Cannabis Use as a Protective Factor Against Overweight in HIV-Hepatitis C Virus Co-Infected People (ANRS CO13 HEPAVIH Cohort)

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Abstract

Overweight is increasingly prevalent in people living with HIV (PLWH), and is a high risk factor for metabolic disorders in this population. PLWH co-infected with hepatitis C virus (HCV) have a higher risk of metabolic disorders than their mono-infected counterparts. The putative relationship between cannabis use and body weight found in the general population has never been documented in HIV-HCV co-infected people. We tested whether cannabis use is associated with body mass index (BMI), overweight, and underweight in HCV co-infected PLWH (n=992). Mixed-effects linear and logistic regression models were used to study the association between cannabis use and the three outcomes over time. After multivariable adjustment, cannabis use was inversely associated with BMI. Cannabis use was associated with a lower and higher risk of overweight and underweight, respectively. Cannabis use should be assessed and taken into account in the clinical management of the HIV-HCV co-infected population.

Keywords: HIV; hepatitis C, chronic; cannabis; marijuana; obesity; body mass index.

Introduction

Elevated body weight is increasingly prevalent in people living with HIV (PLWH) in high-income countries (Crum-Cianflone et al., 2010; Koethe et al., 2016; Pourcher, Costagliola, & Martinez, 2015). Antiretroviral therapy (ART) is a risk factor for weight gain (Buzón-Martín, 2020; Sax et al., 2020), which in turn may lead to an unhealthy body mass index (BMI) (Jiang et al., 2019; Kumar & Samaras, 2018; Yuh et al., 2015). For instance, in pooled analyses of eight phase 3 ART trials, Sax et al. found a 96-week median weight gain of 2 kg, the proportion of participants with obesity rising from 16.3% at baseline to 21.2% at week 96 (Sax et al., 2020). In PLWH taking ART, maintaining normal weight is associated with a lower risk of cardiovascular diseases, cancer, and mortality (Achhra et al., 2018; Jiang et al., 2019; Sharma et al., 2015). BMI seems to be linearly associated with the risk of diabetes in this population (Achhra et al., 2018). At the upper end of the BMI spectrum, obesity is a risk factor for several conditions. PLWH are at a higher risk of these conditions than the general population, including diabetes mellitus, cardiovascular diseases, liver steatosis and neurocognitive impairments (Bailin, Gabriel, Wanjalla, & Koethe, 2020). For instance, in treated PLWH, the relative risk for cardiovascular disease and cancers known to be associated with BMI were estimated at 1.31 and 1.92 for a BMI>30 and BMI 23-25, respectively (Achhra et al., 2018). Underweight is also a risk factor for comorbidities (e.g., non-AIDS-defining cancers) and for AIDS and non-AIDS-related mortality (Achhra et al., 2018; Jung et al., 2019). Co-infection with hepatitis C virus (HCV) also represents an excess risk for all-cause, non-liver related and cancer mortality (Chalouni et al., 2021), as well as cardiovascular diseases (Osibogun et al., 2017) in PLWH. Managing and preventing elevated and low body weight is therefore crucial in PLWH - especially HCV co-infected PLWH - to limit the risk of comorbidities and mortality.

Weight gain is multifactorial (Goupil de Bouillé et al., 2021); factors associated with it, and with elevated body weight in HCV co-infected PLHW need to be identified in order to prevent their deleterious consequences. Studies in other populations have found that

cannabis use is a potential modifiable protective factor for weight gain and elevated body weight (Alshaarawy & Anthony, 2019; Clark, Jones, Hall, Tabner, & Kmiec, 2018; Meier, Pardini, Beardslee, & Matthews, 2019). Cannabis use is common among PLWH and HIV-HCV co-infected people (Brunet et al., 2013; Funke et al., 2020; Pacek, Towe, Hobkirk, Nash, & Goodwin, 2018), and is sometimes used as a strategy to cope with symptoms related to HIV infection and its treatment (Costiniuk et al., 2019; Towe, Horton, Martin, & Meade, 2018). Regular and daily cannabis use are associated with a lower HCV-related mortality rate (72% reduction) and a lower risk of liver steatosis (36% reduction) in HIV-HCV co-infected persons, independently of BMI (Santos et al., 2020; Nordmann S. et al., 2017). However, its impact on body weight is poorly documented in this population, and the only related result to date found no association with changes in BMI (Lee et al., 2019).

