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**A University of Sussex DPhil thesis**

**Neuropsychiatric manifestations of hepatitis C treatment in HIV/HCV co-infection**

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**Submitted in fulfilment of the requirements for the degree of Doctor of Philosophy  
in Psychology**

**School of Psychology  
University of Sussex**

**March, 2017**

## DECLARATION

The thesis conforms to an ‘article format’ in which the middle chapters consist of discrete articles written in a style that is appropriate for publication in peer-reviewed journals in the field. The first and final chapters present synthetic overviews and discussions of the field and the research undertaken.

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Chapter 2 article 1 is published in *AIDS Care* as:

Fialho, R., Pereira, M., Bucur, M., Fisher, M., Whale, R., & Rusted, J. (2016). Cognitive impairment in HIV and HCV co-infected patients: A systematic review and meta-analysis. *AIDS Care*, 28(12), 1481-1494.

The author contributions are as follows: I was responsible for all aspects of data collection, data analysis, writing of the manuscript; Professor Marco Pereira was responsible for data extraction and providing feedback on study analysis; Dr Mihaela Bucur, Professor Martin Fisher, Dr Richard Whale and Professor Jennifer Rusted were collectively responsible for responsible for providing feedback on study design and corrections to the manuscript.

Chapter 2 article 2 is published in *Psychology, Health & Medicine* as:

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Chapter 3 article 1 is submitted (after first revision) in *Psychiatric Research* as: “Co-infection with HIV associated with reduced vulnerability to symptoms of depression during antiviral treatment for hepatitis C”.

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**University of Sussex**

**Renata Fialho**

**Doctor of Philosophy**

## **Neuropsychiatric manifestations of HCV treatment**

### **Summary**

Hepatitis C (HCV) infection is associated with high rates of mortality and morbidity. Interferon alpha based treatment for HCV offers a good rate of viral clearance, however the associated neuropsychiatric side effects increase the risk of treatment interruption and disease progression. The HIV/HCV coinfection is of particular interest due to association with higher rates of HCV treatment side effects and earlier treatment discontinuation when compared with HCV mono-infection. Therefore, the aim of the thesis was to further explore the effect of coinfection on mood and cognition and how HCV interferon based treatment influences neuropsychiatric side effects in mono and co-infected samples. Firstly a meta-analysis was performed to explore cognitive impairment and depression in HIV HCV co-infection. The results suggested that there was consistent literature indicating that the coinfecting group were more cognitively impaired and more likely to be depressed than the HCV and HIV monoinfected groups. Secondly empirical studies were conducted to analyse the profile of depression during interferon-based treatment, and explore potential risk factors, such as gender and immune profile. Co-infected patients appeared less vulnerable to the emergence of depressive symptoms during HCV treatment than HCV mono-infected patients. Additionally, neither female gender nor immune response were associated with increased vulnerability to depression. Finally, a longitudinal study investigating cognitive performance during interferon-based treatment was conducted. A significant effect of treatment on information processing speed level of executive function was observed. Overall the research reported in this thesis further clarifies the nature of interferon induced depression and cognitive effects differences between mono and coinfecting groups. Having identified a neurovegetative symptom profile and speed of processing impairment of executive function during HCV treatment, the discussion considers the potential of targeted interventions via psychotropic medication and cognitive interventions to minimise the impact of these treatment effects and optimise outcomes in this clinical group.

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## **1. INTRODUCTION**

## 1. Introduction

### 1.1. General Introduction

Infection with Hepatitis C virus (HCV) is a major health burden in England as evidenced by the Department of Health initiated **Hepatitis C strategy and Action Plan** (Public Health England [PHE], 2015). Estimates on the prevalence of HCV worldwide indicate that three to four million are newly infected per year and approximately 180 million people are believed to be currently chronically HCV infected (Mohd et al., 2013). However, according to a World Health Organisation report (2017) 1.75 million new infected HCV cases were reported in 2015, representing a global incidence rate of 23.7 per 10,000. Chronic hepatitis C is the leading cause of end-stage liver disease, hepatocellular carcinoma and liver related deaths (Westbrook & Dusheilo, 2014). HCV infection is associated with high fatality rates (Mohd et al., 2013). The evolution of better treatment for HCV in the form of Direct Acting Antivirals mean that at last eradication of hepatitis C may be possible but only if all with HCV are treated.

An estimated 2.3 million people living with HIV are coinfectd with hepatitis C virus (HCV) globally (Platt et al., 2016). Of these, more than half, or 1.3 million, are people who inject drugs (PWID). The study also found that HIV-infected people are on average 6 times more likely than HIV-uninfected people to have HCV infection, pointing to a need to improve integrated HIV/HCV services (Platt et al., 2016). Since 2000, the incidence of HCV infection among HIV-positive men who have sex with men (MSM) population has dramatically increased in Europe, USA and Australia (Fox et al., 2008; Martin et al., 2013; Van de Laar et al., 2011). More specifically, in the UK HIV/HCV co-infection in MSM enhanced from 0% in 1999 to 4% in 2006 (Fox et al., 2008). A significant change in the epidemiology of HIV HCV coinfection has definitely occurred. In particular, acute HCV infection in HIV-positive MSM is an emerging problem. Additionally, several studies have reported a high risk of reinfection in HIV-positive MSM in both treated and those who spontaneously cleared the virus (Stellbrink et al., 2010; Martin et al, 2013).

HIV and HCV viruses share common routes of infection, but they have differences regarding types of exposure and disease progression. HIV is a chronic disease manageable with treatment (antiretroviral therapy-ART). The medication redefined the concept of quality of life improving health and prolongs life (Deeks, Lewin & Havlir, 2013). HCV infection is characterized by an acute stage that is typically mild and



undiagnosed (Westbrook & Dusheiko, 2014). After six months of persistent HCV RNA, the possibility of spontaneous clearance is significantly reduced and the infection is defined as chronic. However, treatments now exist with 95% response rates for HCV so the chance of cure in chronic HCV is high. In coinfection there is an accelerated liver disease that has been associated with immune activation and dysregulation causing complications such as bone disorders, metabolic disorders, kidney disease, cardiovascular disease, and neurologic disease (Opskalski & Kovacs, 2011). Overall, the burden of HCV indicates that treatment could be a strategy to prevent progression of disease, eliminate infection and improve quality of life (Bernstein et al., 2002; Fried et al., 2002; Jacobson et al., 2011; Poordad et al., 2001).

## **1.2. Psychopathology of Inflammation**

Evidence has emerged to suggest that inflammation is a response involving cytokine activation and changes in both adaptive and innate immunity (Irwin, 2011; Haapakoski et al., 2016). The relationship between inflammatory immune response and neuropsychiatric changes has been noted (McNamara & Lotrich, 2012), establishing that inflammatory reactions and neuro-immune changes have an effect on behaviour. These inflammatory processes seem to regulate mood, which affects alteration in serotonin levels (Lotrich et al., 2013; Wichers & Maes, 2004), activation of microglia (Fenn et al., 2014) and local invasion of circulating immune cells (Nathan, 2002).

The cytokines are divided into pro-inflammatory and anti-inflammatory cytokines. For the purpose of this thesis we will focus on the role of pro-inflammatory cytokines, in particular interferon alpha ( $\alpha$ ), which is involved in facilitating an inflammatory response associated with depressive mood, anhedonia, sleep changes, fatigue, anorexia and cognitive impairment (Anisman & Merali, 2002; Capuron et al., 2000, 2002; Whale et al., 2015).

### **1.2.1. The inflammatory Paradigm**

Cytokine induced sickness behaviour was proposed by Hart (1988), as an adaptive response to infection. Increasing evidence suggest that activation of pro-inflammatory cytokines leads to a behavioural repertoire that is associated with the pathophysiology of psychiatric disorders (Dantzer et al., 2008; Haapakoski et al., 2016; Miller et al., 2009).

Pro-inflammatory cytokines production has been implicated in influencing behaviour, due to penetration of the central nervous system (CNS), inducing sleep changes, anhedonia, cognitive disturbances, psychomotor retardation and depressive mood (Harrison et al., 2009; Maes et al., 1993). These symptoms are known as sickness behaviour and some symptoms overlap with major depressive disorders symptoms (Dantzer, 2001, Dantzer & Kelley, 2007).

The blood brain barrier (BBB) controls the exchanges between the blood and the brain in order to prevent diseases. Failing to control this dynamic communication causes neuroinflammatory events that have been associated with the emergence of diseases (Banks, 2015; Banks & Erickson, 2010). Neuroinflammation is the result of transmitting inflammatory signals to the brain that may lead to depression. Peripherally administered cytokines can penetrate the brain by directly crossing the blood-brain barrier (BBB) (Banks, 2015), interaction with circumventricular organs (Blatteis et al., 1983), immune cell trafficking (Wetzel et al., 2000) or induction of release from BBB cells (Verma et al., 2006).

Microglia, a type of glial cell, which resides within CNS, has an important role regulating neuronal activities and immune functions (Fenn et al., 2014). When the brain presents changes as a result of an infection, microglia boost pro-inflammatory cytokine release (Lehnardt, 2010) in order to restore the neural integrity. Persistent activation of microglia may induce a behaviour state of depressive disorder via this cytokine release. (Hanisch & Kettenman, 2007; Maes, 2011). According to recent evidence, microglia has an important implication in depression-like behaviour due to a direct effect of interferon- $\alpha$  (Zheng et al., 2015). In particular, in the hippocampus it seems that the density of microglia was increased and significantly associated with depression (Belzung et al., 2014; Zheng et al., 2015).

### **1.2.2. Inflammation and Cognitive Impairment**

In the context of chronic inflammation such as HIV and HCV infections, the viruses can contribute to the disturbance of CNS function. HIV crosses the BBB through infected immune cell migration, which induces neuropathology (Hong & Banks for review, 2015). These processes are aggravated by pro-inflammatory reactions mediated by the HIV itself (Alonso et al., 1997). The severe impact on behaviour - in particular in neurocognitive performance - is facilitated by the difficulty to suppress HIV replication

on the CNS due to compartmentalisation of virus within the CNS and differing CNS penetration of antiretroviral drugs. In fact it seems that the CNS is a potential reservoir for HIV causing a systemic inflammation (Hayashi et al., 2006).

It has been suggested that HCV also crosses the BBB and microglia cells may be the reservoir of HCV infection (Aloisi, 2001). There is evidence for HCV affecting the cerebral function with significant correlation between cognitive impairment and changes in cerebral metabolism (Forton et al., 2008).

In HIV HCV co-infection, having both viruses insulting the CNS, a significant inflammatory response is expected, as confirmed by changes in microglia and a significant association with neuroinflammation that may be causing cognitive performance impairment (Garvey et al., 2012). Additionally under interferon- $\alpha$  external exposure, measured by interferon-based treatments, the likelihood of inflammatory activation is high, increasing the risk of cognitive impairment.

### **1.2.3. Inflammation and Depression in clinical settings**

An increased prevalence of mood symptoms was found in several inflammatory conditions, such as cardiovascular diseases, diabetes, obesity, autoimmune diseases, HCV and metabolic syndrome (Walker et al., 2011, Whale et al., 2015). The immune reaction activates cellular responses that have a toxic effect on cells identified as harmful and release cytokines to recruit additional immune cells - such as macrophages - lymphocytes and neutrophils, to induce a response against pathogens (Abbas et al., 2012).

The association between inflammation and depression has been supported by the key idea that inflammation causes immune changes and those alterations have an impact in the pathophysiology of depression (Kim & Maes, 2003, Reyes-Vasquez, 2012). There are several lines of research that explore this model. Inducing a pro-inflammatory response in healthy and non-healthy populations seems to increase pro-inflammatory cytokines levels that have been significantly associated with mood disorders (Capuron et al., 2000; Capuron & Miller, 2004, 2011; Harrison et al., 2009; Wichers et al., 2007). Previous studies reported that the levels of pro-inflammatory cytokines were significantly higher in depressed patients (Dowlati et al., 2010; Kim et al., 2007). Conversely, high levels of inflammation were associated with resistance to treatment

with anti-depressant medication (Strawbridge et al., 2015). Peripheral levels of inflammatory markers were associated with MDD (Felger & Lotrich 2013).

In studies with exogenous pro-inflammatory exposure, there was a significant association with depression (Liang & Ghany, 2013, Whale et al., 2015). Furthermore, meta-analytic data reported that emotional stress was associated with high levels of inflammatory markers such as IL-6, IL-1 $\beta$ , TNF- $\alpha$ , and CRP (Steptoe et al., 2007). The idea that psychological or physical stress can trigger an inflammatory response has also been documented (Miller et al., 2013; Abbas et al., 2012). Overall, it seems that the relationship between inflammation and mood disorders is bidirectional.

The mechanisms of interferon-induced depression includes upregulation of the central serotonin transporter molecule (Zhu et al., 2006), alteration in T cell activation (Felger & Lotrich, 2013; Maes et al., 2001a), changes in tryptophan metabolism including activation of indoleamine-2,3-dioxygenase - IDO (Christmas et al., 2011), changes in glutamate metabolism (Taylor et al., 2013) and activation of the hypothalamic-pituitary-adrenal axis (Eccles et al., 2012). Despite the complexity of these pathways that trigger immune and inflammatory reactions, the common result is depressive associated behaviour.

Peripheral inflammation, such as exogenous administration of interferon- $\alpha$ , has been associated with changes in cortical and sub-cortical structures. The areas more sensitive to behavioural change include the ventral striatum regions (Capuron et al., 2012; Harrison et al., 2015), and hippocampus (Harrison et al., 2015). In HCV patients receiving interferon- $\alpha$  based treatment changes were found in the whole brain functional network architecture within 4 hours after interferon- $\alpha$  administration, which was correlated with mood and cognitive changes (Dispaquale et al., 2015). A study by Dowell and colleagues (2015) showed in HCV patients that peripheral administration of interferon- $\alpha$  rapidly changed striatal regions that were significantly associated with interferon induced fatigue at week 4 of treatment.

Overall it seems clear that interferon- $\alpha$  affects the brain resulting in behavioural changes including depression, fatigue, motivation and cognitive impairment (Capuron et al., 2002; Dantzer et al., 2008). What is unclear are the specific brain areas involved in these neuropsychiatric manifestations, the underlying mechanisms and the nature of the mood and cognitive alterations.

### 1.3.Hepatitis C Treatment

Until 2015 the standard of care (SoC) for chronic hepatitis C treatment was a combination of pegylated interferon- $\alpha$  (INF- $\alpha$ ) and ribavirin for 24 to 48 weeks, depending on HCV genotype and treatment response (Vogel & Rockstroh, 2009). HCV viral load is normally measured at week 4, 12 and week 24. These time points are used to compare response in HCV RNA to baseline levels in order to assess the type of response. If negative HCV viral load is achieved at week 4, a rapid virological response is considered, if negative at week 12 it is defined as early virological response, if negative at week 24 it is a delayed virological response.

The therapy goal is to clear the virus at the end of treatment (ETR) leading to a sustained virological response (SVR) defined as negative HCV viral load 6 months after treatment exposure. Historically HCV genotypes 2 and 3 present higher rates of positive treatment response than genotype 1 and 4 to treatment with INF- $\alpha$  and ribavirin (Antaki et al., 2010).

In special groups such as HIV/HCV co-infected patients, early HCV treatment is recommended due to the accelerated progression of liver disease. The indications for HCV treatment are similar to HCV mono-infection. However, if the immune profile is poor, with CD4 cell count <200 cells/ $\mu$ l, it is recommended to improve CD4 cell count based on HIV therapy (cART) (EASL, 2011). cART has been significantly associated with controlling HIV viral load (Maartens et al., 2014). As result the patients present high CD4 counts, which have been previously correlated with the less likelihood of liver fibrosis progression (Puoti et al., 2001).

Previously treating HCV in co-infection was associated with a poorer response to HCV treatment than treatment of HCV mono-infection and faster liver fibrosis progression (Rockstroh et al., 2008; Soriano et al., 2007). Regarding the response to HCV therapy with INF- $\alpha$  and ribavirin the rates of SVR were 40-50% in genotype 1 (GT1) and 70-80% in GT2 and 3 in mono-infected groups (Ilyas et al, 2011). As mentioned above, co-infected patients presented SVR rates of 17-36% in GT1 and 4 (Carrat et al., 2004; Chung et al., 2004).

Since 2011, the emergence of direct acting antivirals (DAAs) has been a landmark for the treatment of HCV. DAAs protease inhibitors such as telaprevir, boceprevir or faldaprevir in combination with pegylated interferon and ribavirin were the first generation of triple therapy that have reported high cure rates of HCV (Zeuzem et al.,

2011; Bacon et al., 2011). In particular, they presented a high curative rate in patients with advanced liver disease and GT1 (Back & Else, 2013; Ryder, 2015). Promising results with telaprevir and boceprevir were reported with similar SVR rates in mono-infected and co-infected patients (Sitole et al., 2013; Jacobson et al., 2011; Higgins et al., 2003). Therefore, the co-infected patients appear to be “equivalent” to mono-infected groups with satisfactory SVR rates.

Hepatitis C treatment has undergone several changes since the widespread use of interferon- $\alpha$  mono-therapy. Initially ribavirin was added in 2001 to increase the rate of sustained virological response (SVR). SVR was defined as an undetectable HCV viral load at 6 months after completion of HCV treatment. Ribavirin is a synthetic nucleoside antiviral agent that acts via polymerase inhibition and is shown to be effective against HCV replication (Davis et al., 1989). Ribavirin can cause reduction in T cell numbers that in combination with interferon- $\alpha$  exacerbates immune function impairment and has been hypothesised as a mechanism to induce depression of mood (Miller & Raison, 2016). The mechanism of action of interferon-induced depression includes direct effect of interferon- $\alpha$  and ribavirin in the immune system via tryptophan metabolism (Lotrich, 2015; Huckans et al., 2015) that accelerates spontaneous apoptosis in CD4<sup>+</sup> T-cells (Fallarino et al., 2002; Ivanova et al., 2007). The peripheral administration of HCV therapy disturbs the tryptophan (trp) mechanism by activating indoleamine 2,3 dioxygenase (IDO) which is an enzyme expressed in different cell types, such as microglia, astrocytes, macrophages, that when up-regulated cause trp depletion. Tryptophan depletion has been significantly associated with depression related symptoms (Schaefer et al., 2005; Christmas et al., 2011; Oxenkrug et al., 2014; Comai et al., 2011, Zignego et al., 2007). A different potential pathway of interferon- $\alpha$  induced IDO activity was suggested involving serotonin (5-HT) metabolism (Loftis et al., 2013). In patients with HCV interferon based treatment a significant association was found between lower plasma concentrations of 5-HT and increased symptoms of depression (Raison et al., 2009). It has been suggested that IDO converts trp into kynurenine and as a consequence of this reduction in the trp availability, there is decreased serotonin (5-HT) in the brain. In the context of serotonin depletion researchers have reported a significant association with interferon-induced depression (Zhu et al., 2006).

Changes in basal ganglia due to interferon- $\alpha$  exposure have also been suggested as a possible mechanism for interferon-induced depression (Capuron et al., 2004). Several

studies have speculated that interferon- $\alpha$  via dopamine neurotransmission might induce depression like behaviour (Capuron et al., 2002a; Capuron et al., 2004); however this hypothesis requires further testing to develop a clear model of the pathways involved. Another mechanism proposed to underlie interferon- $\alpha$  induced depression includes activation of the hypothalamic-pituitary-adrenal (HPA) axis (Eccles et al., 2012). It has been suggested that interferon- $\alpha$  induces hyperactivity of HPA axis by releasing high levels of corticotropin-releasing hormone that have been associated with depressive like behaviour (Udina et al., 2014). In addition interferon- $\alpha$  induces the production of pro-inflammatory cytokine IL-6 that has been shown to induce HPA activity leading to emergence of depressive symptoms (Capuron et al., 2004). Despite the complexity and diversity of these proposed HCV treatment mechanisms that trigger immune and inflammatory reactions, the common result is depressive associated behaviour (Felger & Lotrich, 2013; Bufalino et al., 2013).

This combination therapy was poorly tolerated, with associated severe neuropsychiatric side effects (Chasser et al., 2017). When the first generation of protease inhibitors (boceprevir and telaprevir) was introduced in 2013, these were combined with interferon  $\alpha$  and ribavirin (Ryder, 2015). These protease inhibitors were expected to increase efficacy due to higher antiviral activity. This combination had over 90% efficacy. Subsequently in 2014 oral direct-acting antiviral regimes were introduced (DAA), enabling interferon free -treatment regimes, with initial research indicating higher HCV cure rates than previous treatments (Chasser et al., 2017). These DAA interferon-free therapies are shorter in treatment duration but appear to remain associated with mild neuropsychiatric effects, in particular fatigue (Zopf et al., 2016).

The primary outcome with DAA treatment is to achieve undetectable HCV RNA at week 12 or 24 after initiation, which implies permanent elimination of HCV infection (European Association for the Study of the Liver, 2017). This more effective treatment with DAA is more likely to eliminate the risk of liver disease progression (Gelson & Alexander., 2017) including regression of fibrosis, reduction in risk of hepatocellular carcinoma and 90% reduction in liver related mortality (Bidel et al., 2016). It may also reduce the rate of HCV related extra-hepatic diseases such as stroke (Hsu et al., 2013), diabetes (Milner et al., 2014), lymphoma (Kawamura et al., 2007) and cognitive function impairment. (Kraus et al., 2013).

The development of DAAs was based on targeting structural proteins that take part in every stage of the HCV life cycle (Li, & De Clercq, 2017). For example, NS3/4A inhibitors (boceprevir; telaprevir); NS5A inhibitors (velpatasvir); nucleotide inhibitors (sofosbuvir) and non-nucleotide inhibitors (dasabuvir). In comparison, interferon- $\alpha$  controls viral infection by activating a number of cellular genes and these genes inhibit viral infection (Chung et al., 2008). This mechanism is less effective than the direct effect of DAAs on the HCV life cycle.

According to the National Institute for Health and Care Excellence (NICE) guidelines these newer DAA preparations have 90% cure rate (Gelson & Alexander., 2017). The treatment options include simeprevir, sofosbuvir, daclatasvir, a combination of ledipasvir and sofosbuvir, a combination of ombitasvir, paritaprevir and ritonavir, taken with or without dasabuvir and a combination of sofosbuvir and velpatasvir. However, new agents of treatment are under development and several clinical trials are on-going to attempt to increase cure rates with shorter treatment durations and lesser neuropsychiatric side effects.

As we move into an era of DAA use, there are several factors that may have an impact on who receives this treatment. DAAs are highly cost effective but virological response may be impaired by interactions with other HIV drugs and resistance associated with HCV variants (Back & Else, 2013; Paolucci et al., 2015) in particular GT 3 (Ryder, 2015).

Among co-infected patients, a high rate of HCV reinfection has been observed (Hullegie et al., 2015). The incidence of reinfection in co-infected MSM per 100 patient's years of follow-up, increased from 7.8 to 15.2 (Lambers et al., 2011; Martin et al., 2013). Several studies have identified risk behaviours as cause of reinfections (Ingiliz et al., 2014; Martin et al., 2013; Micallef et al., 2007; van de Laar et al., 2009). It seems that reinfection is a behavioural-based issue with severe consequences. The risk of reinfection and DAA use is potential emergence of DAA-resistance, impairing the efficacy of the new treatments (Franco et al., 2014), however this has not yet emerged. These barriers continue to make interferon- $\alpha$  a valid option for treatment. Nevertheless it is remarkable that interferon free therapies present cure rates in excess of 90%, are safe and need shorter treatment duration (12 weeks) (Ryder, 2015).



#### **1.4. Outcomes of Meta-Analysis on behavioural changes in HIV HCV co-infection**

Neuropsychiatric aspects in HIV mono infection (Ford et al, 2015) and HCV mono-infection are well known (Schaefer et al, 2012). Conversely, the co-infected group has been understudied, probably because of the high level of clinical and psychosocial complexity and small samples (Operskalski & Kovacs, 2011). However, recently it has become an important clinical group to look at due to the increasing rates of (re) infection, particularly among MSM populations.

In order to clarify the nature of neuropsychiatric manifestations associated with co-infection and to explore knowledge gaps in the literature, it was important to search the symptom profiles of co-infected samples. We aimed to synthesize results of studies on depression and cognitive aspects in co-infection; for that purpose systematic reviews and meta-analysis were performed.

##### **1.4.1. Cognitive Impairment in HIV HCV Co-infected Patients: A Systematic Review and Meta-analysis**

Cognitive impairment has been well described in HIV and HCV mono-infection, however in the context of co-infection, research is more limited. The aim of this systematic review was to describe the characteristics of cognitive impairment in HIV/HCV co-infection and to determine whether, in the current literature, there is evidence for differences on cognitive performance between co-infected HIV/HCV, and HIV and HCV mono-infected groups.

From the narrative analysis, some studies highlighted that HIV/HCV co-infected patients had a higher degree of cognitive impairment than HIV mono-infected patients. However, no significant difference on cognitive impairment between groups was also reported. The meta-analysis indicated a significantly higher global deficit score in co-infected patients than in HIV mono-infected patients. Information processing speed was also significantly different, suggesting that the co-infected patients are more likely to be impaired than HIV mono-infected patients. No significant differences between co-infected group and HCV group were reported.

As expected the presence of two viruses insulting the CNS will probably explain the greater cognitive performance impairment. These findings can be challenged by bias factors such as a small number of studies, heterogeneity of the studied population, and the large variety of methodological procedures. Future research with more consistent measures between studies is needed in order to clarify whether being co-infected with

HIV/HCV is associated with an increased risk of cognitive impairment. Such knowledge will drive clinical service development to address the needs of this specific group of patients.

#### **1.4.2. Depressive disorder in HIV HCV Co-infected Patients: A Systematic Review and Meta-analysis.**

Depression has been the most commonly reported neuropsychiatric disorder in HIV and HCV (Nanni, Caruso, Mitchell, Meggiolaro, & Grassi, 2015; Schaefer et al., 2012). However, data in the co-infected population is not clear. The key aim of our systematic review and meta-analysis was to describe and explore differences in depression rates between HIV/HCV co-infected, and HIV and HCV mono-infected samples. From the narrative analysis, studies with retrospective design reported a high prevalence of depression among co-infected patients. From prospective studies, mixed findings were reported. Some studies suggested that co-infected groups reported higher depression levels than mono-infected groups (Baillargeon et al., 2008; Braitstein et al., 2005; Butt et al., 2009; Clifford et al., 2005; Sun et al., 2013; Yoon et al., 2011). In contrast, it was also reported that diagnosis of depression was significantly less common in co-infection patients than HCV mono-infection patients (Tavakkoli et al., 2013). In studies including HCV treatment, depression was commonly reported (Alavi et al., 2012; Fumaz et al., 2007) and considered to be a risk factor for discontinuation of HCV treatment within co-infected patients (Laguno et al., 2004; Landau et al., 2001; Myers et al., 2004; Moreno et al., 2004; Rockstroh et al., 2002).

Our meta-analytic results showed that, as measured by depression scales, the co-infected group was more depressed than either the HIV or the HCV mono-infected groups. The variations among the results of the reviewed studies suggest that a clear interpretation of how depression outcomes are affected by HIV/HCV co-infection is still needed. Clinically, this finding is particularly relevant in that it offers an opportunity for targeted screening for depression in populations most at risk. This also allows for the potential to diagnose depression early and treat in a timely way before symptoms are exacerbated. This is particularly important given that depression is associated with stressful life, self-reported poor health, unhappiness with current life, non-adherence to treatment, financial problems, psychiatric history and lack of satisfaction with sexual life (Slot et al., 2015).

In summary, these qualitative and quantitative narratives have given us a better understanding of the neuropsychiatric aspects associated with HIV/HCV co-infection. In particular, there is clearly a lack of studies on the neuropsychiatric manifestations during hepatitis C treatment within this group. Interestingly, our data are starting to shape a profile of the co-infection clinical group. The meta-analytic data indicated that the co-infected group is more vulnerable - on depression and cognitive performance - as previously predicted. In view of these results, we could start to (re) think potential factors that could impact the emergence of neuropsychiatric manifestations, which have not been explored within co-infection, such as aetiology of depression factors and cognitive vulnerabilities: (1) Is it idiopathic depression different from interferon-induced depression? If so, does the co-infection cohort are more vulnerable to develop depression? (2) Is T cell activation a protective mechanism involved in emergence of depression? (3) Does gender plays a role in MDD emergence? (4) Is co-infection associated with a poorer cognitive performance, in particular on executive function level?

### **1.5. Neuropsychiatric Side Effects in HCV Treatment: Interferon Induced Depression**

Unfortunately, there are a significant number of individuals who are not offered treatment because they are unaware of their positive HCV status (Ryder, 2015), poorly engage with health services (Grebely et al, 2008), or have psychiatric co-morbidities (Nunes et al, 2006). Interferon- $\alpha$  is routinely administered to treat HCV infection as well as other inflammatory viral infections or cancer (Fritz-French & Tyor, 2012). There is a solid body of evidence that interferon- $\alpha$  induces neuropsychiatric side effects associated with high levels of inflammation (Capuron et al., 2012; Hoyo-Becerra et al., 2014, Maes, 2011; Miller, 2009; Raison & Miller, 2013). These neuropsychiatric manifestations occurring during conventional hepatitis C treatment have been well studied, particularly major depressive disorder (MDD) and cognitive impairment (Capuron & Miller, 2004; Fialho et al., 2017; Whale et al., 2015; Udina et al., 2012) which have been associated with treatment interruption and negative treatment response (Landau et al., 2001; Laguno et al., 2004; Meyers et al., 200; Moreno et al., 2004; Rockstroh et al., 2002).

