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Suicidal risk among patients enrolled in methadone maintenance treatment: HCV status and implications for suicide prevention (ANRS Methaville)

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Abstract

Background: Suicide is a critical issue among opioid users. The aim of this study was to assess the relationship between HCV status and suicidal risk in patients receiving methadone treatment.
Methods: We used data from Methaville, a multicenter, pragmatic randomized trial designed to evaluate the feasibility of methadone induction in primary care compared with induction in specialized centers. Suicidal risk was assessed at enrollment and after one year of methadone treatment using the suicidality module in the MINI International Neuropsychiatric Interview. Socio-demographic characteristics, drug and alcohol consumption, behavioral and personality factors, history of drug use and health indicators were also assessed.
Results: A total of 195 individuals were enrolled from January 2009 to December 2010. Suicidal risk assessment was available at month 0 (M0) and M12 for 159 (72%) and 118 (73%) individuals, respectively. Forty-four (28%) were at risk of suicide at M0 and 17 (14%) at M12 ($p = 0.004$). One patient attempted suicide by overdose during the one-year follow-up. The following three factors were associated with suicidal risk: hepatitis C virus (HCV) positive status (OR [95%CI] = 17.25 [1.14–161.07]; $p = 0.04$), receiving food assistance (OR [95%CI] = 0.05 [0.00–1.05]; $p = 0.05$) and a higher number of health problems (OR [95%CI] = 1.24 [1.08–1.44]; $p = 0.003$).
Conclusions: Special attention should be given to HCV-positive patients through suicidal risk prevention strategies and routine suicide assessment as part of a comprehensive approach to prevention and care for opioid users. Our results represent a new and powerful argument for the expansion of access to HCV treatment to drug users with chronic infection.

1. Introduction

Suicide is a major issue among opioid users [1,2]. Heroin users are 14 times more likely to die from suicide than their counterparts in the general population [2]. Suicide is also one of the major causes of death among opioid users [3], annual suicide rates being estimated at between 6% and 10% [4]. A recent study conducted in opioid-dependent individuals prior to methadone maintenance treatment induction showed a prevalence of recent suicide attempts of 11% and a lifetime prevalence of 18% [5]. A clear overlap between suicide and overdose exists, mainly explained by the fact that overdosing is a common method of suicide [6]. Although associated with a decrease after treatment initiation irrespective of the treatment used [3], suicide attempts and suicide ideation rates in treated patients are nevertheless usually higher than in the general population [3,7]. Worldwide HCV prevalence

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among injecting drug users (IDU) is over 60% [8] and liver disease has become one of the most common causes of mortality among aging opioid-dependent populations [9]. Asthenia together with cognitive, depressive, and anxiety-based disorders are frequent in those with chronic hepatitis C and increase the burden of hepatitis infection [10]. Hepatitis C is therefore a major health concern for IDU, and HCV testing is systematically proposed in most addiction units throughout the territory in France. Using data from the Methaville trial, we aimed to assess the relationship between HCV status and suicidal risk in methadone-treated patients when accounting for other potential correlates of suicidal risk.

2. Material and methods

2.1. Study design

ANRS Methaville is a multicenter, pragmatic randomized trial, designed to evaluate the feasibility of methadone induction in opiate-dependent patients in primary care compared with induction in specialized centers.

Between January 2009 and January 2010, 195 men and women were recruited in 10 sites randomly allocated to initiate methadone either in specialized centers (hereafter standard care) or with primary care physicians. The full protocol is described elsewhere [11,12].

Participants were followed up at months 0 (M0, enrolment), 3, 6 and 12 months (M3, M6 and M12) through medical visits where medical and self-reported questionnaires were completed by the physician and patient, respectively, and through computer-assisted telephone interviews (CATI) after each medical visit, conducted by a trained non-judgmental interviewer.

For safety reasons, patients screening positive for opioids/benzodiazepines/alcohol triple co-dependence in the semi-structured MINI questionnaire (Mini International Neuropsychiatric Interview — French Version 5.0.0) [13] were not included in the study.

