HCV Cure and Cannabis Abstinence Facilitate Tobacco Smoking Quit Attempts in HIV-HCV Co-Infected Patients (ANRS CO13 HEPAVIH Cohort Study)

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HCV cure and cannabis abstinence facilitate tobacco smoking quit attempts in HIV-HCV co-infected patients (ANRS CO13 HEPAVIH cohort study)

Abstract

Background and aims. In Western countries, tobacco smoking is highly prevalent among patients co-infected with HIV and hepatitis C virus (HCV). In the era of antiretrovirals and HCV cure, smoking-related health damages contribute greatly to morbidity and mortality in HIV-HCV co-infected patients. We used longitudinal data from the ANRS CO13 HEPAVIH cohort to identify the correlates of tobacco smoking quit attempts (TSQA) in HIV-HCV co-infected patients.

Methods. TSQA were modelled using a multivariable discrete-time Cox proportional hazards model in 695 HIV-HCV co-infected tobacco smokers.

Results. HCV cure was associated with a 76% higher chance of TSQA (adjusted hazard ratio [95% confidence interval]: 1.76 [1.06-2.93], p=0.029), and cannabis use with a 37% lower chance (0.63 [0.40-1.00], p=0.049), independently of the mode of HIV transmission, other psychoactive substance use, and body mass index.

Conclusions. Patients should be screened for tobacco and cannabis use at HCV treatment initiation and during follow-up. They should also be provided with comprehensive counselling and referral to addiction services. Non-smoking routes of cannabis administration should be promoted for cannabis users who wish to quit smoking tobacco.

Key words: cannabis; tobacco; smoking cessation; human immunodeficiency virus; hepatitis C, chronic.

Introduction

Tobacco smoking prevalence among people living with HIV (PLWH) is over 50% in high-income Western countries (1). In France, it was estimated at 37.5% in a national representative survey of PLWH conducted in 2011, with variations according to both sex and epidemiological group (from 7.9% among female migrants from Sub-Saharan Africa to 74.3% and 79.9% for past or current male and female injecting drug users (IDU), respectively) (2). More recent hospital-based data (FHDH-ANRS CO4, 2014) showed a tobacco smoking prevalence of 43.2% among French PLWH (3), which is nearly twice that observed in the French general population (4). This high prevalence could be explained by several factors including socioeconomically deprived status, stress, depression, other substance use and poor access to tobacco cessation treatment (5), as well as an overrepresentation of men who have sex with men (MSM) and IDU, two populations with a high prevalence of tobacco smoking, irrespective of HIV status (6,7). Hepatitis C virus (HCV)-infected individuals are also more likely to smoke tobacco. A cohort representative of HCV-infected persons in France highlighted an estimated tobacco smoking prevalence of 62% (8), while in the United States, the estimated prevalence in this population was three times higher than in HCV-uninfected people (9). Similarly, tobacco smoking is very prevalent in HIV-HCV co-infected people (10,11), a population prone to both depression (12) and psychoactive substance use (13,14), two known risk factors of low success rates in smoking cessation in PLWH (15).

Thanks to highly active antiretroviral therapy (ART), the life expectancy of PLWH has dramatically increased in recent decades (16), while AIDS-related mortality has decreased (17). Today, cancer and cardiovascular diseases are two leading causes of death in this population. ART-treated PLWH who smoke tobacco

may now lose more life-years through smoking than through HIV infection (18). Similarly, thanks to the scaling up of direct-acting antiviral treatment against HCV, it is expected that the related decrease in mortality in HCV mono-infected patients and HIV-HCV co-infected patients will be partially offset by tobacco-related mortality if nothing is done to reduce associated harms (19,20).

Engagement in HCV treatment has a positive impact on drug use and injection equipment sharing behaviors in IDU (21), but no such association with tobacco use has been found for HIV-HCV co-infected patients (22). Furthermore, data on changes in tobacco smoking behaviors following HCV cure in HIV-HCV co-infected patients are scarce.

Using data from the French National Agency for Research on Aids and Viral Hepatitis (ANRS) CO13 HEPAVIH cohort of HIV-HCV co-infected patients, we aimed to identify potential clinical (including HCV cure) and socio-behavioral correlates of tobacco smoking quit attempts (TSQA).