Studies on neuropsychiatric side effects on triple therapy are scarce, although it has been reported that there was no significant difference in risk of developing MDD between pegylated interferon and ribavirin, and triple therapy (Fialho et al., 2014). Regarding the interferon free regimens, we can't discard the possibility of emergence of neuropsychiatric side effects due to the influence of risk factors, such as previous history of depression and or mental illness (Basseri et al., 2010, Schaefer et al., 2012), HCV itself (Carta et al., 2012), drug use and alcohol use and adverse social circumstances (Hilsabeck, Castellon & Hinkin, 2005). Data on the effect of interferon free regimes and psychiatric side effects is scarce.

In summary, we expect that in the presence of inteferon- $\alpha$ , the side effects may be exacerbated due to a state of an overstimulation of pro-inflammatory cytokines. Furthermore, the potential causes for emergence of neuropsychiatric side effects during hepatitis C treatment do not rely exclusively on the inflammatory hypothesis. The multifactorial aspects of treatment and co factors (host, viral and environment) also contribute to an aggravated negative emotional response.

#### **1.5.1. Co-infection with HIV Associated With Reduced Vulnerability to Depressive Symptoms in Hepatitis C Patients**

As mentioned above, the co-infected patients were more likely to experience worse neuropsychiatric side effects during interferon-based therapies. The factors underlying this increased vulnerability are currently unclear. The natural research question that emerged was exploring potential differences between HCV and co-infected patients undergoing HCV treatment, expecting higher rates of MDD and depression symptoms severity in the co-infected group than the HCV mono-infected group.

Interferon- $\alpha$  treatment may be responsible for the emergence of two distinct behavioural syndromes; the neurovegetative and mood-cognitive syndrome (Capuron et al., 2002a, Capuron & Miller, 2004). The neurovegetative syndrome tends to appear rapidly, associated with symptoms such as anorexia; fatigue and psychomotor slowing. The development of this syndrome has been associated with changes in the basal ganglia functions (Capuron et al., 2007; Dowell et al., 2015 Kamata et al., 2000). Neuroimaging studies strongly suggested that interferon- $\alpha$  rapidly induces changes in striatal structure causing fatigue (Dowell et al., 2015). In contrast, the mood- cognition

syndrome implicates symptoms of anxiety, depressive mood and cognitive dysfunction. These symptoms are common at a later stage of the treatment. The pathophysiological mechanisms may involve alterations in the serotonin metabolism that is related with tryptophan metabolism (Capuron et al., 2003a, Raison et al., 2010b).

In HCV chronic patients treated with INF $\alpha$ , it was found that kynurenine (kyn) levels and kyn/tryptophan (trp) ratio were high in the presence of depressive symptoms (Comai et al, 2011). These data suggest that INF- $\alpha$  boosts indoleamine-2,3-dioxygenase (IDO) activity, enhancing trp metabolism into kyn overstimulation and serotonin depletion (Capuron et al., 2004; Wichers et al., 2005). Another potential pathway is the hypothalamic-pituitary-adrenal (HPA) mechanism. INF $\alpha$  induces pro-inflammatory cytokines that trigger HPA axis via overproduction of corticotropin-releasing factor (CRF) that has been associated with mood and cognitive symptoms (Capuron & Miller, 2004; Eccles et al., 2012).

Despite the mechanisms underlying interferon therapy, it seems that interferon-induced depressive disorder is a specific sub-type of mood disorders that are exclusively associated with higher expression of the neurovegetative syndrome. Most of the evidence comes from the HCV mono-infected population leaving a research gap within the HIV HCV co-infected group. The key aim of our study was determine if there were differences in the expression of depressive symptoms during INF $\alpha$  treatment between HCV mono-infected and HIV/HCV co-infected patients. In particular, we investigated the depressive symptoms subtypes associated with the emergence of depression during HCV treatment, and investigated whether this association was different across the two study groups.

A prospective study design was conducted at the outpatients HCV clinic at the Royal Sussex County Hospital, Brighton, UK. All patients eligible to start hepatitis C treatment with pegylated INF $\alpha$  and ribavirin, or DAA triple therapy (composed of pegylated INF $\alpha$ , ribavirin and telaprevir) were included. Both treatments involved 24 weeks of pegylated INF $\alpha$ . Ethical approval was obtained and all participants gave written consent. Behavioural and clinical data were gathered at baseline, before starting treatment, during and after finishing treatment, with a 6 months period of follow-up (SVR endpoint). Depression assessments were conducted through a semi-structured clinical interview (SCID-I) and with the Hamilton Depression Rating Scale (HAMD).

Our results confirmed the depressogenic nature of  $\text{INF}\alpha$  with the greatest increase in neurovegetative symptoms. Surprisingly, the HIV-HCV co-infected group appeared less vulnerable to develop depression when compared with the HCV mono-infected group. There are several explanations for our findings, such as the nature of our cohort, potential influence of behavioural and genetic moderators, HCV chronicity and psychosocial variables. The clinical relevance of our findings are associated with developing better strategies to help patients going through treatment, taking into account the specific neurovegetative symptoms. If not screened and treated, depression can become recurrent and resistant to treatment. Additionally, what stood out was the resilience to develop severe depression symptoms in the HIV-HCV co-infected group. It seems that being co-infected is a protective factor to developing depression, under an inflammatory acute condition, such as HCV interferon based treatment.

These findings started to draw a specific co-infection signature. The need to understand what factors could interfere with the resilience to develop depression within co-infection was emerging. Regardless, it is noteworthy to point out that the emergence of neuropsychiatric aspects remains, even without  $\text{INF-}\alpha$  treatment. In chronic infection, several factors have been associated with high rates of MDD, such as personal and familiar previous history of mental illness (Carta et al., 2012), alcohol and drug abuse (Boscarino et al., 2015) and immune mechanisms (Lotrich, 2015). It seemed that, we were not looking at a vulnerable group; instead our data were suggesting a resilient clinical cohort less likely to be depressed and with similar rates of SVR when compared with the HCV mono-infected group. Taking our data into account and the hypothesis that alteration in T cell activation is one protective mechanism involved in emergence of depression, a sub study was developed to explore the potential association between depression and immune markers in a co-infected MSM sample.

### **1.5.2. Major depressive disorder and immune response in HIV HCV co-infection men during hepatitis C treatment.**

In chronic somatic diseases, MDD is 1.5 to 2 times higher than when compared with the general population (Harter et al., 2007). MDD is characterized by somatic symptoms, cognitive impairment, low mood and anxiety mapping a heterogeneous disease profile. According with meta-analysis, the co-infected group were more likely to present depressive symptoms than the HIV and HCV mono-infected groups (Fialho et

al., 2017). Several risk factors were identified as predictors of greater depression symptoms in co-infection, such as high rates of intravenous drug abuse (Clifford et al., 2005, Backus et al., 2005), alcohol abuse (Pantalone et al., 2012), psychiatric comorbidities (Backus et al., 2005) and risky sexual behaviour (Martin et al., 2013).

In the context of inflammation, as seen in HIV and HCV infection, depression symptoms may be a response to the infection itself, or side effects to treatment, or an adjustment disorder to receiving a diagnosis of HIV and or HCV, or the combination of these factors. Nevertheless, it seems that inflammation remains the common denominator for the development of depression in chronic somatic diseases (Haroon et al., 2012). Furthermore, patients who are under a chronic low-grade of inflammation are at a higher risk of developing depression (Danzter et al., 2008). Considering the interactions between MDD and immune dysregulation, the emergence of depression symptoms may depend on the onset, duration and intensity of the immune markers (Capuron et al., 2011; Sperner-Unterwieser et al., 2014).

In patients with HIV, depression has been associated with a decreased CD4 T cell count and increased rate of progression to AIDS related death (Lesernam, 2008; Ickovics et al., 2001; Stommel et al., 2002). Interestingly, it seems that depression and T cell dysfunction share the same pathways, highlighting the role of T cells in the emergence of depression via immune-inflammatory processes (Miller, 2010).

T cells are part of the immune system and it has been reported an association between low T cells count and depression (Zorilla et al., 2001), with evidence of T cell alterations in patients with MDD (Irwin & Miller, 2007; Zorilla et al., 2001). The mechanisms involved in T cell alterations are not clear, however it has been reported that in depressed patients CD4 T cells exhibited accelerated spontaneous apoptosis (Szuster-Ciesielska et al., 2008). Another hypothesis that has been proposed to explain the relationship between MDD and reduced T cells is glucocorticoid function (Bauer et al., 2002, Pariante & Miller, 2001) and inflammatory cytokines (Miller et al., 2009).

The role of T cells in emergence of depression is not clear. It is well known that decreases in T cell response are associated with depression (Irwin & Miller, 2007; Zorilla et al., 2001). There is however, emerging data suggesting that T cells might be a protective factor against depression (Brackman et al., 2015; Lewitus et al., 2008) through their neuroprotective and anti-inflammatory effects (Miller, 2010). In animal models it was observed that enhanced trafficking of T-cells to the brain was associated with an increased ability to adjust to stress (Lewitus et al., 2008). The T cells seem to

have a “protective auto-immunity” response that could represent a mechanism to control negative emotional states (Brackman et al., 2015; Lewitus et al., 2008; Schwartz, 2001; Raison & Miller, 2016).

MDD is the most common side effect of interferon-based therapies in patients with hepatitis C (Whale et al., 2015; Fialho et al., 2014; Lotrich et al., 2009) and with co-infection (Alavi et al., 2012; Fumaz et al., 2007). Particularly, in the co-infected group, depression has been reported as the major cause of treatment discontinuation (Laguno et al., 2004; Landau et al., 2001; Myers et al., 2004; Moreno et al., 2004; Rockstroh et al., 2002).

MDD as behaviour response is caused by inflammation and immune activation (Wirleitner et al, 2003; Neurauter et al, 2008a, Danzter et al, 2008). As stated previously the potential mechanisms that immune activation and interferon treatment share are the serotonergic system and IDO pathway (Myint et al., 2012). IDO activity integrates endogenous regulator mechanisms of T cells proliferation (Mellor et al., 1999). On the other hand, interferon- $\alpha$  induces increased IDO expression causing up-regulation of trp/kynurenine metabolism (Capuron et al., 2009, Wishers et al., 2005). As a consequence, serotonin synthesis is reduced leading to depression (Nemeroff & Owens, 2009). Several studies in chronic hepatitis C infection found that elevated concentrations of trp levels were associated with the deficiency of serotonin expression (Raison et al, 2009) and with depression (Oxenkrug et al., 2014). In contrast, there is evidence that failed to find differences in KTR (trp/kynurenine ratio concentrations), defined as a marker of IDO activity, and between HCV patients with and without interferon induced depression (Oxenkrug et al., 2014). Another study found that depression was associated with trp depletion without an enhanced kynurenine pathway (Hughes et al., 2012). Cytokine genes may also influence trp breakdown affecting depression emergence (Mynt et al., 2013; Oxenburg et al., 2012, 2014). Despite the mechanisms involved, the association between immune response and an inflammatory cascade on depression, activated by interferon treatment is clear.

According with the aforementioned paradigm, we aimed to explore if immune response, measured by CD4 T cell count, was correlated with depression during HCV interferon based therapy in MSM HIV-HCV patients. As expected, there was a significant increase in depression symptoms at the beginning of treatment and those symptoms remitted at a later stage. There was a significant reduction of CD4 T cells



from baseline to week 4, and we did not find a correlation between CD4 T cell count and depression and SVR. The depressogenic effect of interferon seems to be transitory, and more research is needed in order to clarify the role of T cell on depression emergence.

### **1.5.3. Does Gender Play a Role in new-onset depression during HCV Treatment?**

A research gap in the literature exists about HCV treatment in women. Potential reasons for this are the lower rates of treatment prescription due to small cohort numbers alongside slow progression of liver disease and they are more likely to spontaneously clear the virus when compared with men (Beste, Bondurant, & Ioannou, 2015). However, risk factors for HCV infection in women have been reported, such as substance abuse, HIV infection, smoking and age being over 35 years (Operskalski et al., 2008).

Regarding depression subtyping, increased somatic symptoms were suggested as a significant predictor of changes in inflammatory markers, in particular in TNF-alpha in females with MDD (Dannehl et al., 2014). In contrast, MDD was not associated with inflammatory markers possibly due to an impact of estrogen use (hormonal contraceptives) on the inflammatory cascade (Vogelzangs et al., 2012). In the non-iatrogenic model of depression it is well established that females are more vulnerable to depression (Whale et al., 2015). However, it is not so clear in the inflammatory model of depression. Nevertheless, with the vulnerability risk of being a female and adding the effects of INF- $\alpha$  therapy, a higher rate of depression is expected than men.

A prospective study design was adopted, including a HCV infection cohort only. Of 167 participants, 55 were women. The aim of this study was determine if there were gender differences in emergence of MDD during treatment, including expression of depression symptoms. Participants were assessed for depression before the start of the treatment, during and 6 months after treatment ended, defined as SVR.

During HCV therapy, there was a significant increase in depression from baseline to week 4 and a significant decrease from week 24 to SVR. These results are in accordance with our previous report, which confirms the depressogenic nature of interferon as transient. Regarding the syndrome type, the neurovegetative and mood-cognitive syndrome were significantly increased at the beginning of the treatment and markedly dropped at the end. Our data suggested that women were more likely to

present MDD at later stage of treatment (week 24). The influence of gender on depression emergence at a later stage may be due to the influence of vulnerability factors. We found that telaprevir was associated with lower depression rates in women, leading us to the possibility notion that the protease inhibitor may play a role in the inflammatory model of depression.

### **1.6. Executive function and Hepatitis C treatment in HIV acute HCV MSM sample**

As previous reported the cytokines induce changes in cognition due their over-expression (McAfoose & Baune, 2009; Irwin & Miller, 2007; Raison et al., 2006). The neuropsychological abnormalities occurring in viral hepatitis, such as HCV, suggest that greater disease severity is significantly associated with greater cognitive impairment (Cordoba et al., 2003).

Data on HCV population infers a direct association between HCV infection and development of cognitive abnormalities (Monaco et al., 2015; Forton et al., 2008; Kenelly, 2013) suggesting that the cognitive impairment is observed even in non-severe liver pathology. The profile of cognitive impairment in HCV infected patients (HCV-associated neurocognitive disorder – HCV-AND) is similar to the HIV associated neurocognitive disorders - HAND, composed of executive function, attention, working memory, psychomotor speed, verbal learning and verbal recall abnormalities (Monaco et al., 2015).

The hypothesis of a cognitive model of inflammation is based on the neurotoxic effect of HCV in the CNS that causes an increased inflammatory response mediated by overstimulation of cytokines (Senzolo et al., 2011). On the other hand, in the context of interferon-based therapies, it has been reported that there is a functional link between IFN- $\alpha$  and the brain, which ultimately contribute for cognitive impairment (Lieb et al., 2006).

IFN- $\alpha$  activation on cognition is not clear in HCV. Some studies have not found cognitive impairment (Fontana et al., 2010), whereas other reports observed cognitive impairment (Lieb et al., 2006; Pawelczyk et al., 2008). Cognitive impairment associated with IFN- $\alpha$  has been associated with prefrontal cortex dysfunctions and hippocampus (Juengling et al., 2000). It seems that the effect of IFN- $\alpha$  on cognition is dose dependent and the cognitive features associated are mainly subcortical resulting in executive

function, attention, working memory, psychomotor speed, verbal learning and verbal recall impairment (Meyers et al., 1991; Fritz-French & Tyor, 2012).

In HIV patients with identified HIV associated dementia (HAD) was found elevated levels of CSF levels of IFN- $\alpha$  than in HIV with no HAD (Rho et al., 1995) highlighting the potential negative effect of IFN- $\alpha$  on neurocognitive status. A subsequent study performed on post-mortem brain tissue from HAD individuals showed an up regulation of IFN- $\alpha$  genes compared with HIV without HAD (Valcour, 2010). Cognitive function in co-infected patients appears more impaired than in HIV mono-infection as highlighted in the post-cART era (Heaton et al., 2011) due to the insult of both virus to the CNS and the inflammatory cascade activated by IFN- $\alpha$  treatment.

As previously reported IFN- $\alpha$  based therapies induce changes in cognition. One of the research avenues that were relevant to explore was the cognitive cluster, in particular EF, associated with inflammation in clinical samples, such as HIV and HCV infection. Neuroimaging and neuropsychological data revealed a greater impairment in EF among HIV HCV co-infected patients when compared with HIV mono-infected patients (Winston et al., 2013; Sun et al., 2013; Thiagarajan et al., 2010). Cerebral changes in particular basal ganglia myo-inositol/creatine ratio was strongly associated with poor EF performance in acute HIV HCV group (Winston et al., 2013). Additionally the acute HCV stage in HIV patients, lower nadir CD4 T cell count stood out as factors associated with EF impairment (Winston et al., 2013). Overall it seems that acute HCV stage and cerebral changes are associated with EF dysfunction in HCV non-treated co-infected samples.

Cognitive impairment is reported as part of the neuropsychiatric side effects of IFN- $\alpha$  (Okanoue et al., 1996; Capuron & Miller, 2004) with evidence of EF impairment (Majer et al., 2008, Monchi et al., 2001). However, data on interferon induced cognitive impairment - in particular in DAAS - is scarce and the mechanisms underlying the EF impairment are multifactorial and understudied.

Executive function is a complex cognitive domain that facilitates behaviour and allows us to approach and adjust to unfamiliar circumstances integrating the ability to planning, decision-making and intentionally inhibits a dominant response (Miyaki et al., 2000; Mendelsohn et al., 2009). These cognitive features are implicated on overall functioning (Royall et al., 2002) and map updating, shifting and inhibiting components.

The aim of our last study was to explore the EF status in a co-infected and control HIV mono-infected group using EF tasks. We expected that the co-infected group presented a poor EF performance than the HIV group and during HCV therapy.

A total of 25 HIV MSM participants enrolled in our study, 12 were HIV asymptomatic and 13 were acute HCV HIV assigned for HCV treatment with DAAs. Patients were assessed prospectively using a comprehensive EF battery. Our data indicated that there was an effect of DAAs on cognition, in particular with the co-infected group showing a disadvantage on information processing speed, with a significant increase on speed of processing performance under prospective memory conditions. Clearly more research is needed in order to explore if this cognitive impairment is due to the effect of DAAs, the HIV virus or residual effect of both.

## References

- Abbas, A. K., Lichtman, A. H., & Pillai, S. (2012). *Cellular and molecular immunology*. Elsevier Health Sciences.
- Aitken, C. K., Lewis, J., Tracy, S. L., Spelman, T., Bowden, D. S., Bharadwaj, M., ... Hellard, M. (2008). High incidence of hepatitis C virus reinfection in a cohort of injecting drug users. *Hepatology*, 48(6), 1746-1752.
- Alavi, M., Grebely, J., Matthews, G. V., Petoumenos, K., Yeung, B., Day, C., ... Dore, G. J. (2012). Effect of pegylated interferon- $\alpha$ -2a treatment on mental health during recent hepatitis C virus infection. *Journal of Gastroenterology and Hepatology*, 27(5), 957-965.
- Aloisi, F. (2011). Immune function of microglia. *Glia*, 36, 165-179.
- Alonso, K., Pontiggia, P., Medenica, R., & Rizzo, S. (1997). Cytokine patterns in adults with AIDS. *Immunological Investigations*, 26(3), 341-350.
- Anisman, H., & Merali, Z. (2002). Cytokines, stress, and depressive illness. *Brain, behavior, and immunity*, 16(5), 513-524.
- Antaki, N., Craxi, A., Kamal, S., Moucari, R., Van der Merwe, S., Haffar, S., ... Heathcote, E. J. (2010). The neglected hepatitis C virus genotypes 4, 5 and 6: an international consensus report. *Liver International*, 30(3), 342-355.
- Back, D., & Else, L. (2013). The importance of drug–drug interactions in the DAA era. *Digestive and Liver Disease*, 45, S343-S348.
- Backus, L. I., Boothroyd, D., & Deyton, L. R. (2005). HIV, hepatitis C and HIV/Hepatitis C virus co-infection in vulnerable populations. *AIDS*, 19(Suppl. 3), S13-S19.
- Bacon, B. R., Gordon, S. C., Lawitz, E., Marcellin, P., Vierling, J. M., Zeuzem, S., ... Burroughs, M. (2011). Boceprevir for previously treated chronic HCV genotype 1 infection. *New England Journal of Medicine*, 364(13), 1207-1217.
- Baillargeon, J. G., Paar, D. P., Wu, H., Giordano, T. P., Murray, O., Raimer, B. G., ... Pulvino, J. S. (2008). Psychiatric disorders, HIV infection and HIV/hepatitis co-infection in the correctional setting. *AIDS Care*, 20(1), 124-129.
- Banks, W. A. (2015). The blood-brain barrier in neuroimmunology: Tales of separation and assimilation. *Brain, Behavior, and Immunity*, 44, 1-8.
- Banks, W. A., & Erickson, M. A. (2010). The blood–brain barrier and immune function and dysfunction. *Neurobiology of Disease*, 37(1), 26-32.

- Basseri, B., Yamini, D., Chee, G., Enayati, P. D. P., Tran, T., & Poordad, F. (2010). Comorbidities associated with the increasing burden of hepatitis C infection. *Liver International*, 30(7), 1012-1018.
- Bassett, S. E., Guerra, B., Brasky, K., Miskovsky, E., Houghton, M., Klimpel, G. R., & Lanford, R. E. (2001). Protective immune response to hepatitis C virus in chimpanzees rechallenged following clearance of primary infection. *Hepatology*, 33(6), 1479-1487.
- Bauer, M. E., Papadopoulos, A., Poon, L., Perks, P., Lightman, S. L., Checkley, S., & Shanks, N. (2003). Altered glucocorticoid immunoregulation in treatment resistant depression. *Psychoneuroendocrinology*, 28(1), 49-65.
- Belzung, C., Willner, P., & Philippot, P. (2014). Depression: From psychopathology to pathophysiology. *Current Opinion in Neurobiology*, 30, 24-30.
- Bernstein, D., Kleinman, L., Barker, C. M., Revicki, D. A., & Green, J. (2002). Relationship of health-related quality of life to treatment adherence and sustained response in chronic hepatitis C patients. *Hepatology*, 35(3), 704-708.
- Beste, L. A., Bondurant, H. C., & Ioannou, G. N. (2015). Prevalence and management of chronic hepatitis C virus infection in women. *Medical Clinics of North America*, 99(3), 575-586.
- Bing EG, Burnam MA, Longshore D, Fleishman JA, Sherbourne CD, London AS, et al. (2001). Psychiatric disorders and drug use among human immunodeficiency virus-infected adults in the United States. *Archives of General Psychiatry*, 58, 721-728.
- Blatteis, C. M., Bealer, S. L., Hunter, W. S., Llanos, J. Q., Ahokas, R. A., & Mashburn, T. A. (1983). Suppression of fever after lesions of the anteroventral third ventricle in guinea pigs. *Brain Research Bulletin*, 11(5), 519-526.
- Boscarino, J. A., Lu, M., Moorman, A. C., Gordon, S. C., Rupp, L. B., Spradling, P. R., ... & Holmberg, S. D. (2015). Predictors of poor mental and physical health status among patients with chronic hepatitis C infection: The Chronic Hepatitis Cohort Study (CHeCS). *Hepatology*, 61(3), 802-811.
- Brachman, R.A., Lehmann, M.L., Maric, D., Herkenham, M., (2015). Lymphocytes from chronically stressed mice confer antidepressant-like effects to naive mice. *J. Neurosci.* 35, 1530–1538.
- Braitstein, P., Montessori, V., Chan, K., Montaner, J. S. G., Schechter, M. T., O'shaughnessy, M. V., & Hogg, R. S. (2005). Quality of life, depression and

- fatigue among persons co-infected with HIV and hepatitis C: outcomes from a population-based cohort. *AIDS Care*, 17(4), 505-515.
- Butt, A. A., Khan, U. A., Shaikh, O. S., McMahon, D., Dorey-Stein, Z., Tsevat, J., & Lo Re III, V. (2009). Rates of HCV treatment eligibility among HCV-monoinfected and HCV/HIV-coinfected patients in tertiary care referral centers. *HIV Clinical Trials*, 10(1), 25-32.
- Bidell, M. R., McLaughlin, M., Faragon, J., Morse, C., & Patel, N. (2016). Desirable characteristics of hepatitis C treatment regimens: a review of what we have and what we need. *Infectious diseases and therapy*, 5(3), 299-312.
- Bufalino, C., Hepgul, N., Aguglia, E., & Pariante, C. M. (2013). The role of immune genes in the association between depression and inflammation: a review of recent clinical studies. *Brain, behavior, and immunity*, 31, 31-47.
- Chung, R. T., Gale, M., Polyak, S. J., Lemon, S. M., Liang, T. J., & Hoofnagle, J. H. (2008). Mechanisms of action of interferon and ribavirin in chronic hepatitis C: Summary of a workshop. *Hepatology*, 47(1), 306-320
- Capuron, L., & Miller, A. H. (2004). Cytokines and psychopathology: Lessons from interferon- $\alpha$ . *Biological Psychiatry*, 56(11), 819-824.
- Capuron, L., & Miller, A. H. (2011). Immune system to brain signaling: Neuropsychopharmacological implications. *Pharmacology & Therapeutics*, 130(2), 226-238
- Capuron, L., Neurauter, G., Musselman, D. L., Lawson, D. H., Nemeroff, C. B., Fuchs, D., & Miller, A. H. (2003a). Interferon-alpha-induced changes in tryptophan metabolism: relationship to depression and paroxetine treatment. *Biological Psychiatry*, 54(9), 906-914.
- Capuron, L., Pagnoni, G., Demetrashvili, M. F., Lawson, D. H., Fornwalt, F. B., Woolwine, B., ... Miller, A. H. (2007). Basal ganglia hypermetabolism and symptoms of fatigue during interferon- $\alpha$  therapy. *Neuropsychopharmacology*, 32(11), 2384-2392.
- Capuron, L., Pagnoni, G., Drake, D. F., Woolwine, B. J., Spivey, J. R., Crowe, R. J., ... Miller, A. H. (2012). Dopaminergic mechanisms of reduced basal ganglia responses to hedonic reward during interferon alfa administration. *Archives of General Psychiatry*, 69(10), 1044-1053.

- Capuron, L., Ravaud, A., & Dantzer, R. (2000). Early depressive symptoms in cancer patients receiving interleukin 2 and/or interferon alfa-2b therapy. *Journal of Clinical Oncology*, 18(10), 2143-2151
- Capuron, L., Ravaud, A., Neveu, P. J., Miller, A. H., Maes, M., & Dantzer, R. (2002). Association between decreased serum tryptophan concentrations and depressive symptoms in cancer patients undergoing cytokine therapy. *Molecular Psychiatry*, 7(5), 468-473.
- Carrat F, Bani-Sadr F, Pol S, Rosenthal E, Lunel-Fabiani F, Benzekri A, et al. (2004). Pegylated interferon alfa-2b vs. standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: A randomized controlled trial. *JAMA*, 292, 2839–2848
- Carta, M. G., Angst, J., Moro, M. F., Mura, G., Hardoy, M. C., Balestrieri, C., ... Farci, P. (2012). Association of chronic hepatitis C with recurrent brief depression. *Journal of Affective Disorders*, 141(2), 361-366.
- Chibanda, D., Cowan, F. M., Healy, J. L., Abas, M., & Lund, C. (2015). Psychological interventions for common mental disorders for people living with HIV in low- and middle-income countries: Systematic review. *Tropical Medicine & International Health*, 20 (7), 830-839.
- Christmas, D. M., Potokar, J., & Davies, S. J. (2011). A biological pathway linking inflammation and depression: Activation of indoleamine 2,3-dioxygenase. *Neuropsychiatr Dis Treat*, 7, 431-439.
- Chung RT, Andersen J, Volberding P, Robbins GK, Liu T, Sherman KE, et al.(2004) Peginterferon Alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. *New England Journal of Medicine*, 351, 451-459.
- Ciccarelli, N., Fabbiani, M., Grima, P., Falasca, K., Tana, M., Baldonero, E., ... Di Giambenedetto, S. (2013). Comparison of cognitive performance in HIV or HCV mono-infected and HIV-HCV co-infected patients. *Infection*, 41, 1103-1109. doi:10.1007/s15010-013-0503-2
- Clifford, D. B., Evans, S. R., Yang, Y., & Gulick, R. M. (2005). The neuropsychological and neurological impact of hepatitis C virus co-infection in HIV-infected subjects. *AIDS*, 19, S64-S71
- Comai, S., Cavalletto, L., Chemello, L., Bernardinello, E., Ragazzi, E., Costa, C. V. L., & Bertazzo, A. (2011). Effects of PEG-interferon alpha plus ribavirin on



- tryptophan metabolism in patients with chronic hepatitis C. *Pharmacological research*, 63(1), 85-92
- Córdoba, J., Flavià, M., Jacas, C., Sauleda, S., Esteban, J. I., Vargas, V., ... Guardia, J. (2003). Quality of life and cognitive function in hepatitis C at different stages of liver disease. *Journal of Hepatology*, 39(2), 231-238.
- Dannehl, K., Rief, W., Schwarz, M. J., Hennings, A., Riemer, S., Selberdinger, V., Stapf, T., Euteneuer, F. (2014). The predictive value of somatic and cognitive depressive symptoms for cytokine changes in patients with major depression. *Journal of Neuropsychiatric Disease and Treatment* 10, 1191–1197.
- Dantzer, R. (2001). Cytokine-induced sickness behavior: where do we stand?. *Brain, Behavior, and Immunity*, 15(1), 7-24.
- Dantzer, R., & Kelley, K. W. (2007). Twenty years of research on cytokine-induced sickness behavior. *Brain, Behavior, and Immunity*, 21(2), 153-160.
- Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W., & Kelley, K. W. (2008). From inflammation to sickness and depression: When the immune system subjugates the brain. *Nature Reviews Neuroscience*, 9(1), 46-56.
- Dantzer, R., O'Connor, J. C., Lawson, M. A., & Kelley, K. W. (2011). Inflammation-associated depression: from serotonin to kynurenine. *Psychoneuroendocrinology*, 36(3), 426-436
- Deeks, S. G., Lewin, S. R., & Havlir, D. V. (2013). The end of AIDS: HIV infection as a chronic disease. *The Lancet*, 382(9903), 1525-1533.
- den Hollander JG, Rijnders BJ, van Doornum GJ, van der Ende ME. (2005). Sexually transmitted reinfection with a new hepatitis C genotype during pegylated interferon and ribavirin therapy. *AIDS*; 19: 639–40.
- Dipasquale, O., Cooper, E. A., Tibble, J., Voon, V., Baglio, F., Baselli, G., ... Harrison, N. A. (2016). Interferon- $\alpha$  acutely impairs whole-brain functional connectivity network architecture – A preliminary study. *Brain, Behavior, and Immunity*, 58, 31-39.
- Dowell, N. G., Cooper, E. A., Tibble, J., Voon, V., Critchley, H. D., Cercignani, M., & Harrison, N. A. (2016). Acute changes in striatal microstructure predict the development of interferon-alpha induced fatigue. *Biological Psychiatry*, 79(4), 320-328.

- Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, Lanctot KL (2010) A meta-analysis of cytokines in major depression. *Biological Psychiatry*, 67, 446–457.
- Eccles, J., Lallemand, C., Mushtaq, F., Greenwood, M., Keller, M., Golding, B., ... Whale, R. (2012). Pre-treatment waking cortisol response and vulnerability to interferon  $\alpha$  induced depression. *European Neuropsychopharmacology*, 22(12), 892-896.
- European Association For The Study Of The Liver. (2011). EASL Clinical Practice Guidelines: management of hepatitis C virus infection. *Journal of Hepatology*, 55(2), 245-264.
- European Association for the Study of the Liver. (2017). Response to the Cochrane systematic review on DAA-based treatment of chronic hepatitis C. *Journal of Hepatology*. 32129-3 DOI: <http://dx.doi.org/10.1016/j.jhep.2017.06.022>
- Felger, J. C., & Lotrich, F. E. (2013). Inflammatory cytokines in depression: Neurobiological mechanisms and therapeutic implications. *Neuroscience*, 246, 199-229.
- Fenn, A. M., Gensel, J. C., Huang, Y., Popovich, P. G., Lifshitz, J., & Godbout, J. P. (2014). Immune activation promotes depression 1 month after diffuse brain injury: A role for primed microglia. *Biological Psychiatry*, 76(7), 575-584.
- Fialho, R., Keller, M., File, A., Woods, C., Pereira, M., Yousseff, E., ... Whale, R. (2014). HCV triple therapy in co-infection HIV/HCV is not associated with a different risk of developing major depressive disorder. *Journal of the International AIDS Society*, 17(4).
- Fialho, R., Pereira, M., Bucur, M., Fisher, M., Whale, R., & Rusted, J. (2016). Cognitive impairment in HIV and HCV co-infected patients: a systematic review and meta-analysis. *AIDS Care*, 28(12), 1481-1494.
- Fialho, R., Pereira, M., Rusted, J., & Whale, R. (2017). Depression in HIV and HCV co-infected patients: a systematic review and meta-analysis. *Psychology, Health & Medicine*, 1-16.
- Ford, N., Shubber, Z., Meintjes, G., Grinsztejn, B., Eholie, S., Mills, E. J., ... Doherty, M. (2015). Causes of hospital admission among people living with HIV worldwide: A systematic review and meta-analysis. *The Lancet HIV*, 2(10), e438-e444.

- Forton, D. M., Hamilton, G., Allsop, J. M., Grover, V. P., Wesnes, K., O'Sullivan, C., ... Taylor-Robinson, S. D. (2008). Cerebral immune activation in chronic hepatitis C infection: a magnetic resonance spectroscopy study. *Journal of Hepatology*, 49(3), 316-322.
- Fox, J., Nastouli, E., Thomson, E., Muir, D., McClure, M., Weber, J. & Fidler, S. (2008). Increasing incidence of acute hepatitis C in individuals diagnosed with primary HIV in the United Kingdom. *AIDS*, 22(5), 666-668.
- Franco S, Tural C, Nevot M, Molto J, Rockstroh JK, Clotet B, et al. (2014). Detection of a sexually transmitted hepatitis C virus protease inhibitor-resistance variant in a human immunodeficiency virus-infected homosexual man. *Gastroenterology*, 147, 599–601.
- Fried, M. W., Shiffman, M. L., Reddy, K. R., Smith, C., Marinos, G., Gonçalves Jr, F. L., ... Craxi, A. (2002). Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *New England Journal of Medicine*, 347(13), 975-982.
- Fritz-French, C., & Tyor, W. (2012). Interferon- $\alpha$  (IFN $\alpha$ ) neurotoxicity. *Cytokine & Growth Factor Reviews*, 23(1), 7-14.
- Fumaz, C. R., Munoz-Moreno, J. A., Ballesteros, A. L., Paredes, R., Ferrer, M. J., Salas, A., ... Tural, C. (2007). Influence of the type of pegylated interferon on the onset of depressive and neuropsychiatric symptoms in HIV-HCV coinfecting patients. *AIDS Care*, 19(1), 138-145.
- Garvey, L. J., Pavese, N., Ramlackhansingh, A., Thomson, E., Allsop, J. M., Politis, M., ... Winston, A. (2012). Acute HCV/HIV coinfection is associated with cognitive dysfunction and cerebral metabolite disturbance, but not increased microglial cell activation. *PloS One*, 7(7), e38980.
- Gelson, W., & Alexander, G. (2017). Is elimination of hepatitis C from the UK by 2030 a realistic goal?. *British Medical Bulletin*, 1-9.
- Goulet, J. L., Fultz, S. L., McGinnis, K. A., & Justice, A. C. (2005). Relative prevalence of comorbidities and treatment contraindications in HIV-mono-infected and HIV / HCV-co-infected veterans. *AIDS*, 19(Suppl. 3), S99-S105.
- Grebely J, Conway B, Raff a JD, Lai C, Krajden M, Tyndall MW. (2006). Hepatitis C virus reinfection in injection drug users. *Hepatology*, 44, 1139-1145.
- Grebely, J., Genoway, K. A., Raffa, J. D., Dhadwal, G., Rajan, T., Showler, G., ... Fischer, B. (2008). Barriers associated with the treatment of hepatitis C virus infection among illicit drug users. *Drug and Alcohol Dependence*, 93(1), 141-147.

- Haapakoski, R., Ebmeier, K. P., Alenius, H., & Kivimäki, M. (2016). Innate and adaptive immunity in the development of depression: An update on current knowledge and technological advances. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 66, 63-72.
- Hanisch, U. K., and Kettenmann, H. (2007). Microglia: Active sensor and versatile effector cells in the normal and pathologic brain. *Nat. Neurosci.* 10, 1387–1394.doi: 10.1038/nn1997
- Haroon, E., Raison, C. L., & Miller, A. H. (2012). Psychoneuroimmunology meets neuropsychopharmacology: Translational implications of the impact of inflammation on behavior. *Neuropsychopharmacology*, 37(1):137–162.
- Harrison NA, Brydon L, Walker C, Gray MA, Steptoe A, Critchley HD (2009) Inflammation causes mood changes through alterations in subgenual cingulate activity and meso- limbic connectivity. *Biological Psychiatry*, 66, 407–414.
- Harrison, N. A., Cercignani, M., Voon, V., & Critchley, H. D. (2015). Effects of inflammation on hippocampus and substantia nigra responses to novelty in healthy human participants. *Neuropsychopharmacology*, 40(4), 831-838
- Hart, B. L. (1988). Biological basis of the behavior of sick animals. *Neuroscience & Biobehavioral Reviews*, 12(2), 123-137
- Harter M, Baumeister H, Reuter K, Jacobi F, Höfler M, Bengel J, et al. (2007). Increased 12-month prevalence rates of mental disorders in patients with chronic somatic diseases. *Psychother Psychosomatics*, 76, 354-360.
- Härter, M., Baumeister, H., Reuter, K., Jacobi, F., Höfler, M., Bengel, J., & Wittchen, H. U. (2007). Increased 12-month prevalence rates of mental disorders in patients with chronic somatic diseases. *Psychotherapy and Psychosomatics*, 76(6), 354-360.
- Hayashi, K., Pu, H., Andras, I. E., Eum, S. Y., Yamauchi, A., Hennig, B., & Toborek, M. (2006). HIV-TAT protein upregulates expression of multidrug resistance protein 1 in the blood–brain barrier. *Journal of Cerebral Blood Flow & Metabolism*, 26(8), 1052-1065.
- Heaton, R.K., Franklin, D.R., Ellis, R.J., McCutchan, J.A., Letendre, S.L., Leblanc, S., ... Grant, I., (2011). HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. *J. Neurovirol.* 17, 3–16.

- Higgins JPT, Thompson SG, Deeks JJ, et al. (2003). Measuring inconsistency in meta-analyses. *British Med Journal*, 327, 557–560.
- Hilsabeck, R. C., Castellon, S. A., & Hinkin, C. H. (2005). Neuropsychological aspects of coinfection with HIV and hepatitis C virus. *Clinical Infectious Diseases*, 41(Supplement 1), S38-S44.
- Hong, S., & Banks, W. A. (2015). Role of the immune system in HIV-associated neuroinflammation and neurocognitive implications. *Brain, Behavior, and Immunity*, 45, 1-12.
- Hoyo-Becerra, C., Schlaak, J. F., & Hermann, D. M. (2014). Insights from interferon- $\alpha$ -related depression for the pathogenesis of depression associated with inflammation. *Brain, Behavior, and Immunity*, 42, 222-231.
- Hughes, M. M., Carballedo, A., McLoughlin, D. M., Amico, F., Harkin, A., Frodl, T., & Connor, T. J. (2012). Tryptophan depletion in depressed patients occurs independent of kynurenine pathway activation. *Brain, Behavior, and Immunity*, 26(6), 979-987.
- Hullegie, S. J., Arends, J. E., Rijnders, B. J., Irving, W. L., Salmon, D., Prins, M., ... & Rockstroh, J. K. (2015). Current knowledge and future perspectives on acute hepatitis C infection. *Clinical Microbiology and Infection*, 21(8), 797-e9.
- Hsu, C. S., Kao, J. H., Chao, Y. C., Lin, H. H., Fan, Y. C., Huang, C. J., & Tsai, P. S. (2013). Interferon- based therapy reduces risk of stroke in chronic hepatitis C patients: a population- based cohort study in Taiwan. *Alimentary pharmacology & therapeutics*, 38(4), 415-423
- Ickovics, J. R., Hamburger, M. E., Vlahov, D., Schoenbaum, E. E., Schuman, P., Boland, R. J., ... & HIV Epidemiology Research Study Group. (2001). Mortality, CD4 cell count decline, and depressive symptoms among HIV-seropositive women: longitudinal analysis from the HIV Epidemiology Research Study. *JAMA*, 285(11), 1466-1474.
- Ilyas JA, Vierling JM. (2011). An overview of emerging therapies for the treatment of chronic hepatitis C. *Clin Liver Dis*, 15, 515–536.
- Ingiliz, P., Krznaric, I., Stellbrink, H. J., Knecht, G., Lutz, T., Noah, C., ... Rockstroh, J. K. (2014). Multiple hepatitis C virus (HCV) reinfections in HIV-positive men who have sex with men: No influence of HCV genotype switch or interleukin-28B genotype on spontaneous clearance. *HIV Medicine*, 15(6), 355-361.

- Irwin, M. R., & Cole, S. W. (2011). Reciprocal regulation of the neural and innate immune systems. *Nature Reviews Immunology*, 11(9), 625-632.
- Irwin, M. R., & Miller, A. H. (2007). Depressive disorders and immunity: 20 years of progress and discovery. *Brain, Behavior, and Immunity*, 21(4), 374-383
- Jacobson IM, McHutchison JG, Dusheiko G, et al. (2011). Telaprevir for previously untreated chronic hepatitis C virus infection. *New England Journal of Medicine*, 364, 2405–2416.
- Juengling, F. D., Ebert, D., Gut, O., Engelbrecht, M. A., Rasenack, J., Nitzsche, E. U., ... Lieb, K. (2000). Prefrontal cortical hypometabolism during low-dose interferon alpha treatment. *Psychopharmacology*, 152(4), 383-389.
- Kamata M, Higuchi H, Yoshimoto M, Yoshida K, Shimizu T (2000): Effect of single intracerebroventricular injection of alpha-interferon on mono-amine concentrations in the rat brain. *European Neuropsychopharmacology*, 10, 129-132.
- Kennelly, S. P. (2013). Cognitive dysfunction: an important extrahepatic manifestation of hepatitis C infection? *Postgraduate Medical Journal*. doi:10.1136/postgradmedj-2012-131337
- Kim, Y. K., & Maes, M. (2003). The role of the cytokine network in psychological stress. *Acta Neuropsychiatrica*, 15(3), 148-155.
- Kim, Y.K., Na, K.S., Shin, K.H., Jung, H.Y., Choi, S.H., Kim, J.B., (2007). Cytokine imbalance in the pathophysiology of major depressive disorder. *Prog Neuropsychopharmacol Biological Psychiatry* 31, 1044-1053.
- Kawamura, Y., Ikeda, K., Arase, Y., Yatsuji, H., Sezaki, H., Hosaka, T., ... & Kumada, H. (2007). Viral elimination reduces incidence of malignant lymphoma in patients with hepatitis C. *The American journal of medicine*, 120(12), 1034-1041.
- Kraus, M. R., Schäfer, A., Teuber, G., Porst, H., Sprinzl, K., Wollschläger, S., ... & Scheurlen, M. (2013). Improvement of neurocognitive function in responders to an antiviral therapy for chronic hepatitis C. *Hepatology*, 58(2), 497-504.
- Laguno, M., Murillas, J., Blanco, J. L., Martínez, E., Miquel, R., Sánchez-Tapias, J. M., ... & León, A. (2004). Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for treatment of HIV/HCV co-infected patients. *AIDS*, 18(13), 27-36.
- Lai ME, Mazzoleni AP, Argioli F, et al. (1994). Hepatitis C virus in multiple episodes of acute hepatitis in polytransfused thalassaemic children. *Lancet*; 343: 388-390.

- Lai, H. M. X., Cleary, M., Sitharthan, T., & Hunt, G. E. (2015). Prevalence of comorbid substance use, anxiety and mood disorders in epidemiological surveys, 1990-2014: A systematic review and meta-analysis. *Drug and Alcohol Dependence*, 154, 1-13.
- Lambers, F. A., Prins, M., Thomas, X., Molenkamp, R., Kwa, D., Brinkman, K., ... MOSAIC (MSM Observational Study of Acute Infection with hepatitis C) study group. (2011). Alarming incidence of hepatitis C virus re-infection after treatment of sexually acquired acute hepatitis C virus infection in HIV-infected MSM. *AIDS*, 25(17), F21-F27.
- Landau, A., Batisse, D., Piketty, C., Van Huyen, J. P. D., Bloch, F., Belec, L., ... Kazatchkine, M. D. (2001). Long-term efficacy of combination therapy with interferon- $\alpha$ 2b and ribavirin for severe chronic hepatitis C in HIV-infected patients. *AIDS*, 15(16), 2149-2155
- Lehnardt, S., (2010). Innate immunity and neuroinflammation in the CNS: The role of microglia in Toll-like receptor-mediated neuronal injury. *Glia* 58, 253–263.
- Leserman, J. (2008). Role of depression, stress, and trauma in HIV disease progression. *Psychosomatic Medicine*, 70(5), 539-545
- Lewitus, G.M., Cohen, H., Schwartz, M. (2008). Reducing post-traumatic anxiety by immunization. *Brain, Behavior, and Immunity*, 22, 1108-1114.
- Liang, T. J., & Ghany, M. G. (2013). Current and future therapies for hepatitis C virus infection. *New England Journal of Medicine*, 368(20), 1907-1917.
- Lieb, K., Engelbrecht, M. A., Gut, O., Fiebich, B. L., Bauer, J., Janssen, G., & Schaefer, M. (2006). Cognitive impairment in patients with chronic hepatitis treated with interferon alpha (IFN $\alpha$ ): results from a prospective study. *European Psychiatry*, 21(3), 204-210.
- Lotrich, F. E. (2015). Inflammatory cytokine-associated depression. *Brain research*, 1617, 113-125
- Lotrich, F. E., Albusaysi, S., & Ferrell, R. E. (2013). Brain-derived neurotrophic factor serum levels and genotype: association with depression during interferon- $\alpha$  treatment. *Neuropsychopharmacology*, 38(6), 985-995.
- Lotrich, F. E., Ferrell, R. E., Rabinovitz, M., & Pollock, B. G. (2009). Risk for depression during interferon-alpha treatment is affected by the serotonin transporter polymorphism. *Biological Psychiatry*, 65(4), 344-348.

- Maartens, G., Celum, C., & Lewin, S. R. (2014). HIV infection: Epidemiology, pathogenesis, treatment, and prevention. *The Lancet*, 384(9939), 258-271.
- Maes M, Capuron L, Ravaud A, Gualde N, Bosmans E, Egyed B, Dantzer R, Neveu PJ. (2001) Lowered serum dipeptidyl peptidase IV activity is associated with depressive symptoms and cytokine production in cancer patients receiving interleukin-2- based immunotherapy. *Neuropsychopharmacology* 24(2):130–40.
- Maes M, Meltzer HY, Scharpé S, Cooreman W, Uyttenbroeck W, Suy E, ... Cosyns P (1993). Psychomotor retardation, anorexia, weight loss, sleep disturbances, and loss of energy: Psychopathological correlates of hyperhaptoglobinemia during major depression. *Psychiatr. Research*, 47(3), 229-241.
- Maes M. (1993). A review on the acute phase response in major depression. *Reviews in the Neuroscience*, 4(4), 407-416.
- Maes, M. (2011). Depression is an inflammatory disease, but cell-mediated immune activation is the key component of depression. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 35, 664–675.
- Majer, M., Welberg, L. A., Capuron, L., Pagnoni, G., Raison, C. L., & Miller, A. H. (2008). IFN- $\alpha$ -induced motor slowing is associated with increased depression and fatigue in patients with chronic hepatitis C. *Brain, Behavior, and Immunity*, 22(6), 870-880.
- Martin, E. M., DeHaan, S., Vassileva, J., Gonzalez, R., Weller, J., & Bechara, A. (2013). Decision making among HIV+ drug using men who have sex with men: A preliminary report from the Chicago Multicenter AIDS Cohort Study. *Journal of Clinical and Experimental Neuropsychology*, 35(6), 573-583.
- Martin, T. C., Martin, N. K., Hickman, M., Vickerman, P., Page, E. E., Everett, R., ... Nelson, M. (2013). Hepatitis C virus reinfection incidence and treatment outcome among HIV-positive MSM. *AIDS*, 27(16), 2551-2557.
- McAfoose, J., & Baune, B. T. (2009). Evidence for a cytokine model of cognitive function. *Neuroscience & Biobehavioral Reviews*, 33(3), 355-366
- McNamara, R. K., & Lotrich, F.E. (2013). Elevated immune-inflammatory signaling in mood disorders: A new therapeutic target? *Expert Rev Neurother*, 12(9), 1143–1161.
- Mehta SH, Cox A, Hoover DR, et al. (2002). Protection against persistence of hepatitis C. *Lancet*, 359, 1478-1483.



- Mellor, A. L., & Munn, D. H. (1999). Tryptophan catabolism and T-cell tolerance: immunosuppression by starvation?. *Immunology today*, 20(10), 469-473.
- Mendelsohn, D., Riedel, W. J., & Sambeth, A. (2009). Effects of acute tryptophan depletion on memory, attention and executive functions: a systematic review. *Neuroscience & Biobehavioral Reviews*, 33(6), 926-952
- Meyers, C. A., Scheibel, R. S., & Forman, A. D. (1991). Persistent neurotoxicity of systemically administered interferon-alpha. *Neurology*, 41(5), 672-676
- Micallef JM, Macdonald V, Jauncey M et al. (2007). High incidence of hepatitis C virus reinfection within a cohort of injecting drug users. *J Viral Hepat*; 14: 413–418.
- Miller AH, Haroon E, Raison CL, Felger JC. (2013). Cytokine targets in the brain: Impact on neurotransmitters and neurocircuits. *Depression and Anxiety*, 30(4), 297–306.
- Miller, A. H. (2010). Depression and immunity: a role for T cells?. *Brain, Behavior, and Immunity*, 24(1), 1-8.
- Miller, A. H., & Raison, C. L. (2016). The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nature Reviews Immunology*, 16(1), 22-34
- Miller, A. H., Maletic, V., & Raison, C. L. (2009). Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biological Psychiatry*, 65(9), 732-741.
- Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex “frontal lobe” tasks: A latent variable analysis. *Cognitive psychology*, 41(1), 49-100.
- Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST.(2013). Global epidemiology of hepatitis C virus infection: new estimates of age- specific antibody to HCV seropre- valence. *Hepatology*; 57, 1333-1342.
- Monaco, S., Mariotto, S., Ferrari, S., Calabrese, M., Zanusso, G., Gajofatto, A., ... Dammacco, F. (2015). Hepatitis C virus-associated neurocognitive and neuropsychiatric disorders: Advances in 2015. *World Journal of Gastroenterology*, 21(42), 11974.
- Monchi, O., Petrides, M., Petre, V., Worsley, K., & Dagher, A. (2001). Wisconsin Card Sorting revisited: distinct neural circuits participating in different stages of the

- task identified by event-related functional magnetic resonance imaging. *Journal of Neuroscience*, 21(19), 7733-7741
- Moreno, L., Quereda, C., Moreno, A., Perez-Elías, M. J., Antela, A., Casado, J. L., ... Moreno, S. (2004). Pegylated interferon  $\alpha 2b$  plus ribavirin for the treatment of chronic hepatitis C in HIV-infected patients. *AIDS*, 18(1), 67-73.
- Mustanski BS, Newcomb ME, Du Bois SN, Garcia SC, Grov C. (2011). HIV in young men who have sex with men: a review of epidemiology, risk and protective factors, and interventions. *Journal of Sexual Research*, 48:218–253.
- Myers, R. P., Benhamou, Y., Bochet, M., Thibault, V., Mehri, D., & Poynard, T. (2004). Pegylated interferon alpha 2b and ribavirin in HIV/hepatitis C virus-co-infected non-responders and relapsers to IFN-based therapy. *AIDS*, 18(1), 75-79.
- Myint, A. M., Bondy, B., Baghai, T. C., Eser, D., Nothdurfter, C., Schüle, C., ... Schwarz, M. J. (2013). Tryptophan metabolism and immunogenetics in major depression: A role for interferon- $\gamma$  gene. *Brain, Behavior, and Immunity*, 31, 128-133.
- Myint, A. M., Schwarz, M. J., & Müller, N. (2012). The role of the kynurenine metabolism in major depression. *Journal of Neural Transmission*, 119(2), 245-251.
- Nanni, M. G., Caruso, R., Mitchell, A. J., Meggiolaro, E., & Grassi, L. (2015). Depression in HIV infected patients: A review. *Current Psychiatry Reports*, 17(1), 1-11.
- Nascimbeni M, Mizukoshi E, Bosmann M, et al. (2003). Kinetics of CD4+ and CD8+ memory T-cell responses during hepatitis C virus rechallenge of previously recovered chimpanzees. *Journal of Virology*; 77, 4781-4793.
- Nathan, C. (2002). Points of control in inflammation. *Nature*, 420(6917), 846-852.
- Nemeroff, C. B., & Owens, M. J. (2009). The role of serotonin in the pathophysiology of depression: as important as ever. *Clinical Chemistry*, 55(8), 1578-1579.
- Neurauter, G., Grahmann, A. V., Klieber, M., Zeimet, A., Ledochowski, M., Sperner-Unterweger, B., & Fuchs, D. (2008a). Serum phenylalanine concentrations in patients with ovarian carcinoma correlate with concentrations of immune activation markers and of isoprostane-8. *Cancer Letters*, 272(1), 141-147.
- Nunes, D., Saitz, R., Libman, H., Cheng, D. M., Vidaver, J., & Samet, J. H. (2006). Barriers to Treatment of Hepatitis C in HIV/HCV-Coinfected Adults with

- Alcohol Problems. *Alcoholism: Clinical and Experimental Research*, 30(9), 1520-1526.
- Okanoue, T., Sakamoto, S., Itoh, Y., Minami, M., Yasui, K., Sakamoto, M., ... Kashima, K., (1996). Side effects of high-dose interferon therapy for chronic hepatitis C. *Journal of Hepatology*, 25, 283–291.
- Operskalski, E. A., & Kovacs, A. (2011). HIV/HCV co-infection: pathogenesis, clinical complications, treatment, and new therapeutic technologies. *Current HIV/AIDS Reports*, 8(1), 12-22.
- Osburn, W. O., Fisher, B. E., Dowd, K. A., Urban, G., Liu, L., Ray, S. C., ... Cox, A. L. (2010). Spontaneous control of primary hepatitis C virus infection and immunity against persistent reinfection. *Gastroenterology*, 138(1), 315-324.
- Oxenkrug, G. F., Reuintina, P. J., Mikolich, D. L., Ruthazer, R., Viveiros, K., Lee, H., & Summergrad, P. (2012). Neopterin as a marker of response to antiviral therapy in hepatitis C virus patients. *Hepatitis Research and Treatment*, vol 2012, Article ID 619609, 4 pages, 2012 doi: 10.1155/2012/619609..
- Oxenkrug, G. F., Turski, W. A., Zgrajka, W., Weinstock, J. V., Ruthazer, R., & Summergrad, P. (2014). Disturbances of tryptophan metabolism and risk of depression in HCV patients treated with IFN-alpha. *Journal of infectious disease and therapy*, 2(2), 131. <http://doi.org/10.4172/2332-0877.1000131>
- Page, K., Hahn, J. A., Evans, J., Shiboski, S., Lum, P., Delwart, E., ... Busch, M. P. (2009). Acute hepatitis C virus infection in young adult injection drug users: a prospective study of incident infection, resolution, and reinfection. *Journal of Infectious Diseases*, 200(8), 1216-1226.
- Pantalone, D. W., Hessler, D. M., Barkoff, S. M., & Shah, B. J. (2012). Psychosocial correlates of HIV-monoinfection and HIV/HCV-coinfection among men who have sex with men. *Journal of Behavioral Medicine*, 35, 520-528.
- Paolucci, S., Fiorina, L., Mariani, B., Landini, V., Gulminetti, R., Novati, S., ... Baldanti, F. (2015). Development and persistence of DAA resistance associated mutations in patients failing HCV treatment. *Journal of Clinical Virology*, 72, 114-118.
- Pariante, C. M., & Miller, A. H. (2001). Glucocorticoid receptors in major depression: relevance to pathophysiology and treatment. *Biological Psychiatry*, 49(5), 391-404.

- Pawelczyk, R. J., Bieliauskas, L. A., Back-Madruga, C., Lindsay, K. L., Kronfol, Z., Lok, A. S., ... HALT-C Trial Group. (2005). Cognitive function in hepatitis C patients with advanced fibrosis enrolled in the HALT-C trial. *Journal of Hepatology*, 43, 614-622.
- Pawelczyk, T., Pawelczyk, A., Strzelecki, D., & Rabe-Jablonska, J. (2008). Pegylated interferon  $\alpha$  and ribavirin therapy may induce working memory disturbances in chronic hepatitis C patients. *General Hospital Psychiatry*, 30(6), 501-508.
- Platt, L., Easterbrook, P., Gower, E., McDonald, B., Sabin, K., McGowan, C., ... Vickerman, P. (2016). Prevalence and burden of HCV co-infection in people living with HIV: A global systematic review and meta-analysis. *The Lancet Infectious Diseases*, 16(7), 797-808.
- Poordad, F., McCone Jr, J., Bacon, B. R., Bruno, S., Manns, M. P., Sulkowski, M. S., ... DiNubile, M. J. (2011). Boceprevir for untreated chronic HCV genotype 1 infection. *New England Journal of Medicine*, 364(13), 1195-1206.
- Public Health England (2015). Hepatitis C in the UK 2015 report. London: Author. Retrieved from <https://www.gov.uk/government/publications/hepatitis-c-in-the-uk>
- Puoti, M., Bonacini, M., Spinetti, A., Putzolu, V., Govindarajan, S., Zaltron, S., ... Carosi, G. (2001). Liver fibrosis progression is related to CD4 cell depletion in patients coinfecting with hepatitis C virus and human immunodeficiency virus. *Journal of Infectious Diseases*, 183(1), 134-137.
- Raison CL, Dantzer R, Kelley KW, Lawson MA, Woolwine BJ, Vogt G et al. (2010b). CSF concentrations of brain tryptophan and kynurenines during immune stimulation with IFN- $\alpha$ : relationship to CNS immune responses and depression. *Molecular Psychiatry*, 15, 393-403.
- Raison, C. L., & Miller, A. H. (2013). The evolutionary significance of depression in Pathogen Host Defense (PATHOS-D). *Molecular Psychiatry*, 18(1), 15-37.
- Raison, C. L., Borisov, A. S., Majer, M., Drake, D. F., Pagnoni, G., Woolwine, B. J., ... Miller, A. H. (2009). Activation of central nervous system inflammatory pathways by interferon- $\alpha$ : relationship to monoamines and depression. *Biological Psychiatry*, 65(4), 296-303.
- Reyes-Vázquez, C., Prieto-Gómez, B., & Dafny, N. (2012). Interferon modulates central nervous system function. *Brain Research*, 1442, 76-89.

