# Impact of HCV treatment and depressive symptoms on adherence to HAART among coinfected HIV-HCV patients: results from the ANRS-CO13-HEPAVIH cohort.

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**Abstract**

Background: The additional burden of HCV infection in HIV-HCV coinfected individuals may have some consequences on adherence to highly active antiretroviral therapy (HAART). Few studies have explored the pattern of correlates of non-adherence to HAART while simultaneously considering the impact of HCV treatment and depressive symptoms on adherence to HAART. We used longitudinal data to assess factors associated with non-adherence to HAART. Methods: The French national prospective cohort ANRS-CO-13-HEPAVIH is a multi-center cohort which recruited 1175 HIV-HCV coinfected patients in 17 hospital outpatient units delivering HIV and HCV care in France between October 2006 and June 2008. For this analysis, we selected participants on HAART with self-reported data for adherence to HAART (n = 727 patients, 1190 visits). Data were collected using self-administered questionnaires and medical records. A mixed logistic regression model based on an exchangeable correlation matrix was used to identify factors associated with non-adherence to HAART. Results: Patients reported non-adherence to HAART in 808 (68%) of the 1190 visits. Four variables remained associated with non-adherence to HAART after multivariate analysis: hazardous alcohol consumption, cocaine use and depressive symptoms, regardless of whether treatment for depression was being received. Finally, patients being treated for HCV infection were less likely to be non-adherent to HAART. Conclusions: Besides the problem of polydrug use, two other dimensions deserve special attention when considering adherence to HAART in HIV-HCV coinfected patients. Access to HCV treatment should be encouraged as well adequate treatment for depression in this population to improve adherence and response to HAART.

**Key words:** adherence, coinfection, depressive symptoms, HIV, HCV, treatment.

## Introduction

Adherence to highly active antiretroviral therapy (HAART) is a crucial aspect of medical care in HIV infected patients and has been widely investigated [1, 2]. Many factors have been identified as potential determinants of non-adherence to HAART among monoinfected HIV patients, including medical factors related to care and treatment [3] and non-medical factors such as socio-economic, behavioral and structural determinants e.g. incarceration [4, 5]. The identification of these factors has led to the development of a multidisciplinary approach towards improving adherence to HAART, wherein new interventions to tackle these factors are continuously incorporated. [6]. Part of this approach is to provide improved mental healthcare services for HIV infected persons, the main reason being that psychiatric comorbidities are often associated with chronic diseases [7] in this population [8]. Moreover, mental health and depressive symptoms have a large impact on adherence to HAART [9] and have been the subject of many studies exploring effective clinical strategies to prevent or treat depression [10, 11].

In HIV-HCV coinfected patients, HCV infection seems to be an independent factor associated with poorer adherence to HAART [12]. In addition, the burden of depression is a challenging concern for HIV clinicians as HIV-HCV individuals are characterized by more severe depression than are their HIV monoinfected counterparts [13]. Moreover, a recent study has shown the first evidence of an association between chronic HCV and recurrent brief episodes of depression, independent of HCV treatment (IFN-alpha) and substance or alcohol abuse [14]. HCV treatment initiation is known to induce depressive symptoms independently of any inherent patient susceptibility to major depression [15]. Besides the fear of HCV treatment inducing depressive symptoms in coinfected individuals, there is also the worry that it may

have a negative impact of adherence to HAART in this population. This fear was expressed during the most recent IAS conference [16].

The ANRS CO13 HEPAVIH cohort gave us the opportunity to explore the impact of HCV treatment, depressive symptoms and antidepressant treatment on adherence to HAART in a cohort of HIV-HCV coinfected patients.

## Methods

### Study design

The French ANRS-CO13-HEPAVIH cohort was designed to study the clinical, immunological, virological, and socio-behavioral course of HIV-HCV coinfected individuals. This longitudinal study recruited 1175 HIV-HCV coinfected individuals in 17 outpatient hospital units delivering care to HIV and HCV positive individuals in France between October 2006 and June 2008 and monitored them for 60 months [17].

Individuals enrolled had to be HIV-positive with chronic HCV infection. Those with sustained virological response (undetectable HCV viral load for more than 6 months after treatment for HCV) were not included. Patients who agreed to participate signed a letter of informed consent and were given a self-administered questionnaire at every annual visit (visits were annual) that included items on socio-demographic characteristics, past and current drug and alcohol use, treatment history, HAART adherence and psychosocial factors.