After the study was fully explained to the patients, we obtained their written informed consent to participate. This study was approved by the Ethics Committee of Persons Protection in Paris, France. The procedures followed were in accordance with the Revised Declaration of Helsinki (Edinburgh 2000).

2.2. Data collection

2.2.1. Outcome

Suicidal risk was assessed at enrolment and M12 using the suicidality module of the MINI questionnaire [13]. This module assesses suicidal risk according to the following factors: attempted suicide, self-harm, death and/or suicide ideation. Suicidal risk is considered present if a patient answers "yes" to at least one question in the module.

2.2.2. Socio-demographic characteristics

Data for the following socio-demographic characteristics were collected at baseline: sex, age, educational level, child(ren), employment status, housing (owner or renter, living with family, living in an hospital or clinic, living in a social care institute, living at a friend's home, living in a hotel room, having no home, other), history of incarceration and receiving food assistance. Unstable housing was defined as not being the owner or renter of one's housing. Employment status, housing and receiving food assistance were reassessed at M12.

2.2.3. Drug and alcohol consumption

At each visit, drug use in the previous month was assessed using the Opiate Treatment Index (OTI).

Individuals who reported using opiates, cocaine or injecting drugs at least once in the previous month were defined as opiate users, cocaine users or current injectors, respectively. Those who consumed cannabis in the 3 consecutive days before the questionnaire was administered were defined as daily cannabis users.

If OTI data for cocaine were missing, we used the results from the urine drug test performed during the same medical visit when available. Urine drug tests were performed at the discretion of the physician at each follow-up visit. Drugs which we tested for included opiates, benzodiazepines, buprenorphine, cocaine/crack, and methadone. At enrolment and M12, the prescribing physician was also interviewed about his/her patient's opiate consumption. We used this information when OTI data for opiate consumption were missing.

To identify prescribed and non-prescribed benzodiazepine users at both M0 and M12 we used different questions: the first question in the OTI (CATI) documented anxiolytics' use and type (including benzodiazepine). The second question, contained in the self-administered questionnaire, asked patients if they were taking pain killers. This was an open question, so we recoded all the drugs reported and reclassified them when a benzodiazepine was mentioned. The third question, contained in the medical questionnaire and answered by the physician, concerned the different medications prescribed to the patient.

During the medical visit physicians could perform a urine analysis for benzodiazepine.

A patient was defined a benzodiazepine user if benzodiazepine use was mentioned at least once in the three questions described above, or if urine analysis resulted positive.

We assessed alcohol consumption at M0 and M12 during the CATI using the Alcohol Use DIsorders Test (AUDIT) with a cut-off of 13 or more being used to identify alcohol dependence [14].

During the phone interview, patients were asked about their daily methadone dose. At each follow-up visit physicians also indicated the methadone dose they were prescribing to their patient in the medical questionnaire.

We assessed tobacco dependence using the Fagerstrom scale, which comprises 6 items. A cut-off value of at least 5 out of 10 defined a high or very high level of dependence [15].

2.2.4. History of drug use

At enrolment and during the phone interviews, patients were asked about their history of drug use. More specifically, they were asked whether they were switching from buprenorphine maintenance to methadone maintenance, whether they had a history of drug overdose, their drug injection history, age at first regular drug use, and age at first injection.

2.2.5. Health indicators

During the phone interview after each follow-up visit, patients were asked a list of questions about 50 health-related issues. The latter were grouped into more specific sections (general health condition, injection-related health problems, cardio-respiratory health, genito-urinary function, gyneco-logical issues, muscular-skeletal problems, neurological concerns, gastro-intestinal difficulties) occurring in the month prior to the visit. During each medical visit, physicians collected data about withdrawal symptoms using the Objective Opioid Withdrawal Scale (OOWS) which consists of a list of 13 withdrawal symptoms [16].

Positive or negative results of the patients' most recent hepatitis C virus (HCV) test were indicated at each medical visit in the medical questionnaire. If no test had been carried out or if the result of a test was not known, the "unknown" option was used. Systematic screening did not occur at every medical visit. However, information was collected at each visit.

