Abstract

In this prospective study, we examined new-onset major depressive disorder (MDD) and the differential expression of depressive symptoms in a sample of 132 HCV mono-infected and 40 HIV/HCV co-infected patients initiating pegylated interferon-based treatment, including protease inhibitor therapy. The semi-structured clinical interview (SCID-I) was used to assess MDD. Severity of depressive symptoms was assessed using the Hamilton Depression Rating Scale. Of the total sample, 60 patients (34.9%) developed SCID-I defined MDD during antiviral treatment. The proportion of HCV mono- and HIV/HCV patients developing MDD during treatment was not significantly different (37.9% vs. 25%; \( p = 0.185 \)). In both groups, there was a significant increase in HAMD total score from baseline to week 4, and a significant decrease between week 24 and 6 months post-treatment cessation. The greatest increase was observed in the symptoms of the neurovegetative syndrome. HCV mono-infected patients reported higher scores than co-infected patients, particularly impaired activity and somatic symptoms, but the differences were only significant at week 12. The finding that co-infected patients appear less vulnerable to the development of depressive symptoms during HCV treatment than HCV mono-infected patients warrants further exploration, including a thorough analysis of the biological and psychosocial factors associated with this emergence.

**Keywords:** HIV; hepatitis C; co-infection; interferon; triple therapy; depression
1. Introduction

Based on current estimates, 170 million people worldwide are chronically infected with hepatitis C virus (HCV) (Mohd Hanafiah et al., 2013). HCV infection is also prevalent among HIV-infected patients (Chen et al., 2009), especially among intravenous drug users (IDU; Baum et al., 2008) and is increasing among men who have sex with men (MSM; Martin et al., 2013; Webster et al., 2013). When untreated, HCV can cause liver cirrhosis and hepatocellular carcinoma (Westbrook and Dusheiko, 2014). Meta-analytic data indicated that HIV/HCV co-infected patients are significantly more likely to present with cirrhosis than HCV mono-infected patients (relative risk: 2.1) (Thein et al., 2008), further highlighting the importance of addressing HCV treatment among the co-infected population.

Conventionally, chronic HCV infection has been treated using a combination of interferon-alpha (IFN-α) and ribavirin. The addition of a protease inhibitor (triple therapy) has been associated with significantly higher rates of viral clearance in both HCV mono- and HIV/HCV co-infected patients (Rockstroh and Bhagani, 2013; Sulkowski et al., 2013). However, IFN-α is also associated with neuropsychiatric effects, which may diminish treatment compliance and constitute risk factors for treatment failure (Martin-Subero and Diez-Quevedo, 2016). The most common effects associated with conventional IFN-α treatment in HCV mono-infected patients are major depressive disorder (MDD), cognitive impairment, sleep disorders, anxiety and fatigue (Schaefer et al., 2002). Among co-infected patients, depression, irritability, sleep disorders and weight loss were reported as the most common neuropsychiatric adverse events during IFN-α treatment (Sulkowski, 2008). Data on neuropsychiatric effects of triple therapy are currently limited, but the prevalence of interferon-induced depression remains a significant issue (Alavi et al., 2012; Fialho et al., 2014; Whale et al., 2015).

The prevalence of new-onset depression during HCV treatment among HIV/HCV co-infected patients is high (Fumaz et al., 2007), and has been related to treatment disruption (Laguno et al., 2004; Landau et al., 2001; Moreno et al., 2004; Myers et al., 2004; Rockstroh et al., 2002). In the population without HCV treatment, one study found that co-infected patients had higher prevalence of depression than mono-infected patients (Butt et al., 2006) and another study reported that co-infected patients
were more likely to report depressive symptoms than HCV mono-infected patients (Sun et al., 2013). In contrast, it was found that a diagnosis of MDD was significantly less common among co-infected patients than among mono-infected patients (Tavakkoli et al., 2013). During HCV treatment, Alavi and colleagues (2012) found recently similar rates of new-onset depression during HCV treatment between HCV mono-infected (33%) and co-infected patients (38%), although depression at baseline was more common among HCV mono-infected patients. However, though numerous studies assessed depression during treatment, those examining the emergence of depression during antiviral treatment for hepatitis C, and particularly the differences in the emergence of depression between HCV mono-infected and co-infected patients, are still rather limited.