Based on data from the French National Agency for Research on AIDS and Viral Hepatitis (ANRS) CO13 HEPAVIH cohort study, we aimed to test whether cannabis use was associated with BMI, overweight, and underweight in ART-treated HCV co-infected PLWH.

Material and Methods

Cohort design

ANRS CO13 HEPAVIH is an ongoing French national prospective cohort of PLWH co-infected with HCV (Loko et al., 2010). Consecutive patients attending outpatient services in 17 different hospitals throughout the country were enrolled in its first phase (2005-2008) with 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 after treatment. Annual clinical follow-up visits (or biannual for patients with cirrhosis) were scheduled. Patients who initiated HCV treatment during follow-up had additional visits. Patients were invited to complete a self-administered questionnaire collecting socio-behavioral data at enrollment (M0) and yearly thereafter until the scheduled 60-month clinical follow-up visit (M60). The study was designed and implemented in accordance with the Declaration of

Helsinki, and the protocol was approved by the Ethics Committee of the Cochin University Hospital in Paris. Participants provided informed consent before participating.

Collected data

Clinical, biological, and histological data were collected using standardized medical forms completed by medical staff at each follow-up visit. Collected data included HIV transmission mode, time since HIV and HCV diagnoses, current and past ART regimens, HCV treatment status and information on sustained virological response (HCV cure), height and weight. Annual self-administered questionnaires documented patients' socio-demographic characteristics (education level, employment status, housing comfort), consumption behaviors (alcohol, cannabis, other psychoactive substances, coffee), and depressive symptoms.

Study population and study period

For the present study, we used data from annual visits of ANRS CO13 HEPAVIH participants recruited during the cohort's first enrollment phase (2005-2008). Given the impact of ART regimens on body weight, cohort participants who were ART-naive at enrollment were excluded. Participants with no visit where both BMI and cannabis use were available were secondarily excluded. For each participant, the beginning of the study period (i.e., baseline) corresponded to the first cohort visit with simultaneously available data for both BMI and cannabis use. All subsequent follow-up visits with a self-administered questionnaire available until M60 were included in the longitudinal analyses.

Outcomes and explanatory variables

Outcomes

The following three different time-varying outcomes were separately analyzed based on BMI and World Health Organization cut-off values (World Health Organization, 2019) i) BMI as a continuous variable, ii) underweight (BMI<18.5), and iii) overweight (BMI≥25).

Explanatory variables

Gender and HIV transmission mode: a combination of the variables 'gender' and 'transmission mode' (men who have sex with men (MSM), injecting drug use (IDU), other) led to a five-category explanatory variable with ‘MSM’, ‘male IDU’, ‘female IDU’, ‘male other’ and ‘female other’ as modalities.

ART and HCV cure: Current protease inhibitor (PI) intake was dichotomized into ‘yes’ and ‘no’. The PI drugs considered were amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir/ritonavir, nelfinavir, ritonavir, saquinavir, tipranavir, and TMC114. Patients who had a 12-week sustained virological response at a given follow-up visit were classified as HCV cured at that visit. Patients who cleared HCV before enrollment in the cohort were also classified as cured.

Self-reported psychoactive substance use and coffee consumption: Current, former, and no lifetime tobacco use were the three categories created for the variable ‘tobacco use. Alcohol use was categorized into abstinence or low (≤1 standard drink per day), moderate (>1-4 and >1-3 standard drinks per day for males and females, respectively) and elevated (>4 and >3 standard drinks per day for males and females, respectively). Cannabis use frequency was recorded as ‘never’, ‘sometimes’, ‘regularly’ and ‘daily’, and subsequently categorized into a three-category explanatory variable: no use (never), occasional (sometimes), and regular use (regularly or daily). Use of psychoactive substances other than cannabis during the previous four weeks (cocaine, heroin, crack, ecstasy, street buprenorphine, amphetamines and LSD/other hallucinogens) was coded as ‘yes’ or ‘no’. Coffee consumption was categorized into low (≤ 1 cup per day), moderate (2 cups per day) and elevated (≥3 cups per day), reflecting a threshold previously highlighted as beneficial for health outcomes in this population (Carrieri, Protopopescu, Marcellin, Rosellini, et al., 2017; Carrieri, Protopopescu, Marcellin, Wittkop, et al., 2017; Protopopescu et al., 2018).