Depressive symptoms were assessed at M0 and M12 using the CES-D scale. We used the validated French cut-off points of 17 for men and 23 for women [17].

At enrolment and M12, during the phone interview, patients were asked if they had visited a psychiatrist, psychologist or psychotherapist in the previous 6 months, or if they had been hospitalized for at least 24 hours in the same period for mental health reasons.

2.3. Statistical analyses

We used a chi-squared test for categorical variables and a Wilcoxon test for continuous variables to compare: (1) the characteristics of patients included in this analysis with those not included and (2) the characteristics of patients at enrolment according to suicidal risk.

As the outcome was measured only at M0 and M12, we only focused on these two follow-up visits.

We used mixed logistic regression models to test for any association between suicidal risk and the following factors: (1) Socio-demographic characteristics: sex, age, certified educational level, child(ren), employment, unstable housing, receiving food assistance and experience of incarceration; (2) Drug and alcohol consumption: opiate use, cocaine use, benzodiazepine use, current injection, alcohol and tobacco dependence, daily cannabis use and methadone dose; (3) History of drug use: switching from buprenorphine maintenance, history of drug overdose, history of drug injection, age at first regular drug use and age at first injection; and (4) Health indicators: depressive symptoms, visiting a psychiatrist, psychologist or psychotherapist at least once in the previous 6 months, number of health problems, number of withdrawal symptoms, HCV status.

We first performed a univariate mixed logistic regression analysis to assess the association between HCV status and suicidal risk and to test the effect of other known correlates/confounders on suicidal risk. Variables were considered eligible for the final model if $p < 0.25$ or if they significantly modified the strength of the association when introduced together with HCV status. A stepwise procedure was used to identify the final multivariate model, and variables were then removed one at a time based on a p-value of >0.05.

A sensitivity analysis was performed by testing the association between receiving methadone treatment and suicide risk after removing the variable "history of attempted suicide" from the outcome. All analyses were performed using the SPSS v15.0 (SPSS, Inc, Chicago, IL) and Intercooled Stata 10 (StataCorpLP, College Station, TX) software packages.

3. Results

Baseline data were available for 188 individuals among the 195 recruited and at M12, 162 patients were still participating. Suicidal risk assessment was available at M0 and M12 for 159 (72%) and 118 (73%) patients, respectively (Table 1). Overall, 169 had at least one assessment of suicidal risk at M0 and/or at M12. They constituted our study population.

At enrolment, no difference was observed in terms of socio-demographic characteristics and drug use between patients included in this analysis and those not included because of missing data on suicidal risk (data not shown).

At M0, patients included in this analysis were mainly males 136 (86%), median [IQR] age was 32 [27–38] years and 81 (51%) were switching from buprenorphine. Twenty-six (17%) patients had a history of suicide attempt, 20 (13%), a history of overdose and 7 (4%) both. During the 12-month period of assessment, one patient with a history of attempted suicide intentionally overdosed.

With respect to suicidal risk assessment, 44 (28%) were at risk of suicide at M0 (including 26 who had a history of attempted suicide) and 17 (14%) at M12 (including 11 with a history of attempted suicide).

The variables associated with suicidal risk in the univariate model are presented in Table 2. We decided to remove the "history of overdose" variable from the initial multivariate model as it was collinear with the outcome and consequently would have hidden the role of important correlates.

In the multivariate model (Table 3), the relationship between testing positive for HCV and suicidal risk at any visit was confirmed (OR [95%CI] = 13.52 [1.14–161.07]; $p = 0.04$), after adjustment for receiving food assistance (OR [95%CI] = 0.05 [0.00–1.05]; $p = 0.05$) and a greater number of reported health problems (OR [95%CI] = 1.24 [1.08–1.44]; $p = 0.003$). Among the 25 HCV-positive

Table 1
Patient characteristics at enrolment according to suicidal risk (ANRS Methaville trial, N = 159).