Clinical and biological data, including HIV viral load, CD4 count and liver fibrosis stage, were evaluated using a different questionnaire given to each clinical center's medical staff.

The study was approved by a French institutional review board.

## Study population

Among the 1175 patients included in the cohort, individuals with decompensated cirrhosis, those who had undergone a liver transplantation, those who had hepatocellular carcinoma and those who had been cured of their HCV infection were initially excluded. Of the remaining 1021 patients, only those receiving HAART (n=954) and whose data on adherence to HAART and on depressive symptoms were available for at least one visit (n=727) - accounting for 1190 visits - were included in the analyses.

## Questionnaires

### *Self-administered questionnaires*

The self-administered questionnaires collected psychosocial and behavioral characteristics at enrolment and at each follow-up visit. They consisted of several sections accounting for approximately 100 items focusing on socio-demographic characteristics, history of drug use, addictive behaviors, adherence to HAART, side effects and depressive symptoms. Demographic information and details about educational level, employment and housing were also collected. For history of drug use and current drug and alcohol use, we documented the year of first drug injection. Each patient's history of substance use was assessed using the Addiction Severity Index (ASI) [18], the substances included for assessment being cannabis, cocaine, heroin, crack, ecstasy, buprenorphine, methadone, amphetamines and hallucinogens.

Alcohol consumption was measured using the AUDIT-C questionnaire. Hazardous alcohol consumption was defined as a score $\geq 4$ for men and $\geq 3$ for women [19].

Data about patients' perceptions of treatment side effects were collected using a section in the questionnaires exploring the occurrence of 39 symptoms over the previous four weeks, and

the discomfort these symptoms had caused. This section was based on the Symptoms Distress Module proposed by Justice et al. [20] which lists symptoms known to occur while on HAART. It was broadened to include questions on lipodystrophy symptoms and symptoms associated with interferon-based therapy.

Patients' depressive symptomatology was assessed using the Center for Epidemiological Studies Depression scale (CES-D) [21]. Patients' feelings and behaviors over the previous week were used to calculate a global depression score ranging from 0 to 60. The cut-off points 17 and 23 for men and women, respectively, were chosen as indicative of depressive symptoms (DS) [22]. This variable was then combined with the information about use of antidepressant treatment(s) (ADT) during the previous 6 months in order that patients could be classified according to the following categories: *"no depressive symptoms and no ADT"* (which was used as the reference group in the analysis), *"no depressive symptoms and ADT", "depressive symptoms and no ADT"* and *"depressive symptoms and ADT"*.

*Measurement of adherence to HAART*

In the self-administered questionnaire, a set of seven questions was used to assess adherence to HAART. At each clinical visit, all HAART-treated patients were asked to list, for each antiretroviral drug, the daily number of prescribed pills they had taken during the four days prior to that particular visit. They were also asked if they had "totally" or "partially" taken their prescribed doses of HAART or had "interrupted their treatment" during the same 4-day period. Patients were considered non-adherent if they reported that they had taken <100% of the total dose of antiretroviral drugs prescribed, and/or if they had not totally followed their prescribed regimen during the 4-day period prior to that particular visit. In addition, the visual analogue scale was used to reclassify those patients whose scale score was <100% as non-adherent. In other words, a patient who reported that he/she was adherent in all previous

questions in the adherence section was nonetheless reclassified as non-adherent if he/she reported a score different from 100% in the visual analog scale (from 1 to 6). This approach has been previously validated using protease inhibitor dosage measurement via urine analysis [23].

*Medical questionnaire*

A medical questionnaire at enrolment collected retrospective data about the patient's history, including clinical and biological data (HIV viral load, CD4 count, and liver fibrosis stage based on Metavir score, and provided either by biopsy, transient elastometry (Fibroscan™) or FibroTest™ results), together with other data on treatment history, including HAART regimen and HCV treatment.

Statistical analysis

Analyses were performed for the 727 coinfected patients (accounting for 1190 visits) who were receiving HAART and who had available data on both depressive symptoms and adherence to HAART. Clinical and psychosocial characteristics of patients, including depressive symptoms, access to HCV therapy, self-reported treatment-related side effects, and drug and alcohol use were tested for their association with adherence to HAART.