Education level and housing: Education level was characterized as ‘< upper secondary school certificate’ or ‘≥ upper secondary school certificate’, and employment status as ‘having a job’ or ‘not’. Perceived comfort of housing was recorded with the question ‘Would you say

that your current housing is…?:' with four possible answers. It was subsequently dichotomized into 'not comfortable' (which included the answers 'not at all comfortable', 'barely comfortable' and 'quite comfortable') and 'very comfortable'. This variable was designed and used as a proxy for standard of living.

Depressive symptoms: The presence of depressive symptoms ('yes' vs. 'no') was assessed using the CES-D scale (with cut-offs of 17 and 23 for males and females, respectively) (Fuhrer & Rouillon, 1989; Radloff, 1977).

Except for gender and HIV transmission category, all the explanatory variables were evaluated at each visit and used as time-varying covariates in the statistical analyses.

Statistical analyses

Missing data on time-varying explanatory variables, including cannabis use, were imputed during the longitudinal follow-up using the last observation carried forward method. For each variable, this consisted in imputing each missing value with the last observed available value of the individual, if this value existed. The outcome variable BMI was not imputed.

The study population's main characteristics were considered using data from the baseline visit self-administered questionnaire. These characteristics were then compared between participants with underweight, participants with overweight, and those with normal weight (18.5≤ BMI <25) (using Chi-squared and Mann-Whitney tests for categorical and continuous variables, respectively).

Mixed-effects linear (for continuous BMI) and logistic (for underweight and overweight) regression models were used to estimate the association between the explanatory variables and each outcome, while accounting for correlations between repeated measures for each individual.

For both model types, variables were considered eligible for inclusion in the multivariable analyses if they had a p-value < 0.20 (Wald test) in the univariable analyses. A

backward procedure based on the Wald test was used to select variables for the three final multivariable models (significance p-value threshold ≤ 0.05).

In a sensitivity analysis, we forced tobacco use into the final models to test the robustness of the cannabis use effect independently of the tobacco smoking effect.

All analyses were performed with STATA version 16.1 for Windows software (StataCorp LP, College Station, TX).

Results

Study sample characteristics

Of the 1246 participants from the cohort's first enrollment phase, we excluded 17 because they were ART-naive at enrollment, and 237 others, as they had no visit with simultaneous data for cannabis use and BMI. The study sample therefore comprised 992 patients, accounting for 4485 visits. Seventy percent were male, 12.4% were HCV-cured at baseline (24.2% at last available follow-up visit), 26.6% were regular or daily cannabis users, 70.0% had normal weight, and 17.8% were overweight. Median age was 45 years (interquartile range (IQR) [42-48]) (**Table 1**).

Median follow-up time in the present study was 4 years (IQR [3-5]). The completion rate of the self-administered questionnaire varied from 98.6 to 53.6% in the M0-M24 period, and from 46.0 to 22.7% in the M36-M60 period. There were 800, 819, 803, 770, 710, and 583 participants included in the longitudinal analyses at M0, M12, M24, M36, M48 and M60, respectively.

Relationship between cannabis use and BMI level

Results from mixed-effects univariable and multivariable linear regression models are given in **Table 2**. In univariable analyses, both regular and occasional cannabis use were inversely associated with BMI. After multivariable adjustment, regular cannabis use was inversely associated with BMI (adjusted regression coefficient: -0.53 [95% CI] [-0.82; -0.24], p<0.001); however, occasional use was not (p=0.100) (**Table 2**). Moreover, a linear trend test confirmed the dose-response association between cannabis use frequency and BMI

(p<0.001). BMI was also inversely associated with being a female IDU (vs. being a male IDU), time since HIV diagnosis, current HCV treatment, former or current tobacco smoking, and reporting very comfortable housing. Conversely, BMI was positively associated with follow-up time.

Relationship between cannabis use and BMI categories

Results from the multivariable logistic regression models are provided in **Table 3**. After multiple adjustment, both occasional (adjusted odds ratio (aOR) [95% confidence interval (CI)]: 0.26 [0.11; 0.58], p=0.001) and regular (aOR [95% CI]: 0.13 [0.05; 0.31], p<0.001) cannabis use were inversely associated with overweight, as were being an MSM, being a female IDU (vs. a male IDU), time since HIV diagnosis, and having depressive symptoms. Conversely, elevated alcohol use and follow-up time were positively associated with overweight (**Table 3**).