	HCV status			
	Negative or missing	Positive	Total	p*
Socio-demographic characteristics				
Sex				
Male	115 (85.8)	21 (84.00)	136 (85.53)	*0.51*
Female	19 (14.2)	4 (16.00)	23 (14.47)	
Age — in years	32 (27–36)	42 (32–46)	32 (27–38)	*0.0004*
Certified educational level				
<High-school diploma	88 (65.67)	17 (70.83)	105 (66.46)	*0.62*
≥High-school diploma	46 (34.33)	7 (29.17)	53 (33.54)	
Having child(ren)				
No	84 (63.16)	15 (62.50)	99 (63.06)	*0.95*
Yes	49 (36.84)	9 (37.50)	58 (36.94)	
Employment				
No	57 (42.24)	12 (54.55)	69 (46.62)	*0.42*
Yes	69 (54.76)	10 (45.45)	79 (53.38)	
Unstable housing				
No	41 (35.71)	10 (45.45)	55 (37.16)	*0.38*
Yes	81 (64.29)	12 (54.55)	93 (62.84)	
Receiving food assistance				
No	109 (87.90)	18 (81.82)	127 (86.99)	*0.31*
Yes	15 (12.10)	4 (18.18)	19 (13.01)	
History of incarceration				
No	98 (73.13)	15 (60.00)	113 (71.07)	*0.18*
Yes	36 (26.87)	10 (40.00)	46 (28.93)	
Drug consumption				
Benzodiazepine use				
No	98 (73.13)	16 (64.00)	114 (71.10)	*0.35*
Yes	36 (26.87)	9 (36.00)	45 (28.30)	
Alcohol dependence (AUDIT)				
No	105 (84.68)	18 (85.71)	123 (84.83)	*0.60*
Yes	19 (15.32)	3 (14.29)	22 (15.17)	
Tobacco dependence				
None/low/medium	87 (71.31)	13 (65.00)	100 (70.42)	*0.57*
High/very high	35 (28.69)	7 (35.00)	42 (29.58)	
Cocaine consumption[a]				
No	88 (70.97)	14 (58.33)	102 (68.92)	*0.22*
Yes	36 (29.03)	10 (41.67)	46 (31.08)	
Opiate consumption[a]				
No	32 (24.06)	11 (44.00)	43 (27.22)	*0.04*
Yes	101 (75.94)	14 (56.00)	115 (72.78)	
Daily cannabis use[a]				
No	105 (83.33)	17 (77.27)	122 (82.43)	*0.34*
Yes	21 (16.67)	5 (22.73)	26 (17.57)	
Drug injection[a]				
No	98 (86.73)	13 (61.90)	111 (82.84)	*0.01*
Yes	15 (13.27)	8 (38.10)	23 (17.16)	
Methadone dose — in mg				
<60	102 (77.27)	22 (88.00)	124 (78.98)	*0.18*
≥60	30 (22.73)	3 (12.00)	33 (21.02)	
History of drug use				
Switching from buprenorphine maintenance				
No	70 (52.24)	8 (32.00)	78 (49.06)	*0.06*
Yes	64 (47.76)	17 (68.00)	81 (50.94)	
History of drug overdoses				
No	128 (95.52)	11 (44.00)	139 (87.42)	$<10^{-3}$
Yes	6 (4.48)	14 (56.00)	20 (12.58)	
History of drug injection				
No	73 (58.40)	1 (4.55)	74 (50.34)	
Yes	52 (41.60)	21 (95.45)	73 (49.66)	
Age at first regular drug use	20 (18–25)	19 (18–23)	20 (18–24)	*0.12*
Age at first injection	22 (19–26)	19 (18–24)	21 (19–25)	*0.10*

Table 1 (*continued*)

	HCV status			
	Negative or missing	Positive	Total	p*
Health indicators				
Consulting a psychiatrist, psychologist or psychotherapist[b]				
No	97 (76.98)	16 (72.73)	113 (76.35)	*0.67*
Yes	29 (23.02)	6 (27.27)	35 (23.65)	
CES-D				
No	72 (59.02)	10 (47.62)	82 (57.34)	*0.33*
Yes	50 (40.98)	11 (52.38)	61 (42.66)	
Suicidal risk at enrolment — MINI				
No	101 (75.37)	14 (56.00)	115 (72.33)	*0.05*
Yes	33 (24.63)	11 (44.00)	44 (27.67)	
No. of health problems[a]	11 (6–16)	12 (6–14)	12 (6–16)	*0.77*
No. of withdrawal symptoms	2 (0–3)	2 (1–2)	2 (0–3)	*0.94*

