

# Determinants of antiviral treatment initiation in a hepatitis C-infected population benefiting from universal health care coverage

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**BACKGROUND AND AIMS:** In view of increasing therapeutic efficacy, the delivery of hepatitis C virus (HCV) antiviral treatment is expected to increase. Yet practical experience reveals a low rate of treatment, particularly among intravenous drug users. The aim of the present study was to examine the prevalence of HCV treatment and identify factors associated with HCV treatment in a population of patients evaluated in an academic hepatology outpatient clinic between 2001 and 2002.

**PATIENTS AND METHODS:** The charts of HCV-infected patients who attended the outpatient clinic of the liver division between January 2001 and December 2002 were retrospectively reviewed. Regression analyses were conducted to compare patients according to HCV treatment initiation.

**RESULTS:** Of 378 eligible patients (past intravenous drug users 61%), 143 (38%) initiated antiviral treatment. Enrolment in a methadone maintenance program and a strong willingness to get treatment were independently associated with treatment initiation, while current intravenous drug use, alcoholic liver damage on biopsy, precarious housing arrangements and personality disorders were negatively associated with treatment initiation. Among patients who were offered treatment, 40% refused (they did not differ from the treated group for past or current substance abuse).

**CONCLUSIONS:** Only 38% of eligible patients initiated treatment; treatment refusal was very common. The results of the present study showed that a significant barrier to therapy involved patient perceptions.

**Key Words:** Alcohol intake; Hepatitis C; Interferon treatment; Substance-related disorders

The treatment efficacy of patients infected with hepatitis C virus (HCV) has improved significantly over the past 10 years, reaching sustained virological response rates of over 50% (1). HCV antiviral treatment is unfortunately associated with a number of side effects, some of which are severe and can lead to significant disability (2). Furthermore, HCV treatment is very expensive. Therefore, the treatment decision is subject to controversies and has compelled the adoption of national and international expert panel consensus statements (3-5).

## Les déterminants de l'instauration d'un traitement antiviral au sein d'une population infectée par l'hépatite C profitant du système de soins de santé universels

**HISTORIQUE ET OBJECTIFS :** Afin d'en accroître l'efficacité thérapeutique, la prestation du traitement antiviral contre le virus de l'hépatite C (VHC) devrait augmenter. Pourtant, l'expérience pratique révèle un faible taux de traitement, notamment chez les utilisateurs de drogues injectables. La présente étude visait à examiner la prévalence du traitement au VHC et à repérer les facteurs associés à ce traitement au sein d'une population de patients évalués dans une clinique ambulatoire universitaire d'hépatologie entre 2001 et 2002.

**PATIENTS ET MÉTHODOLOGIE :** On a procédé à l'examen rétrospectif des dossiers des patients infectés par le VHC qui ont fréquenté la clinique ambulatoire de la division hépatique entre janvier 2001 et décembre 2002. Des analyses de régression ont permis de comparer les patients d'après l'instauration d'un traitement contre l'hépatite C.

**RÉSULTATS :** Des 378 patients admissibles (anciens utilisateurs de drogues intraveineuses, 61 %), 143 (38 %) ont entrepris un traitement antiviral. La participation à un programme d'entretien à la méthadone et une forte volonté de se faire traiter s'associaient de façon indépendante à l'instauration du traitement, tandis que l'utilisation courante de drogues intraveineuses, une atteinte hépatique alcoolique révélée à la biopsie, un logement précaire et des troubles de la personnalité s'associaient négativement à l'instauration du traitement. Chez les patients à qui on avait offert le traitement, 40 % l'ont refusé (ils ne différaient pas du groupe traité pour l'utilisation courante ou passée de drogues).

**CONCLUSIONS :** Seulement 38 % des patients admissibles ont entrepris le traitement, et le refus de traitement était très courant. Les résultats de la présente étude révèlent que les perceptions des patients constituent un important obstacle au traitement.

It has been observed that patients with mental disorders or drug dependence (6-8) are often denied treatment on the assumption that they would experience severe side effects (in particular depression), and are subject to continuous risk of reinfection because of potential re-exposure to the virus after treatment (6-10). Ongoing alcohol abusers are also denied treatment on the basis of overall lower response rates because of the persistent liver damage caused by alcohol despite the potential for viral eradication (9,10). In many countries, the

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treatment cost also represents a significant treatment barrier among populations with insufficient medical insurance coverage.