Materials and methods

Design of the cohort

ANRS CO13 HEPAVIH is an ongoing French national multicenter prospective cohort of HIV-HCV co-infected patients initiated in 2005 (recruitment ended in 2016) which provides a representative sample of the French co-infected population receiving care in hospitals (23). Only patients from the first recruitment phase (2005-2008) were included in the present study population, as the content and timing of the cohort study's socio-behavioral questionnaires were subsequently modified. In the first phase, consecutive patients attending outpatient services in 17 different hospitals were enrolled according to the following selection criteria: aged ≥18 years; infected with HIV-1; either chronically co-infected with HCV (as confirmed by an HCV

RNA assay) or HCV cured thanks to treatment. These participants had annual clinical follow-up visits (biannual (i.e., six-monthly) for patients with cirrhosis), with additional intermediate visits for patients initiating HCV treatment during follow-up.

Clinical data

Clinical, biological, and histological data were collected using standardized medical forms completed by medical staff at each clinical visit. Collected data included CD4-T cell count, plasma HIV RNA level, HIV transmission mode, time since HIV and HCV diagnosis, HCV treatment status and information on sustained virological response (HCV cure), serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, platelet counts, height and weight.

Socio-behavioral data

All patients (including cirrhotic patients) completed a self-administered questionnaire at enrolment and at each annual visit during the five-year follow-up. This questionnaire detailed sociodemographic characteristics (age, sex, living with a partner or not, employment status, perceived comfort of housing, educational level), psychosocial (depressive symptoms, previous treatment for depression, HIV-related self-reported symptoms) and behavioral data (alcohol and coffee consumption, and psychoactive substance use).

Tobacco smoking status

Tobacco smoking status was collected through a face-to-face interview with a physician at each clinical visit and categorized as a time-dependent variable with the following categories: ‘non-smoker’, ‘former smoker’, or ‘current smoker’.

Study population

The present study used data from the five-year follow-up of HIV-HCV co-infected patients enrolled in the first phase of HEPAVIH cohort between 2005 and 2008.

The study population comprised patients who had at least one follow-up visit where they both reported being a current smoker and had available data from the self-administered questionnaire, and whose smoking status was available for at least one subsequent follow-up visit.

Study period

For each patient, the study period began at the first clinical visit where the patient reported being a current smoker and where a self-administered questionnaire was also available (hereafter ‘baseline’). The study period ended at the first clinical visit where the participant reported being a former smoker (corresponding to a TSQA), or the last clinical visit with available tobacco smoking status during the follow-up period (hereafter ‘end-of-study visit’).

Outcome

The study outcome was time to the first TSQA during follow-up, defined as the time between baseline and the first transition from ‘current smoker’ to ‘former smoker’ status. Accordingly, duration was not considered when defining TSQA, and therefore TSQA included both temporary and definitive cessation events. As tobacco status was recorded annually (biannually for patients with cirrhosis), the study outcome was interval-censored.

Explanatory variables

All variables except sex, educational level and HIV transmission mode were time-dependent.

HCV cure was evaluated at each follow-up visit. Patients who had a 12-week sustained virological response at a given clinical follow-up visit, and those who cleared HCV before enrolment in the cohort, were classified as cured.

Given the potential therapeutic use of cannabis in the course of HIV and HCV infections (24–26) and the fact that its primary route of administration (i.e., smoking) is the same as that for tobacco (27), cannabis use was tested separately from other psychoactive substances (grouped together in the analysis) as a potential correlate of TSQA. The frequency of recent cannabis use - understood here as during the previous four weeks - was categorized as ‘never’, ‘sometimes’, ‘regular’ or ‘daily’, with two variables tested as follows: never *versus* sometimes and more frequently (i.e., a dichotomous variable), and never / sometimes / regular or daily (i.e., a three-level variable). HIV transmission mode was categorized as ‘IDU’, ‘MSM’ and ‘other’. Recent use (i.e., in the previous four weeks) of psychoactive substances other than cannabis (cocaine, heroin, crack, ecstasy, street buprenorphine, amphetamines and LSD/other hallucinogens) was coded as ‘yes’ or ‘no’.

Plasma HIV viral load was categorized as detectable *versus* undetectable, according to the limit of detection of the laboratory test used in each of the participating hospitals. Liver fibrosis was assessed using the FIB-4 index, which is a non-invasive marker of fibrosis calculated using age, AST level, ALT level, and platelet count with the following formula: age [years] * AST [IU/L])/(platelet count [10^9/L] * (ALT [IU/L])$^{1/2}$. The presence of advanced fibrosis was defined as a FIB-4 index >3.25 (28). Body mass index (BMI) was calculated as the weight [kg] divided by height squared [m^2].