Although the exact neurobiological basis of interferon-induced depression is not known, there is evidence that HCV can replicate in extra-hepatic sites and has been shown to replicate in microglia, macrophages and astrocytes, triggering the release of pro-inflammatory cytokines, which are associated with the emergence of depression (Loftis et al., 2008). Cytokines, such as IFN-α may directly enter the brain (Banks, 2005; Banks and Erickson, 2010) via parenchyma cells causing an activation of IFN-α gene expression (Wang et al., 2008), and by leaky regions in brain blood barrier (BBB) at circumventricular organs (Pan and Kastin, 2003), or non-directly through effects on the central nervous system (CNS) by induction of cytokines and growth factors that are able to cross the BBB (Reyes-Vázquez et al., 2012; Schaeffer et al., 2002). During HCV treatment, depressive disorders may therefore emerge due to IFN-α acting on the CNS causing a neuro-inflammatory response (Capuron and Miller, 2004; Dantzer et al., 2008; Raison et al., 2005). The hypothesis that inflammatory cytokines are involved in the pathogeneses of depression has been well supported (Hoyo-Becerra et al., 2014). Across multiple studies and medical conditions, there is evidence that the administration of cytokines to humans boosts depressive symptoms in healthy subjects (Harrison et al., 2009), in HCV treatment (Udina et al., 2013), as well as in cancer (Archer et al., 2012), kidney disease (Taraz et al., 2012) and HIV (Poudel-Tandukar et al., 2014).

During HCV therapy, higher levels of depression have been reported (Udina et al., 2012), particularly at earlier stages of treatment. It has also been suggested that patients with IFN-induced
depression show significantly more symptoms of the neurovegetative syndrome and less cognitive-affective symptoms (e.g., guilt) (Capuron et al., 2009). In this context, and considering this biphasic model of depression, it was found that neurovegetative symptoms tend to develop early and depressive-cognitive symptoms tend to occur later (Capuron et al., 2002a). Regarding the specific symptoms of the neurovegetative syndrome, psychomotor slowing was shown to be a consistent predictor of later emergence of depression (Capuron et al., 2001; Raison et al., 2005; Whale et al., 2015). Recently, in a sample of HCV mono-infected patients, Loftis et al. (2013) found that neurovegetative symptoms increased at an early stage of interferon treatment (week 2), though no significant changes in the cognitive-affective factor were observed. Though more limited, there is also evidence in co-infected populations indicating that depressive symptoms emerge in the first months after IFN-α treatment initiation (Fumaz et al., 2007; Laguno et al., 2004).

These findings seem to suggest that continuing interferon tends to induce a specific sub-type of mood disorder, characterised by a high expression of neurovegetative symptoms. However, most of the existing evidence in support of this comes from HCV mono-infection studies, leaving a significant research gap in the context of HIV/HCV co-infection. Thus, the objective of this study was to compare the new-onset IFN-α-induced MDD (defined as the development of depression during treatment among participants who were not depressed prior to the initiation of treatment) and the expression of depressive symptoms in HCV mono- and HIV/HCV patients. Specifically, we analysed the clusters of depressive symptoms associated with the new-onset depression during HCV treatment, and investigated whether this association was different across the two study groups. Based on the existing literature, although mostly outside the context of HCV treatment, we expected that the co-infected group would be more likely to present higher prevalence of depression than the HCV group. We also expected that the expression of the neurovegetative syndrome would be more prominent than that of the mood-cognitive syndrome in both groups.

2. Methods

2.1. Participants and procedure

This prospective study was conducted at the outpatient HCV clinic at the Royal Sussex County Hospital, Brighton UK. All participants gave informed written consent for participation.
Ethical approval was obtained through the National Research Ethics Service (NRES) Committee South East Coast.

A cohort of 176 patients initiating hepatitis C treatment with a combination of pegylated interferon-α and ribavirin, or pegylated interferon-α, ribavirin and teleprevir were consecutively recruited between June 2014 and October 2015. The following exclusion criteria were applied: female, autoimmune disorder or any cause of liver disease other than HCV, history of neurological disease, acute psychiatric illness, current diagnosis of MDD, being on methadone, and intravenous drug or alcohol abuse within the month prior to the beginning of hepatitis C treatment. All HIV-infected patients had HIV infection confirmed by a positive ELISA positive and Western-blot analysis. Positive HCV RNA confirmed HCV infection by polymerase chain reaction (PCR) assay. Four participants were excluded from the analyses because of current IDU and to missing information in the main outcome at week 24 and at SVR. Therefore, the final sample consisted of 172 participants.