Most studies published so far on the efficacy of HCV treatment were conducted among carefully selected patient populations with none of the previously discussed conditions, for whom the treatment was paid by the sponsors of the clinical trials (6). Yet, a growing number of studies have demonstrated the feasibility of treating HCV infections among intravenous drug user (IDU) populations (11-14). Data in IDUs successfully treated for HCV suggest that reinfection is rare even if drug injection behaviour continues, as long as high-risk behaviours are minimized (12,13,15-17).

From a public health perspective, treating IDUs could yield a significant decrease in the reservoir of HCV-infected individuals, and can potentially decrease the rate of transmission in a population where public health measures have failed to control the HCV epidemic until now (8,18).

We report herein the results of a study undertaken to assess the importance of the different biopsychosocial parameters involved in the physician's decision to administer treatment and in the patient's decision to accept the proposed therapy. The present study was conducted in a large referral-based liver disease clinic in Montreal, Quebec, where the cost of treatment was fully covered by either private or government-based insurances.

## PATIENTS AND METHODS

### Setting

The liver unit of the St Luc Hospital of the Centre Hospitalier de l'Université de Montréal (Montreal, Quebec) is the largest specialized hospital-based facility for the treatment of liver diseases in Quebec. Between January 1, 2001, and December 31, 2002, a total of 3300 patients, 1317 of whom were HCV-infected individuals, were followed by trained hepatologists. Most patients came from the greater Montreal metropolitan area. Antiviral HCV treatment was prescribed almost exclusively by specialists at the time of the investigation. The only treatment available during the study period was interferon in combination with ribavirin. Patients were treated 24 to 48 weeks, according to their HCV genotype. At the time of the study, it was considered that HCV genotype and viral load should not be factored in the decision to treat, and thus genotype testing was performed only after the treatment offer to determine its duration. All patients benefited from full coverage of all medical and pharmaceutical costs through the province of Quebec's universal mixed insurance plan. Of note, pegylated interferon became available in December 2002 through private insurance and in February 2003 through the government drug insurance plan. Yet patients who were offered antiviral therapy in the transition period (eg, between federal approval in March 2002 and provincial coverage in February 2003) were counselled as to whether they should wait until the medication became freely available before initiating their treatment. These patients were included in the present analysis if they accepted to receive pegylated interferon during the study period, although treatment initiation was delayed.

### Patients

A retrospective chart review of all 1317 HCV-infected patients seen between January 1, 2001, and December 31, 2002, at the outpatient clinic of the liver unit was conducted. Approval from the local Research Ethics Board of the Centre Hospitalier de l'Université de Montréal was granted. To be included in the

investigation, patients had to be eligible for HCV antiviral therapy at least once during the study period. Criteria included age older than 18 years, serum HCV RNA positivity, abnormal alanine aminotransferase (ALT) levels and a fibrosis stage greater than 1 on liver biopsy according to the Knodell classification (19). Patients with symptomatic cryoglobulinemia or acute HCV infection were also eligible regardless of the other criteria. Exclusion criteria included prior antiviral treatment for HCV, major contraindications for antiviral therapy (decompensated liver disease, severe thrombopenia or neutropenia, pregnancy, renal failure and major uncontrolled psychiatric disease) and coinfection with HIV or hepatitis B virus.

### Study methods

All charts from HCV-infected patients followed at the liver unit between January 2001 and December 2002 were initially identified using the centralized appointment hospital database (MEDITECH, USA). A pilot compilation of 30 patients was conducted to identify information usually available in the charts. All data were retrieved by the same research assistant, who was trained and knowledgeable in the field of HCV diagnosis and treatment.

Information from several visits was available for the same patient in most cases. Information was preferentially retrieved from the physician's notes. For those patients who were followed without being offered treatment throughout the study period, variables from their last visit were used. Variables on sociodemographic data, alcohol and drug use patterns, addiction treatment exposure, psychiatric condition and biological liver parameters were retrieved.