Employment status was categorized as ‘unemployed’ *versus* all other situations (employed, retired, housewife/househusband). Perceived comfort of

housing was derived from the question 'Would you say that your current housing is…?:' with 4 possible answers subsequently categorized as 'not comfortable' (which included the answers 'not at all comfortable' and 'barely comfortable') *versus* 'comfortable' (which included 'quite' and 'very comfortable'). This variable was designed and used as a proxy for standard of living. Educational level was categorized as having a high-school certificate or not. The presence of depressive symptoms was assessed using the CES-D scale (with cut-offs of 17 and 23 for men and women, respectively) (29,30). The total number of HIV-related self-reported symptoms in the previous four weeks was based on the 39-item ANRS AC24 self-reported symptoms checklist (31), itself derived from the AIDS Clinical Trials Group (ACTG) Symptom Distress Module (32). Alcohol consumption was assessed using the Alcohol Use Disorders Identification Test-Concise (AUDIT-C) questionnaire (33), and categorized as hazardous (score ≥ 4 and ≥ 3 for men and women, respectively) or not. Coffee intake was categorized as daily (≥ 1 cup per day) *versus* non-daily.

Statistical analyses

We described the study population's main characteristics at the end-of-study visit, and the number of events occurring during the study period for each category of each explanatory variable.

For HEPAVIH participants (first phase of enrolment) who reported at least once during their follow-up that they currently smoked tobacco, we compared age and gender between included individuals (i.e., study population) and those excluded, using Mann-Whitney and chi-squared tests.

Associations between clinical (including HCV cure) and socio-behavioral characteristics and TSQA were assessed using a multivariable discrete-time proportional hazards Cox model with the exact partial-likelihood method to deal with

tied failures. This type of model is recommended for survival analyses with interval-censored data (34) - as was the case in the present study - where follow-up data are collected on an annual or biannual basis. Missing values for explanatory time-dependent variables were imputed according to the last observation carried forward (LOCF) method. For each variable, this consisted in imputing each missing value with the last observed available value of the individual, if such a value existed. In order to minimize the risk of reverse causality, values at the *n-1* visit for all time-dependent variables were used in the model to explain tobacco status at the following *n* visit. Depressive symptoms and a history of treatment for depression were tested alternatively in the multivariable model.

Explanatory variables with a p-value < 0.20 (Wald test) in the univariable analyses were tested in the multivariable analysis. Variables were then selected using a stepwise backward procedure, based on the Wald test. Only those with a p-value < 0.05 were retained in the final multivariable model.

The proportionality of hazards assumption was tested for all explanatory variables in the final multivariable Cox model using graphical examination of Kaplan-Meier estimates and statistical testing based on rescaled Schoenfeld residuals. We hypothesized that loss-to-follow-up (due to missed clinical visits, cohort attrition, and death) was non-informative (i.e., patients were lost to follow-up due to reasons unrelated to the study outcome, and therefore Cox model results were unbiased).

Stata/SE 14.2 software (StataCorp LP, College Station, TX) was used for all analyses.

Results

Characteristics of the study population

The study population comprised 695 participants (Figure 1), representing 59.1% of the individuals enrolled in the first phase of the HEPAVIH cohort, and 77.0% of the individuals who declared at least once during the follow-up that they currently smoked tobacco. Mann-Whitney and chi-squared tests revealed that that women accounted for a greater proportion of the participants, and that participants were slightly older than persons not included (data not shown). During the study period- which represented 2485 person-years - 88 TSQA were observed, leading to an incidence rate of 3.5 TSQA/100 person-years (95% confidence interval (CI) [2.87-4.36]). The median follow-up time of study participants was 48 months (interquartile range (IQR) [24-60]).

The study population's characteristics at the end-of-study visit are provided in Table 1. Patients were mainly male (70.5%) and HIV-infected through drug injection (72.5%). Median age was 47.0 years (IQR [44.0-50.0]). Median time since HIV and HCV diagnosis was 21 (IQR [16-24]) and 13 years (IQR [10-17]), respectively. At baseline, 10.7% were HCV cured, while at the end-of-study visit, 19.6% were HCV cured.

Factors associated with TSQA

In univariable analyses (Table 1), the following explanatory variables were associated with TSQA: HCV cure, cannabis use (dichotomous variable (see above)), age, BMI, HIV transmission mode, and recent substance use.