* Chi-squared or Wilcoxon test.
[a] In the preceding month.
[b] In the preceding 6 months.

patients, 6 received HCV treatment until M12, 2 initiated HCV treatment but did not finish it, and 1 was still on treatment at the time of the study. High/very high tobacco dependence is also associated with higher suicidal risk but only as a statistical tendency (OR [95%CI] = 5.98 [0.91–39.43]; p = 0.06).

No correlation was found between HCV serostatus and social vulnerability (OR [IC95%] = 0.91 [0.00–38.465]; p = 0.76 for receiving food assistance, OR [IC95%] = 0.43 [0.04–4.10]; p = 0.46 for unstable housing and OR [IC95%] = 0.67 [0.08–5.49]; p = 0.46 for employment) or between HCV serostatus and alcohol use (OR [IC95%] = 0.76 [0.01–38.46]; p = 0.76).

The sensitivity analysis removing the variable "history of attempted suicide" from the outcome confirmed the association between HCV status and suicidal risk. Moreover, at enrolment and after one year of methadone treatment, thirty (18.87%) and 5 (4.24%) participants were, respectively, at risk of suicide, confirming the greater significance (p = 0.005) of the protective effect of methadone on suicidal risk.

4. Discussion

The main result of our study is that hepatitis C seropositivity is associated with suicidal risk even when accounting for known correlates of suicidal risk. To our knowledge, this association has never previously been clearly identified in opioid-dependent individuals. Suicidal risk and suicide have already been documented in the general population of treated and untreated chronically infected HCV patients [18,19] and share several common associated factors including drug use, excessive alcohol consumption and related social conditions, and psychiatric comorbidities [18]. It is therefore possible that this association between suicidal risk and hepatitis C seropositivity is more likely linked to the burden associated with HCV disease, including the physical consequences of liver dysfunction [20], as well as to the direct effect of the virus on the brain [21]. Nevertheless, in our survey, when looking at the correlation between HCV serostatus and social vulnerability or alcohol use, no clear association was observed. Neither could any association be found with the side effects of an IFN alpha anti-HCV treatment, as few patients were prescribed such treatment during the 12-month follow-up period. This result is a new and powerful argument to expand access to treatment to drug users with chronic HCV infection, especially since second generation antiviral agents (DAA) without psychiatric side-effects have started to become available.

The correlation between receiving food assistance (a proxy of social vulnerability/disability) and suicidal risk is not surprising. It underlines the importance of providing comprehensive care to opioid users, including assessment and coverage of social needs.

The literature consistently highlights that suicidal risk is highly prevalent among opioid-dependent patients before treatment initiation [2]. However it is important to underline that in our study, although suicidal risk was no longer significant after multiple adjustment (because of its collinearity with the number of health problems, which are significantly reduced during methadone treatment), initiating methadone was associated with a 70% reduced suicidal risk.

Although not confirmed in multivariate analysis, our results on the protective effect of methadone are consistent with those found in previous studies on suicide among opioid-dependent patients [2], and in other studies emphasizing the benefits of methadone treatment initiation with respect to suicidal ideation [7].

The association between suicidal risk and the number of health problems is also strong. Health indicators are rarely assessed in drug users despite the frequency of physical problems related to chronic drug use [22–25] and the burden of the side effects of methadone treatment (mainly sweating, weight gain, sexual dysfunction, sedation, constipation and drowsiness) [26,27]. Suicidal ideation has been associated with physical health in epileptic patients [28], self-perceived burden in chronic pain [29]

Table 2
Factors associated with suicidal risk during methadone treatment: univariate logistic regression (ANRS Methaville trial, N = 277 visits; 169 persons).