All participants were eligible to start hepatitis C treatment with the standard combination of PEG-IFN 2α 180 μg weekly sub-cutaneously and oral ribavirin 800-1200mg daily (depending on weight and HCV genotype) or PEG-IFN 2α 180 μg weekly sub-cutaneously and oral ribavirin 800-1200mg daily and protease inhibitor telaprevir orally (750 mg) every 8 hours. Both treatments involved 24 weeks of interferon exposure.

Participants were assessed at five time points: baseline, week 4, week 12, week 24, and six months after treatment completion (sustained virological response [SVR] endpoint).

2.2. Measures

At baseline, socio-demographic information (e.g., age, gender), HCV-related variables (e.g., mode of HCV acquisition, HCV stage, genotype), and information such as past psychiatric history, past drug use and HCV re-infection (defined as having detectable HCV RNA following a positive treatment outcome or spontaneous self-clearance) were collected. Positive response to treatment was measured by the SVR, defined as negative HCV viral load measured by polymerase chain reaction assay (PCR, HCV RNA < 1.9 log IU/mL) six months after treatment completion.
The diagnosis of MDD was determined through a semi-structured clinical interview (SCID-I) (First et al., 1996) for the major DSM-IV Axis I diagnosis. For the purpose of defining depression threshold, criterion A12D of the SCID-I (excluding other organic aetiologies) was discarded.

Severity of depression and sub-syndrome features were assessed with the Hamilton Depression Rating Scale (HAMD; Hamilton, 1960), which consists of 21 items answered on a three-point (0-2), four-point (0-3) or five-point (0-4) response scale. The total score ranges between 0 and 66, and higher scores correspond to higher severity of depressive symptoms. This scale provided detailed rating of both somatic and non-somatic components of depression. In this study, the dimensional structure suggested by Capuron et al. (2009) was used: (1) depressive symptoms composed of depressed mood, feelings of guilt and suicide items; (2) anxiety symptoms composed of anxiety psychological, hypochondriasis, agitation and anxiety somatic items; (3) impaired activity/decreased tone composed of work/activities and retardation; (4) sleep alterations composed of early, middle and late insomnia items; and (5) somatic symptoms composed of somatic symptoms gastrointestinal, somatic symptoms general, genital symptoms and loss of weight. The neurovegetative syndrome aggregates impaired activity, sleep alterations and somatic symptoms. The mood-cognitive syndrome combines depressive and anxiety symptoms. Alpha reliability in this sample ranged from .84 (Week 4) to .94 (SVR).

2.3. Data analysis

Data were analysed using the Statistical Package for Social Sciences (IBM SPSS 20.0). A Chi-square ($\chi^2$) analysis was conducted to assess whether both groups had statistically different proportions in categorical variables, and Student’s $t$ tests were used for comparisons in continuous variables. Repeated-measures multivariate analysis of covariance (MANCOVA) was used to assess changes in depressive symptoms across groups (between-subjects) and over time (within-subjects). Bonferroni adjustments were applied to correct for multiple comparisons ($p < 0.01$). Logistic regressions were performed to examine the association between the study variables and the development of MDD during treatment. Participants were coded for either transition to MDD or no transition to MDD at any time point during the study period. Effect sizes were calculated for all analyses. For Chi-square: small: Cramer’s $V \geq 0.10$; medium: Cramer’s $V \geq 0.30$; large: Cramer’s $V \geq$
0.50. For t-test: small: Cohen’s $d \geq 0.20$, medium: Cohen’s $d \geq 0.50$; large: Cohen’s $d \geq 0.80$) (Cohen, 1992).