To identify factors associated with non-adherence to HAART, we used a mixed logistic regression based on an exchangeable correlation matrix. To avoid situations where strong confounding could have hidden important predictors of non-adherence, a liberal p-value of $<0.20$ in the univariate analyses was chosen to define the variables to be entered into the selection procedure for the multivariate model. A step-by-step backward procedure based on

the log-likelihood ratio test was used to identify the variables, with a p-value of <0.05, in the multivariate model.

The association between "depressive symptoms and anti-depressant treatment" and two other variables, "the number of perceived symptoms" and "daily cannabis use", was also tested.

## Results

### Descriptive analysis

First, no significant difference was found between participants included in the analyses and those who were not, in terms of socio-demographic and clinical characteristics.

The baseline characteristics of the 727 patients included in the analyses are described in **Table 1**.

From a total of 1190 visits, 296 patients (808 visits, 68% of the 1190 visits) reported being non-adherent to HAART, 346 patients (484 visits, 41%) had depressive symptoms and 196 patients (261 visits, 22%) reported having received ADT in the previous 6 months.

Of the 484 visits where patients reported depressive symptoms, 238 patients (312 visits, 64%) were not being treated for their depression, while 136 patients (172 visits, 36%) were receiving ADT. Of the 706 visits where patients had no depressive symptoms, 421 patients (617 visits, 52%) were not being treated and 76 patients (89 visits, 7%) were receiving ADT.

Hazardous alcohol consumption was reported by 286 patients (397 visits, 33%), daily cannabis use by 125 patients (171 visits, 16%), cocaine use by 78 patients (98 visits) and heroin use by 25 patients (32 visits, 3%). The median [IQR] number of self-reported side effects was 9[4-14].

Finally, 223 patients were receiving HCV therapy (354 visits, 30%).

**Factors associated with non-adherence to HAART**

*Univariate analysis*

**Table 2** shows the crude and adjusted ORs of possible correlates of non-adherence to HAART. The variables which were eligible for the final model are indicated in bold. Some socio-demographic characteristics were found to be associated with adherence: Older patients, those who were employed, those living in a couple and those having comfortable housing were all less likely to be non-adherent to HAART. Certain behavioral and psychological outcomes influenced adherence to HAART in the univariate model: depressive symptoms, antidepressant treatment, daily alcohol consumption, daily cannabis use and cocaine use. Experience of progression to AIDS (CDC stage C) was found to be associated with adherence to HAART. Patients who were being treated for their HCV infection were more likely to be adherent to HAART.

Two additional variables - the number of symptoms and daily cannabis use - were found to be correlates of non-adherence to HAART in the univariate analysis but were not included in the final model as they were collinear with "depressive symptoms and antidepressant treatment" which had a stronger association with the outcome. **Tables 3 and 4** show the significant association between the DS/ADT variable and the number of symptoms or daily cannabis use. Even though the number of symptoms was associated with being treated with antidepressants without having any depressive symptoms, the strongest association (a greater than five-fold higher risk of perceiving depressive symptoms) was in patients who had depressive symptoms, whether they were being treated with antidepressants or not. However, daily cannabis use was associated only with those patients who had depressive symptoms while on antidepressant treatment.

*Multivariate analyses*

The results show that, after multiple adjustments (**Table 2**), patients who reported hazardous alcohol consumption (OR[95%CI]=1.91[1.27-2.87], p=0.002) and cocaine use (OR[95%CI] =2.26[1.15-4.43], p=0.02) were significantly more likely to be non-adherent to HAART. Patients who reported depressive symptoms were also significantly less adherent to HAART, whether they were being treated for depression (OR [95%CI]= 1.83[1.05-3.22], p=0.03) or not (OR[95%CI]= 1.63[1.04-2.54], p=0.03). Finally, patients who were being treated for HCV infection were less likely to be non-adherent to HAART (OR[95%CI]=0.38 [0.17-0.84], p=0.02).

## Discussion

The main results of this study suggest that HIV-HCV coinfected patients with depressive symptoms are at higher risk of non-adherence to HAART - whether they are on antidepressant treatment or not - and that being treated for HCV has a positive impact on adherence to HAART. Not surprisingly, we also found that cocaine use and alcohol consumption continue to be factors associated with non-adherence to HAART.