	Number of visits (%) or median (IQR)	Number of patients	OR	[IC95%]	p
Socio-demographic characteristics					
Methadone maintenance treatment					
No	159 (57.40)	159	1		
Yes	118 (42.60)	118	0.33	[0.11–1.01]	*0.05*
Sex					
Male	238 (85.92)	145	1		
Female	39 (14.08)	24	1.47	[0.11–18.44]	*0.77*
Age — in years	33 (27–39)		1.08	[0.96– 1.21]	*0.21*
Certified educational level[a]					
<High school diploma	186 (67.39)	113	1		
≥High school diploma	90 (32.51)	55	4.00	[0.62– 25.92]	*0.15*
Having child(ren)[a]					
No	170 (62.04)	103	1		
Yes	104 (39.96)	64	0.82	[0.14– 4.73]	*0.82*
Employment					
No	102 (40.80)	83	1		
Yes	148 (59.20)	103	0.11	[0.02–0.52]	*0.005*
Unstable housing					
No	84 (33.60)	65	1		
Yes	166 (66.40)	111	0.75	[0.17–3.39]	*0.71*
Receiving food assistance					
No	222 (89.52)	144	1		
Yes	26 (10.48)	24	0.11	[0.01– 1.90]	*0.13*
History of incarceration[a]					
No	200 (72.20)	119	1		
Yes	77 (27.80)	50	3.22	[0.37–28.18]	*0.29*
Drug consumption					
Benzodiazepine use					
No	204 (73.65)	135	1		
Yes	73 (26.35)	59	2.96	[0.68–12.83]	*0.15*
Alcohol dependence (AUDIT)					
No	216 (87.45)	135	1		
Yes	31 (12.55)	25	28.35	[1.79–447.92]	*0.02*
Tobacco dependence					
None/low/medium	182 (74.90)	119	1		
High/very high	61 (25.10)	47	32.41	[4.04–259.81]	*0.001*
Cocaine consumption[b]					
No	197 (76.06)	133	1		
Yes	62 (23.94)	52	4.37	[1.06–18.06]	*0.04*
Opiate consumption[b]					
No	123 (45.05)	93	1		
Yes	150 (54.95)	122	4.72	[0.84–26.46]	*0.08*
Daily cannabis use[b]					
No	205 (82.00)	134	1		
Yes	45 (18.00)	37	0.63	[0.11– 3.42]	*0.59*
Drug injection[b]					
No	209 (88.56)	133	1		
Yes	27 (11.44)	24	9.98	[1.43–69.80]	*0.02*
Methadone dose — in mg					
<60	157 (57.09)	130	1		
≥60	118 (42.91)	103	0.89	[0.26–3.04]	*0.86*
History of drug use					
Switching from buprenorphine maintenance[a]					
No	132 (47.65)	83	1		
Yes	118 (52.35)	86	0.92	[0.17– 5.13]	*0.93*
History of drug overdoses[a]					
No	242 (87.36)	149	1		
Yes	35 (12.64)	20	43.21	[1.94– 961.54]	*0.02*
History of drug injection[a]					
No	209 (88.56)	133	1		
Yes	27 (11.44)	24	13.67	[2.42– 77.10]	*0.003*
Age at first regular drug use	20 (18–25)		0.93	[0.79–1.10]	*0.41*
Age at first injection	22 (19–26)		0.95	[0.73– 1.24]	*0.73*

Table 2 (*continued*)

	Number of visits (%) or median (IQR)	Number of patients	OR	[IC95%]	p
Health indicators					
Consulting a psychiatrist, psychologist or psychotherapist[c]					
No	207 (82.80)	136	1		
Yes	43 (17.20)	39	3.16	[0.53–18.89]	*0.21*
CES-D					
No	157 (64.34)	109	1		
Yes	87 (35.66)	69	25.17	[4.35–145.79]	$<10^{-3}$
No. of health problems[b]	9 (4–15)		1.23	[1.10–1.38]	$<10^{-3}$
No. of withdrawal symptoms	0 (0–2)		1.35	[1.01–1.82]	*0.05*
HCV status					
Negative or unknown	222 (83.46)	134			
Positive	44 (16.54)	26	12.41	[0.84– 182.77]	*0.07*

[a] At enrolment.
[b] In the preceding month.
[c] In the preceding 6 months.

and, among drug users, HIV infection [30]. Health should be considered in a comprehensive way, incorporating physical problems due to drug use and withdrawal symptoms, but also methadone related side-effects which may tend to be underreported.