3. Results

3.1. Participants’ characteristics

The sample comprised 172 participants, with a mean age at treatment initiation of 46.58 years ($SD = 10.44$). Forty patients were co-infected with HIV and 132 patients were HCV mono-infected. Most participants were infected with genotype 2 virus ($n = 77; 44.8\%$), followed by genotype 1 ($n = 58; 33.7\%$). Regarding antiviral treatment, most patients received pegylated INFα and ribavirin dual therapy ($n = 113; 65.7\%$). Seventy-seven patients (44.8\%) reported past psychiatric history, out of which 65 (84.4\%) specified previous history of depression. A SVR response was achieved in 150 patients (87.2\%). HIV/HCV co-infected patients were less likely than HCV mono-infected patients to report a past psychiatric history and HCV infection through IDU. As summarised in Table 1, no significant differences were found between HCV and HIV/HCV patients in the remaining baseline study variables.

[Insert_Table_1]

3.2. Depressive symptoms at baseline and development of MDD during treatment

At baseline, the mean HAMD total score across groups was 4.10 ($SD = 5.51$; range: 0-23). Four patients had a HAMD total score at baseline $> 20$, suggesting moderate depressive symptoms, despite not having a SCID defined MDD. No significant differences were found between HCV ($M = 4.13, SD = 5.31$) and HIV/HCV co-infected patients ($M = 4.03, SD = 6.19$) regarding baseline HAMD score, $F(1, 170) = 0.10, p = 0.917$.

A total of 60 patients (34.9\%) developed SCID defined MDD during HCV treatment of the whole sample. Twenty-eight patients developed MDD by week 4 and 40 patients by week 12 representing a cumulative percentage of 66.7\% of patients with new-onset depression within the first 12 weeks of treatment. Regarding differences between groups in each time point, the results indicated that HCV mono-infected patients were more likely than co-infected patients to have a MDD diagnosis at week 4 (26.5\% vs. 10\%; $\chi^2(1) = 4.78, p = 0.029$, Cramer’s $V = 0.17$), week 12 (31.1\% vs. 15\%);
\( \chi^2(1) = 3.99, p = 0.046, \) Cramer’s \( V = 0.15 \) and week 24 (24.6% vs. 7.9%; \( \chi^2(1) = 4.99, p = 0.026, \) Cramer’s \( V = 0.17 \)).

3.3. Depressive symptoms during HCV treatment

In order to control for potential confounders associated with the severity of depressive symptoms during treatment, preliminary univariate logistic regressions were conducted to examine the associations between baseline factors (age, marital status, HCV stage, past drug use, genotype, type of treatment and prior treatment status) and the emergence of MDD, in the total sample, as well as in each group separately. No baseline variables were significantly associated with increased odds of developing MDD during treatment. Nevertheless, analyses of the changes of symptoms of depression during treatment were adjusted for anti-depressant treatment, as this was defined a priori as a potential confounder.

Regarding HAMD total score, the multivariate analysis, adjusted for antidepressant treatment, indicated a significant effect of time, Wilk’s \( \lambda = 0.45, F(4, 166) = 51.47, p < 0.001, \eta_p^2 = 0.55, \) group, \( F(1, 169) = 9.34, p = 0.003, \eta_p^2 = 0.05, \) and time x group interaction, Wilks’ \( \lambda = 0.93, F(4, 166) = 3.05, p = 0.018, \eta_p^2 = 0.07. \) Regarding time, subsequent univariate analyses (Bonferroni corrected) indicated a significant increase in HAMD total score from baseline to week 4 (Mean difference = 7.20, \( p < 0.001 \)), and a significant decrease between week 24 and SVR endpoint (Mean difference = 9.74, \( p < 0.001 \)). No significant differences were found between week 4 and week 12, or between week 12 and week 24.

In relation to group comparisons, HCV mono-infected patients reported higher scores than HIV/HCV co-infected patients. The group x time interaction, after Bonferroni’s correction, indicated that the between-group differences in HAMD total score were only significant at week 12, \( F(1, 169) = 13.82, p < 0.001. \) Longitudinal changes in depressive symptoms during and following treatment are shown in Figure 1.
3.4. Changes in depressive symptoms subtypes during HCV treatment

Regarding the five HAMD factors, the descriptive results are summarised in Table 2. Repeated measures MANCOVA indicated a significant main effect of time, Wilks’ $\lambda = 0.25$, $F(20, 150) = 22.43$, $p < 0.001$, $\eta^2_p = 0.75$. The main effect of group was not significant, Wilks’ $\lambda = 0.95$, $F(5, 165) = 1.84$, $p = 0.109$, $\eta^2_p = 0.05$. The time by group interaction was significant, Wilks’ $\lambda = 0.81$, $F(20, 150) = 1.77$, $p = 0.029$, $\eta^2_p = 0.19$, suggesting that the groups present with significant behavioural differences.