Sociodemographic indicators were sex, age, marital and familial status including living arrangements, occupation, and social disorganization indicators such as incarceration and drunk-driving offences. Information on alcohol and drug use was available in most charts and included duration of drug use and length of abstinence (in years). Patients were categorized as former IDUs if they reported having stopped prior injection drug use (there was no required period of abstinence). Active injection drug use referred to current injection practice. Current alcohol-related problems were defined as either current hazardous, harmful drinking (including current alcoholic hepatitis) or alcohol dependence. Hazardous drinking corresponded to alcohol intake likely to increase the risk of developing alcohol-related harm (greater than 14 units/week for women and greater than 21 units/week for men); harmful drinking corresponded to a pattern of drinking associated with the development of alcohol-related harm.

Resolute request for treatment was defined as an unambiguous and insistent request from the patient to receive antiviral treatment. HCV-related symptoms were also retrieved and categorized dichotomously.

Clinical indicators of liver disease included hepatic enzyme assessment (eg, ALT, aspartate aminotransferase and liver biopsy). Only liver biopsies performed the year before the treatment decision were considered (41.5% of patients). Liver fibrosis was expressed according to the Knodell histological score and further categorized into five groups (0 to 4). The presence of alcoholic liver damage suggested that the liver disease was partly or mainly alcohol-related.

### Statistical analysis

Sociodemographic characteristics, symptom-related factors and drug use factors were compared between patients who decided to initiate an antiviral treatment during the observation period and those who did not. Logistic regression was used to calculate crude

ORs and respective 95% CIs of the association of HCV antiviral treatment with each category of variable defined on the basis of information provided during the chosen visit. Nonparametric tests were used to compare continuous values. Data were analyzed using SAS version 8.0 (SAS Institute Inc, USA) for Windows (Microsoft Corporation, USA).

Independent factors associated with antiviral treatment were assessed using a stepwise logistic regression. Only the most informative variables were used at this stage, based on substantive knowledge, preliminary univariate analysis and assessment of collinearity. P values of 0.05 and 0.15 were used for entry and removal of variables, respectively.

Similar analyses, using logistic regression, were also conducted to calculate crude and adjusted ORs and respective 95% CIs of the association between treatment acceptance and individual characteristics among those patients who were offered treatment.

## RESULTS

Of the 1317 patient charts examined, only 378 patients (29%) were eligible to receive antiviral treatment according to the aforementioned criteria. Reasons for noneligibility included previous treatment (n=364), liver transplantation (n=47) or HIV positivity (n=36); contraindication to antiviral treatment (severe liver disease, and cardiac or renal conditions [n=159]); absence of medical indication for treatment (no HCV replication, normal ALT and no fibrosis [n=319]); and incomplete chart data (n=14). Included in the 378 eligible patients were six patients with cryoglobulinemia and seven patients with acute HCV (five from active intravenous drug use, one from professional exposure and one from unknown cause). Eligible patients were predominantly male (n=256 [68%]) with a mean age of 45.4 years (interquartile range of 39 to 51 years). Two hundred six (54.5%) patients had a past history of injection drug use and 139 (37%) patients reported a past history of alcohol-related problems. Current alcohol or drug use was reported by 97 patients (25.7%), and of those, 27 (7%) were active IDUs.

Of the 378 eligible patients, 238 (63%) were offered treatment and 143 actually initiated antiviral therapy. Thus, only 60% of patients who were offered treatment actually underwent therapy. Five of six patients with cryoglobulinemia and three patients with acute HCV (one from professional exposure, one from unknown cause, and one of five from intravenous drug use) underwent therapy. Forty-one (29%) patients were treated with pegylated interferon and 102 with interferon alpha in combination with ribavirin. Physicians recorded the following justifications when they denied treatment to those eligible (n=140) – loss to follow-up after the assessment of eligibility (n=45 [32.1%]), current drug- or alcohol-related problems (n=47 [33.6%]), active psychiatric condition (n=27 [19.3%]) and the remainder being unspecified (n=21 [15%]). No information was available on the patients' reasons for refusing therapy.

