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

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1 **Cannabis use as a protective factor against overweight in HIV-hepatitis C virus co-**
2 **infected people (ANRS CO13 HEPAVIH cohort)**

3

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124 Abstract

125

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

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

139 Introduction

140 Elevated body weight is increasingly prevalent in people living with HIV (PLWH) in
141 high-income countries (Crum-Cianflone et al., 2010; Koethe et al., 2016; Pourcher,
142 Costagliola, & Martinez, 2015). Antiretroviral therapy (ART) is a risk factor for weight gain
143 (Buzón-Martín, 2020; Sax et al., 2020), which in turn may lead to an unhealthy body mass
144 index (BMI) (Jiang et al., 2019; Kumar & Samaras, 2018; Yuh et al., 2015). For instance, in
145 pooled analyses of eight phase 3 ART trials, Sax et al. found a 96-week median weight gain
146 of 2 kg, the proportion of participants with obesity rising from 16.3% at baseline to 21.2% at
147 week 96 (Sax et al., 2020). In PLWH taking ART, maintaining normal weight is associated
148 with a lower risk of cardiovascular diseases, cancer, and mortality (Achhra et al., 2018; Jiang
149 et al., 2019; Sharma et al., 2015). BMI seems to be linearly associated with the risk of
150 diabetes in this population (Achhra et al., 2018). At the upper end of the BMI spectrum,
151 obesity is a risk factor for several conditions. PLWH are at a higher risk of these conditions
152 than the general population, including diabetes mellitus, cardiovascular diseases, liver
153 steatosis and neurocognitive impairments (Bailin, Gabriel, Wanjalla, & Koethe, 2020). For
154 instance, in treated PLWH, the relative risk for cardiovascular disease and cancers known to
155 be associated with BMI were estimated at 1.31 and 1.92 for a BMI>30 and BMI 23-25,
156 respectively (Achhra et al., 2018). Underweight is also a risk factor for comorbidities (e.g.,
157 non-AIDS-defining cancers) and for AIDS and non-AIDS-related mortality (Achhra et al.,
158 2018; Jung et al., 2019). Co-infection with hepatitis C virus (HCV) also represents an excess
159 risk for all-cause, non-liver related and cancer mortality (Chalouni et al., 2021), as well as
160 cardiovascular diseases (Osibogun et al., 2017) in PLWH. Managing and preventing
161 elevated and low body weight is therefore crucial in PLWH - especially HCV co-infected
162 PLWH - to limit the risk of comorbidities and mortality.

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

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

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

180 **Material and Methods**

181 **Cohort design**

182 ANRS CO13 HEPAVIH is an ongoing French national prospective cohort of PLWH
183 co-infected with HCV (Loko et al., 2010). Consecutive patients attending outpatient services
184 in 17 different hospitals throughout the country were enrolled in its first phase (2005-2008)
185 with the following selection criteria: aged ≥ 18 years; infected with HIV-1; either chronically
186 co-infected with HCV (as confirmed by an HCV RNA assay) or HCV cured after treatment.
187 Annual clinical follow-up visits (or biannual for patients with cirrhosis) were scheduled.
188 Patients who initiated HCV treatment during follow-up had additional visits. Patients were
189 invited to complete a self-administered questionnaire collecting socio-behavioral data at
190 enrollment (M0) and yearly thereafter until the scheduled 60-month clinical follow-up visit
191 (M60). The study was designed and implemented in accordance with the Declaration of

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

194 Collected data

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

203 Study population and study period

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

212 Outcomes and explanatory variables

213 Outcomes

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

217 Explanatory variables

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

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

228 Self-reported psychoactive substance use and coffee consumption: Current, former, and no
229 lifetime tobacco use were the three categories created for the variable 'tobacco use. Alcohol
230 use was categorized into abstinence or low (≤ 1 standard drink per day), moderate ($>1-4$ and
231 $>1-3$ standard drinks per day for males and females, respectively) and elevated (>4 and >3
232 standard drinks per day for males and females, respectively). Cannabis use frequency was
233 recorded as 'never', 'sometimes', 'regularly' and 'daily', and subsequently categorized into a
234 three-category explanatory variable: no use (never), occasional (sometimes), and regular
235 use (regularly or daily). Use of psychoactive substances other than cannabis during the
236 previous four weeks (cocaine, heroin, crack, ecstasy, street buprenorphine, amphetamines
237 and LSD/other hallucinogens) was coded as 'yes' or 'no'. Coffee consumption was
238 categorized into low (≤ 1 cup per day), moderate (2 cups per day) and elevated (≥ 3 cups per
239 day), reflecting a threshold previously highlighted as beneficial for health outcomes in this
240 population (Carrieri, Protopopescu, Marcellin, Rosellini, et al., 2017; Carrieri, Protopopescu,
241 Marcellin, Wittkop, et al., 2017; Protopopescu et al., 2018).

242 Education level and housing: Education level was characterized as '< upper secondary
243 school certificate' or ' \geq upper secondary school certificate', and employment status as 'having
244 a job' or 'not'. Perceived comfort of housing was recorded with the question 'Would you say

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

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

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

254 **Statistical analyses**

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

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

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

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

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

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

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

277 Results

278 Study sample characteristics

279 Of the 1246 participants from the cohort's first enrollment phase, we excluded 17
280 because they were ART-naive at enrollment, and 237 others, as they had no visit with
281 simultaneous data for cannabis use and BMI. The study sample therefore comprised 992
282 patients, accounting for 4485 visits. Seventy percent were male, 12.4% were HCV-cured at
283 baseline (24.2% at last available follow-up visit), 26.6% were regular or daily cannabis users,
284 70.0% had normal weight, and 17.8% were overweight. Median age was 45 years
285 (interquartile range (IQR) [42-48]) (**Table 1**).