The following variables were retained in the final multivariable model: HCV cure, BMI, HIV transmission mode, cannabis use and other illegal substance use. The multivariable analysis confirmed the positive associations between HCV cure

and TSQA (adjusted hazard ratio (HR) [95% CI]: 1.76 [1.06-2.93], p=0.029) (Figure 2), between a higher BMI and TSQA (1.06 [1.00-1.13], p=0.040), and between MSM transmission mode and TSQA (2.60 [1.44-4.70], p=0.002, *versus* IDU) (Table 1). By contrast, cannabis use (0.63 [0.40-1.00], p=0.049) (Figure 3) and recent illegal psychoactive substance use (0.35 [0.13-0.99], p=0.048) were independently negatively associated with TSQA. Older age was no longer significantly associated with the outcome in the multivariable analysis. The proportionality of hazards assumption was verified for all explanatory variables in the final multivariable Cox model (see Figure 2 for HCV cure status and Figure 3 for cannabis use).

Discussion

In this large cohort of HIV-HCV co-infected people in France, HCV cure was associated with more than a 75% higher chance of TSQA. Recent cannabis use was associated with a 37% lower chance of TSQA. Other illegal psychoactive substance use was also identified as a main barrier to TSQA.

To our knowledge, the association we found between HCV cure and TSQA has not been previously reported. However, it does reflect data from a large cohort of HCV-infected veterans in the USA, where those who were treated were less likely to be current smokers than the control group (35). Moreover, our results for TSQA reflect observations in HCV-infected IDU, for whom treatment appeared to have a positive impact on injecting behaviors, injection equipment sharing behaviors (21), and hazardous alcohol use (36).

From a wider perspective, TSQA may be a manifestation of the psychosocial benefits of HCV cure. More specifically, it has been shown that HCV cure has a short-term positive impact on health-related quality of life, with noticeable improvements in anxiety/depression (37). One could expect therefore that the

disappearance of HCV-related stress (38) alleviates the need to smoke in order to cope with stress (39,40) and therefore fosters TSQA. In people with a history of substance use, HCV treatment and/or HCV cure has been associated with increased self-care (41,42), ability and motivation to plan for the future, self-confidence and empowerment (42,43). These benefits are likely to foster TSQA. As smoking-related deaths become more common than liver-related deaths in HIV-HCV co-infected patients - thanks to HCV treatment scale-up (20) - HCV cure may participate in raising awareness of tobacco-related harms and promote TSQA. HCV cure may also be a proxy of social support (44), which fosters TSQA (45,46). Furthermore, it may also reflect better engagement in care (47–49), implying more frequent exposure to and/or better accepted short interventions or counselling about tobacco use (50,51). All these results from the literature highlight the opportunity that medical visits - whether during or after HCV treatment - represent for screening, interventions and referral to a specialist smoking cessation service (50,52–54).

To our knowledge, this is also the first longitudinal study to show an association between cannabis use and TSQA in PLWH, in HCV mono-infected persons, and in HIV-HCV co-infected persons. Our results reflect those in other studies on PLWH which found associations between cannabis use and tobacco smoking status (55,56). A lower likelihood of smoking cessation in cannabis users than in non-users has also been documented in the general population, both for non-treatment seeking (57) and treatment-seeking smokers (58). Larger studies are needed to confirm our primary result of the association between cannabis use and TSQA. However, given the negative impact of tobacco smoking on survival in HIV-HCV co-infected patients (26,59), we strongly recommend that this result be taken into account immediately in clinical management and public health strategies.

Mechanisms fostering co-occurring tobacco and cannabis use have been identified, as have the potential benefits of dual abstinence (60). One possible major reason for cannabis use being a barrier to TSQA is that smoking is the primary route of cannabis administration. This is especially true in Europe (27). Other possible mechanisms include exposure to smoking cues (60) (which are maintained when tobacco is substituted with cannabis (61)), the putative potentiation of nicotine dependence by cannabis (62,63), and a desire to attenuate nicotine's undesirable effects or withdrawal symptoms (64). There is also evidence that detrimental neurocognitive effects in long-term cannabis users (65) may foster persistent tobacco use (66). Interestingly, we did not find any dose-dependent relationship between the frequency of cannabis use and tobacco TSQA.