In sensitivity analysis, forcing the tobacco use variable into the final model had no impact on non-tobacco associations. Furthermore, tobacco modalities (former, current vs. non-smoker) were not statistically significantly associated with being overweight (data not shown).

After multivariable adjustment, both occasional (aOR [95% CI]: 2.08 [1.06; 4.05], p=0.033) and regular (aOR [95% CI]: 3.56 [1.86; 6.79], p<0.001) cannabis use were associated with underweight, as were being a female (whether IDU or not, vs. a male IDU), older age, and current HCV treatment. Conversely, underweight was inversely associated with elevated alcohol use (**Table 3**).

Forcing the tobacco use variable into the final model led to a non-significant association between former tobacco use and underweight, and an association approaching statistical significance for current tobacco use and underweight (aOR 3.57, p=0.056). Occasional cannabis use was no longer associated with this outcome (aOR 1.68, p=0.133), while regular use was (aOR 2.68, p=0.003). The other associations were not substantially impacted.

Discussion

In the present study, regular and occasional cannabis use were associated with lower BMI, a lower risk of overweight, and a higher risk of underweight in ART-treated HCV co-infected PLWH. This inverse relationship between cannabis use and body weight is in line with findings for other populations. In the general population, cannabis use is associated with lower body weight, lower BMI, and a lower risk of obesity and weight gain (Alshaarawy & Anthony, 2019; Clark et al., 2018; Meier et al., 2019; Ngueta, Bélanger, Laouan-Sidi, & Lucas, 2015; Sidney, 2016). The largest genome-wide association study for lifetime cannabis use conducted to date, revealed a genetic overlap between lifetime cannabis use and low BMI (Pasman et al., 2018). This relationship was also found in patients infected with chronic hepatitis B (Barré, Pol, et al., 2021). However, to our knowledge, no such data exist for HCV-infected persons, and the only results available for HIV-infected people found no evidence for an effect of cannabis use on changes in BMI (Lee et al., 2019). We did not find a significant dose-response relationship, despite the fact that aOR values for former and current use suggested the contrary.

In our study, tobacco use was inversely associated with BMI. However, unlike cannabis use, it was not associated with underweight or overweight. This inverse relationship with BMI reflects findings in the literature and is probably related to both lower food intake and greater energy expenditure in tobacco smokers (Audrain-McGovern & Benowitz, 2011). The stronger impact of cannabis use than tobacco smoking on BMI which we found must be put into context. First, the regression coefficient was higher in magnitude for current tobacco use than for current cannabis use in the model for continuous BMI. Second, current use of the two substances was not assessed in the same way; current tobacco use encompassed all smoking frequencies, whereas a frequency distinction was made for cannabis. Finally, we were not able to construct a tobacco-cannabis combined variable because of the very low prevalence of cannabis-only use in the study population. In Europe, most cannabis users - including HCV co-infected PLWH (Barré, Mercié, et al., 2021) - co-use tobacco (Hindocha,

Freeman, Ferris, Lynskey, & Winstock, 2016). However, sensitivity analyses showed that if we had relaxed the significance threshold (i.e., from 0.05 to 0.10), current tobacco use would have been associated with underweight with a higher odds ratio than for regular cannabis use. We acknowledge that tobacco smoking intensity (i.e., number of cigarettes per day) may also influence those relationships. Unfortunately, these data were not available.

The above results would therefore suggest that cannabis use, just like tobacco use, acts as an agent for lowering body weight. It has been suggested that while acute stimulation of cannabinoid receptor 1 (CB1) by Δ9-tetrahydrocannabinol (THC) in cannabis initially leads to increased food intake (Foltin, Fischman, & Byrne, 1988), overstimulation of the receptor by chronic cannabis consumption may lead to long-lasting downregulation of CB1 (Clark et al., 2018). The latter may in turn reduce energy storage and increase metabolic rates, leading to a lower BMI (Clark et al., 2018). Indeed, it was recently documented that the endocannabinoid system - an endogenous lipid signaling system comprising cannabinoid receptors and their ligand (among other molecules) - is widely and complexly involved in energy homeostasis (Di Marzo & Silvestri, 2019). This finding led to the development of a CB1 antagonist by the drug industry. Despite positive results in the treatment of obesity, this antagonist was subsequently discarded because of adverse psychiatric effects (Di Marzo & Després, 2009).