Table 1 outlines the differences in sociodemographic characteristics, past and current drug and alcohol history, and health indicators between patients who initiated antiviral therapy and those who did not. Age was negatively associated with treatment. Individual characteristics, generally consistent with a better social integration, such as family support; stable living arrangements; reporting a social occupation; and being on methadone maintenance treatment were associated with treatment initiation. Although reporting a history of

**TABLE 1**  
**OR and 95% CI of hepatitis C virus (HCV)-infected patients who initiated antiviral treatment and those who did not**

	All eligible patients, n=378		
	All eligible patients, n (%)	Frequency of treated patients, n (%)	OR (95% CI)
<b>Sociodemographic characteristics</b>			
Sex			
Male, 256 (67.7)	100 (39.1)	1	
Female, 122 (32.3)	43 (35.2)	0.85 (0.5–1.3)	
Age			
≤45 years, 196 (51.8)	85 (43.4)	1	
>45 years, 182 (48.1)	58 (31.9)	0.61 (0.4–0.9)	
Married or common law			
No, 154 (43.6)	49 (31.8)	1	
Yes, 199 (56.4)	91 (45.7)	1.81 (1.2–2.8)	
Family support*			
No, 139 (39.6)	40 (28.8)	1	
Yes, 212 (60.4)	96 (45.3)	2.04 (1.3–3.2)	
Accommodation			
With others, 218 (57.6)	98 (45.0)	1	
Alone, 112 (29.6)	38 (34.0)	0.63 (0.4–1.0)	
Precarious†, 26 (6.9)	4 (15.4)	0.22 (0.1–0.60)	
Unspecified, 22 (5.8)	3 (13.6)	0.19 (0.1–0.6)	
Occupation‡			
No, 129 (35.0)	39 (30.2)	1	
Yes, 240 (65.0)	101 (42.1)	1.75 (1.1–2.8)	
Past history of incarceration			
No, 318 (84.1)	120 (37.7)	1	
Yes, 60 (15.9)	23 (38.3)	1.02 (0.6–1.8)	
Past history of prostitution			
No, 368 (97.3)	140 (38.0)	1	
Yes, 10 (2.7)	3 (30.0)	0.70 (0.2–2.7)	
<b>Alcohol- and drug-related characteristics</b>			
Methadone maintenance treatment			
No, 358 (94.7)	130 (36.3)	1	
Yes, 20 (5.3)	13 (65.0)	3.26 (1.3–8.3)	
Current injection drug use			
No, 351 (92.9)	142 (40.5)	1	
Yes, 27 (7.1)	1 (3.7)	0.06 (0.0–0.4)	
Past history of illicit drug use			
No, 249 (65.9)	94 (37.8)	1	
Yes, 129 (34.1)	49 (38.0)	1.01 (0.7–1.5)	
Current illicit drug use			
No, 332 (87.8)	130 (39.2)	1	
Yes, 46 (12.2)	13 (28.3)	0.61 (0.3–1.2)	
Past history of alcohol-related problems			
No, 239 (63.2)	83 (34.7)	1	
Yes, 139 (36.8)	60 (43.2)	1.43 (0.9–2.2)	
Current alcohol-related problems			
No, 329 (87.0)	134 (40.7)	1	
Yes, 49 (13.0)	9 (18.4)	0.32 (0.2–0.7)	
<b>Mental health-related characteristics</b>			
Past history of psychiatric diagnosis			
No, 259 (68.5)	99 (38.2)	1	
Yes, 119 (33.5)	54 (45.3)	1.06 (0.7–1.7)	

Continued on next page

**TABLE 1 – CONTINUED****OR and 95% CI of hepatitis C virus (HCV)-infected patients who initiated antiviral treatment and those who did not**

All eligible patients, n (%)	All eligible patients, n=378	
	Frequency of treated patients, n (%)	OR (95% CI)
<b>Mental health-related characteristics - continued</b>		
Current depression		
No, 334 (88.4)	127 (38.0)	1
Yes, 44 (11.6)	16 (36.4)	0.93 (0.5–1.8)
Personality disorder		
No, 351 (92.9)	139 (39.6)	1
Yes, 27 (7.1)	4 (14.8)	0.26 (0.1–0.8)
Resolute request for treatment		
No, 351 (92.9)	122 (34.8)	1
Yes, 27 (7.1)	21 (77.8)	6.57 (2.6–16.7)
<b>Clinical indicators of liver disease</b>		
Reported HCV-related symptoms		
No, 256 (67.7)	88 (34.4)	1
Yes, 122 (32.3)	55 (45.1)	1.56 (1.0–2.4)
Liver biopsy year before treatment decision		
No, 221 (58.5)	51 (23.1)	1
Yes, 157 (41.5)	92 (58.6)	4.72 (3.0–7.4)
Fibrosis on liver biopsy (n=157)		
2 – reference group, 79 (50.3)	37 (46.8)	1
0 or 1, 10 (6.4)	8 (80.0)	4.54 (0.9–22.7)
3, 22 (14.0)	15 (68.2)	2.43 (0.9–6.6)
4 – cirrhosis, 46 (29.3)	32 (69.6)	2.60 (1.2–5.6)