Our results add evidence to the need to manage addictive behaviors using a holistic approach. It has been shown that having multiple concurrent substance use disorders is associated with a greater likelihood of substance use disorder persistence at a distance of three years (compared with having only one such disorder), and also with nicotine dependence (67). The positive effects of smoking cessation on substance use outcomes have previously been highlighted (68). However, substance substitution mechanisms have also been reported (69,70). Moreover, as some genetic vulnerabilities to addictions are related to pathways which are common to different substances (e.g., the reward pathway) (71), therapeutic programs targeting multiple substance use are likely to bring greater benefits than those only focusing on one substance. However, these programs would require treatment providers to undergo more in-depth training in order to be able to provide addiction care for a wide range of substances rather than just one. They would also

require patients who are willing and motivated to simultaneously reduce or stop co-use.

It is increasingly recognized that cannabis- and cannabinoid-based medicines provide relief for PLHW and HCV-infected persons (24–26). In the general population, cannabis - whether used for recreational or medical purposes - is a barrier to tobacco cessation (58). Accordingly, improving access to medical cannabis and cannabinoids which are tobacco-free and which are not administered through smoking (72,73), would appear to be an urgent public health issue, especially for PLWH and HCV-infected people. Our findings may also encourage research on 'cannabis substitution' as a therapeutic support mechanism for HIV-infected, HCV-infected and HIV-HCV co-infected patients who attempt to stop smoking tobacco. To date, nabiximols have shown mixed results as a cannabinoid agonist treatment (74–76).

More generally, substance use, including alcohol, has been identified as a barrier to smoking cessation in HIV-infected populations (77). Unsurprisingly therefore, in our study, recent use of psychoactive substances other than cannabis was associated with a 65% lower chance of TSQA. This reflects Encrenaz et al.'s finding of a lower TSQA incidence in IDU-infected PLWH (78). This finding may be partly due to greater baseline cigarette use and/or nicotine dependence (6), although we did not have these data in the present study. Furthermore, in line with Encrenaz *et al*. 's findings, the positive relationship we found between MSM HIV transmission mode and TSQA is likely due to the fact that our study population mainly comprised participants infected by HIV through IDU.

The positive association we found between BMI and TSQA is counter-intuitive. As weight gain is a widely-known consequence of tobacco cessation, it may hinder

motivation or confidence to stop tobacco smoking (79,80). Consequently, one would expect people with higher BMI to be less likely to try to quit. However, it is also possible that a higher BMI is a proxy for previous TSQA (81).

Depression was not a barrier to TSQA in our study. This reflects Benard *et al.* who found no association between depressive symptoms and motivation to stop smoking in a French cohort of HIV-infected people (55). In the general population, depression appeared to be a barrier to quitting (82). This absence of any association may be due to collinearity with cannabis use. Indeed, cannabis is frequently used by PLWH to cope with depression (83), and depression and cannabis use have been associated with each other in the general population (84), as well as in PLWH (85). Unlike Regan et al., who found that patients with a detectable HIV viral load were significantly less likely to quit smoking than their virologically suppressed counterparts (86), we did not find any association between HIV plasma load and our study outcome.

The large sample size and the relatively long follow-up duration are the main strengths of our study. However, several limitations must be acknowledged. First, unfortunately, our study sample selection did not lead to a study sample representative of the smokers in the original cohort (which is itself representative of HIV-HCV co-infected people engaged in care in French hospitals), and duplication of our results would be needed to ensure their generalizability. Second, due to the interval-censored nature of the smoking status data collected during follow-up in the cohort, we may have missed short-lived TSQA which occurred between two annual or biannual (for people with cirrhosis) follow-up visits. Third, the LOCF method used to account for missing data on explanatory variables is grounded in the assumption of stability of these variables over time. As variables were mainly socio-behavioral, we

expect this assumption to be true, although we cannot confirm it. Fourth, we were not able to characterize the duration of tobacco use or abstinence, and did not have information on whether TSQA were self-helped or assisted. Finally, many patients did not provide information on the number of cigarettes they smoked, and therefore data on this variable could not be used here. Moreover, we had no information about the factors related to people's motivation to quit smoking. However, as TSQA may be considered part of the process leading to quitting (81), identifying modifiable factors which facilitate them is of great clinical importance. Along with modifiable factors, future research should explore the possible environmental factors (e.g., the presence of smokers in the household) which may facilitate or impede TSQA.