Moreover, we cannot definitively rule out reverse causality, that is to say the possibility that participants with poorer health status (i.e., too low a body weight) turned to cannabis for therapeutic reasons.

The positive relationships we found between both age and time since HIV diagnosis and both continuous BMI and the risk of overweight reflect observed increases in body weight across the lifespans of PLWH on ART in the Unites States (Erlandson et al., 2016). However, contrary to Buzón-Martín's findings for weight change (Buzón-Martín, 2020), we found no impact of PI intake on corpulence. This difference may be explained by the follow-up time in our study, which was not long enough to be able to adequately capture such an

effect. It may also be related to the fact that most of our study participants had been on ART for a long time (median time since ART initiation was 10.6 years (IQR [7.7 ; 13.2]), while studies reporting weight changes related to ART often focus on ART initiation or regimen switching periods. Moreover, we did not consider a pre-inclusion history of different ART regimens. Such a history may have impacted participants' BMI more strongly than their current regimen.

We found that current HCV treatment was associated with a lower BMI and therefore a higher risk of underweight. This reflects research findings for interferon therapy and body weight changes (Alam, Ullah, Alam, & Ali, 2013) (we remind the reader that our data were collected before the Direct Acting Antivirals era). Furthermore, elevated alcohol use was associated with both categorical outcomes in our study; this reflects previous findings on alcohol intake and obesity (Traversy & Chaput, 2015).

Being a female PLHW was associated with a higher risk of underweight. This association was even stronger for females HIV-infected through IDU. While this finding is in line with previous results from another study on HIV-HCV co-infected patients, where females had a lower BMI than males, and higher rates of adverse events during HCV treatment (Bhattacharya et al., 2010), it contrasts with those from a study which showed a higher risk of underweight in HIV-infected males (Huis In 't Veld, Pengpid, Colebunders, & Peltzer, 2018), and a greater increase in BMI following ART initiation in females than males (Bares, Smeaton, Xu, Godfrey, & McComsey, 2018), in particular in persons taking recommended ART regimens including integrase inhibitors, such as dolutegravir and bictegravir (Shah, Hindley, & Hill, 2021).

A history of drug injection has been associated with lower BMI and percent body fat (McCombie et al., 1995; Tang et al., 2010). Moreover, females who inject drugs face a range of unique, gender-specific, and often additional challenges and barriers, leading to higher vulnerability to a range of health-related harms than males, including blood-borne viral and sexually transmitted infections, injection-related injuries, mental health issues, physical and

sexual violence, poor sexual and reproductive health, issues in relation to childbearing and child care, and pervasive stigma and discrimination (Iversen, Page, Madden, & Maher, 2015). Those conditions are likely to favor weight loss.

Our results have several implications. First, stopping cannabis (as well as tobacco) use can be considered an immediately available tool to improve the health status of HCV co-infected PLWH with underweight. Accordingly, smoking behaviors should be taken into account when providing HIV and/or HCV care, in order to carefully assess related risks and benefits. Although cannabis use cannot be currently advised for weight loss, our results reinforce evidence for the relevance of developing cannabis-based medicine to treat metabolic disorders in people with overweight, (Bielawiec, Harasim-Symbor, & Chabowski, 2020; Cluny, Keenan, Reimer, Le Foll, & Sharkey, 2015). This is of particular importance for PLWH, a population with an increasing prevalence of overweight, and who may have a higher risk of dysglycemia than non-infected people for a given BMI (Hanttu et al., 2021). Moreover, HIV infection is already a risk factor for type 2 diabetes (Noubissi, Katte, & Sobngwi, 2018), hypertension (Davis et al., 2021; Fahme, Bloomfield, & Peck, 2018; Schouten et al., 2014), dyslipidemia (Maggi et al., 2017; Russell et al., 2020) and liver steatosis (Bj, T, A, Aim, & Je, 2019), which are all related to an excess body weight gain. Finally, when considering the implications of our results, it should be kept in mind that the risk associated with underweight or overweight in PLWH depends on the BMI score (Achhra et al., 2018). One can expect graduated levels of risk within those categories. However, these were not investigated here.

One limitation of the present study is the assessment of cannabis use. The terms used to characterize the frequency of use may have been interpreted differently by participants. However, the fact that only regular cannabis use remained significant in the final model in the sensitivity analysis, suggests that a large part of the variability was captured. The major strengths of the present study are the large study sample size, its longitudinal design, and the large panel of socio-behavioral variables studied.

