study based on data collected in the pre-HAART era in HIV-infected patients had demonstrated that patients HIV-infected through drug injection report more symptoms and higher overall and physical symptom distress than those belonging to other HIV-transmission categories (25), which can result in exacerbated angry feelings. In addition, these patients may not be adequately treated for their side effects including anger (26). However, we pointed out a significant difference concerning angry feelings between HCV treated and not treated patients despite well-balanced proportions of former or active drug users in these two groups, which underlines the determinant impact of HCV treatment on anger.

The failure of the study to find differences on anger dimensions other than control-out between those patients being treated for HCV and those who were not may be due to limited statistical power. Besides, the use of a self-administered questionnaire to address anger issues may be limiting, as it does not take into account perceptions of the patients' environment regarding this problem. Therefore, studies including anger assessment of the patient's environment should be conducted for complementary information. Finally, studies among HCV-infected patients not infected by routes other than drug injection need to be developed in order to disentangle the impact of drug use on anger's dimensions.

Conclusion. Findings indicate that routine psychosocial assessment of patient's pattern of symptoms should be integrated into HCV and HIV services in order to develop programs to reduce anger expression and to increase anger control ability. Indeed, anger behaviors can potentially be changed using group therapy (27). Our results need to be taken into account when individualising treatment strategy in co-infected patients in order to minimise possible side effects and optimize patient's clinical outcomes and quality of life.

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Table 1 - Socio-demographic, behavioral and clinical characteristics of HIV/HCV coinfecting patients receiving antiretroviral therapy - comparison of those patients treated and those not treated for HCV infection (n=139, cross-sectional survey on HIV/HCV coinfecting patients' QOL, France, 2005)

	All patients n=139	Patients treated for HCV infection n=24	Patients not treated for HCV infection n=115	P-value ¹
Number of patients (%)				
Male gender	89 (64.0%)	13	76	0.35
Mean age (SD) - years	42.9 (5.4)	43.6 (5.4)	42.7 (5.5)	0.73
Mean time since HIV diagnosis (SD) - years	15.5 (4.4)	15.9 (3.4)	15.5 (4.6)	0.97
HIV infection transmission category				
- sexual contact	24 (17.3%)	2	22	0.49
- intravenous drug use	113 (81.3%)	22	91	
- other	2 (1.4%)	0	2	
Mean HIV viral load (SD) - log₁₀ copies/ml	2.26 (1.06)	1.89 (0.70)	2.34 (1.11)	0.23
CD4 count - cells/mm³				
- below 350	54 (39.7%)	13	41	0.14
- between 350 and 500	31 (22.8%)	6	25	
- above 500	51 (37.5%)	5	46	
Mean duration of HIV treatment (SD) - years	9.4 (3.8)	10.6 (2.7)	9.1 (4.0)	0.09
Mean time since HCV diagnosis (SD) - years	10.9 (5.4)	11.6 (4.8)	10.7 (5.6)	0.43
HCV infection transmission category				
- sexual contact	25 (18.0%)	2	23	0.44
- intravenous drug use	102 (73.4%)	20	82	
- other	12 (8.6%)	2	10	
Fibrosis stage²				
- 0 to 1	29 (37.7%)	7	22	1.00
- 2 to 4	48 (62.3%)	11	37	
Alcohol consumption during the previous six months				
- less than two times a week	111 (79.9%)	23	88	0.05
- at least two times a week	28 (20.1%)	1	27	
Number of glasses consumed per day				
- less than 3 (2 for women)	107 (79.3%)	21	86	0.16
- at least 3 (2 for women)	28 (20.7%)	2	26	
Drug use³ during the previous four weeks - n=121				
- none	95 (78.5%)	14	81	0.08
- at least one	26 (21.5%)	8	18	
Depression global score (CES-D) median [IQR]	18 [11 ; 27]	20 [14 ; 27]	18 [11 ; 27]	0.22

SD = standard deviation; IQR = interquartile range

¹ comparison of those patients treated and those not treated for HCV infection (Fisher's exact test for categorical variables, Wilcoxon rank-sum test for continuous variables)

² data on fibrosis stage (biopsy results or FibroTestTM score) are available for half of the patients

³ Use of at least one of the following products: cannabis, cocaine, heroin, crack, ecstasy, amphetamins, buprenorphine without medical prescription, LSD or other hallucinogens

Table 2 - State-Trait Anger Expression Inventory-2 (STAXI-2) scores in HIV/HCV coinfecting patients receiving antiretroviral therapy: comparison of those patients treated and those not treated for HCV infection (n= 139, cross-sectional feasibility survey for the HEPAVIH project, 2005, French National Agency for AIDS and viral hepatitis Research - ANRS)

median [interquartile range]	Patients treated for HCV infection n=24	Patients not treated for HCV infection n=115	P-value ¹
State Anger n=107	22 [15; 30]	17 [15; 21]	0.07
Trait Anger n=109	20.5 [13; 23.5]	17 [14; 21]	0.27
Anger Expression-Out n=108	16 [11; 18]	14 [13; 17]	0.78
Anger Expression-In n=109	18 [14.5; 21]	18 [15; 21]	0.83
Anger Control-Out n=110	18.5 [17.5; 23]	23 [18; 26]	0.02
Anger Control-In n=103	20 [18; 23]	22 [17.5; 25]	0.47

¹ nonparametric two-sided Wilcoxon rank-sum test