Subsequent tests indicated that, with the exception of the factor ‘depressive symptoms’ ($p = 0.035$), there was a significant increase in all other factors during treatment (anxiety symptoms, impaired activity symptoms, sleep alterations and somatic symptoms), most notably between baseline and week 4 (all $p < 0.001$). Overall, the depressive symptoms subtypes with the greatest increase from baseline to week 4 were impaired activity (Mean difference = 0.78, $p < 0.001$), somatic symptoms (Mean difference = 0.56, $p < 0.001$) and sleep alterations (Mean difference = 0.50, $p < 0.001$). In addition, a significant decrease in all factors was observed between week 24 and the SVR endpoint (all $p < 0.001$) – see Supplementary Figure.
Group comparisons, after Bonferroni correction, indicated that HCV mono-infected patients reported significantly higher scores than HIV/HCV patients only in impaired activity. The interaction between group and time indicated that differences between co-infected and mono-infected patients were only significant at week 12 in respect to sleep alterations (Mean difference = 0.37, \( p = 0.004 \)) and somatic symptoms (Mean difference = 0.37, \( p < 0.001 \)).

To further examine the longitudinal changes in the two clusters of depressive symptoms, a repeated measures MANCOVA was conducted. The results indicated a significant main effect of time, Wilks’ \( \lambda = 0.29, F(8, 162) = 50.07, p < 0.001, \eta_p^2 = 0.71 \), group, Wilks’ \( \lambda = 0.95, F(2, 168) = 3.91, p = 0.022, \eta_p^2 = 0.05 \), and time x group interaction, Wilks’ \( \lambda = 0.87, F(8, 162) = 2.95, p = 0.004, \eta_p^2 = 0.13 \). Follow-up ANCOVAs indicated a significant increase in both mood-cognitive and neurovegetative syndromes during treatment, particularly between baseline and week 4 (\( p < 0.001 \)). Consistent with prior findings, a significant decrease in both syndromes between week 24 and SVR endpoint was found (all \( p < 0.001 \)) – see Figure 2.

Group comparisons indicated that HCV mono-infected patients reported significantly higher symptoms scores than HIV/HCV patients in both the mood-cognitive, \( F(1, 169) = 5.79, p = 0.017, \eta_p^2 = 0.03 \), and neurovegetative syndrome, \( F(1, 169) = 6.55, p = 0.011, \eta_p^2 = 0.04 \). The group x time was only significant for the neurovegetative syndrome, \( F(8, 162) = 5.10, p = 0.001, \eta_p^2 = 0.03 \). Subsequent ANCOVAs indicated that the differences were only significant at week 12 (Mean difference = 0.35, \( p < 0.001 \)), with the HCV group showing higher scores at this time point.
Figure 2. Time course of HAMD syndromes mean scores and standard errors (SE) in HCV mono-infected and HIV/HCV co-infected patients during HCV treatment. Neurovegetative syndrome (A) was defined by HAMD criteria by impaired activity; sleep alterations and somatic symptoms. Mood-cognitive syndrome (B) defined by HAMD criteria by depressive and anxiety symptoms.

4. Discussion

In this study, it was found a high prevalence of new-onset MDD during interferon-based treatment (34.9%), with no significant differences between HCV mono-infected and HIV/HCV co-infected patients. However, our findings also indicated that HCV mono-infected patients were more likely to develop MDD earlier in treatment (week 4). This early emergence of symptoms has been previously been reported and should be considered, as it may be a significant factor in treatment
compliance and drop outs. For both study groups, the severity of depressive symptoms increased significantly during treatment and showed a significant decrease after treatment ended. The cluster of depressive symptoms showing the greatest increase during treatment includes the neurovegetative syndrome (impaired activity, somatic symptoms and sleep alterations), with the HCV mono-infected group reporting significantly higher scores than the co-infected group, particularly at week 12.