- Rho, M. B., Wesselingh, S., Glass, J. D., McArthur, J. C., Choi, S., Griffin, J., & Tyor, W. R. (1995). A potential role for interferon- $\alpha$  in the pathogenesis of HIV-associated dementia. *Brain, Behavior, and Immunity*, 9(4), 366-377
- Richardson, J. L., Nowicki, M., Danley, K., Martin, E. M., Cohen, M. H., Gonzalez, R., ... Levine, A. M. (2005). Neuropsychological functioning in a cohort of HIV- and hepatitis C virus-infected women. *AIDS*, 19, 1659-1667.
- Rockstroh, J. K., Bhagani, S., Benhamou, Y., Bruno, R., Mauss, S., Peters, L., ... Tural, C. (2008). European AIDS Clinical Society (EACS) guidelines for the clinical management and treatment of chronic hepatitis B and C coinfection in HIV-infected adults. *HIV Medicine*, 9(2), 82-88.
- Rockstroh, J. K., Mudar, M., Lichterfeld, M., Nischalke, H. D., Klausen, G., Göltz, J., et al. (2002). Pilot study of interferon alpha high-dose induction therapy in combination with ribavirin for chronic hepatitis C in HIV coinfecting patients. *AIDS*, 16, 2083-2085.
- Royall D. R., Lauterbach, E. C., Cummings, J. L., Reeve, A., Rummans, T. A., Kaufer, D. I., et al. (2002). Executive control function: A review of its promise and challenges for clinical research. *Journal of Neuropsychiatry and Clinical Neurosciences*, 14(4), 377-405.
- Ryder, S. D. (2015). Chronic hepatitis C—what do the new drugs offer and who should get them first?. *Clinical Medicine*, 15(2), 197-200.
- Schaefer, M., Capuron, L., Friebe, A., Diez-Quevedo, C., Robaeys, G., Neri, S., ... Pariante, C. M. (2012). Hepatitis C infection, antiviral treatment and mental health: a European expert consensus statement. *Journal of Hepatology*, 57(6), 1379-1390.
- Schwartz, M. (2001). Protective autoimmunity as a T-cell response to central nervous system trauma: prospects for therapeutic vaccines. *Progress in neurobiology*, 65(5), 489-496.
- Senzolo, M., Schiff, S., D'Aloiso, C. M., Crivellin, C., Cholongitas, E., Burra, P., & Montagnese, S. (2011). Neuropsychological alterations in hepatitis C infection: the role of inflammation. *World J Gastroenterol*, 17(29), 3369-3374
- Sherman K, Roustrer S, Chung R, & Rajicic N. (2000). Hepatitis C: Prevalence in HIV-infected patients across sectional analysis of the US ACTG. *Antiviral Ther*, 5(Suppl. 1), 64-65.

- Shoukry, N. H., Grakoui, A., Houghton, M., Chien, D. Y., Ghrayeb, J., Reimann, K. A., & Walker, C. M. (2003). Memory CD8+ T cells are required for protection from persistent hepatitis C virus infection. *Journal of Experimental Medicine*, 197(12), 1645-1655
- Sitole, M., Silva, M., Spooner, L., Comee, M. K., & Malloy, M. (2013). Telaprevir versus boceprevir in chronic hepatitis C: A meta-analysis of data from phase II and III trials. *Clinical Therapeutics*, 35(2), 190-197.
- Slot, M., Sodemann, M., Gabel, C., Holmskov, J., Laursen, T., & Rodkjaer, L. (2015). Factors associated with risk of depression and relevant predictors of screening for depression in clinical practice: A cross-sectional study among HIV-infected individuals in Denmark. *HIV Medicine*, 16(7), 393-402.
- Soriano, V., Puoti, M., Sulkowski, M., Cargnel, A., Benhamou, Y., Peters, M., ... Rockstroh, J. (2007). Care of patients coinfectd with HIV and hepatitis C virus: 2007 updated recommendations from the HCV–HIV International Panel. *AIDS*, 21(9), 1073-1089.
- Soriano, V., Sulkowski, M., Bergin, C., Hatzakis, A., Cacoub, P., Katlama, C., ... Rockstroh, J. (2002). Care of patients with chronic hepatitis C and HIV co-infection: Recommendations from the HIV–HCV International Panel. *AIDS*, 16(6), 813-828.
- Sperner-Unterweger, B., Kohl, C., & Fuchs, D. (2014). Immune changes and neurotransmitters: possible interactions in depression?. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 48, 268-276.
- Stellbrink, H. J., Schewe, C. K., Vogel, M., & Noah, C. (2010). Increasing numbers of acute hepatitis C infections in HIV-infected MSM and high reinfection rates following SVR. *Journal of the International AIDS Society*, 13(S4), P200..
- Steptoe, A., Hamer, M., & Chida, Y. (2007). The effects of acute psychological stress on circulating inflammatory factors in humans: A review and meta-analysis. *Brain, Behavior, and Immunity*, 21(7), 901-912.
- Stommel, M., Given, B. A., & Given, C. W. (2002). Depression and functional status as predictors of death among cancer patients. *Cancer*, 94(10), 2719-2727.
- Strawbridge, R., Arnone, D., Danese, A., Papadopoulos, A., Vives, A. H., & Cleare, A. J. (2015). Inflammation and clinical response to treatment in depression: A meta-analysis. *European Neuropsychopharmacology*, 25(10), 1532-1543.

- Sun, B., Abadjian, L., Rempel, H., Monto, A., & Pulliam, L. (2013). Differential cognitive impairment in HCV coinfectd men with controlled HIV compared to HCV monoinfection. *Journal of Acquired Immune Deficiency Syndromes*, 62(2), 190-196.
- Szuster-Ciesielska, A., Słotwińska, M., Stachura, A., Marmurowska-Michałowska, H., Dubas-Ślomp, H., Bojarska-Junak, A., & Kandefer-Szerszeń, M. (2008). Accelerated apoptosis of blood leukocytes and oxidative stress in blood of patients with major depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 32(3), 686-694.
- Tavakkoli, M., Ferrando, S. J., Rabkin, J., Marks, K., & Talal, A. H. (2013). Depression and fatigue in chronic hepatitis C patients with and without HIV co-infection. *Psychosomatics*, 54(5), 466-471.
- Taylor, M. J., Godlewska, B., Near, J., Christmas, D., Potokar, J., Collier, J., ... Cowen, P. J. (2014). Effect of interferon- $\alpha$  on cortical glutamate in patients with hepatitis C: A proton magnetic resonance spectroscopy study. *Psychological Medicine*, 44(04), 789-795
- Thiyagarajan, A., Garvey, L. J., Pflugrad, H., Maruffc, P., Scullard, G., Main, J., ... Winston, A. (2010). Cerebral function tests reveal differences in HIV-infected subjects with and without chronic HCV co-infection. *Clinical Microbiology and Infection*, 16, 1579-1584.
- Udina, M., Castellví, P., Moreno-España, J., Navinés, R., Valdés, M., Forns, X., ... Martín-Santos, R. (2012). Interferon-induced depression in chronic hepatitis C: A systematic review and meta-analysis. *Journal of Clinical Psychiatry*, 73(8), 1-478.
- Valcour, V. G., Shiramizu, B. T., & Shikuma, C. M. (2010). HIV DNA in circulating monocytes as a mechanism to dementia and other HIV complications. *Journal of Leukocyte Biology*, 87(4), 621-626.
- van de Laar, T. J., Molenkamp, R., van den Berg, C., Schinkel, J., Beld, M. G., Prins, M., ... Bruisten, S. M. (2009). Frequent HCV reinfection and superinfection in a cohort of injecting drug users in Amsterdam. *Journal of Hepatology*, 51(4), 667-674
- Verma, S., Nakaoke, R., Dohgu, S., & Banks, W. A. (2006). Release of cytokines by brain endothelial cells: A polarized response to lipopolysaccharide. *Brain, Behavior, and Immunity*, 20(5), 449-455.

- Vogel, M., & Rockstroh, J. K. (2009). Treatment of acute hepatitis C in HIV infection. *Journal of Antimicrobial Chemotherapy*, 65(1), 4-9.
- Vogelzangs, N., Duivis, H. E., Beekman, A. T., Kluft, C., Neuteboom, J., Hoogendijk, W., ... Penninx, B.W. (2012). Association of depressive disorders, depression characteristics and antidepressant medication with inflammation. *Translational Psychiatry* 2, e79.
- Walker, J. R., Graff, L. A., Dutz, J. P., & Bernstein, C. N. (2011). Psychiatric disorders in patients with immune-mediated inflammatory diseases: Prevalence, association with disease activity, and overall patient well-being. *The Journal of Rheumatology*, 88, 31-35.
- Westbrook, R. H., & Dusheiko, G. (2014). Natural history of hepatitis C. *Journal of Hepatology*, 61(1), S58-S68.
- Wetzel, M.A., Steele, A.D., Eisenstein, T.K., Adler, M.W., Henderson, E.E., Rogers, T.J. (2000). Mu-opioid induction of monocyte chemoattractant protein-1, RANTES, and IFN-gamma-inducible protein-10 expression in human peripheral blood mononuclear cells. *Journal of Immunology*, 165, 6519–6524.
- Whale, R., Fialho, R., Rolt, M., Eccles, J., Pereira, M., Keller, M., ... Tibble, J. (2015). Psychomotor retardation and vulnerability to interferon alpha induced major depressive disorder: Prospective study of a chronic hepatitis C cohort. *Journal of Psychosomatic Research*, 79(6), 640-645
- Wichers, M. C., & Maes, M. (2004). The role of indoleamine 2, 3-dioxygenase (IDO) in the pathophysiology of interferon-[alpha]-induced depression. *Journal of psychiatry & neuroscience*, 29(1), 11-17.
- Wichers, M. C., Koek, G. H., Robaey, G., Verkerk, R., Scharpe, S., & Maes, M. (2005). IDO and interferon- $\alpha$ -induced depressive symptoms: a shift in hypothesis from tryptophan depletion to neurotoxicity. *Molecular Psychiatry*, 10(6), 538-544
- Wichers, M., Myin-Germeys, I., Jacobs, N., Peeters, F., Kenis, G., Derom, C., ... Van Os, J. (2007). Genetic risk of depression and stress-induced negative affect in daily life. *The British Journal of Psychiatry*, 191(3), 218-223.
- Winston, A., Arenas-Pinto, A., Stöhr, W., Fisher, M., Orkin, C. M., Aderogba, K., ... Dunn, D. (2013). Neurocognitive function in HIV infected patients on antiretroviral therapy. *PloS One*, 8(4), e61949.



- Wirleitner, B., Neurauter, G., Schrocksnadel, K., Frick, B., & Fuchs, D. (2003). Interferon- $\gamma$ -induced conversion of tryptophan: immunologic and neuropsychiatric aspects. *Current Medicinal Chemistry*, 10(16), 1581-1591
- Yoon, J. C., Crane, P. K., Ciechanowski, P. S., Harrington, R. D., Kitahata, M. M., & Crane, H. M. (2011). Somatic symptoms and the association between hepatitis C infection and depression in HIV-infected patients. *AIDS Care*, 23(10), 1208-1218.
- Zeuzem, S., Andreone, P., Pol, S., Lawitz, E., Diago, M., Roberts, S., ... Ferenci, P. (2011). Telaprevir for retreatment of HCV infection. *New England Journal of Medicine*, 364(25), 2417-2428.
- Zheng, L. S., Kaneko, N., & Sawamoto, K. (2015). Minocycline treatment ameliorates interferon-alpha-induced neurogenic defects and depression-like behaviors in mice. *Frontiers in cellular neuroscience*, 9, 5.
- Zhu, C. B., Blakely, R. D., & Hewlett, W. A. (2006). The proinflammatory cytokines interleukin-1beta and tumor necrosis factor-alpha activate serotonin transporters. *Neuropsychopharmacology*, 31(10), 2121-2131.
- Zorrilla, E. P., Luborsky, L., McKay, J. R., Rosenthal, R., Houldin, A., Tax, A., ... Schmidt, K. (2001). The relationship of depression and stressors to immunological assays: A meta-analytic review. *Brain, Behavior, and Immunity*, 15(3), 199-226.
- Zopf, S., Kremer, A. E., Neurath, M. F., & Siebler, J. (2016). Advances in hepatitis C therapy: What is the current state - what come's next? *World Journal of Hepatology*, 8(3), 139-147. <http://doi.org/10.4254/wjh.v8.i3.139>

## **2. OUTCOMES OF META-ANALYSIS ON BEHAVIORAL CHANGES IN HIV/HCV CO-INFECTION**

## **2.1. Cognitive impairment in HIV and HCV co-infected patients: A systematic review and meta-analysis**

### **Abstract**

Cognitive impairment has been well documented in HIV and hepatitis C virus (HCV) mono-infections. However, in the context of HIV/HCV co-infection the research is more limited. The aim of this systematic review was to describe the characteristics of cognitive impairment in HIV/HCV co-infection and to examine the differences in cognitive performance between HIV/HCV and HIV and HCV mono-infected patients. Of the 437 records initially screened, 24 papers met the inclusion criteria and were included in the systematic review. Four studies were included in the meta-analysis. Most studies indicated that HIV/HCV co-infected patients had a higher level of cognitive impairment than HIV mono-infected patients. Meta-analysis also indicated that HIV mono-infected patients had a significantly lower global deficit score than co-infected patients. The results also indicated that co-infected patients were more likely to be impaired in information processing speed than HIV mono-infected patients. These findings can be challenged by biasing factors such as the small number of included studies, heterogeneity of the samples, and a large diversity of methodological procedures. Future research with consistent and comprehensive neuropsychological batteries and covering a greater diversity of risk factors is needed, in order to clarify the effects of both viruses on cognitive function and the mechanisms that underlie these effects. Because cognitive impairments may pose significant challenges to medication adherence, quality of life and overall functioning, such knowledge may have important implications to the planning and implementation of effective interventions aimed at optimising the clinical management of these infections.

## **Introduction**

Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) have been individually associated with cognitive impairment. Despite the era of combination antiretroviral therapy, the incidence of HIV-associated neurocognitive disorders (HAND) in milder and mild forms, defined respectively as asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disorder (MND), has remained stable but still prevalent (Letendre, 2011; Simioni et al., 2010). There is evidence indicating that cognitive impairment occurs in a substantial proportion (15-50%) of HIV-infected patients (Schouten, Cinque, Gisslen, Reiss, & Portegies, 2011). Cognitive impairment has been associated with disease stage (Woods, Moore, Weber, & Grant, 2009), poor adherence to treatment, HCV infection and other comorbid conditions such as substance use and mental illness (Anand, Springer, Copenhaver, & Altice, 2010; Cysique et al., 2009; Martin-Thormeyer & Paul, 2009). Abnormalities in the neurocognitive profile of HAND have been shown in executive function, memory, information processing speed, attention/working memory, motor skills, language/verbal fluency and sensoriperception (Grant, 2008; Woods et al., 2009). The prevalence of HIV-associated cognitive impairment is high even in patients with undetectable HIV RNA. The cause of this remains unclear, although there is evidence that immune activation, neuroinflammation, genetic and behavioural factors may have an important role (Hong & Banks, 2015; Simioni et al., 2010).

In hepatitis C, the rates of cognitive impairment described range from 0% to 82% (Hilsabeck, Perry, & Hassanein, 2002), and several studies demonstrated evidence of cognitive impairment across a variety of domains. Particularly, attention, concentration, working memory, executive function and psychomotor speed have been shown to be the cognitive domains most likely to be impaired (Perry, Hilsabeck, & Hassanein, 2008; Posada et al., 2009). Several risk factors for cognitive impairment in HCV have been identified. Among these, history of alcohol and drug misuse (Foster, Goldin, & Thomas, 1998), depression (Fontana et al., 2005), severity of liver disease (Hilsabeck et al., 2002; Letendre et al., 2005) and high levels of pro-inflammatory cytokines (Gershon, Margulies Gorczynski, & Heathcote, 2000) were the most consistent. Despite the complexity of mechanisms and associated risk factors, investigations of cognition in viral hepatitis have one common finding of greater disease

severity being associated with more significant cognitive impairment (Córdoba et al., 2003).

Among HIV/HCV co-infected patients, the rates of cognitive impairment are less well-defined, although it appears prevalent (Hilsabeck, Castellon, & Hinkin, 2005; Hinkin, Castellon, Levine, Barclay, & Singer, 2008; Martin-Thormeyer & Paul, 2009). Existing literature suggests that the presence of co-infection with both viruses leads to greater cognitive deficit than in mono-infection, though with a different pattern of cognitive impairment (Letendre et al., 2005; Martin et al., 2004). The aim of this systematic review and meta-analysis was to bring more clarity to this area by analysing the differences on cognitive domains between HIV/HCV co-infection and HIV and HCV mono-infections, as well as to describe the characteristics of cognitive impairment in HIV/HCV co-infected patients.

## **Methods**

### **Information sources and search strategy**

The Cochrane Central Registered of Control Trials Library, SCOPUS, Medline, PsycINFO and ScienceDirect were systematically searched for records from the earliest data available online to April 2014. Each database was searched separately using the following key terms “*cognitive impairment*” AND “*HIV HCV co-infection*”, where AND was the Boolean operator. The search was supplemented with information from references lists of the eligible articles, conferences abstracts, and contact with the key academics in the field of cognitive impairment and HIV/HCV. The selection was limited to publications written in English. The study was designed according to the PRISMA statement (Moher, Liberati, Tetzlaff, & Altman, 2009).

### **Eligibility criteria**

Study inclusion criteria were: (1) type of studies: prospective experimental studies concerning cognitive aspects in co-infection with HIV and HCV; retrospective cohort studies with data collected from previous medical records on cognitive domains; (2) Participants: individuals diagnosed with HIV/HCV co-infection and individuals with HIV and HCV mono-infection; (3) interventions: no intervention and all interventions, including HCV treatment. No description of intervention was necessary, as this review did not aim to compare intervention between groups; (4) primary outcome measures:

any cognitive outcome measure described in the HIV/HCV co-infected group.

### **Data extraction**

Two authors (RF and MB) independently reviewed references from electronic and non-electronic sources and selected the relevant studies. Data extraction was conducted independently (by RF and MB) and reviewed by the lead author. Disagreements were resolved by consensus. Information on the following items was extracted from each study: year of publication, design, sample size, and population characteristics (e.g., gender, age, clinic stage of HIV and HCV, past and/or current intravenous drug use (IDU), and domains and measures of cognitive impairment). If the full-text article did not provide sufficient data, the authors of the studies were contacted for clarification or additional data. Risk of bias assessment was undertaken on each selected study. A checklist was created based on a quality assessment instrument, and included the following items: aims explicitly stated, selection and representativeness of the sample, inclusion/exclusion criteria, measures clearly identified, data adequately reported, and discussion addressing cognitive outcomes (Higgins & Green, 2011).

### **Primary outcomes**

Data were extracted to address all cognitive domains available. For the meta-analysis, the global deficit score (GDS) was also extracted, which was defined as a unitary global score representing overall neuropsychological tests performances. Each individual cognitive test score was converted to T-scores demographically corrected (for education, age and gender) (Rempel et al., 2013; Letendre et al., 2005; Sun, Abadjian, Rempel, Monto, & Pulliam, 2013). The meta-analyses were performed for: (a) the studies that provided a GDS score; and (b) the studies that reported specific neurocognitive domains.

### **Data analysis**

Meta-analyses quantifying the differences in cognitive impairment between co-infected and mono-infected groups were performed using the Review Manager software (RevMan; version 5.2, The Cochrane Collaboration, 2012). The meta-analysis was carried out for continuous variables using inverse variance with standardised mean differences (SMD) and 95% confidence intervals (CI). Heterogeneity was assessed using  $\chi^2$  and  $I^2$  tests, with an  $I^2$  more than 50% being regarded as substantial

heterogeneity (Higgins & Thompson, 2002; Higgins, Thompson, Deeks, & Altman, 2003). If significant heterogeneity was identified, a random-effects model was adopted.

## Results

### Study selection

The study selection process is described in Figure 1. Briefly, the electronic search identified 434 records. Three additional records were identified by non-electronic methods of searching. After the removal of duplicates and of the initial screening (application of the pre-defined inclusion criteria and of PICO parameters), 40 full-text articles were assessed for eligibility. After full-text reading, 16 studies were further excluded, and 24 studies were included in the systematic review. Four studies (16.7%) were included in the meta-analysis process.

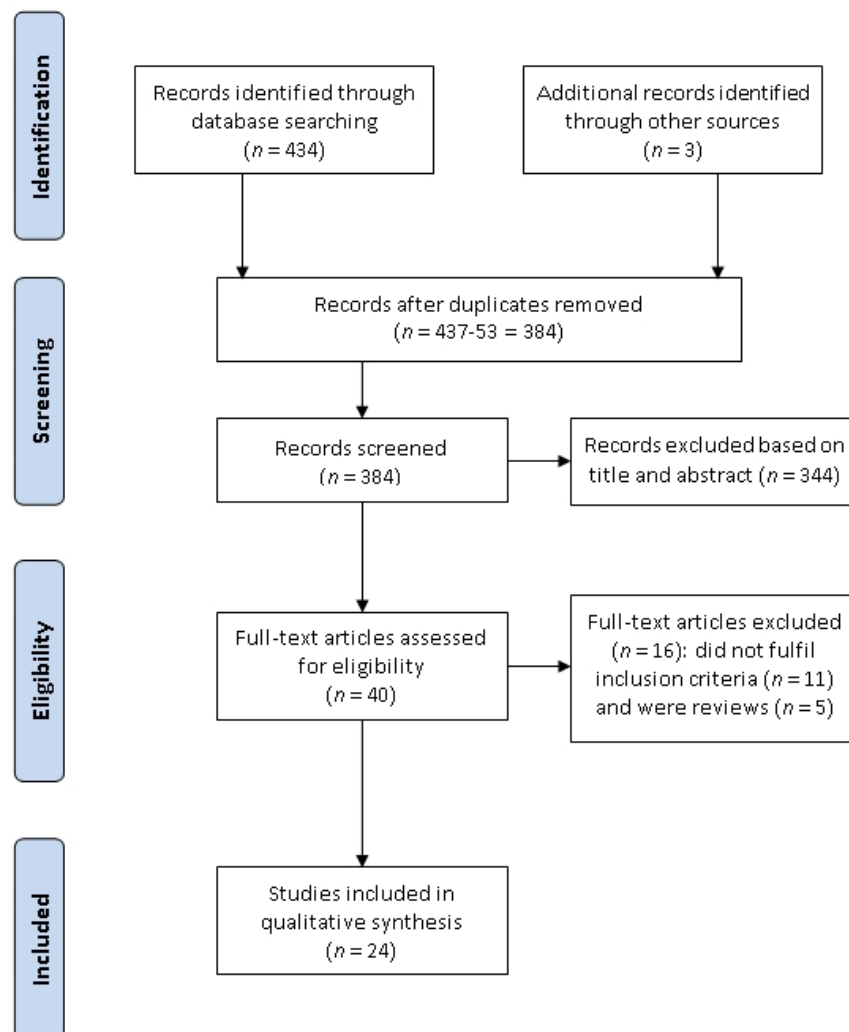


Figure 1. Flow diagram outlining the study selection process

A low risk of bias was observed when considering the identification of aims, inclusion and exclusion criteria, the procedures associated with how outcomes were determined, reporting of relevant results, and discussion addressing cognitive outcomes. However, bias was found, most notably in relation to the selection of participants (e.g., a systematic difference between the characteristics of groups that were compared was identified), which limited their representativeness.

### **Study characteristics**

The 24 studies of this systematic review included a total of 5,674 participants from 6 countries (one study from Australia, Canada, Italy and Germany, three studies from the UK; and 17 studies from the USA). Selected studies were published between 2004 and 2013. Study designs were largely cross-sectional ( $n = 14$ , 58.3%) and cohort ( $n = 8$ , 33.3%), and included a comparison between co-infected and HIV mono-infected groups ( $n = 14$ , 54.2%). The majority of studies included both male and female participants and two studies included only female participants (Crystal et al., 2012; Richardson et al., 2005). The proportion of male participants ranged from 56.2% (von Giesen et al., 2004) to 100% (Martin et al., 2004; Rempel et al., 2013; Sun et al., 2013; Winston et al., 2010). Regarding the clinical stage, 22 studies included participants in HCV chronic stage. In relation to HIV stage, the majority of studies included HIV-infected participants who were chronic and clinically stable ( $n = 16$ ). General characteristics of included studies are described in Table 1.



Table 1. Characteristics of the 24 studies included in the systematic review: study design, sample size, age of participants and clinical stage of HIV and HCV infections

Authors, Year	Study design	Sample size (N)		Sample characteristics (Age) <sup>a</sup>						Clinical stage	
		HIV/ HCV	HCV	HIV	Controls	HIV/HCV	HCV	HIV	Controls	HIV	HCV
Aronow et al., 2008	Cross sectional	31		128		NA		42.6 (7.8)		Late-stage HIV infection	Chronic
Cherner et al., 2005	Cross sectional	83		347		40.9 (7.3)		36.3 (9.3)		Chronic	Chronic
Ciccarelli et al., 2013	Cross sectional	50	50	50		48 (45-53) <sup>b</sup>	48 (42-52) <sup>b</sup>	48 (42-55) <sup>b</sup>		Clinically stable	Chronic
Clifford et al., 2005	Cross sectional	30		234		40.27 (7.75)		38.05 (8.63)		Clinically stable	Chronic
Clifford et al., 2009	Retrospective	249		310		NA		NA		Clinically stable	Chronic
Cohen et al., 2011	Cohort	9		21	34	NA		NA	46.0 (15.9)	Clinically stable	Chronic
Crystal et al., 2012	Cohort	184	42	721	392	47.8 (6.3)	45.9 (8.2)	38.3 (8.8)	36.1 (9.8)	All stages	Chronic
Devlin et al., 2012	Cross sectional	42	9	73	63	NA	NA	45.4 (9.48)	NA	Clinically stable	Chronic
Garvey et al., 2012	Case-control study	24		57		41 (36-44) <sup>b</sup>		47 (39-56) <sup>b</sup>		Clinically stable	Acute
Hinkin et al., 2008	Cohort	35		83		44.7 (8.4)		42.5 (8.3)		HIV in several HAND stages	Chronic
Letendre et al., 2005	Cross sectional	112		414		42		37		Chronic	Chronic
Martin et al., 2004	Cross sectional	28	20	39	69	45.2 (4.2)	44.9 (4.3)	41.6 (5.0)	40 (10.6)	Clinically stable	Chronic
Morgello et al., 2005	Cohort	67		116		NA		NA		Advanced stage	Chronic
Parsons et al., 2006	Cohort	20		45		42.8 (4.9)		40.0 (6.8)		All stages	Chronic
Perry et al., 2005	Cohort	29	47			43.90 (10.27)	47.28 (7.21)			Clinically stable	Chronic
Rempel et al., 2013	Cross sectional	17	19	36	28	54.5 (5.2)	56.6 (4.5)	NA	NA	Clinically stable	Chronic

Richardson et al., 2005	Cross sectional	70	27	75	48	39.6 (6.5)	37.3 (9.2)	33.8 (7.2)	33 (8.6)	Chronic	Chronic
Ryan et al., 2004	Cross sectional	67		49		45.1 (7.2)		41.9 (7.2)		Advanced stage	Chronic
Sun et al., 2013	Cross sectional	17	19	14	28	54.5 (5.2)	56.6 (4.5)	51.6 (7.2)	53.2 (6.0)	Clinically stable	Chronic
Thein et al., 2007	Cross sectional	15	19	30	30	35.5 (7.0)	42.2 (6.5)	34.7 (7.4)	34.8 (8.2)	Clinically stable	Chronic
Thiyagarajan et al., 2010	Cross sectional	27		45		46 (8.0)		48 (11.0)		Clinically stable	Chronic
Vivithanaporn et al., 2012	Cohort	91		365		NA		NA		HIV in several HAND stages	Chronic
von Giesen et al., 2004	Cross sectional	43	44	43		38 (8.1)	43.2 (13.7)	37.4 (7.8)		AIDS and non-AIDS stage	Chronic
Winston et al., 2010	Cohort	10		10	10	40 (9.2)		39 (5.9)	32 (8.9)	Chronic	Acute

*Note:* SD = Standard deviation; HAND: HIV-Associated Neurocognitive Disorder; NA: Not available

<sup>a</sup> Unless indicated, data are presented as mean (SD or range); <sup>b</sup> Data is presented as Median (Interquartile range)

## **Cognitive impairment**

### *Qualitative synthesis of findings*

Regarding cognitive impairment, the existing literature has produced inconsistent findings. Overall, most studies reported that the HIV/HCV co-infected patients were generally more impaired than HIV and HCV mono-infected patients and controls (Cherner et al., 2005; Ciccarelli et al., 2013; Clifford, Evans, Yang, & Gulick, 2005; Devlin et al. 2012; Hinkin et al., 2008; Letendre et al., 2005; Martin et al., 2004; Parsons et al., 2006; Rempel et al., 2013; Ryan et al., 2004; Sun et al., 2013; Vivinhatanaporn et al., 2012; von Giesen et al., 2004). Other studies found no differences on cognitive performance between HIV/HCV and HIV mono-infected groups (Aronow, Weston, Pezeshki, & Lazarus, 2008; Thiagarajan et al., 2010), between HIV/HCV and HCV mono-infected groups (Clifford et al., 2009; Perry et al., 2005), and between HIV/HCV and both HIV and HCV mono-infected groups (Thein et al., 2007). A qualitative synthesis of the relevant findings is presented in Table2.