To conclude, HCV cure was associated with a higher chance of tobacco smoking quit attempts in the present study of HIV-HCV co-infected patients, a population characterized by a high prevalence of both tobacco smoking and cannabis use, and which is especially vulnerable to tobacco-related harms and mortality. Conversely, cannabis use was associated with a lower chance of quit attempts. Tobacco smoking should be systematically addressed during standard care of HIV-HCV infected people. HCV treatment represents a good opportunity for screening, comprehensive counselling, and referral to specialist tobacco cessation services. Cannabis use should be screened concomitantly with tobacco use in HIV-infected, HCV-infected and HIV-HCV co-infected smokers. Finally, for cannabis users who wish to quit smoking tobacco, safer routes of cannabis administration should be promoted which do not involve smoking cues such as vaporization. This would reduce associated harms and help users in future tobacco smoking cessation attempts.

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Table 1: Factors associated with tobacco smoking cessation attempts (Cox proportional hazards models, ANRS CO13 HEPAVIH cohort, n=2485 person-years, n= 88 events)

	n[#]	**% of the study population**	**Number of events**	Univariable analyses (n=695 patients, n=2485 person-years, n=88 events)			Multivariable analysis (n=666 patients, n= 2356 person-years, n= 84 events)		
Variable				Hazard ratio	95% confidence interval	p-value	Adjusted hazard ratio	95% confidence interval	p-value
Age (in years)*	47 [44-50]			1.05	1.01-1.09	0.027			
Sex									
Male (ref.)	490	70.5	68	1					
Female	205	29.5	20	0.67	0.40-1.11	0.119			
Living with a partner* (n=691)									
No (ref.)	376	54.4	43	1					
Yes	315	45.6	45	1.23	0.80-1.88	0.341			
Educational level (n=607)									
No high-school certificate (ref.)	436	71.8	57	1					
High-school certificate	171	28.2	26	1.20	0.75-1.92	0.444			
Perceived comfort of housing (n=692)*									
Not comfortable (ref.)	126	18.2	16	1					
Comfortable	566	81.8	72	0.89	0.51-1.55	0.691			
Employment (n=689)*									

Unemployed	343	49.8	39	0.97	0.63-1.48	0.876			
Other[1] (ref.)	346	50.2	49	1					
Body mass index (n=693)*	21.3 [19.4-23.9]			1.09	1.03-1.15	0.002	1.06	1.00-1.13	0.040
Daily coffee intake (n=693)*									
No (ref.)	175	25.3	26	1					
Yes	518	74.7	62	0.77	0.48-1.23	0.270			
Hazardous alcohol consumption (n=687)*									
No (ref.)	426	62.0	59	1					
Yes	261	38.0	28	0.70	0.44-1.10	0.121			
Cannabis use (n=670)*									
No	284	42.4	48	1			1		
Yes	386	57.6	36	0.49	0.32-0.76	0.001	0.63	0.40-1.00	0.049
Frequency of cannabis use[2] (n=670)*						0.006			
Never (ref.)	284	42.4	48	1					
Sometimes	159	23.7	15	0.50	0.28-0.90	0.022			
Regular or daily	227	33.9	21	0.48	0.29-0.81	0.006			
Recent use of illegal psychoactive substance[3] (n=675)*									
No	590	87.4	81	1			1		
Yes	85	12.6	4	0.32	0.12-0.87	0.026	0.35	0.13-0.99	0.048
HIV transmission mode						0.004			0.006
IDU (ref.)	504	72.5	52	1			1		
MSM	69	9.9	17	2.52	1.44-4.41	0.001	2.60	1.44-4.70	0.002
Other	122	17.6	19	1.49	0.87-2.54	0.143	1.46	0.85-2.52	0.171
Time since HIV diagnosis (in years) (n=692)*	21 [16-24]			1.02	0.98-1.06	0.418			

CD4 count (in 100 cells/mm^3)(n=694)*	5.3 [3.4-7.4]			0.94	0.88-1.02	0.143			
Undetectable plasma HIV viral load (n=691)*									
No (ref.)	162	23.4	27	1					
Yes	529	76.6	60	0.73	0.46-1.17	0.190			
Time since HCV diagnosis (in years) (n=680)*	13 [10-17]			1.01	0.97-1.05	0.707			
HCV cure*									
No (ref.)	559	80.4	66	1			1		
Yes	136	19.6	22	1.94	1.18-3.18	0.009	1.76	1.06-2.93	0.029
Advanced liver fibrosis[4]*									
No (ref.)	569	81.9	74	1					
Yes	126	18.1	14	1.08	0.60-1.92	0.806			
Depressive symptoms (n=660)*									
No (ref.)	394	59.7	58	1					
Yes	266	40.3	28	0.68	0.43-1.08	0.101			
History of treatment for depression[5] (n=694)*									
No (ref.)	354	51.0	54	1					
Yes	340	49.0	34	0.70	0.45-1.08	0.109			
Total number of self-reported symptoms[6] (n=674)*	11 [5-18]			1.00	0.97-1.03	0.962			

[#] Descriptive statistics are given for the end-of-study visit. Median and interquartile range are given for continuous variables.