Results by logistic regression. \*Married, living in common law or have children at home; <sup>†</sup>Homeless or living in monthly rental rooms; <sup>#</sup>Employed, retired, in school or at home with children

incarceration, prostitution, or alcohol- or drug-related problems had no impact on treatment offer, patients who were current IDUs or alcohol users were much less likely to have received treatment. Of the mental health characteristics recorded in the chart, a mention of a personality disorder by the physician was negatively associated with receiving treatment. Of note, when a patient was expressing a resolute request for treatment, as noted by the physician, this patient was 6.5 times more likely to receive antiviral therapy. Finally, patients who reported symptoms attributed to their HCV infection were also more likely to be treated.

There were no significant differences between the treated and the untreated groups in regard to median levels of aspartate aminotransferase (1.6 times the upper limit of normal versus 1.7, respectively) or ALT (2.2 times the upper limit of normal versus 1.9, respectively). Among the 157 patients for whom a liver biopsy was performed in the previous year, only stage 4 fibrosis was significantly associated with more treatment when compared with stage 2 fibrosis. To account for the fact that a non-negligible number of patients in the untreated group were offered treatment yet declined to be treated, treated patients were compared with the restricted group of patients who were never offered treatment, thus excluding those who were offered treatment but declined the offer. Overall, this restriction did not have a significant effect on estimated ORs (results not shown but are available from the corresponding author).

**TABLE 2****Adjusted OR and 95% CI of hepatitis C virus-infected patients who initiated antiviral treatment and those who did not**

Category	OR (95% CI)
Age	
≤45 years	1
>45 years	0.61 (0.38–0.98)
Current injection drug use	
No	1
Yes	0.02 (0.0–0.16)
Accommodation	
Living with other(s)	1
Alone	0.77 (0.46–1.31)
Precarious	0.22 (0.06–0.77)
Unspecified	0.16 (0.04–0.59)
Current alcohol-related problem	
No	1
Yes	0.38 (0.17–0.85)
Methadone maintenance treatment	
No	1
Yes	8.19 (2.08–32.30)
Personality disorder	
No	1
Yes	0.23 (0.10–1.11)
Current depression	
No	1
Yes	0.84 (0.40–1.75)
Resolute request for treatment	
No	1
Yes	8.12 (2.74–24.09)

Results by multivariate regression models

The results of the multivariate logistic regressions are shown in Table 2. Determination to undergo treatment, younger age, being on methadone maintenance therapy and living with other people were all associated with the likelihood of being treated. Patients with personality disorders and current alcohol users or IDUs were less likely to get treated.

Because a substantial proportion of patients declined therapy, factors associated with treatment acceptance were sought after. Table 3 shows crude ORs of treatment acceptance and the multivariate model of individual characteristics independently associated with treatment acceptance among patients who were offered treatment. In univariate analysis, younger age, a past history of alcohol or drug use, methadone maintenance therapy, a past history of psychiatric disorder or current depression were all positively associated with treatment acceptance. Not surprisingly, a resolute determination to be treated was strongly associated with acceptance. In multivariate analysis, a resolute determination, methadone maintenance, a past history of alcohol-related problems and younger age were all independently associated with treatment acceptance.

## DISCUSSION

In the present study, we aimed at identifying factors associated with the initiation of HCV antiviral therapy in patients benefiting from universal health care coverage, in a large

urban setting. Among anti-HCV-positive patients, only 29% of the studied patients were eligible for treatment at the end of the evaluation process. Similar results were reported in recent studies among HCV-infected patients from hepatology units (20,21), past IDUs (11) or United States veterans (22,23), and were mostly associated with absence of viral replication, normal liver enzymes, mild liver disease or contraindication to treatment. Yet, of all eligible patients, only 38% actually initiated anti-HCV therapy.

A combination of factors led to this low proportion of treated patients. First, a significant proportion of patients either withdrew from the evaluation process or refused the treatment offered by their physician. Second, physicians chose not to offer therapy to otherwise eligible patients.