Table 2. Synthesis of findings on cognitive impairment of the 24 studies included in the systematic review

Authors, Year	Cognitive domains	Cognitive measures	Main results	Group more cognitively impaired
Aronow et al., 2008	Verbal fluency, speed of information processing, learning, memory, executive functions, attention and working memory.	Controlled Oral Word Association Test, Wechsler Adult Intelligence Scale (WAIS) III digit symbol and symbol search, letter number sequencing sub tests, Trail Making Test A/B, Hopkins Verbal Learning Test Revised, Brief Visuospatial Memory Test Revised, Wisconsin Card Sorting Test, Grooved Pegboard Test	The co-infected group was more impaired than the HIV mono-infected group.	HIV/HCV > HIV
Cherner et al., 2005	Learning, recall, attention/working memory, speed information processing, verbal fluency, motor ability, abstraction/problem solving	Wide Range Achievement Test-3, Controlled Word Association Test Letters F, A, S; Category Fluency Animals, Paced Auditory Serial Addition Task (PASAT), WAIS III Letter Number Sequencing, Digit Symbol and Symbol Search sub tests, Trail Making Test A/B, Stroop task interference, Heaton Story Memory Test, Hopkins Verbal Learning Test rev, Heaton Figure Memory Test, Brief Visuospatial Memory Test rev, Wisconsin Card Sorting Test, Halsted Category Test, Grooved Pegboard Test	HCV infection has an independent adverse effect on cognitive impairment performance. HIV/HCV co-infection status was a predictor of global impairment.	NA
Ciccarelli et al., 2013	Memory, attention, executive functions, speed of psychomotor processing and language	Rey auditory verbal learning test, Stroop test, Trail Making Test A/B, WAIS R digit symbol, Grooved Pegboard Test and Letter Fluency	The HIV/HCV co-infected group showed lower neuropsychological performance (auditory verbal learning and letter fluency) than the mono-infected groups.	HIV/HCV > HIV HIV/HCV > HCV

			<p>The prevalence of minor cognitive impairment was significantly higher in HIV/HCV co-infected patients (54%) than in mono-infected groups.</p>	
Clifford et al., 2005	Motor persistence, attention, response speed, visuomotor coordination, conceptual shifting/tracking	Trail Making Test A/B, Digit Symbol sub test from WAIS III	<p>The HIV/HCV co-infected group performed worse on attention and psychomotor speed than HIV mono-infected group.</p> <p>There were no differences in the proportion of patients with neurological impairment (HIV/HCV: 33%; HIV: 25%).</p>	HIV/HCV > HIV
Clifford et al., 2009	Attention and motor persistence	Trail Making Test A/B, WAIS R digit symbol test	<p>There were no significant differences on cognitive performance between HIV mono-infected and HIV/HCV co-infected groups. The cognitive impairment was not exacerbated by HCV viral load.</p>	HIV/HCV $\cong$ HIV
Cohen et al., 2011	Attention, executive function and psychomotor processing speed	Trail Making Test A/B, Stroop Test, Grooved Pegboard Test, WAIS-III Digit Symbol Coding, Letter Number sequencing and Symbol Search sub tests	<p>The cognitive performance in HIV/HCV co-infection was associated with high levels of specific cytokines (IL-6, IL-16,</p>	NA

MIP-1β).

Crystal et al., 2012	Speed information processing, perceptual motor ability and cognitive flexibility	Symbol Digit Modalities Test, Trail Making Test A/B, Stroop Test	HCV infection was not associated with cognitive status.	NA
Devlin et al., 2012	Speed of information processing, attention/working memory, executive functioning, learning, memory, verbal fluency and psychomotor speed	Hopkins Verbal Learning Test – revised, Brief visuospatial memory test- revised, Controlled Oral Word Association Test, Stroop Color and Word Test, Trail Making Test A/B, Digit Symbol Coding, Symbol Search, Letter-number sequencing sub tests from WAIS III	No significant differences were found in cognitive performance between the study groups. HIV viral load and HIV/HCV co-infection were significant predictors of overall cognitive performance. HIV/HCV co-infection was associated with reduced processing speed, learning and memory.	HIV/HCV $\cong$ HIV HIV/HCV $\cong$ HCV HIV/HCV $\cong$ Controls
Garvey et al., 2012	Psychomotor function, identification, learning, working memory and executive function	CogState Battery	No significant differences were observed on overall cognitive tests between HIV mono-infected and HIV/HCV co-infected groups. The acute HIV/HCV co-infection was independently associated with poorer executive function scores. Disturbance of cerebral	HIV/HCV $\cong$ HIV

			metabolites were poorer in the acute HIV/HCV group.	
Hinkin et al., 2008	Attention/working memory, speed of information processing, learning, memory, verbal fluency, abstract executive functioning, motor/psychomotor speed	A comprehensive battery of neuropsychological tests	The HIV/HCV co-infected group was significantly more likely to be globally cognitively impaired than was the HIV mono-infected group (63% vs. 43%). Learning and memory domains were the most impaired cognitive domains.	HIV/HCV > HIV
Letendre et al., 2005	Verbal fluency, attention and working memory, speed of information processing, learning, delayed recall, abstraction, problem solving and motor ability	Letter fluency, Category fluency, Paced Auditory Serial Addition Task and WAIS-III Letter Number Sequencing, Digit Symbol, Symbol Search sub tests and Trail Making Test A/B, Stroop Test, Heaton Story Memory Test and Hopkins Verbal Learning Test, Heaton Figure Memory Test, Brief Visuospatial Memory Test, Wisconsin Card Sorting Test, Halstead Category Test and Grooved Pegboard Test	The HIV/HCV co-infected group had worse cognitive performance, as measured by the GDS, which was independent of methamphetamine dependence. Higher HCV viral load was associated with neurocognitive impairment.	HIV/HCV > HIV
Martin et al., 2004	Executive functions, attention	Stroop Test	The HIV mono-infected group was impaired on the executive component of the Stroop task while the HCV mono-infected group presented overall slowed information processing.	NR

Morgello et al., 2005	Psychomotor speed, attention, memory, verbal fluency, executive function and premorbid cognitive function	Grooved Pegboard Test, Trail Making Test A/B, Digit Symbol, Symbol Search, Letter Number Sequencing, Paced Auditory Serial Addition Task, Hopkins Verbal Learning Test, Brief Visual Memory Test, Wisconsin Card Sorting Test, Wide Range Achievement Test-3	HIV/HCV co-infected patients were more likely to have previous history of drug misuse, greater impairment in executive function and meet diagnostic criteria for AIDS dementia when compared with the HIV mono-infected group.	HIV/HCV > HIV
Parsons et al., 2006	Attention/concentration, psychomotor speed, executive functioning, verbal memory, visual memory, motor functioning	Paced Auditory Serial Addition Task (PASAT), Stroop Test, Digit Symbol, Trail Making Test A/B, Auditory Verbal Learning Test, Complex Figure Test, Finger Tapping, Timed Gait	The co-infected group showed poorer visual memory and motor functioning than the HIV mono-infected group prior to antiretroviral therapy. Before cART, a greater percentage of co-infected patients performed poorly on the neuropsychology summary score (HIV/HCV: 50%; HIV: 20%). After being exposed for six months to antiretroviral therapy, no differences were found between groups.	HIV/HCV > HIV before cART HIV/HCV $\cong$ HIV after cART
Perry et al., 2005	Attention, concentration, psychomotor speed and working memory	Trail Making Test A/B, Symbol Digit Modalities test, WAIS-III symbol search sub test	No significant differences were found in cognitive performance between HIV/HCV co-infected and HCV mono-infected	HIV/HCV $\cong$ HCV



			patients. Greater fibrosis was associated with poorer cognitive status.	
Rempel et al., 2013	Attention, working memory, information processing speed, executive functions, motor ability, verbal fluency, visual and verbal learning	A comprehensive battery of neuropsychological tests	The HIV/HCV group was significantly more cognitively impaired than the HIV and HCV mono-infected groups. HIV/HCV co-infection was associated with a type 1 interferon monocyte activation profile that was correlated with cognitive impairment.	HIV/HCV > HIV HIV/HCV > HCV HIV/HCV > Controls
Richardson et al., 2005	Learning, recall, attention, mental flexibility and psychomotor speed	Color trails, WHO/UCLA Auditory Verbal Learning Test, Grooved Pegboard, Symbol Digit Modalities Test, Visual Reproduction subtest of the WAIS, Mental Alternations Test	HIV/HCV co-infected women had increased odds of cognitive impairment.	NR
Ryan et al., 2004	Psychomotor speed, attention, memory, verbal fluency, executive function and premorbid cognitive functioning	Trail Making Test A/B, Grooved Pegboard Test, Hopkins Verbal Learning Test, Brief Visual Memory Test Revised, Digit Symbol, Symbol search, Letter Number Sequencing, Controlled Oral Word Association Test, Wisconsin Card Sorting Test, Reading sub test of the Wide Range Achievement Test-3	The prevalence of impaired neuropsychological performance was equivalent in HIV/HCV (55%) and HIV mono-infected patients (53%). There was a trend however for co-infected patients perform poorly on neurocognitive tests. HIV/HCV co-infected patients performed worse on executive	HIV/HCV $\cong$ HIV

			functioning and were more likely to present previous history of drug abuse than HIV and HCV mono-infected patients.	
Sun et al., 2013	General intellect, attention/working memory, information processing speed, executive function, fine motor skills, verbal fluency, visual learning memory, verbal learning memory	WAIS-III digit span, Brown Peterson 18,36, Symbol digit oral and written, Stroop word and color, Wisconsin Card Sorting Test, Grooved Pegboard Test, Finger Tapping, Controlled Oral Word Association Test, Brief Visuospatial Memory Test, California Verbal Learning Test	The rates of impairment based on GDS were higher in HIV/HCV co-infection (65%) than HCV mono-infection (42%), HIV mono-infection (29%) and controls (18%). HIV/HCV co-infection significantly increased the risk of cognitive impairment in patients with controlled HIV viral loads; HCV RNA in HCV mono-infection was correlated with worsening general cognitive scores but not in HIV/HCV co-infection.	HIV/HCV > HIV HIV/HCV > HCV HIV/HCV > Controls
Thein et al., 2007	Global cognitive function, psychomotor function, visual attention, executive function, learning and memory	National Adult Reading Test, Trail Making Test A/B, CogState battery	No significant difference in cognitive performance was found between study groups. The prevalence of impaired cognition was of 21% for HCV	HIV/HCV $\cong$ HIV HIV/HCV $\cong$ HCV HIV/HCV $\cong$ Controls

			mono-infected patients and 6.7% for HIV-HCV co-infected patients.	
Thiyagarajan et al., 2010	Psychomotor function, nonverbal learning, visual and divided attention, visual learning, memory, working memory and executive functions. Screening test for HIV dementia	CogState, Prospective and Retrospective Memory Questionnaire, International HIV Dementia Scale (IHDS)	No significant differences in cognitive performance were observed between the groups. However, the HIV/HCV co-infected group reported significantly poorer IHDS scores than the HIV mono-infected group. The prevalence of cognitive impairment was of 11% for co-infected patients and of 22% for HIV mono-infected patients.	HIV/HCV $\cong$ HIV
Vivithanaporn et al., 2012	Memory, executive functions, psychomotor function, attention, concentration	Memorial Sloan Kettering Scale (MSK), Symbol Digit Modalities Test, Grooved Pegboard Test, Trail Making Test A/B	The HIV/HCV co-infected group showed a higher prevalence of multiple neurologic disorders compared with the HIV mono-infected group (60.4% vs. 46.6%). Symptomatic HIV associated neurocognitive disorders were more severe in the co-infected group.	HIV/HCV > HIV

von Giesen et al., 2004	Premorbid verbal intelligence, attention, working memory and screening test for HIV dementia	MWT-b and HIV Dementia Scale	The HIV/HCV co-infected group performed slower in reaction time. No significant differences were found on cognitive status among the groups.	HIV/HCV $\cong$ HIV HIV/HCV $\cong$ HCV
Winston et al., 2010	Associated learning, detection identification, congruent reaction, monitoring and one card learning	CogState battery	Abnormalities in cognitive functions were observed with monitoring domain being impaired and significant reductions in RBG mI/ Cr ratio in acute HIV/HCV co-infected group	HIV/HCV $\cong$ HIV

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*Note:* cART; combination antiretroviral therapy; NA: Not applicable; NR: Not reported

## Meta-analyses

Among the studies that measured the GDS (Letendre et al., 2005; Rempel et al., 2013; Sun et al., 2013), the meta-analysis revealed statistically significant differences between groups (SMD = 0.56, 95% CI: 0.36, 0.75,  $p < .00001$ ). Specifically, the results indicated that HIV/HCV co-infected groups were more globally impaired than HIV mono-infected groups. No significant heterogeneity among studies was detected (Figure 2). Due to overlapping samples of the two studies that compared HIV/HCV co-infected and HCV mono-infected groups, the meta-analysis was not performed.

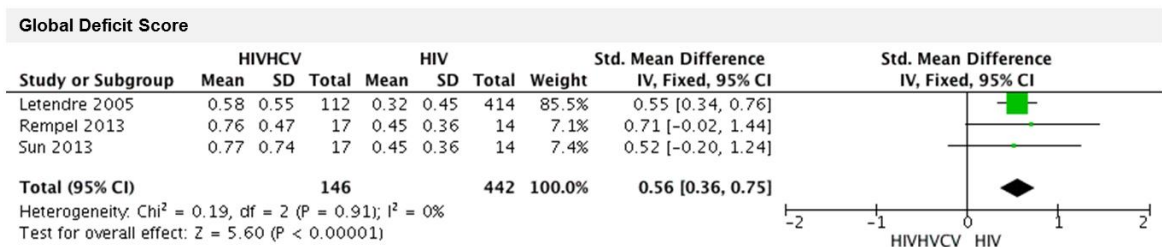


Figure 2. Forest plot of meta-analysis of differences between HIV/HCV co-infected and HIV mono-infected patients in GDS. Abbreviations: SD, standard deviation; CI, confidence interval

In order to explore the existence of differences between HIV/HCV co-infection and HIV and HCV mono-infections on specific cognitive domains, data from each specific domain were also combined and SMD differences with 95%CI were performed. In the meta-analysis, two studies were included (Devlin et al., 2012; Rempel et al., 2013). The forest plots of the assessed cognitive domains are presented in Figures 3 and 4.

Regarding verbal fluency, significant heterogeneity in the meta-analysis was detected ( $I^2 = 61\%$ ;  $p = .11$ ). Consequently, a random effects model meta-analysis was adopted. No significant difference between comparison groups was found (SMD = -0.08, 95%CI: -0.25, 0.42,  $p = .63$ ). The meta-analysis of the two studies assessing information processing speed indicated that the HIV/HCV group was more likely to report impairment in this domain than the HIV mono-infected group (SMD = -0.47, 95% CI: -0.81, -0.14,  $p = .006$ ). In relation to working memory and attention, the meta-analysis revealed no differences between HIV/HCV co-infected and HIV mono-infected

groups (SMD = - 0.00, 95% CI: -0.34, 0.33,  $p = .98$ ). No significant heterogeneity among studies was detected in these two domains.

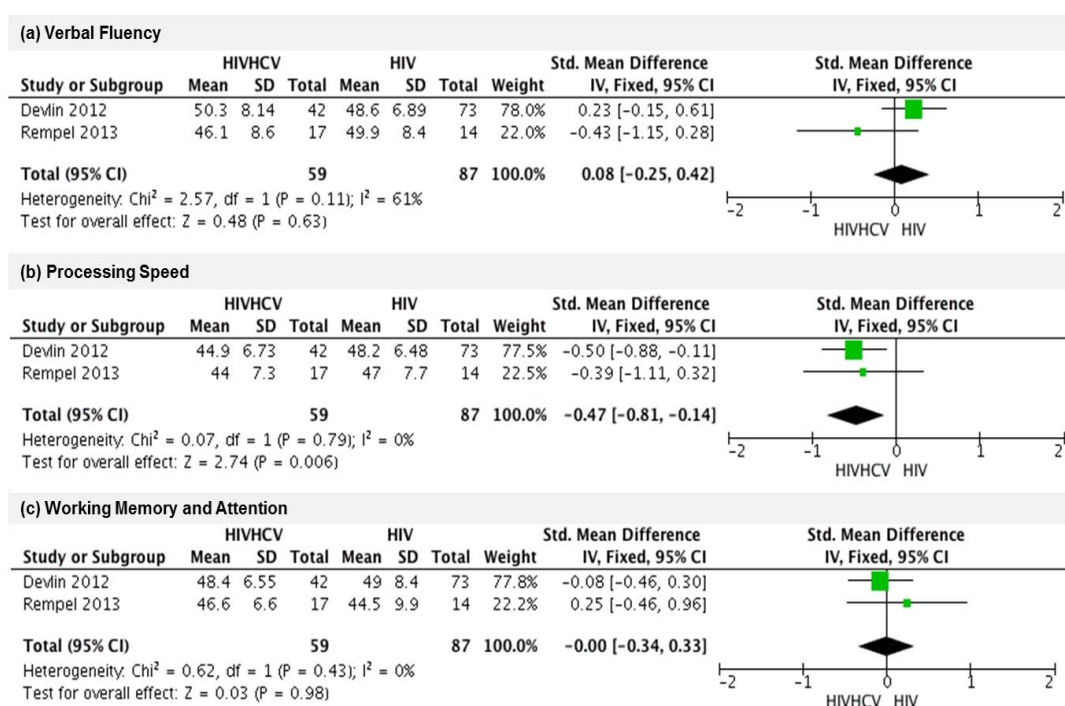


Figure 3. Forest plots of meta-analyses of differences in (a) verbal fluency, (b) processing speed; and (c) working memory and attention between HIV/HCV co-infected and HIV mono-infected patients. Abbreviations: SD, standard deviation; CI, confidence interval

Regarding the comparison between HIV/HCV co-infected and HCV mono-infected patients, no significant differences were found in relation to verbal fluency (SMD = - 0.15, 95% CI: -0.64, 0.33,  $p = .53$ ), information processing speed (SMD = - 0.09, 95% CI: -0.57, 0.40,  $p = .72$ ) and working memory and attention (SMD = 0.34, 95% CI: -0.15, 0.82,  $p = .17$ ). No significant heterogeneity among studies was detected in these three domains.

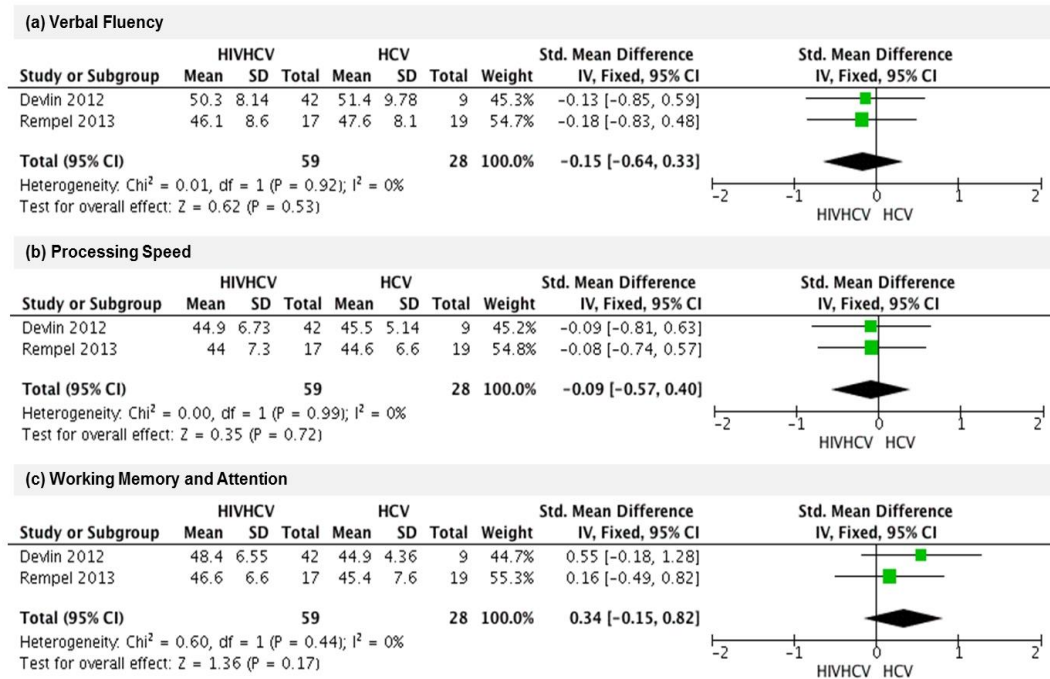


Figure 4. Forest plots of meta-analyses of differences in (a) verbal fluency, (b) processing speed; and (c) working memory and attention between HIV/HCV co-infected and HCV mono-infected patients. Abbreviations: SD, standard deviation; CI, confidence interval

## Discussion

The aim of this systematic review was to explore the differences in cognitive impairment in co-infection with HIV and HCV, being to our knowledge the first to do so. The main contribution of this meta-analytic review is the ascertainment of the magnitude of cognitive impairment among co-infected patients, in comparison with HIV and HCV mono-infected patients. This is particularly relevant for co-infected patients, as cognitive deficits can translate into significant functional consequences, such as patients' difficulties in carrying out a range of important daily routines, which may compromise the adherence to complex treatments for HIV and hepatitis C, difficulties in remembering important information regarding the management of their disease(s), as well as reduced quality of life.

The findings of this meta-analysis indicate that HIV/HCV co-infection is more reliably associated with GDS impairment than HIV mono-infection, reinforcing the conclusions of several individual studies (Ciccarelli et al., 2013; Hinkin et al., 2008; Letendre et al., 2005; Rempel et al., 2013). The meta-analysis also shows that the co-infected group has significantly poorer information processing speed than the HIV

mono-infected group. No differences were found between HIV/HCV co-infected and HCV mono-infected patients in the examined cognitive domains.

Our meta-analysis demonstrates that HIV/HCV patients were more impaired than HIV mono-infected patients on the GDS, which has been suggested to be a useful method to summarise results of neuropsychological assessment in HIV clinical practice (Carey et al., 2004). This finding may reflect differences in immune biomarkers in HIV or HCV mono-infected patients compared to HIV/HCV patients (Kushner et al., 2013; Rempel et al., 2013) and suggest that the presence of HCV may have a greater impact in cognitive impairment in individuals co-infected with HIV, particularly when compared with HIV mono-infected patients. Indeed, some studies reported that HIV/HCV co-infection was an important predictor of neurocognitive impairment, attributing the difference to the adverse effect of HCV on cognition mediated by HCV viral load (Letendre et al., 2005; Sun et al., 2013), monocyte activation (Rempel et al., 2013), plasma inflammatory cytokine levels (Cohen et al., 2011) or the additive effects of both virus on specific brain sites (Hilsabeck et al., 2005). In HIV-infected patients, HCV replication in the brain has been demonstrated in the frontal cortex, white matter and basal ganglia (Letendre et al., 2007). The acute HCV stage is characterized by an active HCV replication in the brain and has been associated with cognitive impairment in HIV/HCV (Winston et al., 2010). It has also been shown that HCV core protein activates human glia and potentiates HIV-associated neurotoxicity (Vivithanaporn et al., 2010). Among HIV/HCV patients, in a study examining the white matter integrity, Stebbins and colleagues (2007) found a trend toward lower fractional anisotropy (FA) and a significant increase in mean diffusivity (MD); lower FA and higher MD values typically refer to reduced neuronal integrity (Martin-Thormeyer & Paul, 2009), therefore suggesting brain compromise among co-infected patients. However, as noted by the authors, a positive history of substance abuse was also common in the sample, which may have influenced the results. This seems to be particularly relevant to justify the lack of differences between HIV/HCV and HCV mono-infected groups. Indeed, in the studies included in the meta-analysis, the participants of both groups had significant rates of drug abuse (> 63%) and lifetime substance dependence. Thus, we cannot exclude the fact that this higher proportion of participants with history of drug misuse, which has been consistently associated with cognitive impairment (Martin-Thormeyer & Paul, 2009) may also have influenced our findings.



In relation to cognitive impairment in HIV, potential influencing factors may be incomplete viral suppression in the central nervous system (CNS) of HIV-infected patients, increased age, poor CNS penetration of some antiretroviral drugs, time of antiretroviral exposure, presence of drug resistance and psychiatric comorbidities (Ciccarelli et al., 2013; Nightingale et al., 2014; Rosca, Rosca, Chirileanu, & Simu, 2011; Woods et al., 2009). It is also noteworthy that persistent cognitive impairment in HIV-infected stable patients is generally attributed to inflammatory influences. An association between inflammation, characterised by high levels of plasma cytokines, and cognitive impairment has been shown in HIV/HCV (Cohen et al., 2011). Moreover, cytokines are involved in neurodevelopmental processes (McAfoose & Baune, 2009). Another mechanism involved in cognitive impairment is immunosuppression; particularly, nadir CD4+ T-cells have been suggested to be an indicator of cognitive decline. For example, ANI has been associated with an increased risk for earlier development of symptomatic HAND (Grant et al., 2014). The authors of this study also noted that those patients with ANI had evidence of lower nadir CD4+ T-cells and were more likely to develop everyday life problems.

Overall, the diverse findings abovementioned are noteworthy and represent important advances in understanding the mechanisms underlying cognitive deficits in HIV and HCV mono-infections. However, as the CNS may be compromised by these comorbid medical conditions via additive or synergistic processes, the field of HIV/HCV co-infection and the study of joint mechanisms in cognitive impairment would still benefit from additional research.

This review also indicates that the HIV/HCV group reported more impairment in information processing speed than the HIV mono-infected group. Information processing speed describes the ability to rapidly process serial cognitive operations; when impaired, information processing speed interferes negatively with other cognitive processes due to the reduction of available information needed and the limited time for task execution (Salthouse, 1996). Earlier studies have reported impairment in this domain as a cognitive marker of HIV-associated dementia, reflecting its broad impact on cognitive flexibility (Becker & Salthouse, 1999). An association between HCV chronic infection and impairment in processing speed has been also reported (Cherner et al., 2005; Vigil et al., 2008). A possible explanation for greater impairment in the co-infected patients may be the higher risk of neurotoxicity due to CNS insults by both viruses in fronto-striatal areas. Particularly, high levels of HIV have been found in the

basal ganglia (notably the substantia nigra) and fronto-cortical areas (Kumar, Borodowsky, Fernandez, Gonzalez, & Kumar, 2007), and it has been shown that fronto-striatal neuronal circuitry mediates processing speed (e.g., Fellows, Byrd, & Morgello, 2014; Kumar, Ownby, Waldrop-Valverde, Fernandez, & Kumar, 2011; Salthouse, 1996). Additionally, there is evidence that fronto-striatal circuits are rich in dopaminergic activity and it is hypothesised that dopamine depletion exacerbates processing speed impairment in HIV (Kumar et al., 2011).

Some limitations in this review should be acknowledged. First, the literature search was restricted to articles written in English. Second, only few studies with consistent measurement methods were identified. The lack of the consistency in the cognitive domains and measures, as well as the inability to compile a GDS from the information supplied, resulted in a rather small number of studies included in the meta-analysis. Methodological differences between the studies should also be noted, including the great heterogeneity of the samples' characteristics, the relatively small sample sizes, the predominance of studies with cross-sectional design and the large variability of cognitive measures and domains. Although the inclusion of studies of varying quality is common in most meta-analyses, these biasing factors are noteworthy and require some caution in the interpretation of the cumulative results. Studies on neurocognitive complications of HIV/HCV (as in the general HIV context) are essentially based on studies involving men, and women are still under-represented in neuropsychological studies. Moreover, it is notable that most studies were conducted in the USA (17 out of 24), and very limited research has been conducted in other settings where these diseases are more widespread.