* Descriptive statistics of time-dependent variables are given for the lagged variables (measured at n-1).

[1] Employed, retired, being a housewife/househusband.

[2] Cannabis use was entered as a dichotomous variable in the final multivariable model as the alternate three-level variable was no longer significantly associated with the outcome during the stepwise procedure.

[3] Illegal psychoactive substance use (excluding cannabis) in the previous 4 weeks. The illegal psychoactive substances evaluated were cocaine, heroin, crack, ecstasy, street Subutex, amphetamines and LSD/other hallucinogens.

[4] Advanced liver fibrosis was defined as an FIB-4 index >3.25.

[5] Depressive symptoms and history of treatment for depression were tested alternatively in the multivariable model.
[6] From the ANRS AC24 self-reported symptoms checklist.
IDU, injecting drug user; MSM, men who have sex with men.

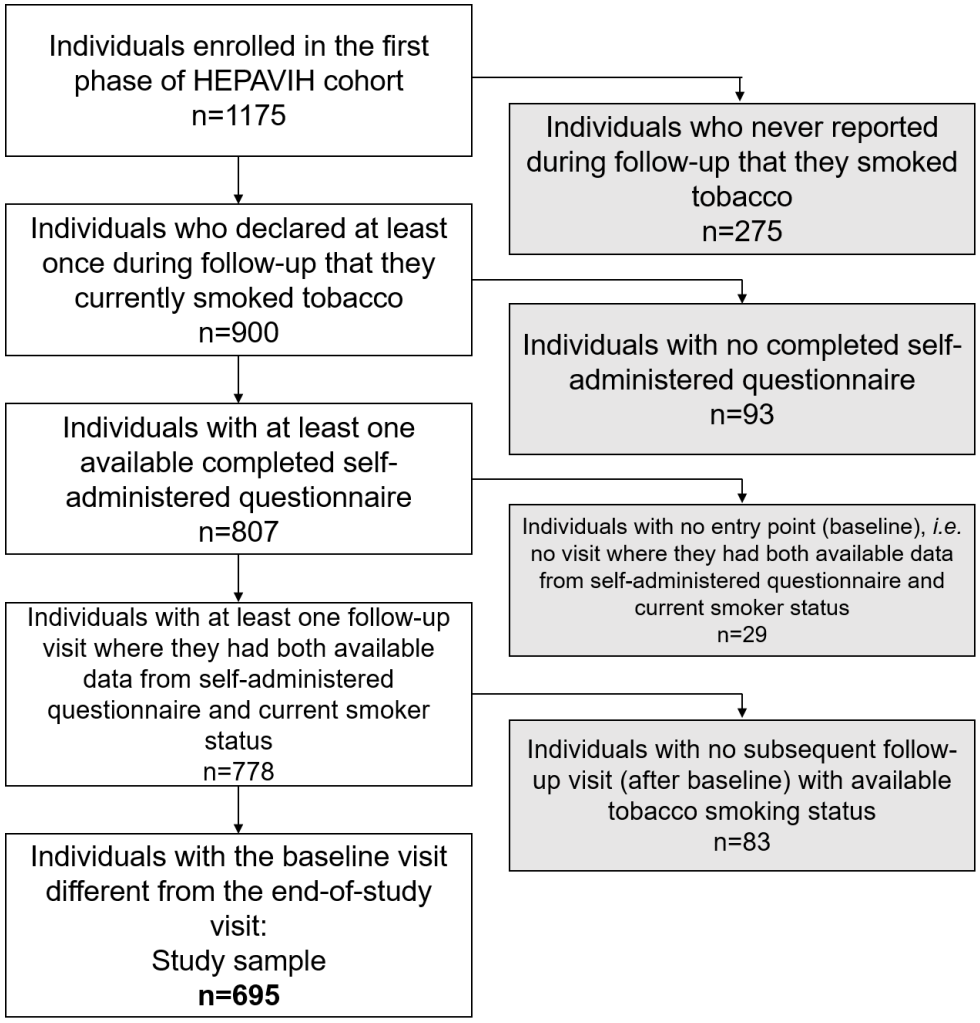

Figure 1: Flow chart of the study population (n=695, ANRS CO13 HEPAVIH cohort).