These results need to be replicated in other populations, particularly in HIV-mono-infected people and individuals with a lower prevalence of history of drug injection.

Conclusions

To conclude, cannabis use in HCV co-infected PLWH appeared to act as an agent for lowering body weight. While this may be beneficial to lower the risk of overweight and related metabolic disorders, it may also favor underweight. The direct cannabis use-underweight relationship which we found deserves more investigation. In the meantime, cannabis use should be regularly assessed and taken into account in the clinical management of this co-infected population.

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668 **Table 1: Study population characteristics at baseline according to body mass index**
669 **status (ANRS CO13 HEPAVIH cohort, n=992)**

Variable (% of missing data)	**Total study population (n=992)**	**Participants with underweight (BMI <18.5) (n=121)**	**Participants with normal weight (18.5≤ BMI <25) (n=694)**	**Participants with overweight (BMI ≥25) (n=177)**	
	n (%) or median [IQR]	n (%) or median [IQR]	n (%) or median [IQR]	n (%) or median [IQR]	p-value*
Age (years)	45 [42 ; 48]	45 [43 ; 48]	44 [41 ; 48]	46 [42 ; 48]	**0.023**
Gender * HIV transmission mode (0.2%)					**<0.001**
Men who have sex with men	112 (11.3)	7 (5.8)	85 (12.3)	20 (11.3)	
Male IDU	459 (46.4)	39 (32.5)	328 (47.3)	92 (52.0)	
Female IDU	180 (18.2)	47 (39.2)	121 (17.5)	12 (6.8)	
Male other	121 (12.2)	9 (7.5)	85 (12.3)	27 (15.3)	
Female other	118 (11.9)	18 (15.0)	74 (10.7)	26 (14.7)	
Educational level (14.4%)					0.716
< upper secondary school certificate	565 (66.6)	69 (69.7)	392 (65.8)	104 (67.5)	
≥ upper secondary school certificate	284 (33.4)	30 (30.3)	204 (34.2)	50 (32.5)	
Housing comfort (n=0.2%)					0.719
Not, barely, or quite comfortable	671 (67.8)	80 (66.7)	475 (68.5)	116 (65.5)	
Very comfortable	319 (32.2)	40 (33.3)	218 (31.5)	61 (34.5)	
Having a job (0.3%)					**0.005**
No	507 (51.3)	78 (64.5)	347 (50.2)	82 (46.3)	
Yes	482 (48.7)	43 (35.5)	344 (49.8)	95 (53.7)	
Time since HIV diagnosis (years) (0.3%)	18 [14; 21]	19 [15 ; 21]	18 [14 ; 21]	16 [11 ; 21]	**0.003**
Taking protease inhibitors					**0.040**
No	316 (31.9)	49 (40.5)	220 (31.7)	47 (26.6)	
Yes	676 (68.2)	72 (59.5)	474 (68.3)	130 (73.4)	
Time since HCV diagnosis (years) (2.1%)	10.0 [7.0 ; 14.0]	11.0 [7.0 ; 14.0]	10.5 [7.0 ; 15.0]	10.0 [8.0 ; 13.0]	0.929
HCV treatment status					0.699
Not yet treated	801 (80.8)	103 (85.1)	555 (80.0)	143 (80.8)	
On treatment	54 (5.4)	3 (2.5)	43 (6.2)	8 (4.5)	
Treated but not cured	14 (1.4)	2 (1.7)	9 (1.3)	3 (1.7)	
Cured	123 (12.4)	13 (10.7)	87 (12.5)	23 (13.0)	