Illicit drug use causes deficits in cognition and in combination with mental health disorders and social/behavioural factors may exacerbate cognitive impairment (Gill & Kolson, 2014; Martin-Thormeyer & Paul, 2009). The variability of age across studies may also affect the classification and rate of patients classified as cognitively impaired. It is possible that HIV-related cognitive impairment reported in this study may be impacted by either advanced age (Rempel et al., 2013; Sun et al., 2013) or by the emergence of cognitive decline due to AIDS indicator conditions (Letendre et al., 2005). Another relevant factor relates to cognitive reserve (CR), which has been demonstrated to modulate cognitive impairment (Stern, 2003), and that has been shown to be protective factor of cognitive impairment, both in HIV (Foley et al., 2012; Morgan et al., 2012; Vázquez-Justo, Piñón, Vergara-Moragues, Guillén-Gestoso, & Pérez-

García, 2014) and HCV (Sakamoto et al., 2013). In future research, it will be important to include appropriate controls/comparison groups, longitudinal follow-up of cohorts with repeated measures, comprehensive neuropsychological batteries, as well as social and behavioural factors and levels of cognitive reserve that may increase the prevalence of cognitive impairment. This will be a significant opportunity to determine whether these effects are independent or additive, to identify similarities and differences in the neuropsychological patterns of HIV/HCV co-infected and HIV and HCV mono-infected patients, as well as to clarify the discrepancies of the prevalence rates of cognitive impairment reported in the literature.

In conclusion, HIV and HCV infections have detrimental effects on neurocognitive function, which in turn may have a significant impact on patients' quality of life and overall functioning, adherence to treatments, and management of risk behaviours. Patients with HIV and HCV usually present several cofactors, where interactions and cumulative effects may well increase their vulnerability to cognitive impairment. Therefore, biological, behavioural and social risk factors that could influence cognitive dysfunction need to be defined more accurately and will require special clinical attention. Moreover, with greater understanding of cognitive dysfunction, new avenues for treatment and prevention can be developed, as this knowledge may contribute to improve disease(s) management and optimise medication adherence, to facilitate treatment decision-making, to reduce risk behaviours and, ultimately, to maximise the patients' health outcomes.

## References

- Anand, P., Springer, S. A., Copenhaver, M. M., & Altice, F. L. (2010). Neurocognitive impairment and HIV risk factors: A reciprocal relationship. *AIDS and Behavior*, 14, 1213-1226. doi:10.1007/s10461-010-9684-1
- Aronow, H. A., Weston, A. J., Pezeshki, B. B., & Lazarus, T. S. (2008). Effects of coinfection with HIV and hepatitis C virus on the nervous system. *The AIDS Reader*, 18, 43-48.
- Becker, J. T., & Salhouse, T. A. (1999). Neuropsychological test performance in the acquired immunodeficiency syndrome: Independent effects of diagnostic group on functioning. *Journal of the International Neuropsychological Society*, 5, 41-47. doi:10.1017/S1355617799511065

- Carey, C. L., Woods, S. P., Gonzalez, R., Conover, E., Marcotte, T. D., Grant, I., ... HNRC Group. (2004). Predictive validity of global deficit scores in detecting neuropsychological impairment in HIV infection. *Journal of Clinical and Experimental Neuropsychology*, 26, 307-319. doi:10.1080/13803390490510031
- Cherner, M., Letendre, S., Heaton, R. K., Durelle, J., Marquie-Beck, J., Gragg, B., ... HIV Neurobehavioral Research Center Group. (2005). Hepatitis C augments cognitive deficits associated with HIV infection and methamphetamine. *Neurology*, 64, 1343-1347. doi:10.1212/01.WNL.0000158328.26897.0D
- Ciccarelli, N., Fabbiani, M., Grima, P., Falasca, K., Tana, M., Baldonero, E., ... Di Giambenedetto, S. (2013). Comparison of cognitive performance in HIV or HCV mono-infected and HIV-HCV co-infected patients. *Infection*, 41, 1103-1109. doi:10.1007/s15010-013-0503-2
- Clifford, D. B., Evans, S. R., Yang, Y., & Gulick, R. M. (2005). The neuropsychological and neurological impact of hepatitis C virus co-infection in HIV-infected subjects. *AIDS*, 19(Suppl. 3), S64-S71. doi:10.1097/01.aids.0000192072.80572.43
- Clifford, D. B., Smurzynski, M., Park, L. S., Yeh, T. M., Zhao, Y., Blair, L., ... Evans, S. R. (2009). Effects of active HCV replication on neurologic status in HIV RNA virally suppressed patients. *Neurology*, 73, 309-314. doi:10.1212/WNL.0b013e3181af7a10
- Cohen, R. A., de la Monte, S., Gongvatana, A., Ombao, H., Gonzalez, B., Devlin, K. N., ... Tashima, K. T. (2011). Plasma cytokine concentrations associated with HIV/hepatitis C coinfection are related to attention, executive and psychomotor functioning. *Journal of Neuroimmunology*, 233(1-2), 204-210. doi:10.1016/j.jneuroim.2010.11.006
- Córdoba, J., Flavià, M., Jacas, C., Sauleda, S., Esteban, J. I., Vargas, V., ... & Guardia, J. (2003). Quality of life and cognitive function in hepatitis C at different stages of liver disease. *Journal of Hepatology*, 39, 231-238. doi:10.1016/S0168-8278(03)00189-2
- Crystal, H., Kleyman, I., Anastos, K., Lazar, J., Cohen, M., Liu, C., ... Manly, J. (2012). Effects of hepatitis C and HIV on cognition in women: Data from the Womens Interagency HIV study. *Journal of Acquired Immune Deficiency Syndromes*, 59, 149-154. doi:10.1097/QAI.0b013e318240566b

- Cysique, L.A., Vaida, F., Letendre, S., Gibson, S., Cherner, M., Woods, S. P., ... Ellis, R. J. (2009). Dynamics of cognitive change in impaired HIV-positive patients initiating antiretroviral therapy. *Neurology*, 73, 342-348. doi:10.1212/WNL.0b013e3181ab2b3b
- Devlin, K. N., Gongvatana, A., Clark, U. S., Chasman, J. D., Westbrook, M. L., Tashima, K. T., ... Cohen, R. A. (2012). Neurocognitive effects of HIV, hepatitis C, and substance use history. *Journal of the International Neuropsychological Society*, 18, 68-78. doi:10.1017/S1355617711001408
- Fellows, R. P., Byrd, D. A., & Morgello, S. (2014). Effects of information processing speed on learning, memory, and executive functioning in people living with HIV/AIDS. *Journal of Clinical and Experimental Neuropsychology*, 36, 806-817. doi:10.1080/13803395.2014.943696
- Foley, J. M., Ettenhofer, M. L., Kim, M. S., Behdin, N., Castellon, S. A., & Hinkin, C. H. (2012). Cognitive reserve as a protective factor in older HIV-positive patients at risk for cognitive decline. *Applied Neuropsychology: Adult*, 19, 16-25. doi:10.1080/09084282.2011.595601
- Fontana, R. J., Bieliauskas, L. A., Back-Madruga, C., Lindsay, K. L., Kronfol, Z., Lok, A. S., ... HALT-C Trial Group. (2005). Cognitive function in hepatitis C patients with advanced fibrosis enrolled in the HALT-C trial. *Journal of Hepatology*, 43, 614-622. doi:10.1016/j.jhep.2005.04.006
- Foster, G. R., Goldin, R. D., & Thomas, H. C. (1998). Chronic hepatitis C virus infection causes a significant reduction in quality of life in the absence of cirrhosis. *Hepatology*, 27, 209-212. doi:10.1002/hep.510270132
- Garvey, L. J., Pavese, N., Ramlackhansingh, A., Thomson, E., Allsop, J. M., Politis, M., ... Winston, A. (2012). Acute HCV/HIV coinfection is associated with cognitive dysfunction and cerebral metabolite disturbance, but not increased microglial cell activation. *Plos ONE*, 7(7), e38980. doi:10.1371/journal.pone.0038980
- Gershon, A., Margulies, M., Gorczynski, R., & Heathcote, E. J. (2000). Serum cytokine values and fatigue in chronic hepatitis C infection. *Journal of Viral Hepatitis*, 7, 397-402. doi:10.1046/j.1365-2893.2000.00249.x
- Gill, A. J., & Kolson, D. L. (2014). Chronic inflammation and the role for cofactors (hepatitis C, drug abuse, antiretroviral drug toxicity, aging) in HAND persistence. *Current HIV/AIDS Reports*, 11, 325-335. doi:10.1007/s11904-014-0210-3

- Grant, I. (2008). Neurocognitive disturbances in HIV. *International Review of Psychiatry*, 20, 33-47. doi:10.1080/09540260701877894
- Grant, I., Franklin, D. R., Deutsch, R., Woods, S. P., Vaida, F., Ellis, R. J., ... Heaton, R. K. (2014). Asymptomatic HIV-associated neurocognitive impairment increases risk for symptomatic decline. *Neurology*, 82, 2055-2062. doi:10.1212/WNL.0000000000000492
- Higgins, J. P. T., & Green, S. (2011). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. The Cochrane Collaboration. Retrieved from [www.cochrane-handbook.org](http://www.cochrane-handbook.org)
- Higgins, J. P. T., & Thompson, S. G. (2002). Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* 21, 1539-1558. doi:10.1002/sim.1186
- Higgins, J. P. T., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *British Medical Journal* 327, 557-560. doi:10.1136/bmj.327.7414.557
- Hilsabeck, R. C., Castellon, S. A., & Hinkin, C. H. (2005). Neuropsychological aspects of coinfection with HIV and hepatitis C virus. *Clinical Infectious Diseases*, 41(Suppl. 1), S38-S44. doi:10.1086/429494
- Hilsabeck, R. C., Perry, W., & Hassanein, T. I. (2002). Neuropsychological impairment in patients with chronic hepatitis C. *Hepatology*, 35, 440-446. doi:10.1053/jhep.2002.31257
- Hinkin, C. H., Castellon, S. A., Levine, A. J., Barclay, T. R., & Singer, E. J. (2008). Neurocognition in individuals co-infected with HIV and hepatitis C. *Journal of Addictive Diseases*, 27, 11-17. doi:10.1300/J069v27n02\_02
- Hong, S., & Banks, W. A. (2015). Role of the immune system in HIV-associated neuroinflammation and neurocognitive implications. *Brain, Behavior, and Immunity*, 45, 1-12. doi:10.1016/j.bbi.2014.10.008
- Kushner, L. E., Wendelboe, A. M., Lazzeroni, L. C., Chary, A., Winters, M. A., Osinusi, A., ... Holodniy M. (2013). Immune biomarker differences and changes comparing HCV mono-infected, HIV/HCV co-infected, and HCV spontaneously cleared patients. *PLoS ONE*, 8(4), e60387. doi:10.1371/journal.pone.0060387
- Kumar, A. M., Borodowsky, I., Fernandez, B., Gonzalez, L., & Kumar, M. (2007). Human immunodeficiency virus type 1 RNA Levels in different regions of human brain: Quantification using real-time reverse transcriptase-polymerase chain reaction. *Journal of Neurovirology*, 13, 210-224. doi:10.1080/13550280701327038

- Kumar, A. M., Ownby, R. L., Waldrop-Valverde, D., Fernandez, B., & Kumar, M. (2011). Human immunodeficiency virus infection in the CNS and decreased dopamine availability: Relationship with neuropsychological performance. *Journal of Neurovirology*, *17*, 26-40. doi:10.1007/s13365-010-0003-4
- Letendre, S., Paulino, A. D., Rockenstein, E., Adame, A., Crews, L., Cherner, M., ... HIV Neurobehavioral Research Center Group. (2007). Pathogenesis of hepatitis C virus coinfection in the brains of patients infected with HIV. *Journal of Infectious Diseases*, *196*, 361-370. doi:10.1086/519285
- Letendre, S. (2011). Central nervous system complications in HIV disease: HIV-associated neurocognitive disorder. *Topics in Antiviral Medicine*, *19*, 137-142.
- Letendre, S. L., Cherner, M., Ellis, R. J., Marquie-Beck, J., Gragg, B., Marcotte, T., ... HNRC Group. (2005). The effects of hepatitis C, HIV, and methamphetamine dependence on neuropsychological performance: Biological correlates of disease. *AIDS*, *19*(Suppl. 3), S72-S78. doi:10.1097/01.aids.0000192073.18691.ff
- Martin, E. M., Novak, R. M., Fendrich, M., Vassileva, J., Gonzalez, R., Grbesic, S., ... Sworowski L. (2004). Stroop performance in drug users classified by HIV and hepatitis C virus serostatus. *Journal of the International Neuropsychological Society*, *10*, 298-300. doi:10.1017/S135561770410218X
- Martin-Thormeyer, E. M., & Paul, R. H. (2009). Drug abuse and hepatitis C infection as comorbid features of HIV associated neurocognitive disorder: Neurocognitive and neuroimaging features. *Neuropsychology Review*, *19*, 215-231. doi:10.1007/s11065-009-9101-6
- McAfoose, J., & Baune, B. T. (2009). Evidence for a cytokine model of cognitive function. *Neuroscience & Biobehavioral Reviews*, *33*, 355-366. doi:10.1016/j.neubiorev.2008.10.005
- Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Medicine*, *6*(6): e1000097. doi:10.1371/journal.pmed1000097
- Morgan, E. E., Woods, S. P., Smith, C., Weber, E., Scott, J. C., Grant, I., & HIV Neurobehavioral Research Program (HNRP) Group. (2012). Lower cognitive reserve among individuals with syndromic HIV-associated neurocognitive disorders (HAND). *AIDS and Behavior*, *16*, 2279-2285. doi:10.1007/s10461-012-0229-7

- Morgello, S., Estanislao, L., Ryan, E., Gerits, P., Simpson, D., Verma, S., ... Manhattan HIV Brain Bank. (2005). Effects of hepatic function and hepatitis C virus on the nervous system assessment of advanced-stage HIV-infected individuals. *AIDS*, *19*(Suppl. 3), S116-S122. doi:10.1097/01.aids.0000192079.49185.f9
- Nightingale, S., Winston, A., Letendre, S., Michael, B. D., Mearthur, J. C., Khoo, S., ... Street, W. D. (2014). Controversies in HIV-associated neurocognitive disorders. *The Lancet Neurology*, *13*, 1139-1151. doi:10.1016/S1474-4422(14)70137-1
- Parsons, T. D., Tucker, K. A., Hall, C. D., Robertson, W. T., Eron, J. J., Fried, M. W., & Robertson, K. R. (2006). Neurocognitive functioning and HAART in HIV and hepatitis C virus co-infection. *AIDS*, *20*, 1591-1595. doi:10.1097/01.aids.0000238404.16121.47
- Perry, W., Carlson, M. D., Barakat, F., Hilsabeck, R. C., Schiehser, D. M., Mathews, C., & Hassanein, T. I. (2005). Neuropsychological test performance in patients co-infected with hepatitis C virus and HIV. *AIDS*, *19*(Suppl. 3), S79-S84. doi:10.1097/01.aids.0000192074.18691.31
- Perry, W., Hilsabeck, R. C., & Hassanein, T. I. (2008). Cognitive dysfunction in chronic hepatitis C: A review. *Digestive Diseases and Sciences*, *53*, 307-321. doi:10.1007/s10620-007-9896-z
- Posada, C., Morgan, E. E., Moore, D. J., Woods, S. P., Letendre, S. L., Grant, I., & HIV Neurobehavioral Research Center Group. (2009). Neurocognitive effects of the hepatitis C virus. *Current Hepatitis Reports*, *8*, 18-26. doi:10.1007/s11901-010-0085-8
- Rempel, H., Sun, B., Calosing, C., Abadjian, L., Monto, A., & Pulliam, L. (2013). Monocyte activation in HIV/HCV coinfection correlates with cognitive impairment. *PloS One*, *8*(2), e55776. doi:10.1371/journal.pone.0055776
- Richardson, J. L., Nowicki, M., Danley, K., Martin, E. M., Cohen, M. H., Gonzalez, R., ... Levine, A. M. (2005). Neuropsychological functioning in a cohort of HIV- and hepatitis C virus-infected women. *AIDS*, *19*, 1659-1667. doi:10.1097/01.aids.0000186824.53359.62
- Rosca, E. C., Rosca, O., Chirileanu, R. D., & Simu, M. (2011). Neurocognitive disorders due to HIV infection. *HIV & AIDS Review*, *10*, 33-37. doi:10.1016/j.hivar.2011.02.003



- Ryan, E. L., Morgello, S., Isaacs, K., Naseer, M. G., Gerits, P., & Manhattan HIV Brain Bank. (2004). The neuropsychiatric impact of hepatitis C on advanced HIV. *Neurology*, 62, 957-962. doi:10.1212/01.WNL.0000115177.74976.6C
- Sakamoto, M., Woods, S. P., Kolessar, M., Kriz, D., Anderson, J. R., Olavarria, H., ... Huckans, M. (2013). Protective effects of higher cognitive reserve for neuropsychological and daily functioning among individuals infected with hepatitis C. *Journal of Neurovirology*, 19, 442-451. doi:10.1007/s13365-013-0196-4
- Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. *Psychological Review*, 103, 403-428. doi:10.1037/0033-295X.103.3.403
- Schouten, J., Cinque, P., Gisslen, M., Reiss, P., & Portegies, P. (2011). HIV-1 infection and cognitive impairment in the cART-era: A review. *AIDS*, 25, 561-575. doi:10.1097/QAD.0b013e3283437f9a
- Simioni, S., Cavassini, M., Annoni, J. M., Rimbault Abraham, A., Bourquin, I., Schiffer, V., ... Du Pasquier, R. A. (2010). Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. *AIDS*, 24, 1243-1250. doi:10.1097/QAD.0b013e3283354a7b
- Stebbins, G. T., Smith, C. A., Bartt, R. E., Kessler, H. A., Adeyemi, O. M., Martin, E., ... Moseley, M. E. (2007). HIV-associated alterations in normal-appearing white matter: a voxel-wise diffusion tensor imaging study. *Journal of Acquired Immune Deficiency Syndromes*, 46, 564-573. doi:10.1097/QAI.0b013e318159d807
- Stern, Y. (2003). The concept of cognitive reserve: A catalyst for research. *Journal of Clinical and Experimental Neuropsychology*, 25, 589-593. doi:10.1076/jcen.25.5.589.14571
- Sun, B., Abadjian, L., Rempel, H., Monto, A., & Pulliam, L. (2013). Differential cognitive impairment in HCV coinfecting men with controlled HIV compared to HCV mono-infection. *Journal of Acquired Immune Deficiency Syndromes*, 62, 190-196. doi:10.1097/QAI.0b013e31827b61f1
- The Cochrane Collaboration. Review Manager, Version 5.2. (RevMan 5.2) [computer program]. Copenhagen, Denmark: The Nordic Cochrane Centre, 2012.
- Thein, H., Maruff, P., Krahn, M., Kaldor, J., Koorey, D., Brew, B., & Dore, G. (2007). Cognitive function, mood and health-related quality of life in hepatitis C virus (HCV)-mono-infected and HIV/HCV-coinfecting individuals commencing HCV treatment. *HIV Medicine*, 8, 192-202. doi:10.1111/j.1468-1293.2007.00452.x

- Thiyagarajan, A., Garvey, L. J., Pflugrad, H., Maruffc, P., Scullard, G., Main, J., ...Winston, A. (2010). Cerebral function tests reveal differences in HIV-infected subjects with and without chronic HCV co-infection. *Clinical Microbiology and Infection*, 16, 1579-1584. doi:10.1111/j.1469-0691.2010.03176.x
- Vázquez-Justo, E., Piñón, A., Vergara-Moragues, E., Guillén-Gestoso, C., & Pérez-García, M. (2014). Influence of cognitive reserve on neuropsychological performance in HIV intravenous drug users. *Applied Neuropsychology: Adult*, 21, 288-296. doi:10.1080/23279095.2013.813852
- Vigil, O., Posada, C., Woods, S. P., Atkinson, J. H., Heaton, R. K., Perry, W., ... HIV Neurobehavioral Research Center (HNRC) Group. (2008). Impairments in fine-motor coordination and speed of information processing predict declines in everyday functioning in hepatitis C infection. *Journal of Clinical and Experimental Neuropsychology*, 30, 805-815. doi:10.1080/13803390701802354
- Vivithanaporn, P., Maingat, F., Lin, L. T., Na, H., Richardson, C. D., Agrawal, B., ... Power, C. (2010). Hepatitis C virus core protein induces neuroimmune activation and potentiates Human Immunodeficiency Virus-1 neurotoxicity. *PloS one*, 5(9), e12856. doi:10.1371/journal.pone.0012856
- Vivithanaporn, P., Nelles, K., DeBlock, L., Newman, S. C., Gill, M. J., & Power, C. (2012). Hepatitis C virus co-infection increases neurocognitive impairment severity and risk of death in treated HIV/AIDS. *Journal of the Neurological Sciences*, 312, 45-51. doi:10.1016/j.jns.2011.08.025
- von Giesen, H.-J., Heintges, T., Abbasi-Boroudjeni, N., Kücükköylü, S., Köller, H., Haslinger, B. A., ... Arendt, G. (2004). Psychomotor slowing in hepatitis C and HIV infection. *Journal of Acquired Immune Deficiency Syndromes*, 35, 131-137. doi:10.1097/00126334-200402010-00005
- Winston, A., Garvey, L., Scotney, E., Yerrakalva, D., Allsop, J. M., Thomson, E. C., ... Taylor-Robinson SD. (2010). Does acute hepatitis C infection affect the central nervous system in HIV-1 infected individuals? *Journal of Viral Hepatitis*, 17, 419-426. doi:10.1111/j.1365-2893.2009.01198.x
- Woods, S. P., Moore, D. J., Weber, E., & Grant, I. (2009). Cognitive neuropsychology of HIV-associated neurocognitive disorders. *Neuropsychological Review*, 19, 152-168. doi:10.1007/s11065-009-9102-5.

## **2.2. Depression in HIV and HCV co-infected patients: A systematic review and meta-analysis**

### **Abstract**

Depression has long been acknowledged as a significant predictor of negative clinical outcomes in HIV and hepatitis C infections. Patients with both viruses may be however at increased risk. The aim of this study was to carry out a systematic review and meta-analysis of the differences in the prevalence of depression and presence of depressive symptoms between HIV/HCV co-infection, HIV mono-infection, and HCV mono-infection. A systematic electronic search of bibliographic databases was performed to locate articles published from the earliest available online until December 2014. Prospective and retrospective studies were included. Outcomes of depression were based on clinical interviews and validated self-reported measures of depression/depressive symptoms. Of the 188 records initially screened, 29 articles were included in the descriptive systematic review and six were included in the meta-analysis. Consistent with the individual conclusions of the studies included in the descriptive review, the meta-analytic results indicated that, as measured by self-reported measures of depression, HIV/HCV co-infected patients were significantly more likely to report depressive symptoms than either HIV (SMD = 0.24, 95% CI: 0.03-0.46,  $p = .02$ ) or HCV mono-infected (SMD = 0.55, 95% CI: 0.17-0.94,  $p = .005$ ) patients. The variability of the results of the reviewed studies, largely dependent on the samples' characteristics and the methods of assessment of depression, suggests that a clear interpretation of how depression outcomes are affected by the presence of HIV/HCV co-infection is still needed. Failing to diagnose depression or to early screen depressive symptoms may have a significant impact on patients' overall functioning and compromise treatments' outcomes.

## Introduction

Depression is the most common neuropsychiatric manifestation in HIV infection (Nanni, Caruso, Mitchell, Meggiolaro, & Grassi, 2015). A meta-analysis examining the risk for depression in HIV found that HIV-infected patients were more likely to have had an episode of major depressive disorder (MDD) than HIV-negative patients (Ciesla & Roberts, 2001). Regarding hepatitis C virus (HCV) infection, there is also evidence of an increased prevalence of neuropsychiatric disorders, with depression being one of the most significant disorders during hepatitis C treatment as well as in untreated HCV-infected patients (Schaefer et al., 2012). The high prevalence of psychiatric comorbidities in HCV-infected patients has been associated with direct effects of the virus on the central nervous system (Raison et al., 2009) or adverse effects of hepatitis C treatment (Udina et al., 2012). Because the diagnosis of MDD during interferon treatment is often missed (Leutscher et al., 2010) and depression is a well-known risk factor for treatment failure (Schaefer et al., 2012), a timely screening and treatment of depression is of major relevance.

This may be more complex in the presence of HIV/HCV co-infection. This is particularly important because dual-diagnosed patients may face numerous emotional and psychosocial stressors (e.g., adjustment to and management of two chronic medical conditions, coping with stigma and discrimination, and coping with changes in relationships and social networks), which pose unique challenges for mental health providers (Silberbogen, Ulloa, Janke, & Mori, 2009). However, the prevalence of depression and depressive symptoms in HIV/HCV has been less studied, and the comparison with mono-infected populations yielded heterogeneous findings. Summarizing the results of studies comparing the prevalence of depression among co-infected patients with HIV and HCV mono-infected patients is needed to improve current understanding of the consequences of depression/depressive symptoms for dual-infected patients, particularly because of the evidence suggesting that depressive symptoms may compromise antiretroviral treatment compliance (Roux et al., 2013) and add complexity to treatment planning (Baillargeon et al., 2008). This knowledge is also of major importance, as it may allow for a closer monitoring of co-infected patients, who may be at increased risk of poorer mental health and thus may benefit from additional psychosocial support or antidepressant treatment.

Accordingly, the aim of this study was to carry out a systematic review and meta-analysis of the differences in the prevalence of depression and of depressive

symptoms between HIV/HCV co-infected, HIV mono-infected, and HCV mono-infected patients.

## **Methods**

### **Search strategy**

The Cochrane Central Registered of Control Trials Library, SCOPUS, Medline and PsycINFO were systematically searched for records from the earliest data available online to December 2014. Each database was searched separately. The key terms “*depress\**” AND “*HIV - HCV co-infection*” were used, combining search strategies using Boolean operator (AND) and (\*) related terms. The search was supplemented with additional information from reference lists and contact with the authors in the field of depression and HIV/HCV co-infection. The selection was limited to English publications only. The study was designed according to the PRISMA statement (Figure 1; Moher, Liberati, Tetzlaff, & Altman, 2009).

### **Eligibility criteria**

Study inclusion criteria were: (1) Type of studies: prospective and retrospective studies assessing depression or presence of depressive symptoms in HIV/HCV co-infection; (2) Participants: individuals diagnosed with HIV/HCV and control subjects from these studies with either HIV or HCV mono-infection; (3) Interventions: with and without HCV treatment; and (4) Primary outcome: incidence of depression/depressive symptoms in co-infected patients, including during HCV treatment, as assessed by clinical interview or any validated depression measure. Secondary outcome: any other reported assessment measure of depressive symptoms. The following exclusion criteria were applied: (1) studies with participants under 18 years; (2) post-mortem studies; (3) articles with overlapping samples (samples duplicated in different research reports); and (4) articles not written in English.

### **Data extraction**

Two authors (RF and MP) independently reviewed all references from electronic and non-electronic sources, selected the relevant studies for the review and extracted relevant data. Disagreements were resolved by discussion. The following information was extracted from each study: year of publication, country, design, sample size,

population characteristics (e.g., age, gender, past and/or current intravenous drug use (IDU) or IDU as risk factor for infection acquisition), measures to assess depression/depressive symptoms and prevalence of MDD and/or symptoms of depression. To assess the risk of bias, a checklist was developed based on a quality assessment instrument, and included the following parameters: objectives explicitly stated, selection and representativeness of the study samples, inclusion/exclusion criteria, clear identification of measures, data adequately reported, and discussion addressing the primary outcome and validity of depression measures (Higgins & Green, 2011).

### **Data analysis**

All studies meeting eligibility criteria were included in the systematic review. Of these, a sub-set of six studies with available data to perform statistical synthesis and appropriate control groups were entered into the meta-analysis. Meta-analysis quantifying the differences in depression outcomes between HIV/HCV, HIV and HCV mono-infected groups was performed with the Review Manager, version 5.3. Because studies whose results were combinable used different measures to assess depressive symptoms, the standardised mean difference (SMD) between HIV/HCV and control groups and its associated 95% confidence interval (CI) were computed as the summary statistic for the estimate of effects. The heterogeneity between-studies was assessed by computing the  $\chi^2$  and  $I^2$  statistics. An  $I^2$  of 0% indicates no heterogeneity and a value above 50% is considered as substantial heterogeneity (Higgins, Thompson, Deeks, & Altman, 2003). Though moderate to substantial heterogeneity was identified, as suggested by Higgins and Green (2011), both fixed and random-effects models were used for testing differences in the summary effects.

### **Results**

#### **Study selection and quality of studies**

The study selection process is described in Figure 1. Briefly, the electronic search identified 188 records. After removal of duplicated articles ( $n=18$ ), 170 were subjected to abstract review. One hundred and thirty-one were excluded, leaving 39 articles for full-text review and further assessment of eligibility. Twenty-nine papers

fulfilled the inclusion criteria and were included in the systematic review. Six of those studies were included in the quantitative analysis. Selected studies were published between 2001 and 2014.