The association we found between tobacco dependence and suicidal risk is coherent with the literature [31] and appears to be independent of psychiatric history and socio-demographic characteristics [32]. The mechanism involved remains unclear [31] but this risk was found to be dose dependent (number of cigarettes smoked per day) [33]. Our population did not differ from the general population with regard to this association. Nevertheless, although not strictly significant in the final model, we needed to control for this important correlate in our model.

Considering the relatively high frequency of suicide and suicide attempts – including voluntary overdoses – in drug users, suicidal risk should be systematically assessed not only in active drug users but also for drug users at maintenance treatment initiation and during follow-up. Furthermore, specialized evaluation and care should be proposed when suicidal risk is confirmed.

This study has strengths and limitations. Its main strength is that it was nested in a pragmatic trial, i.e. designed to assure external validity, which means that participants were representative of individuals seeking care for opioid dependence in France.

Furthermore, the international neuropsychiatric interview MINI is a well-validated diagnostic tool and its suicidality module has been used in several epidemiological studies to assess suicidal risk. However, the module assesses suicidal ideation and attempts through crude questions which could lead to suicidality being underestimated, patients perhaps being embarrassed to admit suicidal behavior and mental problems [34]. In turn, in our study, this may have led to unidirectional misclassification of individuals who were in fact at risk of suicide, and therefore to an underestimation of the strength of the associations found. Moreover, as the MINI classifies patients with a history of attempted suicide as individuals at suicidal risk, their status cannot change while on treatment. When we removed the variable "history of suicide" from the MINI, receiving methadone treatment remained highly protective.

Furthermore, our assessment of drug use and alcohol consumption was also based on patient self-reports and consequently social desirability bias cannot be excluded. Again this bias could have led to a unidirectional misclassification, with participants having a high consumption of alcohol or drugs being misclassified as low or non-consumers of alcohol or drugs. The same argument can be applied for self-reported HCV serostatus as many of those interviewed may have been HCV positive without being aware of it. Nevertheless, all these possible misclassifications could only have resulted in an underestimation of the strength of the association between the behaviors outlined or HCV serostatus and the outcome. Moreover, the sample size was quite small, increasing the risk of missing an existing association. In addition many variables were tested, increasing the risk of finding a statistically significant difference by chance. Nevertheless, all the associations found were consistent with the international literature. Finally, even though our data were longitudinal, no conclusions about causality between HCV status and suicide risk could be drawn.

Table 3
Factors associated with suicidal risk during methadone treatment: multivariate logistic regression (ANRS Methaville trial, n = 139 patients, 217 visits).

N = 139 (217)	OR	[IC95%]	p
Receiving food assistance			
No	1		
Yes	0.05	[0.00–1.05]	0.05
HCV status			
Negative or unknown	1		
Positive	13.52	[1.14–161.07]	0.04
Tobacco dependence			
None/low/medium	1		
High/very high	5.98	[0.91–39.43]	0.06
No. of health problems	1.24	[1.08–1.44]	0.003

5. Conclusions

Suicide is a major issue among drug users. However, it is possible to act on this problem in the following ways: systematic early HCV testing in all facilities where drug users are consulted, treating diagnosed HCV quickly, improving physical health and quality of life by adopting comprehensive care approaches, covering basic social needs and improving patients' social situation with rehabilitation programs. While crucial in the context of drug users, these objectives are also important for many different chronic medical conditions. They need to be included in national public health strategies. The real challenge lies however in their practical implementation.

The Methaville ANRS trial is registered as follows: the French Agency of Pharmaceutical Products (AFSSAPS) under the number 2008-A0277-48; the European Union Drug Regulating Authorities Clinical Trials: Number Eudract 2008-001338-28; the ClinicalTrials.gov Identifier: NCT00657397 and the International Standard Randomized Controlled Trial Number Register ISRCTN31125511.

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