In contrast to our hypothesis, HCV mono-infected patients reported significantly more depressive symptoms than co-infected patients during treatment, a pattern also reported by Tavakkoli et al. (2013). These results suggest that depression in HCV mono-infected patients may has been under diagnosed, therefore increasing the risk of treatment discontinuation and depression severity. It has been indicated that having HCV is itself a risk factor for depression (Carta et al., 2012; Smith et al., 2011), and various studies found high rates of depression and fatigue in chronic untreated HCV-infected patients compared to the general population (Basseri et al., 2010; Poynard et al., 2002). In our study, though current drug use or use of methadone replacement treatment were exclusion criteria at enrolment, these results may potentially be explained by specific characteristics of patients of this HCV cohort, who are more likely to present with a past history of IDU and past psychiatric history. These factors have been identified as underlying a significant risk for developing MDD during HCV treatment (Hilsabeck et al., 2005, Udina et al., 2016). An alternate explanation may be the chronic inflammatory status identified in 85.5% of our participants, which has been also related to depression (Berk et al., 2013), and an association that has been found to be independent of IFN-α treatment, substance and alcohol misuse (Boscarino et al., 2015; Carta et al., 2012). HCV chronicity, characterized by a persistent long term HCV replication, implies a low grade of inflammatory activation that triggers a high level of immune reaction followed by depressive like behaviour (Carta et al., 2012; Maes et al., 2012). The state of chronic inflammation/chronicity when exposed to interferon treatment may increase risk for developing depression, as previously noted (Capuron et al., 2012; Fritz-French and Tyor, 2012; Miller et al., 2009; Raison et al., 2010).

The evidence suggests that neuropsychiatric side effects of IFN-α therapy occur during the time course of treatment, with a tendency to emerge at the beginning of treatment, between week 4
and week 12 (Cunha et al., 2015; Leutscher et al., 2010; Martín-Santos et al., 2007). The HCV monoinfected group reported significantly higher scores on depression than the co-infected group only at week 12, which is consistent with prior findings (Capuron et al., 2003). This may relate to the time frame for specific interferon pathways. Indeed, depression was found to occur in patients who showed a reduction in serum tryptophan concentrations at week 12 of treatment (Capuron et al., 2003), suggesting that tryptophan degradation may be a mechanism in the pathophysiology of interferon-induced depression (Capuron et al., 2003; Réus et al., 2015). Overall, the fact that in both groups the new cases were observed early in treatment are particularly relevant as they suggest that the beginning of treatment is a crucial period, requiring a comprehensive monitoring by clinicians.

Our main findings are consistent with previous reports that have identified a significant prevalence of MDD during HCV treatment (Udina et al., 2012, 2016; Whale et al., 2015). The percentage found in this study is similar to the overall rate of new-onset depression (35%) reported by Alavi et al. (2012). Additionally, a significant decrease from week 24 to SVR was observed, in line with evidence suggesting that the prevalence of depression significantly decrease after cessation of IFN-α exposure (Huckans et al., 2014). Accordingly, our results are compatible with the inflammatory model of depression, showing a pattern of change consistent with the suggestion that inflammation, induced by exogenous administration of IFN-α, triggers an increased risk of depression like behaviour, which may be due to neurotoxic effects in the brain, and despite the presence of potential vulnerability factors, the depressive symptoms remit following INF-α cessation (Lotrich, 2015).

Capuron and colleagues proposed that IFN-α treatment is associated with the emergence of two distinct behavioural syndromes: the mood-cognitive and the neurovegetative, which occur separately by IFN-α effects on the activation of different pathophysiological mechanisms. In this study, all participants showed a significant increase in anxiety symptoms, impaired activity, somatic symptoms and sleep alterations between baseline and week 4. Most of these symptoms are part of the neurovegetative syndrome, which tends to appear rapidly in treatment, as earlier reported (e.g., Loftis et al., 2013). Capuron et al. (2007), in a study with patients with malignant melanoma, found that four
weeks of IFN-α therapy was associated with marked increased in glucose metabolism in basal ganglia, and a significant increase in fatigue, lassitude and “inability to feel”. The same study suggested that changes in basal ganglia activity may play a role in interferon-induced fatigue related syndromes. A recent study using microstructural MR imaging technique confirmed the involvement of basal ganglia structures in development of fatigue at early stage of INF-α exposure, however, an association between changes in the striatum and depressive symptoms at a later stage was not found (Dowell et al., 2016).