In other words, the findings from this large cohort show that initiating HIV-HCV coinfected patients in HCV treatment may facilitate adherence to HAART. Indeed, it was important to adjust the multivariate model for this variable, as patients who were being treated for HCV infection were more likely to be adherent to HAART. Although this paper focuses more on the impact of depression and antidepressant treatment, the latter result deserves attention. It should be confirmed in a more specific study aimed at examining improved access to treatment for HCV in HIV-HCV coinfected population [24]. It is known that HIV-HCV

coinfected patients face particular barriers to accessing HCV care. They are more often past or current drug users [25], have more chaotic lifestyles and are seen as people with disrupted lives who find it difficult to adhere to treatment [26].

The main result of the present article concerns the impact of depressive symptoms on adherence to HAART. It is known that depression is very prevalent in HCV-infected people, whether receiving treatment for their HCV infection or not [27]. In addition, it has been shown that high rates of depressive symptoms are related to comorbidities such as HCV in such individuals [13]. Given the higher prevalence of depressive symptoms among HIV-HCV coinfected individuals [28] and the negative impact of these symptoms on adherence to HAART, optimizing clinical management of depression is crucial. As we expected, our results indicate that depressive symptoms are associated with non-adherence to HAART. This confirms the findings of a recent meta-analysis [29]. However, when we considered those who were receiving ADT, patients who had depressive symptoms while being treated had a higher risk of non-adherence to HAART than those who were not being treated with ADT. This important result may be a sign of inadequacy in the provision of care for depression in some HIV-HCV coinfected patients receiving HAART.

Yun et al. have already demonstrated the positive impact of antidepressant treatment on adherence to HAART in HIV-infected depressed patients [30]. A previous analysis using the baseline data of Hepavih cohort showed that patients successfully treated for their depression exhibited similar levels of fatigue impact to those with no depressive symptoms and not taking antidepressant treatment [31]. However, the lack of ADT effectiveness, as indicated by persistent depressive symptoms, may be a sign of severe depression or treatment inadequacy. It would therefore seem important to diagnose depression early on and to treat it effectively in order to optimize HIV care. This is especially true with respect to improving adherence to HAART among HIV-HCV coinfected patients.

In line with other reports [32, 33] the present study suggests that alcohol use interferes with adherence to HAART. The most worrying issue is that alcohol problems are more prevalent in the HCV-infected population [34] than in their non-HCV infected counterparts. Paying greater attention to heavy alcohol drinkers by proposing psychological and/or pharmacological responses would seem to be of great importance. For instance, some studies have shown interesting findings either using baclofen in HCV-infected patients [35] or behavioral counseling in HCV-infected IDU [36].

In this study, cocaine use was also found to be a factor associated with non-adherence to HAART. Although some studies have found mixed results concerning the negative impact of active drug use on adherence to HAART and viral suppression [37], cocaine use has already been shown to impair a positive response to HAART [38]. The only current therapy offered for cocaine abusers, based on the cognitive behavioral model, seems to be insufficient in terms of reducing cocaine use [39]. New pharmacological responses to cocaine abuse and dependence are needed for HIV-HCV coinfected patients. Furthermore the development of agonist treatments for cocaine dependence would seem to be an interesting avenue of research to pursue for such HIV-HCV coinfected patients as the efficacy of opioid maintenance treatment in HIV-infected opioid dependent populations has already been proven [40, 41].

Regarding daily cannabis use, our results showed that patients reported daily cannabis use in 16% of visits during follow-up. This behavior was found to be associated with non-adherence to HAART and had a strong association with having depressive symptoms and being treated with ADP. This group (17%) of patients had more severe depressive symptoms. **Indeed, it is known that cannabis dependence may increase psychiatric comorbidities [42, 43]** and depressive symptoms have been found to be higher in cannabis users [44]. Moreover, we also found that the higher the number of self-reported symptoms the higher the non-adherence to HAART. This is in line with previous studies that have demonstrated that reporting perceived

side-effects decreased adherence to HAART [45]. However, many other studies have highlighted the relationship between depression and perceived symptoms such as pain or fatigue [46], suggesting that HCV-related somatic symptoms may be part of a causal pathway leading to depression. That is why treating depression in this population is important in order to improve adherence to HAART but also to alleviate HCV related symptoms.