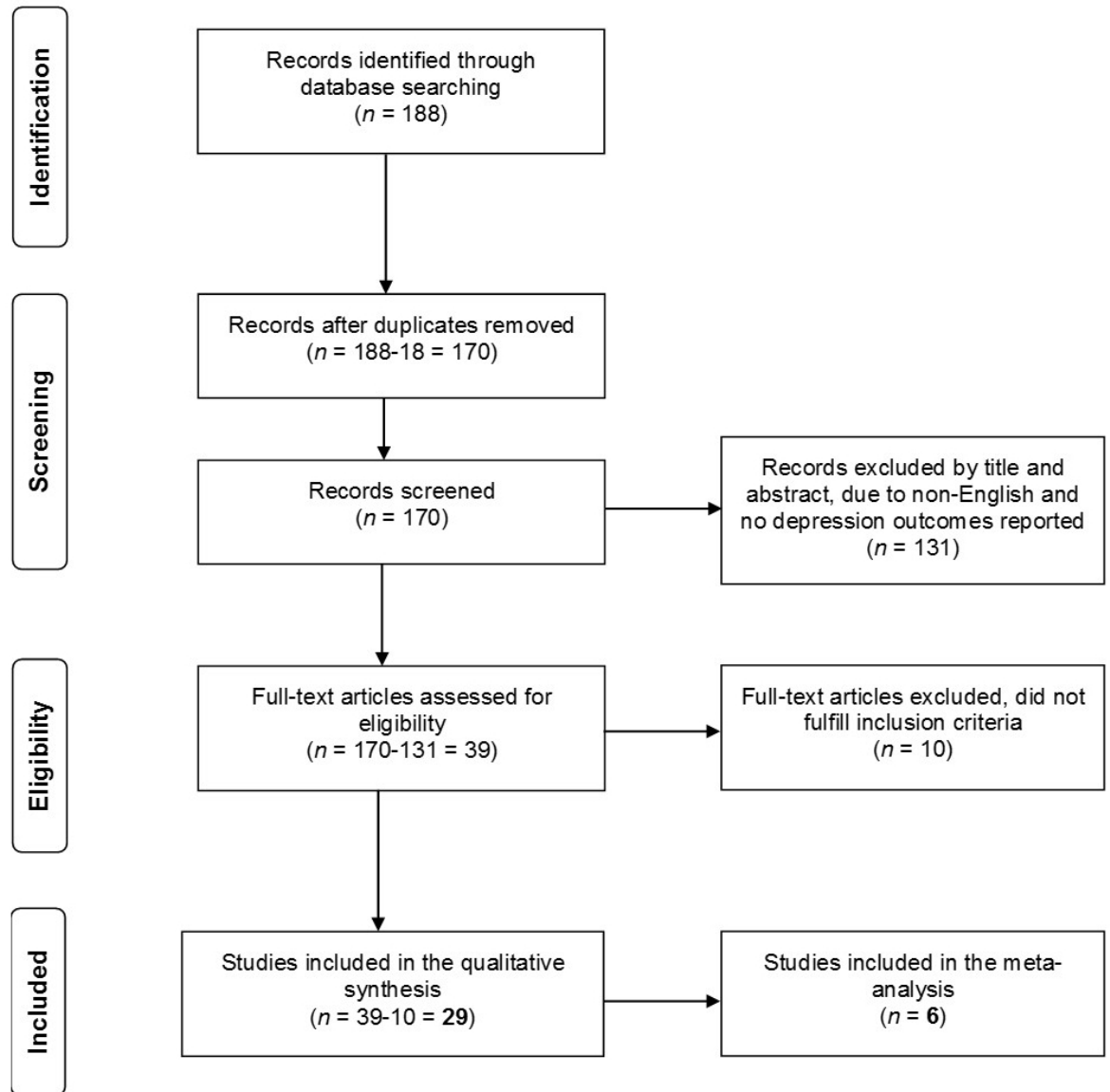


Figure 1. Flow diagram outlining the study selection process

For all studies included in the review, a low risk of bias was observed when considering the identification of the studies' aims, definition of inclusion and exclusion criteria, reporting of results, and discussion of the main outcomes. However, low-moderate to high bias was found regarding the selection of participants (e.g., a systematic difference between the characteristics of groups that were compared was

identified), which limited their representativeness, as well as in identification of the procedures associated with how outcomes were determined (e.g., in six studies it was not clear how depression was assessed). Regarding the six studies included in the meta-analysis, with the exception of two studies (Richardson et al., 2005; von Giesen et al., 2004), in which systematic differences between the comparison groups were identified, a low risk of bias was observed.

### **Study characteristics**

This systematic review covers 29 studies from eight countries (one study from Italy and Portugal, two studies from Australia, France and Germany, three studies from Canada and Spain, and 15 studies from the USA). The number of co-infected participants ranged between 15 and 6,782. Study designs were mostly cross-sectional ( $n = 16$ , 55.2%) and included only a HIV/HCV group ( $n = 10$ , 34.5%) or a comparison between co-infected and HIV mono-infected groups ( $n = 10$ , 34.5%). Most studies included both male and female participants and one study included only females (Richardson et al., 2005). The proportion of co-infected males ranged between 65.1% (von Giesen et al., 2004) and 100% (Pantalone, Hessler, Bankoff, & Shah, 2012; Sun et al., 2013; Thein et al., 2007). Among co-infected patients, the proportion of participants reporting IDU (past and/or current) ranged between 31.5% (Pantalone et al., 2012) and 94% (Landau et al., 2001). In 18 studies, the proportion of IDU was above 60%. General characteristics and comparison groups in each study are described in Table 1.

### **Descriptive analysis**

A summary of the relevant findings of the 29 studies included in the descriptive analysis is presented in Table 2 and briefly described above.



Table 1. General characteristics of the 29 studies included in the systematic review

Authors, Year	Country	Design	Sample (N)	Gender (% male)	Age <sup>a</sup>	IDU
Alavi et al., 2012	Australia	Prospective cohort	Total = 163 HIV/HCV = 50	71%	34.3 ± 9.9	76% history IDU
Backus et al., 2005	USA	Retrospective cohort	HIV = 11,567 HIV/HCV = 6,782	97.4% 98.3%	47.9 ± 10.3 49.8 ± 6.3	20.6% hard drug abuse 62.9% hard drug abuse
Baillargeon et al., 2008	USA	Prospective cohort	HIV = 3,783  HIV/HCV = 2,275	83.2%  87%	NR  NR	NR  NR
Baum et al., 2008	USA	Cross-sectional	HIV = 135 HIV/HCV = 57	75.6% 71.9%	41.0 ± 7.3 45.4 ± 6.5	10.3% history IDU 40.3% history IDU
Braitstein et al., 2005	Canada	Cross-sectional	HIV = 379 HIV/HCV = 105	97% 82%	43 (mean) 42 (mean)	5% history IDU 79% history IDU
Butt et al., 2006	USA	Retrospective cohort	HCV = 114,005 HIV/HCV = 6,502	96.9% 98.2%	50 48	38.9% 56.2%
Butt et al., 2009	USA	Prospective cohort	HCV = 241 HIV/HCV = 158	58.5% 81.6%	49.7 ± 10.9 48.4 ± 7.4	50.6% recent IDU 60.2% recent IDU
Ciccarelli et al., 2013	Italy	Cross-sectional	HIV = 50 HCV = 50 HIV/HCV = 50	64% 72% 78%	48 (45-53) <sup>b</sup> 48 (42-52) <sup>b</sup> 48 (42-55) <sup>b</sup>	4% history IDU 38% history IDU 78% history IDU
Clifford et al., 2005	USA	Cross-sectional	HIV = 234 HIV/HCV = 30	80% 77%	38.05 ± 8.63 40.27 ± 7.75	4% history IDU 47% history IDU

Fumaz et al., 2007	Spain	Prospective longitudinal	Peg-IFN a-2a = 32	71.8%	40.7 ± 4.08	78.1% IDU risk factor
			Peg-IFN a-2b = 31	67.7%	39.2 ± 5.03	90.3% IDU risk factor
Goulet et al., 2005	USA	Retrospective cohort	HIV = 20,627	94%	47.1 (median)	22% <sup>c</sup>
			HIV/HCV = 4,489	98%	46.9 (median)	58% <sup>c</sup>
Kemmer et al., 2012	USA	Prospective longitudinal	HIV/HCV = 329	83.3%	48 (median)	NR
Klein et al., 2014	Canada	Randomized, double-blind placebo-controlled trial	Citalopram = 36	72.2%	45.6 (38.7–50.9) <sup>b</sup>	52.8% IDU risk factor
			Placebo = 40	100%	46.7 (42.6–52.9) <sup>b</sup>	47.5% IDU risk factor
Laguno et al., 2004	Spain	Randomized open-label	Peg-IFN a-2b + RBV = 52	63%	40 (mean)	75% IDU risk factor
			IFN a-2b + RBV = 43	74%	40 (mean)	91% IDU risk factor
Landau et al., 2001	France	Prospective longitudinal	HIV/HCV = 51	76.5%	39 ± 5 (30-59)	94%
Michel et al., 2010	France	Cross-sectional	HIV/HCV = 328	69.8%	42 (40-46) <sup>b</sup>	63.6% IDU risk factor
Moreno et al., 2004	Spain	Prospective longitudinal	HIV/HCV = 35	69%	38 (35-39) <sup>b</sup>	83% IDU risk factor
Myers et al., 2004	Canada	Open-label study	HIV/HCV = 32	78%	40 ± 6 (26-55)	78% history IDU
Pantalone et al., 2012	USA	Cross-sectional	HIV = 117	100%	43.75 ± 8.80	6.1% IDU risk factor
			HIV/HCV = 54	100%	44.80 ± 7.66	31.5% IDU risk factor
Pereira et al., 2014	Portugal	Cross-sectional	HIV = 462		41.19 ± 10.01	19.5% IDU risk factor
			HIV/HCV = 248		38.75 ± 6.54	68.8% IDU risk factor
Richardson et al., 2005	USA	Cross-sectional	HIV = 75	100% female	33.8 ± 7.2	NR
			HCV = 27	100% female	37.3 ± 9.2	NR
			HIV/HCV = 70	100% female	39.6 ± 6.5	NR
Rockstroh et al., 2002	Germany	Prospective longitudinal	HIV/HCV = 23	78.3%	42 (median)	NR

Ryan et al., 2004	USA	Cross-sectional	HIV = 49	77.6%	41.9 ± 7.2	NR
			HIV/HCV = 67	73.1%	45.1 ± 7.2	NR
Sulkowski et al., 2004	USA	Randomized open-label	Daily IFN + RBV = 90	77.8%	43.7 ± 5.7	57.8% history IDU
			TIW IFN + RBV = 90	74.4%	43.7 ± 8.6	65.6% history IDU
Sun et al., 2013	USA	Cross-sectional	HIV = 14	100%	51.6 ± 7.2	NR
			HCV = 19	100%	56.6 ± 4.5	63% history IDU
			HIV/HCV = 17	100%	54.5 ± 5.2	71% history IDU
Tavakkoli et al., 2013	USA	Cross-sectional	HCV = 65	56.9%	47.5 ± 7.1	50.8%
			HIV/HCV = 102	75.5%	49.7 ± 9.6	54.9%
Thein et al., 2007	Australia	Cross-sectional	HIV = 30	100%	34.7 ± 7.4	NR
			HCV = 19	63.2%	42.6 ± 6.5	89.5% history IDU
			HIV/HCV = 15	100%	35.5 ± 7.0	86.7% history IDU
von Giesen et al., 2004	Germany	Cross-sectional	HIV = 43	65.1%	38.0 ± 8.1	62.8% IDU risk factor
			HCV = 44	35.6%	43.2 ± 13.7	18.2% IDU risk factor
			HIV/HCV = 43	65.1%	37.4 ± 7.8	62.8% IDU risk factor
Yoon et al., 2011	USA	Cross-sectional	HIV = 604	88%	45 (median)	15% IDU risk factor
			HIV/HCV = 160	83%		63% IDU risk factor

NR: Not reported; RBV: Ribavirin; Peg-INF: pegylated interferon; INF: interferon; TIW: thrice-weekly.

<sup>a</sup> Unless indicated, data are presented as mean ± SD (or range); <sup>b</sup> Data is presented as Median (Interquartile range); <sup>c</sup> Comorbid drug disorder

Table 2. Synthesis of findings on depression/depressive symptoms of the 29 studies included in the systematic review

Authors, Year	Depression measures	Main Findings
Alavi et al., 2012	Mini International Psychiatric Interview (MINI). Depression, Anxiety and Stress Scale (DASS-21)	Before HCV treatment, at baseline, the co-infected group was significantly less depressed than the HCV mono-infected group. During treatment, the prevalence of new-onset depression was higher among the co-infected group when compared with the HCV mono-infected group (38% vs. 33%), but the difference was not significant.
Backus et al., 2005	Clinical notes based on the International Classification of Diseases, 9th Revision (ICD9)	Both co-infected and HIV mono-infected patients presented high prevalence of mental illness, particularly depression. However, the HIV/HCV co-infected group was more likely to present a diagnosis of depression, alcohol abuse and substance abuse compared with the HIV mono-infected group.
Baillargeon et al., 2008	Clinical appointments using the International Classification of Diseases (ICD-10)	In comparison to HIV mono-infected inmates, those with HIV/HCV co-infection had an elevated prevalence of any psychiatric disorder (20.6% vs. 16.7%). No increased odds were observed in relation to Major Depression (8.4% vs. 7%).
Baum et al., 2008	NR	In comparison to HIV mono-infected patients, the HIV/HCV co-infected patients reported depression (36.8% vs. 8.1%), fatigue, headache, diarrhoea and apathy as the most prevalent physical and mental health symptoms.
Braitstein et al., 2005	Centre for Epidemiologic Studies Depression Scale (CESD)	The co-infected group showed higher scores on symptoms consistent with depression, increased fatigue and poorer quality of life. The impact of HCV on quality of life, depression and fatigue was better explained by socio-demographic factors related to poverty and IDU than by HCV itself.
Butt et al., 2006	Clinical notes using the ICD9 codes	The HIV/HCV co-infected group were more frequently diagnosed with major depression (23% vs. 18.4%) and mild depression (35.4% vs. 32.4%) than the HCV mono-infected group. Additionally, depression was associated with a lower

Butt et al., 2009	Structured questionnaires	likelihood of hepatitis treatment prescription. HIV/HCV co-infected patients were more likely to be depressed (67.4% vs. 39.9%) and tended to present higher prevalence of ongoing alcohol abuse than HCV mono-infected patients.
Ciccarelli et al., 2013*	Zung Depression Scale	No significant differences were found in the depression scores between HIV/HCV co-infected groups and the HIV and HCV mono-infected groups.
Clifford et al., 2005*	Centre for Epidemiologic Studies Depression Scale (CESD)	The HIV/HCV co-infected group presented significantly more depressive symptomatology than the HIV mono-infected group (57% vs. 32%).
Fumaz et al., 2007	Beck Depression Inventory (BDI)	Among HIV/HCV co-infected patients, there were no significant differences in depression scores between types of hepatitis C treatment; however, the rates of depressive symptoms were high in both groups during treatment (overall, 58.7% of patients presented mild to moderate depressive symptoms).
Goulet et al., 2005	Clinical notes using the ICD9 codes	The HIV/HCV co-infected patients were significantly more likely to have psychiatric disorders, including depression (43% vs. 28%), than HIV mono-infected patients.
Kemmer et al., 2012	Centre for Epidemiologic Studies Depression Scale (CESD)	Depression was significantly associated with a decline in role, social and cognitive function in HIV/HCV co-infection.
Klein et al., 2014	Beck Depression Inventory-II (BDI-II) Montgomery–Åsberg Depression Rating Scale (MADRS) Structure Clinical Interview for DSM-IV Axis I Disorders (SCID-I)	Prophylactic citalopram compared to treatment of emergent depression was not associated with a reduction in treatment-limiting depression, nor did significantly reduce depressive symptoms among HIV/HCV co-infected patients during hepatitis C treatment.
Laguno et al., 2004	World Health Organization Scale	A high incidence of depressive symptoms was reported among HIV/HCV co-infected patients (43%); however, most of them were not severe and improved with

Landau et al., 2001	NR	antidepressant therapy, without reduction or cessation of hepatitis C treatment. Depressive symptoms were reported in 8% of HIV/HCV co-infected patients under hepatitis C treatment.
Michel et al., 2010	Centre for Epidemiologic Studies Depression Scale (CESD)	Depressive symptoms and treatment for depressive symptoms was significantly associated with the cognitive, social and physical dimensions of fatigue impact.
Moreno et al., 2004	World Health Organization Scale	A prevalence of 9% of depression was reported as an adverse event during hepatitis C treatment.
Myers et al., 2004	NR	Psychiatric manifestations were the main reason for discontinuation of hepatitis C treatment (19%); depression was the most common reason for discontinuation, followed by agitation and delirium and anxiety.
Pantalone et al., 2012*	Centre for Epidemiologic Studies Depression Scale (CESD)	Depression scores were elevated in HIV mono-infected and HIV/HCV co-infected groups; HIV/HCV co-infected MSM were significantly more depressed than HIV mono-infected MSM.
Pereira et al., 2014	Brief Symptom Inventory (BSI)	HIV/HCV co-infected patients reported significantly higher scores on the subscale Depression of the BSI than HIV mono-infected patients. As well, compared to HIV mono-infected patients, a greater proportion of HIV/HCV co-infected patients met caseness for depression (17.7% vs. 12%).
Richardson et al., 2005*	Centre for Epidemiologic Studies Depression Scale (CESD)	The depression scores were not significantly different between HIV/HCV, HIV and HCV mono-infected groups.
Rockstroh et al., 2002	NR	During hepatitis C treatment, 3 out of 9 patients developed depression, which resulted in treatment discontinuation.
Ryan et al., 2004	Psychiatric Research Interview for Substance and Mental Disorders (PRISM)	There were no significant differences on the prevalence of primary mental disorders between HIV/HCV co-infected and HIV mono-infected patients. However, past and

Sulkowski et al., 2004	NR	current depression was the most common diagnosis in both groups. Depression was observed in patients during hepatitis C treatment among HIV/HCV co-infected patients.
Sun et al., 2013*	Beck Depression Inventory (BDI-II)	The HIV/HCV co-infected group was found to have significantly more depressive symptoms than the HCV mono-infected group and the healthy controls, after adjusting for education and general intellect (IQ).
Tavakkoli et al., 2013	Patient Health Questionnaire -9 (PHQ-9)	A diagnosis of major depression was significantly less common among HIV/HCV co-infected patients, in comparison to HCV mono-infected patients (24.7% vs. 41.4%).
Thein et al., 2007	Depression Anxiety Stress Scales (DAAS)	The mean DAAS scores were similar between HIV/HCV co-infected, HIV and HCV mono-infected patients and uninfected controls prior to hepatitis C treatment.
von Giesen et al., 2004*	Hamilton Depression Rating Scale (HAMD)	HCV mono-infected patients presented significantly lower scores of depression than HIV mono-infected and HIV/HCV co-infected patients.
Yoon et al., 2011	Patient Health Questionnaire -9 (PHQ-9)	A high prevalence and severity of depression was found among HIV/HCV co-infected patients, even adjusting for differences in substance use. The mean depression severity scores for HIV/HCV patients were 3.4 points higher than for HIV mono-infected patients; the association between HCV and greater depression severity remained significant even adjusting for antidepressant medication and current illicit drug use.

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\* Studies included in the meta-analyses

NR: Not reported; MSM: Men who have sex with men

### **Depression in HIV/HCV patients without HCV treatment**

A total of 18 studies assessed depression among co-infected patients outside HCV treatment. The three retrospective studies used the International Classification of Diseases (ICD-9) codes to assess depression. Of these, two studies reported that co-infected patients had a higher prevalence of depression than HIV mono-infected patients (Backus, Boothroyd, & Deyton, 2005; Goulet, Fultz, McGinnis, & Justice, 2005) and one study found that the co-infected group had a higher prevalence of depression than the HCV mono-infected group (Butt, Justice, Skanderson, Good, & Kwoh, 2006).

Cross-sectional and prospective studies similarly indicated that co-infected patients were more likely to report depressive symptoms than HIV mono-infected patients (Baillargeon et al., 2008; Baum, Jayaweera, Duan, & Ms, 2008; Braitstein et al., 2005; Butt et al., 2009; Clifford, Evans, Yang, & Gulick, 2005; Pantalone et al., 2012; Pereira, Fialho, & Canavarro, 2014; Sun et al., 2013; Yoon et al., 2011) and HCV mono-infected patients (Sun et al., 2013). In three studies no significant differences were found between the co-infected group and the HIV and HCV mono-infected groups (Ciccarelli et al., 2013; Richardson et al., 2005; Thein et al., 2007), and one study did not find differences between co-infected and HIV mono-infected patients (Ryan et al., 2004). Additionally, one study indicated that depression was associated with HIV illness progression in co-infection (Michel et al., 2010). Tavakkoli and colleagues (2013) found that a diagnosis of major depression was significantly less common among HIV/HCV patients than among HCV mono-infected patients.

### **Depression in HIV/HCV patients during HCV treatment**

Ten studies assessed depression during hepatitis C treatment. Alavi and colleagues (2012) described similar proportions of new-onset depression during treatment between HCV mono-infected (33%) and co-infected patients (38%). Fumaz and colleagues (2007) indicated that 59% of co-infected patients as having treatment-emergent mild or moderate depression. One study showed that depression did not influence treatment outcomes (Alavi et al., 2012) and another indicated that increased depressive symptoms was significantly associated with reduced role, social and cognitive functioning (Kemmer et al., 2012). Six studies reported occurrence of depression during HCV treatment (Laguno et al., 2004; Landau et al., 2001; Moreno et al., 2004; Myers et al., 2004; Rockstroh et al., 2002; Sulkowski et al., 2004) and five indicated depression as cause of treatment discontinuation (Laguno et al., 2004; Landau



et al., 2001; Moreno et al., 2004; Myers et al., 2004; Rockstroh et al., 2002). Klein and colleagues (2014) found that prophylactic citalopram compared to treatment of depression was not associated with reduce depression symptoms among co-infected patients.

### Meta-analysis: Depression in HIV/HCV vs. HIV and HCV mono-infection

Six out of the 29 studies included data enabling meta-analysis. Because in these studies, depressive symptoms were assessed with different measures (see Table 2), SMD were computed as the summary statistic for the estimate of effects.

The meta-analysis (random-effects model) comparing HIV/HCV and HIV mono-infected patients indicated a significant difference between groups, showing that the HIV mono-infected groups were less likely to report symptoms of clinical depression than the HIV/HCV co-infected groups (SMD = 0.24, 95%CI: 0.03-0.46,  $p = .02$ ). Similarly, the meta-analysis comparing HIV/HCV and HCV mono-infected groups indicated that the latter groups were less likely to exhibit depressive symptoms than the co-infected groups (SMD = 0.55, 95%CI: 0.17-0.94,  $p = .005$ ) (see Figure 2). In both comparisons, moderate to substantial heterogeneity was found ( $I^2$  range = 39%-62%). Data analysis using fixed-effects models yielded similar results in the comparison with HIV mono-infected (SMD = 0.24, 95%CI: 0.08-0.40,  $p = .004$ ) and HCV mono-infected groups (SMD = 0.53, 95%CI: 0.30-0.76,  $p < .00001$ ).

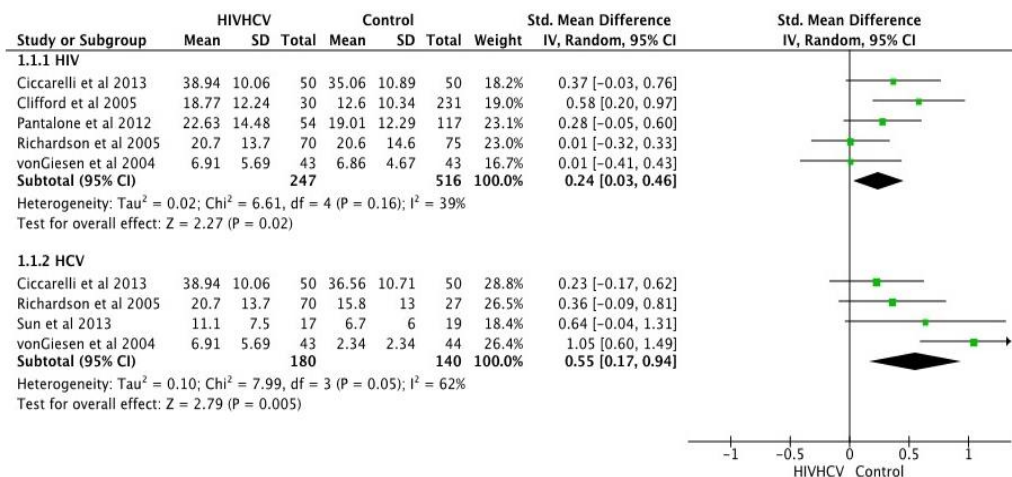


Figure 2. Forest plots of meta-analyses of differences in depression outcomes between study groups. Abbreviations: SD, standard deviation; CI, confidence interval

## Discussion

In this first systematic review and meta-analysis examining the prevalence of depression and depressive symptoms among patients co-infected with HIV and hepatitis C, in comparison to HIV and HCV mono-infected patients, the main findings indicate a significant difference in depression outcomes between the comparison groups, and suggest that patients co-infected with HIV and HCV are more likely to report depressive symptoms than those with mono-infections.

Our results indicate a relevant prevalence of depression/depressive symptoms among co-infected patients, and suggest that the stigmatisation and strain of living with HIV is likely to be greater when coexisting with other medical conditions. Potential explanations for this result may be related to well-known psychosocial factors that are common among co-infected patients, such as the higher prevalence of past history of IDU, ongoing alcohol and drug abuse (Backus et al., 2005; Clifford et al., 2005) and greater psychiatric comorbidity (Backus et al., 2005; Pereira et al., 2014). These factors, cumulatively with antiviral treatments and its side-effects are likely to increase the vulnerability of developing mental health disorders of co-infected patients, particularly in comparison with mono-infected patients. Interestingly, our findings indicated that the SMD was greater in the comparison between HIV/HCV and HCV mono-infected patients. This may be associated with the findings of one study (von Giesen et al., 2004), in which the mean score on depression was significantly lower among HCV mono-infected patients (2.34 vs. 6.86), probably because of the lower proportion of mono-infected patients reporting IDU as risk factor (18.2% vs. 62.8%).

It is also likely that depression may represent a behavioural side effect of these viruses. For instance, research demonstrated that depression associated with HIV is in part driven by immune dysregulation, characterized by an increased production of pro inflammatory cytokines and proliferation of immune cells (Nasi, Pinti, Mussini, & Cossarizza, 2014). Recent evidence also suggested that in a healthy brain, inflammation is an acute and controlled process; but when inflammation is chronic, it may contribute to the development of depression (Jones & Thomsen, 2013). HCV chronic infection also represents a chronic inflamed state that is maladaptive and that has been associated with an elevated choline/creatine ratio in basal ganglia and white matter, depression and cognitive dysfunction (Forton et al., 2008; Weissenborn et al., 2004). Since these same changes would be anticipated in both HIV and HCV, the fact that co-infected patients were more depressed than HIV and HCV mono-infected groups also seems to suggest

that these inflammation-related changes may represent a determinant factor of depression emergence.

Retrospective studies consistently shown a significant prevalence of depression among co-infected patients, and significantly higher than the comparison groups (Backus et al., 2005; Butt et al., 2006; Goulet et al., 2005). The sample sizes of these studies were large suggesting the relevance of the findings. However, retrospective studies may be vulnerable to information bias that can negatively impact the reported outcomes, such as non-standardized observations, use of different measures for assessing depression, and multiple information sources from clinical notes. It is notable that all retrospective studies included veterans with overlapping mental illness comorbidities, which reduces the generalizability of the findings to other populations.

Regarding the descriptive narrative of prospective studies, mixed findings were reported. Some studies found that co-infected groups reported higher depression levels (or symptoms of depression) than mono-infected groups (e.g., Baillargeon et al., 2008; Pereira et al., 2014; Sun et al., 2013) but others did not find such differences (e.g., Ciccarelli et al., 2013; Thein et al., 2007). These differing findings may be related to several factors, including studies' differences in methodological approaches (e.g., study design, variations in the diagnostic/screening tools for assessing depression) and samples' characteristics. It is noteworthy that most studies included significant proportions of participants reporting IDU as a risk factor. However, there is also evidence suggesting changes in the epidemiological patterns of co-infection, particularly a higher incidence of HCV among HIV-infected men who have sex with men (MSM; Pantalone et al., 2012; van de Laar, Matthews, Prins, & Danta, 2010). Thus, future studies considering this emerging sexually transmitted infection are warranted, particularly because of recent evidence suggesting an association between depressive symptoms and higher engagement in sexual risk-behaviours among HIV-infected MSM (O'Cleirigh et al., 2013).

Studies in the context of HCV treatment indicated that depression was common (Alavi et al., 2012; Fumaz et al., 2007) and considered depression to be a risk factor for discontinuation of HCV treatment among co-infected patients (e.g., Laguno et al., 2004; Myers et al., 2004; Rockstroh et al., 2002). However, these results should be carefully interpreted, particularly because of how depression was measured in these studies. Indeed, different measures have been used to assess depression, and in four studies the

measures were not clearly reported, thus leading to likely bias, as well as to under or over-representation of depression and its potential impact on treatment.

Regarding hepatitis C treatment, the interferon-induced depression paradigm has been robustly studied, and it has been reported that 1 out of 4 HCV patients receiving interferon-alpha and ribavirin therapy may develop MDD (Udina et al., 2012). Despite the notable advances of antiviral treatments for hepatitis C, particularly the emergence of direct acting-antivirals (DAAs), interferon-based therapy is still actively prescribed in a sub-set of patients. This means that the risk of depression may remain. Additionally, HCV treatment in co-infection is not as straightforward as in HCV mono-infection due to potential drug-drug interactions (Chen & Jain, 2015). Accordingly, a routine screening of depression in co-infected patients would still be critical to a prompt diagnosis and adequate planning of antidepressant treatment during HCV therapy, which has been however considered safe (Martin-Subero, & Diez-Quevedo, 2016).