Depressive symptoms† (10.0%)					0.736
No	535 (59.9)	68 (61.8)	371 (59.1)	96 (61.9)	
Yes	358 (40.1)	42 (38.2)	257 (40.9)	59 (38.1)	
Cannabis use‡					**<0.001**
No	519 (52.3)	42 (34.7)	345 (49.7)	132 (74.6)	
Occasional	209 (21.1)	31 (25.6)	159 (22.9)	19 (10.7)	
Regular	264 (26.6)	48 (39.7)	190 (27.4)	26 (14.7)	
Tobacco use (1.1%)					**<0.001**
No	117 (11.9)	9 (7.8)	76 (11.0)	32 (18.1)	
Former smoker	138 (14.1)	9 (7.8)	86 (12.5)	43 (24.3)	
Current smoker	726 (74.0)	97 (84.4)	527 (76.5)	102 (57.6)	
Alcohol use§ (3.2%)					0.912
Abstinence or low	725 (75.5)	91 (79.1)	505 (75.0)	129 (75.0)	
Moderate	181 (18.9)	18 (15.7)	130 (19.3)	33 (19.2)	
Elevated	54 (5.6)	6 (5.2)	38 (5.7)	10 (5.8)	
Recent other psychoactive drug use‖ (1.5%)					**0.016**
No	879 (90.0)	107 (91.5)	604 (88.3)	168 (95.5)	
Yes	98 (10.0)	10 (8.4)	80 (11.7)	8 (4.5)	
Coffee consumption (cups/day) (1.6%)					0.508
≤1	486 (49.8)	52 (44.4)	343 (50.3)	91 (51.4)	
2	220 (22.5)	33 (28.2)	146 (21.4)	41 (23.2)	
≥3	270 (27.7)	32 (27.4)	193 (28.3)	45 (25.4)	

* Chi-squared and Kruskal-Wallis tests for categorical and continuous variables, respectively.

† Assessed using the CES-D scale (score > 17 and 23 for men and females, respectively) (Fuhrer & Rouillon, 1989; Radloff, 1977).

‡ In the previous four weeks.

§ Alcohol use was categorized into abstinence or low (≤1 standard drink/day), moderate (>1-4 and >1-3 standard drinks/day for men and women, respectively) and elevated (>4 and >3 standard drinks/day for men and females, respectively).

‖ Use of at least one of the following psychoactive substances in the previous four weeks: cocaine, heroin, crack, ecstasy, street buprenorphine, amphetamines and LSD/other hallucinogens.

BMI, body mass index; HCV, hepatitis C virus; IDU, injecting drug use; IQR, interquartile range.

682 **Table 2: Factors associated with body mass index (mixed-effects linear regression,**
683 **ANRS CO13 HEPAVIH cohort, n=992)**

Variable		**Univariable analysis (n=992)**			**Multivariable analysis (n=977)**	
	Coef	95% CI	p-value	aCoef	95% CI	p-value
Age (years)	0.05	0.02 ; 0.07	<0.001			
Gender * HIV transmission mode						
Men who have sex with men	0.33	-0.28 ; 0.94	0.286	-0.29	-0.93 ; 0.36	0.385
Male IDU (ref.)	0			0		
Female IDU	-1.91	-2.45 ; -1.38	<0.001	-1.80	-2.35 ; -1.26	**<0.001**
Male other	0.67	-0.02 ; 1.37	0.057	0.25	-0.46 ; 0.96	0.498
Female other	0.25	-0.61 ; 1.11	0.570	-0.50	-1.30 ; 0.29	0.215
Educational level						
< upper secondary school certificate (ref.)	0					
≥ upper secondary school certificate	-0.05	-0.54 ; 0.43	0.827			
Housing comfort						
Not or quite comfortable (ref.)	0			0		
Very comfortable	-0.18	-0.38 ; 0.01	0.065	-0.21	-0.40 ; -0.02	**0.030**
Having a job						
No (ref.)	0					
Yes	-0.04	-0.28 ; 0.20	0.758			
Time since HIV diagnosis (years)	0.02	-0.00 ; 0.05	0.055	-0.08	-1.12 ; -0.03	**0.001**
Taking protease inhibitors						
No (ref.)	0					
Yes	-0.03	-0.20 ; 0.14	0.748			
Time since HCV diagnosis (years)	0.04	0.02 ; 0.07	0.001			
HCV treatment status						
Not yet treated (ref.)	0			0		
On treatment	-0.58	-0.74 ; -0.41	<0.001	-0.71	-0.89 ; 0.54	**<0.001**
Treated but not cured	0.06	-0.18 ; 0.30	0.626	-0.17	-0.42 ; 0.07	0.168
Cured	0.30	0.07 ; 0.52	0.011	0.05	-0.20 ; 0.29	0.708
Depression*						
No (ref.)	0					
Yes	-0.15	-0.33 ; 0.04	0.115			
Cannabis use†						
No (ref.)	0			0		
Occasional	-0.32	-0.58 ; -0.07	0.013	-0.21	-0.47 ; 0.04	0.100
Regular	-0.69	-0.99 ; -0.40	<0.001	-0.53	-0.82 ; -0.24	**<0.001**