The mood-cognitive syndrome, encompassing symptoms of depression and anxiety, as well as cognitive dysfunction, appears later during IFN-α therapy, between week 12 and week 24, and is more likely to respond to anti-depressant treatment than neurovegetative symptoms (Capuron et al., 2004). This may imply mechanisms involving monoamine transmission dysfunction for this cluster of symptoms. For example, there is evidence that changes in tryptophan metabolism triggers overstimulation of the enzyme indoleamine-d-oxygenase boosting kynurenine toxicity and serotonin depletion, which represents a risk for the emergence of mood and cognitive symptoms (Capuron et al., 2004; Eccles et al., 2012; Oxenkrug et al., 2014). In our study, the mood-cognitive syndrome was significantly more likely to occur between baseline and week 4. We failed however to find elevated scores of this syndrome at a later stage of treatment, as previously suggested (Dowell et al., 2016; Loftis et al., 2013). A possible explanation may be that the emergence of this syndrome early in treatment may reflect an emotional adjustment response to the treatment, which often combines anxiety and depression symptoms. However, it should also be noted that in healthy volunteers, experimentally-induced inflammation reduce mood within hours (Harrison et al., 2009). The impact of inflammation on behaviour has been related not only to depression but with other neuropsychiatric disorders, such as anxiety and schizophrenia (Fernandes et al., 2015; Miller et al., 2013). Recently, it has been suggested that inflammatory-induced symptoms include positive and negative valence system activity associated with motivation and motor activity changes (anhedonia, fatigue, and psychomotor retardation) and increased threat activity (anxiety, arousal and alarm) (Miller and Raison, 2016).
Several limitations need to be noted. Firstly, the convenience sampling and the relatively small sample size of the co-infected group, which imply that generalisation of our findings should be undertaken with caution. Secondly, our results and conclusions are also limited by the inclusion of only male participants, mostly due to clinical availability, leaving an important research gap in assessing female patients and potential sex-based differences in study outcomes. Thirdly, this study relied mostly on the use of behavioural data, without taking into account other biological markers (which have been proposed to be relevant risk factors for interferon-induced depression; for a review see Udina et al., 2012) and a more detailed psychiatric background (e.g., personal history of psychiatric disorders, prior resistance to anti-depressant treatment), which may have a potential effect on depression outcomes. It is also likely that other variables that were not assessed (e.g., inflammatory markers, such as IL-6, IL-1, CRP; psychosocial factors) may have been able to enhance our interpretations of differences between the HCV and HIV/HCV groups. To overcome these limitations, further studies examining a more complete set of factors associated with interferon-induced depression in mono-infected and co-infected patients would be valuable. Lastly, the introduction of direct-acting antiviral therapy for the treatment of HCV has noticeably transformed the treatment of hepatitis C. We assert however that our findings provide an important description of interferon-induced depression in HCV mono-infected and HIV/HCV co-infected patients during HCV treatment, and are relevant to the current inflammatory paradigm of depression.

Despite these limitations, this study has also important strengths. The study design was prospective and longitudinal and all patients were followed in a single centre. In contrast to many studies that relied only in self-reported symptoms scales to assess depression, this study used both a validated measure for assessing the severity of depressive symptoms (which is useful for examining individual symptoms and changes over time) and a clinical interview based on DSM criteria. Our data suggest that interferon-induced depression presents primary a neurovegetative symptoms profile, highlighting the need to find more specifically effective anti-depressant treatment, particularly because this syndrome appears to be less responsive to anti-depressant treatment (Capuron and Miller, 2004). Despite the advent of IFN-free regimens, INF remains a valid treatment option for several
diseases, such as multiple sclerosis (Calabresi et al., 2014) and leukemia (Bohn et al., 2016). Therefore, these findings may also have important practical implications in such clinical contexts.