Thirty-two patients among those eligible dropped out during the evaluation process, mostly between the baseline clinical and biochemical assessment and the follow-up visit, a situation observed in other studies (20). This high attrition rate was however unexpected, given that most patients were referred by their general practitioners and had waited an average of six to 12 months to get their appointment. In addition, a high proportion of those who were offered treatment after the evaluation process decided not to get therapy. Unfortunately, patients' reasons to withdraw or refuse therapy were not recorded. Nevertheless, our results suggest a deficiency in the provision of adequate counselling and information by primary care physicians before reference, a situation documented elsewhere. Surveys of primary care physicians demonstrated a number of potential knowledge deficits that could impact both the diagnosis and subsequent care of patients with HCV (24). Likewise, only 1% to 5% of surveyed primary care physicians reported having prescribed antiviral therapy (24). Mistrust toward the medical system may have also played a role. In a qualitative study conducted in Montreal, the failure of professionals to provide satisfactory answers on how a person's body gets rid of the virus was interpreted by IDUs as a limit of biomedicine and a reason not to trust current therapies (11,25,26). These studies support our contention that patients consulting in the hepatology clinic may have developed misconceptions and unrealistic expectancies, and even skepticism, toward HCV treatment before getting the proper information. Thus, many could have withdrawn after having received adequate information on HCV therapy, side effects and outcomes. The requirement of a liver biopsy during the evaluation process may have deterred patients from pursuing the evaluation process and may have been an additional barrier to treatment access. Together, these factors may explain the high rate of dropouts during the evaluation process, and treatment refusal when offered.

Barriers to treatment initiation have been raised at the evaluation process by the clinicians. From the hepatologist standpoint, current intravenous drug or alcohol use was among the main barriers to offering antiviral treatment. Factors associated with low social support were also negatively associated with treatment. These variables were correlated with substance abuse, and only precarious or unspecified accommodation remained an independent determinant of treatment in the multivariate model. Nevertheless, a few patients with current abuse were treated, despite the fact that this was considered a contraindication in the 2000 Canadian consensus conference on the management of viral hepatitis (27), a constraint no longer applicable in the most recent version of Canadian guidelines (3). Our results also suggest that patients perceived as being

**TABLE 3**  
Crude and adjusted ORs and 95% CIs of treatment acceptance among 238 patients who were offered hepatitis C virus (HCV) treatment

Category, n (%)	Frequency of patients accepting treatment, n (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Age			
≤45 years, 122 (51.3)	85 (69.7)	1	1
>45 years, 116 (48.7)	58 (50.0)	0.44 (0.26–0.74)	0.47 (0.27–0.83)
Methadone maintenance treatment			
No, 224 (94.1)	130 (58.0)	1	1
Yes, 14 (5.9)	13 (92.9)	9.40 (1.21–73.1)	9.80 (1.24–77.4)
History of injection drug use			
No, 118 (49.6)	61 (51.7)	1	
Yes, 120 (50.4)	82 (68.3)	2.02 (1.19–3.42)	
History of alcohol-related problems			
No, 152 (63.9)	83 (54.6)	1	1
Yes, 86 (36.1)	60 (69.8)	1.92 (1.10–3.36)	1.99 (1.10–3.59)
Past psychiatric disorder			
No, 179 (75.1)	99 (55.3)	1	
Yes, 59 (24.8)	44 (74.6)	2.37 (1.23–4.57)	
Current depression			
No, 219 (92.0)	127 (58.0)	1	
Yes, 19 (8.0)	16 (84.2)	3.86 (1.10–13.6)	
Resolute request for treatment			
No, 215 (90.3)	122 (56.7)	1	1
Yes, 23 (9.7)	21 (91.3)	8.01 (1.83–3.50)	7.97 (1.79–35.5)
Reported HCV-related symptoms			
No, 157 (66%)	88 (56.0)	1	
Yes, 81 (34%)	55 (67.9)	1.65 (0.34–1.06)	

Results by univariate and multivariate regression models

psychologically unstable were more often denied treatment access. Physician's assessment of a personality disorder, mainly of the antisocial or borderline type, was negatively associated with treatment. In contrast, a past history of psychiatric problems was not associated with the decision to treat, as was past drug or alcohol abuse. Borderline and antisocial personality diagnoses are more prevalent among past or current substance abusers (28), yet it seems that it was the personality disorder rather than substance abuse that influenced the physician's decision to treat in the present study.