Tobacco use						
No (ref.)	0			0		
Former smoker	-0.88	-1.50 ; -0.26	0.005	-0.62	-1.21 ; -0.03	**0.041**
Current smoker	-1.36	-1.94 ; -0.78	<0.001	-1.07	-1.62 ; -0.52	**<0.001**
Alcohol use‡						
Abstinence or low (ref.)	0					
Moderate	0.17	-0.05 ; 0.39	0.130			
Elevated	0.19	-0.36 ; 0.73	0.504			
Recent other psychoactive drug use§						
No (ref.)	0					
Yes	-0.04	-0.33 ; 0.24	0.758			
Coffee consumption (cups/day)						
≤1 (ref.)	0					
2	-0.09	-0.31 ; 0.12	0.389			
≥3	-0.02	-0.28 ; 0.24	0.882			
Follow-up time (years)	0.07	0.04 ; 0.10	<0.001	0.14	0.09 ; 0.20	**<0.001**

* Assessed using the CES-D scale (score > 17 and 23 for men and females, respectively) (Fuhrer & Rouillon, 1989; Radloff, 1977).

† In the previous four weeks.

‡ Alcohol use was categorized into abstinence or low (≤1 standard drink/day), moderate (>1-4 and >1-3 standard drinks/day for men and females, respectively) and elevated (>4 and >3 standard drinks/day for men and females, respectively).

§ Use of at least one of the following psychoactive substances in the previous four weeks: cocaine, heroin, crack, ecstasy, street buprenorphine, amphetamines and LSD/other hallucinogens.

aCoef, adjusted regression coefficient; ARV, antiretroviral therapy; CI, confidence interval; Coef, regression coefficient; HCV, hepatitis C virus; IDU, injecting drug use.

Table 3: Factors associated with overweight and underweight (mixed-effects logistic regression, multivariable analysis, ANRS CO13 HEPAVIH cohort, n=942 and n=981, respectively)

Variable		**Overweight (n=942)**			**Underweight (n=981)**	
	aOR	95% CI	p-value	aOR	95% CI	p-value
Age (years)				1.07	1.02 ; 1.11	**0.005**
Gender * HIV transmission mode						
Men who have sex with men	0.35	0.12 ; 0.99	**0.048**	0.44	0.11 ; 1.71	0.234
Male IDU (ref.)	1			1		
Female IDU	0.06	0.03 ; 0.15	**<0.001**	13.18	6.40 ; 27.15	**<0.001**
Male other	1.02	0.34 ; 3.06	0.968	0.65	0.23 ; 1.84	0.421
Female other	0.47	0.16 ; 1.37	0.169	3.08	1.38 ; 6.88	**0.006**
Time since HIV diagnosis (years)	0.85	0.78 ; 0.92	**<0.001**			
HCV treatment status						
Not yet treated (ref.)				1		
On treatment				2.07	1.11 ; 3.85	**0.022**
Treated but not cured				1.12	0.52 ; 2.40	0.775
Cured				0.68	0.35 ; 1.33	0.259
Depressive symptoms*						
No (ref.)	1					
Yes	0.52	0.31 ; 0.87	**0.014**			
Cannabis use†						
No (ref.)	1			1		
Occasional	0.26	0.11 ; 0.58	**0.001**	2.08	1.06 ; 4.05	**0.033**
Regular	0.13	0.05 ; 0.31	**<0.001**	3.56	1.86 ; 6.79	**<0.001**
Alcohol use‡						
Abstinence or low (ref.)	1			1		
Moderate	1.15	0.61 ; 2.15	0.665	0.82	0.44 ; 1.52	0.531
Elevated	2.93	1.13 ; 7.65	**0.028**	0.15	0.04 ; 0.54	**0.003**
Follow-up time (years)	1.60	1.38 ; 1.87	**<0.001**			

* Assessed using the CES-D scale (score > 17 and 23 for males and females, respectively) (Fuhrer & Rouillon, 1989; Radloff, 1977).

† In the previous four weeks.

‡ Alcohol use was categorized into abstinence or low (≤1 standard drink/day), moderate (>1-4 and >1-3 standard drinks/day for males and females, respectively) and elevated (>4 and >3 standard drinks/day for males and females, respectively).

aOR, adjusted odds ratio; CI, confidence interval; HCV, hepatitis C virus; IDU, injecting drug use