Some limitations of this study should be acknowledged. First, the reliability of self-reported adherence remains a concern. However, a meta-analysis has already demonstrated the validity of self-reported measures of adherence [47]. To control for social desirability bias, we used a high cut-off score and an algorithm reclassifying patients reporting non-adherence at least once in the adherence questionnaire as non-adherent. Second, the CES-D scale includes several items that measure somatic and physical symptoms of depression. One limitation of using this tool is that physical symptoms are not specific to depression. In depressed patients with HIV infection, certain symptoms such as loss of appetite, sleep disturbances, difficulty in concentration, fatigue, could be confounded with the physical symptoms of the underlying medical condition. However, as we adjusted the statistical model for HIV variables, any confounding effect of HIV symptoms should be limited. Moreover, the use of the CES-D scale to diagnose depression could be criticized because of its lack of clinical accuracy in terms of measuring major depression. Complementing it with other scales could, potentially, improve its screening power [48]. However, the CES-D scale still remains an appropriate tool for detecting depressive symptoms with gender-specific cut-off values [49]. Another limitation of this study is that we did not study adherence to ADT. Had we done so, we could have investigated whether the inefficacy of ADT among patients who reported depressive symptoms was due to poor ADT treatment adherence.

Our results, which focus on depression management, highlight the need to take into account psychiatric comorbidities among HIV-HCV coinfected persons. The risk of depression induced by HCV therapy is widely recognized [50]. Accordingly, assessment and prompt treatment of depressive symptoms before and after treatment initiation [51] should be recommended. Continuously assessing the effectiveness of such treatment is of paramount importance. While a previous study demonstrated that self-reported fatigue and depression are major components of the different dimensions of the quality of life in HIV-HCV coinfected patients not receiving anti-HCV treatment [52], our findings underline the importance in identifying psychiatric symptoms to help HIV-HCV coinfected patients (on HCV treatment or not) to manage multiple therapeutic regimens. Moreover, increasing the range of available therapeutic options, including adequate antidepressant treatment, treatment for alcohol and cocaine dependence as well as other medications to relieve side-effects, should be considered in the early stages of coinfection in order to provide adequate care to the different profiles of this vulnerable population.

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## Disclosure statement

The authors have no conflict of interest to declare.

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**Table 1.** Baseline characteristics of the sample used for the analyses, n=727.

| | Number of patients (%) | Median [IQR] |
|---|---|---|
| **Female gender** | 224 (31) | |
| **Age**[a] | | 44[41-48] |
| **Being employed** | 371 (51) | |
| **Having children** | 236 (33) | |
| **High school certificate** | 195 (27) | |
| **Living in a couple** | 345 (47) | |
| **Comfortable housing** | 603 (83) | |
| **Owner or tenant of her/his home** | 579 (80) | |
| **HIV transmission group** | | |
| - injecting drug use (IDU) | 472 (65) | |
| - men who have sex with men (MSM) | 85 (12) | |
| - heterosexual | 100 (14) | |
| - "don't know" or "other" | 70 (9) | |
| **Daily cannabis use**[b] | 105 (14) | |
| **Hazardous alcohol consumption**[c] | 251 (35) | |
| **Cocaine use**[b] | 61 (8) | |
| **Heroin use**[b] | 19 (3) | |
| **CDC stage C** | 221 (30) | |
| **CD4 cell count** | | 449 [302-648] |
| **HIV undetectable viral load (<50 copies/ml)** | 533 (73) | |
| **Severe fibrosis** | 219 (30) | |