In sum, our findings indicate that for both HCV mono- and HIV/HCV co-infected patients receiving treatment for hepatitis C, the emergence of depressive symptoms of the neurovegetative syndrome is notable at early stage of IFN-α treatment, and that this cluster of symptoms is significantly more prominent among HCV mono-infected patients than among co-infected patients, particularly at week 12. Additional research is needed however to better understand whether the symptoms of depression clearly reflect the effects of inflammation, what type of anti-depressant treatment may be more effective for neurovegetative symptoms, and which strategies should be adopted to prevent future depression episodes and to improve the quality of life of patients undergoing HCV therapy, even in interferon-free regimens.

Despite the significant advances in HCV therapy with the introduction of IFN-α-free treatment regimens, including in HIV/HCV co-infection (Menard et al., 2016), co-infected patients will continue to be a population with unique characteristics that warrant special attention (Hesamizadeh et al., 2016; Majumdar et al., 2016; Sulkowski, 2016). Factors such as HCV re-infection following successful treatment, drug-drug interactions, and efficacy of HCV shorter treatments should be carefully considered (Sulkowski, 2016). The high cost of the new regimens may also be economically difficult to justify (Chayama et al., 2015). For these reasons, IFN-α may still have a role within co-infection, and is likely to remain a key treatment for HCV worldwide. Nevertheless, important actions on mental health should not be disregarded in the post-interferon era. For example, a recent study found that ongoing substance use weakened the short- and long-term benefits associated with curing HCV (Yeung et al., 2015), suggesting that mental health professionals should continue to take an active role in HCV treatment (Chasser et al., 2017). In our study, a significant proportion of patients reported past drug use and psychiatric history. Because HCV and HIV are prevalent diseases that continue to disproportionately affect these vulnerable populations, reduction of the burden of mental illness and substance misuse before (and during) treatment, identification of barriers to adherence, as well as greater awareness of the drug-drug interactions that
accompany these new treatments (including with psychotropic medication), would be of paramount importance to optimize treatment’s outcomes.
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Table 1. Demographic and clinical characteristics of participants receiving HCV treatment (N = 172)

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<td>18 (13.6)</td>
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<td>4</td>
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<td>5 (12.5)</td>
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<td>0.04</td>
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<tr>
<td>PEG-IFN 2α + Ribavirin +</td>
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<td>0.03</td>
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<td>23 (57.5)</td>
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<td>35 (87.5)</td>
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*** \( p < 0.001 \)
Table 2. Descriptive statistics in HAMD factors during interferon-based therapy for HCV

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<th>Week 4</th>
<th>Week 12</th>
<th>Week 24</th>
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<td>M (SE)</td>
<td>M (SE)</td>
<td>M (SE)</td>
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<td><strong>Depressive symptoms</strong></td>
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<tr>
<td>HCV</td>
<td>0.19 (0.03)</td>
<td>0.43 (0.04)</td>
<td>0.47 (0.04)</td>
<td>0.38 (0.04)</td>
<td>0.04 (0.02)</td>
<td>10.72***</td>
<td>3.86</td>
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<td>HIV/HCV</td>
<td>0.22 (0.06)</td>
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<td>0.32 (0.08)</td>
<td>0.32 (0.07)</td>
<td>0.02 (0.04)</td>
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<td><strong>Anxiety symptoms</strong></td>
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<td>HCV</td>
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<td>0.55 (0.05)</td>
<td>0.63 (0.05)</td>
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<tr>
<td>HCV</td>
<td>0.24 (0.04)</td>
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<td>1.18 (0.06)</td>
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<td>7.30**</td>
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<td>HIV/HCV</td>
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<td>0.93 (0.11)</td>
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<td>0.02 (0.05)</td>
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<td>0.92 (0.06)</td>
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<td>0.05 (0.02)</td>
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<td>HIV/HCV</td>
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<td>0.89 (0.11)</td>
<td>0.55 (0.11)</td>
<td>0.69 (0.11)</td>
<td>0.03 (0.04)</td>
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<td><strong>Somatic symptoms</strong></td>
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<td>HCV</td>
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<td>0.67 (0.09)</td>
<td>0.01 (0.04)</td>
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* p < 0.05; ** p < 0.01; *** p < 0.001
Supplementary Figure. Time course of HAMD factors mean scores and standard errors in HCV mono-infected and HIV/HCV co-infected patients during HCV treatment.