Over the study period, patients with active severe depression or psychosis were systematically excluded because 'major uncontrolled psychiatric disease' (without more precision) was considered a contraindication to treatment in the Canadian consensus guidelines (27). Patients with current depression were considered eligible only if the condition was considered stable by the physician. Of interest, current depression was not associated with the likelihood of being treated, but was associated with a higher acceptance rate. This suggests that patients identified as suffering from depression by the physician may have benefited from a more extensive counselling and informed consent. Depression may deter physicians from treating patients because of fear of the increased suicidal risk. Dieperink et al (29) demonstrated that there was an increase in suicidal ideation during HCV treatment. Recently, it was found that the prophylactic use of specific serotonin reuptake inhibitors was effective in the prevention of interferon-induced depression among patients with a history of interferon-induced major

depression (30), and that patients with mood disorders can be treated with similar results when properly managed during treatment (31). Altogether, these findings suggest that patients with mood disorders or active drug use present challenges to effective treatment that require attention but do not automatically warrant categorical exclusion. We believe that these issues should be addressed on an individual basis.

Our results are quite consistent with recent data from the Veterans Affairs health care system (USA) (32). Although using different design and methodology, both studies identified the role of ongoing substance abuse and psychiatric disorders as an obstacle to treatment, and the high rate of refusal among patients who were offered treatment. The Veterans Affairs study is prospective and is based on a specific group, while our study was retrospective and conducted among a population with universal health coverage insurance, observed by hepatologists in a large urban hospital.

In examining factors associated with treatment initiation and acceptance, we found that participation in a methadone maintenance program was associated with both a higher probability of treatment proposal and a higher acceptance rate. Methadone patients seem to have been considered better candidates by the hepatologists and more likely to accept treatment. This can represent a referral bias because these patients have, by definition, regular medical and psychiatric follow-ups by physicians presumably experienced with chronic viral infections, and are considered to be at low risk of relapsing into drugs. This also suggests that information on HCV treatment before reference and trust in the biomedical care system influences the decision to seek and accept treatment. Some patients expressed the will to be treated so vigorously that it was mentioned in their charts. This was probably more often assessed in those patients for whom treatment indication was debatable. This resolute request from the patient strongly influenced the physician's decision indicating that the decision to treat was not solely dependent on objective medical parameters. Acceptance was also associated with younger age, and this could be due to the fact that elderly patients balance their life expectancy with the risk of developing decompensated liver disease.

There are several limitations to this research design. The study population and the type of medical service are not representative of the whole population of HCV-infected individuals, and results may not be applicable to patients in other settings. Although patients recruited in our study may not be representative, they may well correspond to the next wave of HCV patients because contamination by intravenous drug use is nowadays the major route of transmission.

The period of data collection corresponds to earlier protocols and different Canadian guidelines, and results may not be fully applicable to current practices. Of note, the current standard of care includes the assessment of genotype and viral load to help predict outcomes. This can further affect the decision-making process, by increasing treatment acceptance among those with genotype 2/3- compared with genotype 1-infected individuals. The information was retrospectively retrieved from chart reviews and not prospectively collected for research purposes. For instance, only partial information was collected on psychiatric comorbidities and treatment; no information was gathered on the patient's motivations to accept or decline a treatment offer. Nevertheless, the clinical data collection followed a standard protocol that minimized missing

information and was not subject to information bias. Ultimately, the retrospective chart analysis represents a simple tool to identify some key research questions for the future.

Overall, our results suggest that treatment initiation can be conceptualized as a fine balance on both sides, between physician's perceptions of the patient's competency, and the patient's willingness and motivation to enter such a medical endeavour. In addition, treatment initiation is dependent on the ability of our health system to offer appropriate information at the time of diagnosis, timely referral and adapted services to those seeking treatment for their condition.

To avoid the promised burden of HCV cirrhosis in the next 20 years (33), the proportion of eligible patients actually treated should be increased. In our study, motivation to get the treatment was the strongest determinant of HCV treatment acceptance. With the availability of more effective treatments, research should seek to better understand the relation among the patient, the physician and the decision process. Documenting reasons for patients' refusal could help us better understand and better address misconceptions with therapy that could prevent patients from initiating therapy. Because it has been demonstrated that the rate of treatment initiation was increased in the presence of a multidisciplinary approach (23), further studies are needed to better identify specific components of multidisciplinary approach that are important to enhance the rates of initiation, retention and success for anti-HCV treatment.

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