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

291 Relationship between cannabis use and BMI level

292 Results from mixed-effects univariable and multivariable linear regression models are
293 given in **Table 2**. In univariable analyses, both regular and occasional cannabis use were
294 inversely associated with BMI. After multivariable adjustment, regular cannabis use was
295 inversely associated with BMI (adjusted regression coefficient: -0.53 [95% CI] [-0.82; -0.24],
296 $p < 0.001$); however, occasional use was not ($p = 0.100$) (**Table 2**). Moreover, a linear trend
297 test confirmed the dose-response association between cannabis use frequency and BMI

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

302 Relationship between cannabis use and BMI categories

303 Results from the multivariable logistic regression models are provided in **Table 3**.
304 After multiple adjustment, both occasional (adjusted odds ratio (aOR) [95% confidence
305 interval (CI)]: 0.26 [0.11; 0.58], $p = 0.001$) and regular (aOR [95% CI]: 0.13 [0.05; 0.31],
306 $p < 0.001$) cannabis use were inversely associated with overweight, as were being an MSM,
307 being a female IDU (vs. a male IDU), time since HIV diagnosis, and having depressive
308 symptoms. Conversely, elevated alcohol use and follow-up time were positively associated
309 with overweight (**Table 3**).

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

314 After multivariable adjustment, both occasional (aOR [95% CI]: 2.08 [1.06; 4.05],
315 $p = 0.033$) and regular (aOR [95% CI]: 3.56 [1.86; 6.79], $p < 0.001$) cannabis use were
316 associated with underweight, as were being a female (whether IDU or not, vs. a male IDU),
317 older age, and current HCV treatment. Conversely, underweight was inversely associated
318 with elevated alcohol use (**Table 3**).

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

325 Discussion

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

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

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

357 The above results would therefore suggest that cannabis use, just like tobacco use,
358 acts as an agent for lowering body weight. It has been suggested that while acute stimulation
359 of cannabinoid receptor 1 (CB1) by $\Delta 9$ -tetrahydrocannabinol (THC) in cannabis initially leads
360 to increased food intake (Foltin, Fischman, & Byrne, 1988), overstimulation of the receptor by
361 chronic cannabis consumption may lead to long-lasting downregulation of CB1 (Clark et al.,
362 2018). The latter may in turn reduce energy storage and increase metabolic rates, leading to
363 a lower BMI (Clark et al., 2018). Indeed, it was recently documented that the
364 endocannabinoid system - an endogenous lipid signaling system comprising cannabinoid
365 receptors and their ligand (among other molecules) - is widely and complexly involved in
366 energy homeostasis (Di Marzo & Silvestri, 2019). This finding led to the development of a
367 CB1 antagonist by the drug industry. Despite positive results in the treatment of obesity, this
368 antagonist was subsequently discarded because of adverse psychiatric effects (Di Marzo &
369 Després, 2009).

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

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

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

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

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

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

406 sexual violence, poor sexual and reproductive health, issues in relation to childbearing and
407 child care, and pervasive stigma and discrimination (Iversen, Page, Madden, & Maher,
408 2015). Those conditions are likely to favor weight loss.

409 Our results have several implications. First, stopping cannabis (as well as tobacco)
410 use can be considered an immediately available tool to improve the health status of HCV co-
411 infected PLWH with underweight. Accordingly, smoking behaviors should be taken into
412 account when providing HIV and/or HCV care, in order to carefully assess related risks and
413 benefits. Although cannabis use cannot be currently advised for weight loss, our results
414 reinforce evidence for the relevance of developing cannabis-based medicine to treat
415 metabolic disorders in people with overweight, (Bielawiec, Harasim-Symbor, & Chabowski,
416 2020; Cluny, Keenan, Reimer, Le Foll, & Sharkey, 2015). This is of particular importance for
417 PLWH, a population with an increasing prevalence of overweight, and who may have a
418 higher risk of dysglycemia than non-infected people for a given BMI (Hanttu et al., 2021).
419 Moreover, HIV infection is already a risk factor for type 2 diabetes (Noubissi, Katte, &
420 Sobngwi, 2018), hypertension (Davis et al., 2021; Fahme, Bloomfield, & Peck, 2018;
421 Schouten et al., 2014), dyslipidemia (Maggi et al., 2017; Russell et al., 2020) and liver
422 steatosis (Bj, T, A, Aim, & Je, 2019), which are all related to an excess body weight gain.
423 Finally, when considering the implications of our results, it should be kept in mind that the
424 risk associated with underweight or overweight in PLWH depends on the BMI score (Achhra
425 et al., 2018). One can expect graduated levels of risk within those categories. However,
426 these were not investigated here.

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

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

435 **Conclusions**

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

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Table 1: Study population characteristics at baseline according to body mass index 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)	

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

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

673 ‡ In the previous four weeks.

674 § Alcohol use was categorized into abstinence or low (≤1 standard drink/day), moderate (>1-
675 4 and >1-3 standard drinks/day for men and women, respectively) and elevated (>4 and >3
676 standard drinks/day for men and females, respectively).

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

680 BMI, body mass index; HCV, hepatitis C virus; IDU, injecting drug use; IQR, interquartile
681 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

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

686 † In the previous four weeks.

687 ‡ Alcohol use was categorized into abstinence or low (≤1 standard drink/day), moderate (>1-
688 4 and >1-3 standard drinks/day for men and females, respectively) and elevated (>4 and >3
689 standard drinks/day for men and females, respectively).

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

693 aCoef, adjusted regression coefficient; ARV, antiretroviral therapy; CI, confidence interval;
694 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