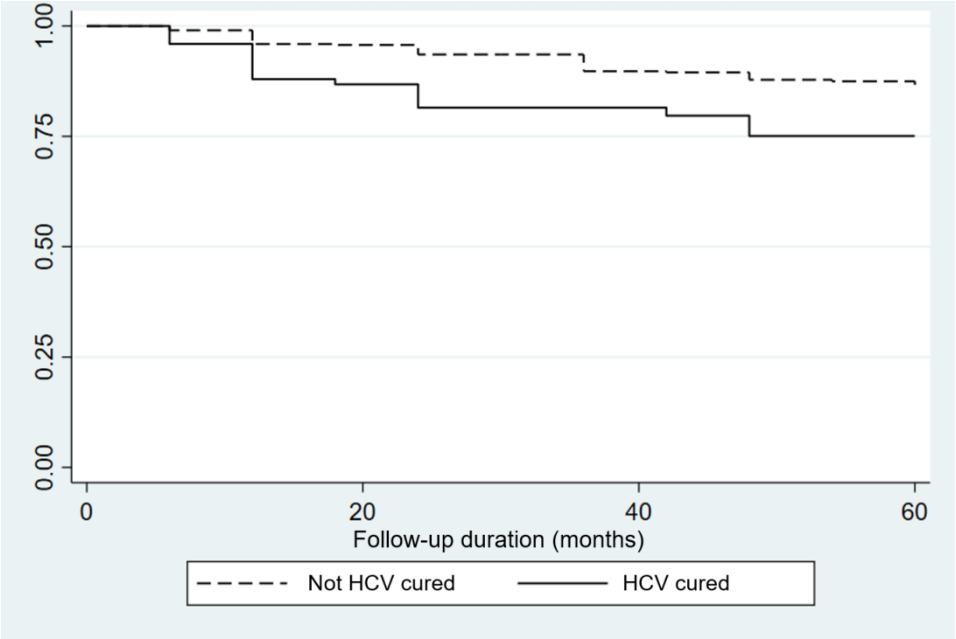

Figure 2: Probability of *no* tobacco smoking cessation attempt during follow-up according to HCV cure status.

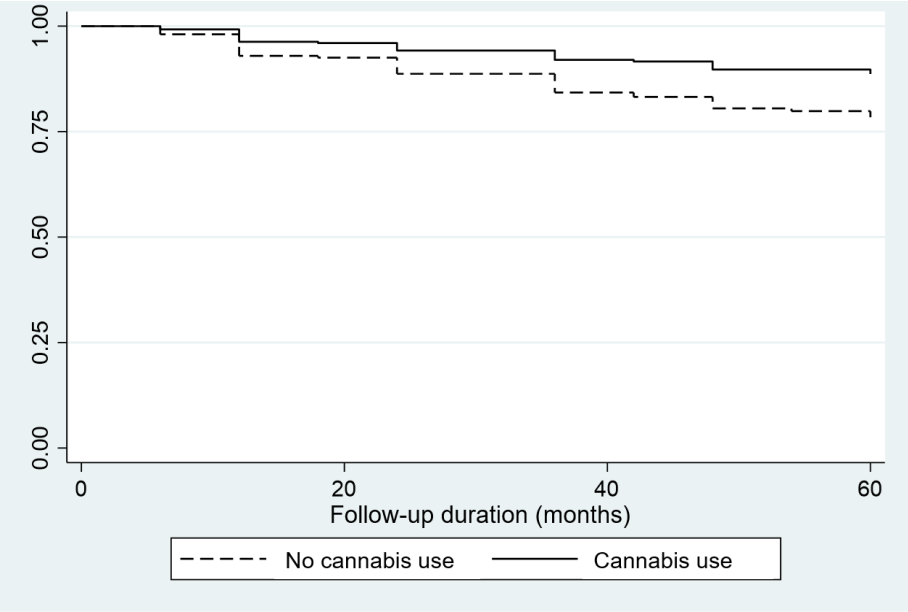

Figure 3: Probability of *no* tobacco smoking cessation attempt during follow-up according to cannabis use.

Figure 1