[a] Per 10-year increase

[b] during the previous month

[c] AUDIT-C score≥4 for men and ≥3 for women

**Table 2.** Factors associated with non-adherence to HAART: mixed logistic model, univariate and multivariate analysis (1190 visits, 727 patients)

| | | | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|---|---|
| | **Number of visits (%) or median [IQR]** | **Number of patients** | **OR [95%CI]** | **p-value** | **aOR [95%CI]** | **p-value** |
| Female gender | 363 (31) | 224 | 0.94 [0.58-1.51] | 0.80 | | |
| **Age**[a] | **45 [42-48]** | | **0.76 [0.54-1.09]** | **0.14** | | |
| **Being employed** | **581 (50)** | **387** | **0.71 [0.47-1.08]** | **0.11** | | |
| Having children | 366 (31) | 247 | 0.99 [0.62-1.57] | 0.96 | | |
| High school certificate | 321 (31) | 185 | 0.73 [0.43-1.23] | 0.24 | | |
| **Living in a couple** | **567 (48)** | **368** | **0.69 [0.45-1.06]** | **0.09** | | |
| **Comfortable housing** | **994 (84)** | **630** | **0.47 [0.25-0.80]** | **0.005** | | |
| Owner or tenant of her/his home | 966 (82) | 604 | 0.89 [0.52-1.50] | 0.65 | | |
| **Depressive symptoms (DS)**[b] **and antidepressant treatment (ADT)** | | | | | | |
| - no DS/no ADT (ref) | 617 (52) | 421 | 1 | | 1 | |
| - no DS/ADT | 89 (7) | 76 | 1.30 [0.62-2.70] | 0.49 | 1.31 [0.64-2.71] | 0.46 |
| **- DS/no ADT** | **312 (26)** | **238** | **1.63 [1.04-2.57]** | **0.03** | **1.63 [1.04-2.54]** | **0.03** |
| **- DS/ADT** | **172 (14)** | **136** | **2.02 [1.15-3.58]** | **0.02** | **1.83 [1.05-3.22]** | **0.03** |
| **Hazardous alcohol consumption**[c] | **397 (33)** | **286** | **2.26 [1.49-3.42]** | **$<10^{-3}$** | **1.91 [1.27-2.87]** | **0.002** |
| **Heroin use**[d] | **32 (3)** | **25** | **3.79 [1.19-12.05]** | **0.02** | | |
| **Cocaine use**[d] | **98 (8)** | **78** | **2.85 [1.43-5.67]** | **0.003** | **2.26 [1.15-4.43]** | **0.02** |
| Number of years since HAART initiation[e] | 3 [1-5] | | 0.87 [0.59-1.27] | 0.46 | | |
| **CDC stage C** | **354 (30)** | **223** | **0.68 [0.42-1.09]** | **0.11** | | |
| **HCV treated** | **88 (7)** | | **0.33 [0.15-0.75]** | **0.008** | **0.38 [0.17-0.84]** | **0.02** |
| Number of HAART pills per day | 4 [3-6] | | 1.01 [0.92-1.09] | 0.90 | | |
| **Number of symptoms**[*] | **9 [4-14]** | | **1.05 [1.02-1.08]** | **0.002** | **-** | **-** |
| **Daily cannabis use**[*] | **171 (16)** | **125** | **2.21 [1.21-4.06]** | **0.01** | **-** | **-** |

[a] Per 10-year increase
[b] CES-D score>17 for men and >23 for women
[c] AUDIT-C score≥4 for men and ≥3 for women
[d] during the previous month
[e] Per 5-year increase
[*] not included in the multivariate model

**Table 3.** Association between depressive symptoms variable and number of symptoms: mixed linear model.

| | Coeff [95%CI] | p-value |
|---|---|---|
| Depressive symptoms[a] and antidepressant treatment | | |
| - no DS/no ADT (ref) | 1 | |
| **- no DS/ADT** | **1.93 [0.66-3.21]** | **0.003** |
| **- DS/no ADT** | **5.45 [4.66-6.25]** | **$<10^{-3}$** |
| **- DS/ADT** | **5.68 [4.66-6.70]** | **$<10^{-3}$** |

Y=number of perceived symptoms

[a] CES-D score>17 for men and >23 for women

**Table 4.** Association between "depressive symptoms and antidepressant treatment" variable and daily cannabis use: mixed logistic model

| | OR [95%CI] | p-value |
|---|---|---|
| Depressive symptoms[a] and antidepressant treatment | | |
| - no DS/no ADT (ref) | 1 | |
| - no DS/ADT | 1.41 [0.44-4.53] | 0.57 |
| - DS/no ADT | 0.96 [0.45-2.08] | 0.93 |
| **- DS/ADT** | **2.65 [1.05-6.70]** | **0.04** |

Y=daily cannabis use

[a] CES-D score>17 for men and >23 for women