This systematic review is not without limitations. First, the literature search was restricted to articles written in English. Second, methodological differences between the studies should be considered in the interpretation of the results, including the heterogeneity of the participants' characteristics, the relatively small sample sizes, the preponderance of cross-sectional studies and the variability of approaches for assessing depression/depressive symptoms (only a limited number of studies performed a clinical diagnosis of depression). Third, the studies' methodological heterogeneity, particularly the lack of information regarding depression measures and quantitative outcomes did not allow us to perform a meta-analysis on depression during HCV treatment. Also, our meta-analysis' results were pooled from a small sample of studies that used different depression measures, which may lead to biased results and explain the substantial heterogeneity. Despite this limitation, restrict the selection of studies to those that used the same instrument would lead to a significant loss of information. Accordingly, the interpretation of these findings should be performed with caution. Finally, because of the emerging epidemiological patterns in HIV/HCV, this review is largely dependent of studies involving participants with history of IDU. Further studies are warranted, particularly those involving MSM as well as women, which are still under-represented in the HIV/HCV literature.

This comparative analysis on the prevalence of depression in HIV, HCV mono-infected and co-infected samples, indicates that depression appears to be more common among co-infected patients. This finding has important clinical implications, as it

provides an opportunity for targeted and timely screening of depression in populations at higher risk, and before the exacerbation of symptoms. In this context, the use of reliable measures of depression is essential. Despite the wide-ranging number of well-established tools for the assessment of depressive symptoms, their scope and scores are often different (Uher et al., 2012) and are not directly comparable (Wahl et al., 2014). A standardized metric for the assessment of depression severity, as the proposed by Wahl and colleagues (2014) may be valuable. For a more complete and accurate assessment, the combination of clinician-rated scales and self-reported measures would also be useful, as it provide unique information that may be important to predict treatment outcomes (Uher et al., 2012).

Finally, there is evidence that the prevalence of depression in HIV and HCV mono-infection as well as in HIV/HCV co-infection vary. Accordingly, a differential diagnosis will be critical, because both host factors (e.g., interferon exposure in HCV treatment) and virus factors (e.g., CNS-related infections) responsible for mood symptoms can be manageable. Moreover, factors such as lack of social support, stress and maladaptive coping strategies are also associated with an increased risk of depression (Slot et al., 2015). Because these factors are amenable to change, addressing these factors may also reduce depressive symptoms and contribute for improved well-being of patients. As recommended by Schaefer et al. (2012), increased education of both patients and health professionals on mental health issues is central to allow early detection of psychological symptoms, particularly those that are likely to contribute to treatments' failure. A close monitoring and comprehensive management of psychological symptoms is also highly recommended, as it may contribute to maximize the likelihood of successful treatments.

## References

- Alavi, M., Grebely, J., Matthews, G. V, Petoumenos, K., Yeung, B., Day, C., ... Haber, P. S. (2012). Effect of pegylated interferon- $\alpha$ -2a treatment on mental health during recent hepatitis C virus infection. *Journal of Gastroenterology and Hepatology*, 27, 957-965. doi:10.1111/j.1440-1746.2011.07035.x
- Backus, L. I., Boothroyd, D., & Deyton, L. R. (2005). HIV, hepatitis C and HIV/Hepatitis C virus co-infection in vulnerable populations. *AIDS*, 19(Suppl. 3), S13-S19. doi:10.1097/01.aids.0000192065.09281.01
- Baillargeon, J. G., Paar, D. P., Wu, H., Giordano, T. P., Murray, O., Raimer, B. G., ... Pulvino, J. S. (2008). Psychiatric disorders, HIV infection and HIV/hepatitis co-infection in the correctional setting. *AIDS Care*, 20, 124-129. doi:10.1080/09540120701426532
- Baum, M. K., Jayaweera, D. T., Duan, R., Sales, S., Lai, S., Rafie, C., ... Campa, A. (2008). Quality of life, symptomatology and healthcare utilization in HIV/HCV co-infected drug users in Miami. *Journal of Addictive Diseases*, 27(2), 37-48. doi:10.1300/J069v27n02\_05
- Braitstein, P., Montessori, V., Chan, K., Montaner, J. S., Schechter, M. T., O'Shaughnessy, M. V., & Hogg, R. S. (2005). Quality of life, depression and fatigue among persons co infected with HIV and hepatitis C: Outcomes from a population based cohort. *AIDS Care*, 17, 505-515. doi:10.1080/09540120412331291733
- Butt, A. A., Justice, A. C., Skanderson, M., Good, C., & Kwoh, C. K. (2006). Rates and predictors of hepatitis C virus treatment in HCV-HIV-coinfected subjects. *Alimentary Pharmacology & Therapeutics*, 24, 585-591. doi:10.1111/j.1365-2036.2006.03020.x
- Butt, A. A., Khan, U. A., Shaikh, O. S., McMahon, D., Dorey-Stein, Z., Tsevat, J., & Lo Re III, V. (2009). Rates of HCV treatment eligibility among HCV-monoinfected and HCV/HIV-coinfected patients in tertiary care referral centers. *HIV Clinical Trials*, 10, 25-32. doi:10.1310/hct1001-025
- Ciesla, J. A., & Roberts, J. E. (2001). Meta-analysis of the relationship between HIV infection and risk for depressive disorders. *American Journal of Psychiatry*, 158, 725-730. doi:10.1176/appi.ajp.158.5.725

- Ciccarelli, N., Fabbiani, M., Grima, P., Falasca, K., Tana, M., Baldonero, E., ... Di Giambenedetto, S. (2013). Comparison of cognitive performance in HIV or HCV mono-infected and HIV-HCV co-infected patients. *Infection*, 41, 1103-1109. doi:10.1007/s15010-013-0503-2
- Clifford, D. B., Evans, S. R., Yang, Y., & Gulick, R. M. (2005). The neuropsychological and neurological impact of hepatitis C virus co-infection in HIV-infected subjects. *AIDS*, 19(Suppl. 3), S64-S71. doi:10.1097/01.aids.0000192072.80572.43
- Forton, D. M., Hamilton, G., Allsop, J. M., Grover, V. P., Wesnes, K., O'Sullivan, C., ... Taylor-Robinson, S. D. (2008). Cerebral immune activation in chronic hepatitis C infection: A magnetic resonance spectroscopy study. *Journal of Hepatology*, 49, 316-322. doi:10.1016/j.jhep.2008.03.022
- Fumaz, C. R., Muñoz-Moreno, J. A., Ballesteros, A. L., Paredes, R., Ferrer, M. J., Salas, A., ... Clotet, B. (2007). Influence of the type of pegylated interferon on the onset of depressive and neuropsychiatric symptoms in HIV-HCV coinfecting patients. *AIDS Care*, 19, 138-145. doi:10.1080/09540120600645539
- Goulet, J. L., Fultz, S. L., McGinnis, K. A., & Justice, A. C. (2005). Relative prevalence of comorbidities and treatment contraindications in HIV-mono-infected and HIV / HCV-co-infected veterans. *AIDS*, 19(Suppl. 3), S99-S105. doi:10.1097/01.aids.0000192077.11067.e5
- Higgins, J. P. T., & Green, S. (2011). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. The Cochrane Collaboration. Retrieved from [www.cochrane-handbook.org](http://www.cochrane-handbook.org)
- Higgins, J. P. T., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *British Medical Journal* 327, 557-560. doi:10.1136/bmj.327.7414.557
- Hilsabeck, R. C., Hassanein, T. I., Carlson, M. D., Ziegler, E. A., & Perry, W. (2003). Cognitive functioning and psychiatric symptomatology in patients with chronic hepatitis C. *Journal of the International Neuropsychological Society*, 9, 847-854. doi:10.1017/S1355617703960048
- Jones, K. A., & Thomsen, C. (2013). The role of the innate immune system in psychiatric disorders. *Molecular and Cellular Neurosciences*, 53, 52-62. doi:10.1016/j.mcn.2012.10.002

- Kemmer, N., Hua, L., Andersen, J. W., Chung, R. T., Butt, A. A., & Sherman, K. E. (2012). Health-related quality of life in subjects with HCV/HIV coinfection: Results from ACTG 5178 study. *Journal of Viral Hepatitis*, 19, 792-800. doi:10.1111/j.1365-2893.2012.01609.x
- Klein, M. B., Lee, T., Brouillette, M. J., Sheehan, N. L., Walmsley, S., Wong, D. K., ... Singer, J. (2014). Citalopram for the prevention of depression and its consequences in HIV-hepatitis C coinfecting individuals initiating pegylated interferon/Ribavirin therapy: A multicenter randomized double-blind placebo-controlled trial. *HIV Clinical Trials*, 15, 161-175. doi:10.1310/hct1504-161
- Laguno, M., Murillas, J., Blanco, J. L., Martínez, E., Miquel, R., Sánchez-Tapias, J. M., ... & Mallolas, J. (2004). Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for treatment of HIV/HCV co-infected patients. *AIDS*, 18, F27-F36. doi:10.1097/00002030-200409030-00003
- Landau, A., Batisse, D., Piketty, C., Paul, J., Huyen, D. Van, Bloch, F., ... Kazatchkine, M. D. (2001). Long-term efficacy of combination therapy with interferon- $\alpha$  2b and ribavirin for severe chronic hepatitis C in HIV-infected patients. *AIDS*, 15, 2149-2155.
- Leutscher, P. D. C., Lagging, M., Buhl, M. R., Pedersen, C., Norkrans, G., Langeland, N., ... & Bech, P. (2010). Evaluation of depression as a risk factor for treatment failure in chronic hepatitis C. *Hepatology*, 52, 430-435. doi:10.1002/hep.23699
- Martin-Subero, M., & Diez-Quevedo, C. (2016). Mental disorders in HIV/HCV coinfecting patients under antiviral treatment for hepatitis C. *Psychiatry Research*, 246, 173-181. doi:10.1016/j.psychres.2016.09.041
- Michel, L., Villes, V., Dabis, F., Spire, B., Winnock, M., Loko, M. A., ... & Carrieri, M. P. (2010). Role of treatment for depressive symptoms in relieving the impact of fatigue in HIV-HCV co - infected patients: ANRS Co13 Hepaviv, France, 2006–2008. *Journal of Viral Hepatitis*, 17, 650-660. doi:10.1111/j.1365-2893.2009.01223.x
- Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Medicine*, 6(6), e1000097. doi:10.1371/journal.pmed1000097
- Moreno, L., Quereda, C., Moreno, A., Perez-Elías, M. J., Antela, A., Casado, J. L., ... Moreno, S. (2004). Pegylated interferon alpha2b plus ribavirin for the treatment



- of chronic hepatitis C in HIV-infected patients. *AIDS*, 18, 67-73. doi:10.1097/00002030-200401020-00008
- Myers, R. P., Benhamou, Y., Bochet, M., Thibault, V., Mehri, D., & Poynard, T. (2004). Pegylated interferon alpha 2b and ribavirin in HIV/hepatitis C virus-co-infected non-responders and relapsers to IFN-based therapy. *AIDS*, 18, 75-79. doi:10.1097/00002030-200401020-00009
- Nanni, M. G., Caruso, R., Mitchell, A. J., Meggiolaro, E., & Grassi, L. (2015). Depression in HIV infected patients: A review. *Current Psychiatry Reports*, 17(1), 530. doi:10.1007/s11920-014-0530-4
- Nasi, M., Pinti, M., Mussini, C., & Cossarizza, A. (2014). Persistent inflammation in HIV infection: Established concepts, new perspectives. *Immunology letters*, 161, 184-188. doi:10.1016/j.imlet.2014.01.008
- O'Cleirigh, C., Newcomb, M. E., Mayer, K. H., Skeer, M., Traeger, L., & Safren, S. A. (2013). Moderate levels of depression predict sexual transmission risk in HIV-infected MSM: A longitudinal analysis of data from six sites involved in a "prevention for positives" study. *AIDS and Behavior*, 17, 1764-1769. doi:10.1007/s10461-013-0462-8
- Pantalone, D. W., Hessler, D. M., Barkoff, S. M., & Shah, B. J. (2012). Psychosocial correlates of HIV-monoinfection and HIV/HCV-coinfection among men who have sex with men. *Journal of Behavioral Medicine*, 35, 520-528. doi:10.1007/s10865-011-9381-1
- Pereira, M., Fialho, R., & Canavarro, M. C. (2014). Prevalence and correlates of emotional distress in HIV/HCV co-infection. *AIDS Care*, 26(Suppl.1), S56-S64. doi:10.1080/09540121.2014.906549
- Raison, C. L., Borisov, A. S., Majer, M., Drake, D. F., Pagnoni, G., Woolwine, B. J., ... Miller, A. H. (2009). Activation of central nervous system inflammatory pathways by interferon-alpha: Relationship to monoamines and depression. *Biological Psychiatry*, 65, 296-303. doi:10.1016/j.biopsych.2008.08.010
- Richardson, J. L., Nowicki, M., Danley, K., Martin, E. M., Cohen, M. H., Gonzalez, R., ... Levine, A. M. (2005). Neuropsychological functioning in a cohort of HIV- and hepatitis C virus-infected women. *AIDS*, 19, 1659-1667. doi:10.1097/01.aids.0000186824.53359.62

- Ryan, E. L., Morgello, S., Isaacs, K., Naseer, M. G., Gerits, P., & Manhattan HIV Brain Bank. (2004). The neuropsychiatric impact of hepatitis C on advanced HIV. *Neurology*, 62, 957-962. doi:10.1212/01.WNL.0000115177.74976.6C
- Rockstroh, J. K., Mudar, M., Lichterfeld, M., Nischalke, H. D., Klausen, G., Götz, J., ... Mauss, S. (2002). Pilot study of interferon alpha high-dose induction therapy in combination with ribavirin for chronic hepatitis C in HIV-co-infected patients. *AIDS*, 16, 2083-2085. doi:10.1097/00002030-200210180-00016
- Roux, P., Lions, C., Cohen, J., Winrock, M., Salmon-Céron, D., Bani-Sadr, F., ... Carrieri, M. P. (2013). Impact of HCV treatment and depressive symptoms on adherence to HAART among coinfecting HIV-HCV patients: Results from the ANRS-CO13-HEPAVIH cohort. *Antiviral Therapy*. Advance online publication. doi:10.3851/IMP2699
- Schaefer, M., Capuron, L., Friebe, A., Diez-Quevedo, C., Robaey, G., Neri, S., ... Pariante, C. M. (2012). Hepatitis C infection, antiviral treatment and mental health: A European expert consensus statement. *Journal of Hepatology*, 57, 1379-1390. doi:10.1016/j.jhep.2012.07.037
- Silberbogen, A. K., Ulloa, E. W., Janke, E. A., & Mori, D. L. (2009). Psychosocial issues and mental health treatment recommendations for patients with hepatitis C. *Psychosomatics*, 50, 114-122. doi:10.1176/appi.psy.50.2.114
- Slot, M., Sodemann, M., Gabel, C., Holmskov, J., Laursen, T., & Rodkjaer, L. (2015). Factors associated with risk of depression and relevant predictors of screening for depression in clinical practice: A cross-sectional study among HIV-infected individuals in Denmark. *HIV Medicine*, 16, 393-402. doi:10.1111/hiv.12223
- Sulkowski, M. S., Felizarta, F., Smith, C., Slim, J., Berggren, R., Goodman, R., ... & Hepatitis Resource Network Clinical Trials Group. (2004). Daily versus thrice-weekly interferon alfa-2b plus ribavirin for the treatment of chronic hepatitis C in HIV-infected persons: A multicenter randomized controlled trial. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, 35, 464-472. doi:10.1097/00126334-200404150-00004
- Sun, B., Abadjian, L., Rempel, H., Monto, A., & Pulliam, L. (2013). Differential cognitive impairment in HCV coinfecting men with controlled HIV compared to HCV mono-infection. *Journal of Acquired Immune Deficiency Syndromes*, 62, 190-196. doi:10.1097/QAI.0b013e31827b61f1

- Tavakkoli, M., Ferrando, S. J., Rabkin, J., Marks, K., & Talal, A. H. (2013). Depression and fatigue in chronic hepatitis C patients with and without HIV co-infection. *Psychosomatics*, 54, 466-471. doi:10.1016/j.psych.2013.02.009
- The Cochrane Collaboration (2014). *Review Manager (RevMan) [Computer program]*, Version 5.3. Copenhagen: The Nordic Cochrane Centre.
- Thein, H., Maruff, P., Krahn, M., Kaldor, J., Koorey, D., Brew, B., & Dore, G. (2007). Cognitive function, mood and health-related quality of life in hepatitis C virus (HCV)-monoinfected and HIV/HCV-coinfected individuals commencing HCV treatment. *HIV Medicine*, 8, 192-202. doi:10.1111/j.1468-1293.2007.00452.x
- Udina, M., Castellví, P., Moreno-España, J., Navinés, R., Valdés, M., Forns, X., ... Martín-Santos, R. (2012). Interferon-induced depression in chronic hepatitis C: A systematic review and meta-analysis. *Journal of Clinical Psychiatry*, 73, 1128-1138. doi:10.4088/JCP.12r07694
- Uher, R., Perlis, R. H., Placentino, A., Dernovšek, M. Z., Henigsberg, N., Mors, O., ... Farmer, A. (2012). Self-report and clinician-rated measures of depression severity: Can one replace the other? *Depression and Anxiety*, 29, 1043-1049. doi:10.1002/da.21993
- van de Laar, T. J., Matthews, G. V., Prins, M., & Danta, M. (2010). Acute hepatitis C in HIV-infected men who have sex with men: An emerging sexually transmitted infection. *AIDS*, 24, 1799-1812. doi:10.1097/QAD.0b013e32833c11a5
- von Giesen, H.-J., Heintges, T., Abbasi-Boroudjeni, N., Kücükköylü, S., Köller, H., Haslinger, B. A., ... Arendt, G. (2004). Psychomotor slowing in hepatitis C and HIV infection. *Journal of Acquired Immune Deficiency Syndromes*, 35, 131-137. doi:10.1097/00126334-200402010-00005
- Weissenborn, K., Krause, J., Bokemeyer, M., Hecker, H., Schüler, A., Ennen, J. C., ... Böker, K. W. (2004). Hepatitis C virus infection affects the brain - Evidence from psychometric studies and magnetic resonance spectroscopy. *Journal of Hepatology*, 41, 845-851. doi:10.1016/j.jhep.2004.07.022
- Wahl, I., Löwe, B., Bjorner, J. B., Fischer, F., Langs, G., Voderholzer, U., ... Rose, M. (2014). Standardization of depression measurement: A common metric was developed for 11 self-report depression measures. *Journal of Clinical Epidemiology*, 67, 73-86. doi:10.1016/j.jclinepi.2013.04.019
- Yoon, J. C., Crane, P. K., Ciechanowski, P. S., Harrington, R. D., Kitahata, M. M., & Crane, H. M. (2011). Somatic symptoms and the association between hepatitis C

infection and depression in HIV-infected patients. *AIDS Care*, 23, 1208-1218.  
doi:10.1080/09540121.2011.555739

**3. NEUROPSYCHIATRIC SIDE EFFECTS IN HCV TREATMENT:  
INTERFERON INDUCED DEPRESSION IN HEPATITIS C TREATMENT**

### **3.1. Co-infection with HIV associated with reduced vulnerability to symptoms of depression during antiviral treatment for hepatitis C**

#### **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.

## 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 & 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- $\alpha$ ) 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- $\alpha$  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- $\alpha$  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- $\alpha$  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- $\alpha$  may directly enter the brain (Banks, 2005; Banks and Erickson, 2010) via parenchyma cells causing an activation of IFN- $\alpha$  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- $\alpha$  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 pathogenesis 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 induces 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- $\alpha$  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- $\alpha$ -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 hypothesized that the co-infected group would be more likely to present higher prevalence of depression than the HCV group. We also hypothesized 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- $\alpha$  and ribavirin, or pegylated interferon- $\alpha$ , ribavirin and telaprevir 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 2 $\alpha$  180  $\mu$ g weekly sub-cutaneously and oral ribavirin 800-1200mg daily (depending on weight and HCV genotype) or PEG-IFN 2 $\alpha$  180  $\mu$ g 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. 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 IFN $\alpha$  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.

Table 1. Demographic and clinical characteristics of participants receiving HCV treatment ( $N = 172$ )

	HCV ( $n = 132$ ) $n$ (%)	HIV/HCV ( $n = 40$ ) $n$ (%)	$\chi^2$	Cramer's $V$
Marital status			2.93	0.13
Single	67 (50.8)	21 (52.5)		
Married/Cohabiting	56 (42.4)	19 (47.5)		
Separated/Divorced	9 (6.8)	-		
HCV stage			1.25	0.09
Chronic	115 (87.1)	32 (80.0)		
Route of HCV infection			30.06***	0.42
IDU	85 (64.4)	6 (15.0)		
Genotype			1.33	0.09
1	45 (34.1)	13 (32.5)		
2	60 (45.5)	17 (42.5)		
3	18 (13.6)	5 (12.5)		
4	9 (6.8)	5 (12.5)		
HCV treatment			0.24	0.04
PEG-IFN 2 $\alpha$ + Ribavirin + Teleprevir	44 (33.3)	15 (37.5)		
PEG-IFN 2 $\alpha$ + Ribavirin	88 (66.7)	25 (62.5)		
Past psychiatric history			0.11	0.03
No	72 (54.5)	23 (57.5)		
Past drug use			23.52***	0.37
Yes	90 (68.2)	10 (25.0)		
Treatment status			0.11	0.03

Naïve	124 (93.9)	37 (92.5)		
Antidepressant treatment during interferon therapy			1.45	0.09
No	82 (62.1)	29 (72.5)		
SVR			0.004	0.01
Yes	115 (87.1)	35 (87.5)		
	<i>M (SD)</i>	<i>M (SD)</i>	<i>t</i>	Cohen's <i>d</i>
Age	47.06 (10.37)	45.00 (10.63)	1.10	0.20

\*\*\*  $p < 0.001$

### 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, Wilks'  $\lambda = 0.45$ ,  $F(4, 166) = 51.47$ ,  $p < 0.001$ ,  $\eta_p^2 = 0.55$ , 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.

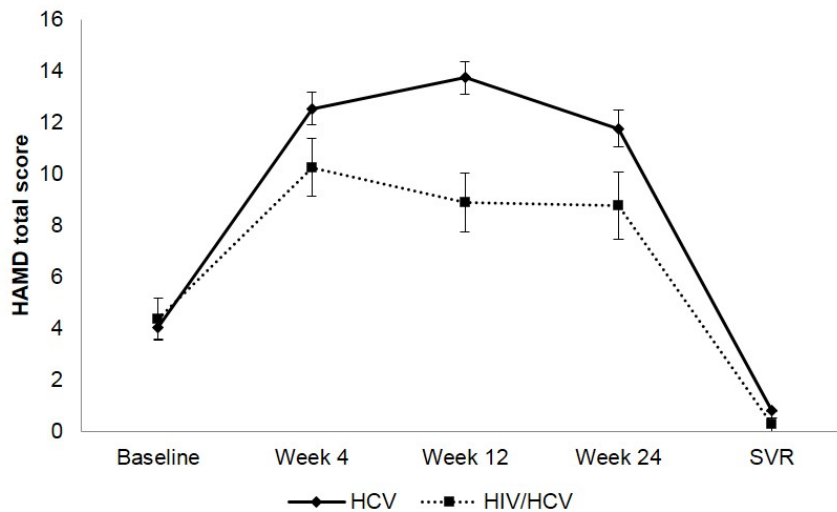


Figure 1. Time course of HAMD mean scores and standard errors (SE) in HCV mono-infected and HIV/HCV co-infected patients during HCV treatment

#### 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'  $\lambda = 0.25$ ,  $F(20, 150) = 22.43$ ,  $p < 0.001$ ,  $\eta_p^2 = 0.75$ . The main effect of group

was not significant, Wilks'  $\lambda = 0.95$ ,  $F(5, 165) = 1.84$ ,  $p = 0.109$ ,  $\eta_p^2 = 0.05$ . The time by group interaction was significant, Wilks'  $\lambda = 0.81$ ,  $F(20, 150) = 1.77$ ,  $p = 0.029$ ,  $\eta_p^2 = 0.19$ , 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.

Table 2. Descriptive statistics in HAMD factors during interferon-based therapy for HCV

	Baseline	Week 4	Week 12	Week 24	SVR	Time ( <i>F</i> )	Group ( <i>F</i> )	Time X Group ( <i>F</i> )
	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>			
Depressive symptoms						10.72***	3.86	1.85
HCV	0.19 (0.03)	0.43 (0.04)	0.47 (0.04)	0.38 (0.04)	0.04 (0.02)			
HIV/HCV	0.22 (0.06)	0.24 (0.07)	0.32 (0.08)	0.32 (0.07)	0.02 (0.04)			
Anxiety symptoms						15.69***	6.09*	1.68
HCV	0.22 (0.03)	0.55 (0.05)	0.63 (0.05)	0.53 (0.05)	0.04 (0.01)			
HIV/HCV	0.21 (0.06)	0.36 (0.09)	0.41 (0.09)	0.35 (0.09)	0.003 (0.03)			
Impaired activity						57.20***	7.30**	1.62
HCV	0.24 (0.04)	1.10 (0.06)	1.18 (0.06)	1.01 (0.07)	0.07 (0.03)			
HIV/HCV	0.23 (0.08)	0.92 (0.11)	0.93 (0.11)	0.70 (0.12)	0.02 (0.05)			
Sleep alterations						35.63***	2.50	2.75*
HCV	0.38 (0.05)	0.87 (0.06)	0.92 (0.06)	0.84 (0.06)	0.05 (0.02)			
HIV/HCV	0.39 (0.09)	0.89 (0.11)	0.55 (0.11)	0.69 (0.11)	0.03 (0.04)			
Somatic symptoms						53.28***	4.77*	5.09**
HCV	0.16 (0.03)	0.81 (0.05)	0.91 (0.04)	0.76 (0.05)	0.05 (0.02)			
HIV/HCV	0.26 (0.05)	0.72 (0.08)	0.55 (0.08)	0.67 (0.09)	0.01 (0.04)			

\*  $p < 0.05$ ; \*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$



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  $\times$  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.

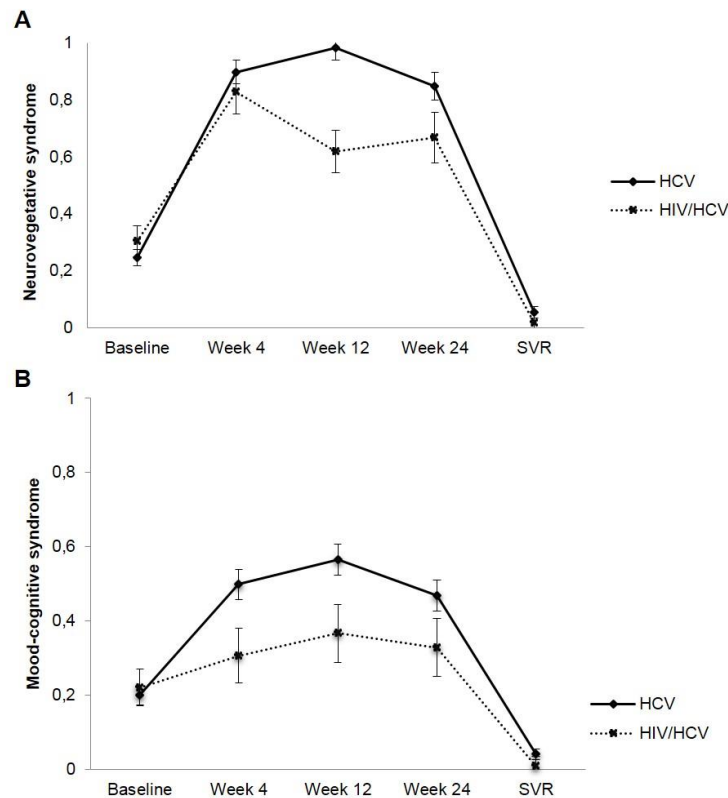


Figure 2. Time course of HAMD syndromes mean scores and standard errors (SE) in HCV mono-infected and HIV/HCV co-infected patients during HCV treatment. Neurovegetative syndrome (A) was defined by HAMD criteria by impaired activity; sleep alterations and somatic symptoms. Mood-cognitive syndrome (B) defined by HAMD criteria by depressive and anxiety symptoms.

#### 4. Discussion

In this study, we found a high prevalence of new-onset MDD during interferon-based treatment in both groups. However, our findings also indicated that the HCV mono-infected patients were more likely to develop MDD earlier in treatment (week 4). This early emergence of symptoms has been previously 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, although not achieving MDD threshold, 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 be 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- $\alpha$  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- $\alpha$  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 mono-infected 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 in depressive symptoms from week 24 to SVR was observed, in line with evidence suggesting that the prevalence of depression significantly decreases after cessation of IFN- $\alpha$  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- $\alpha$ , 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 IFN- $\alpha$  cessation (Lotrich, 2015).

Capuron and colleagues proposed that IFN- $\alpha$  treatment is associated with the emergence of two distinct behavioural syndromes: the mood-cognitive and the neurovegetative, which occur separately by IFN- $\alpha$  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- $\alpha$  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- $\alpha$  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- $\alpha$  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 in 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 primarily 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- $\alpha$  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- $\alpha$ -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- $\alpha$  may still have a role within co-infection. 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.

## References

- Alavi, M., Grebely, J., Matthews, G.V., Petoumenos, K., Yeung, B., Day, C., Day, C., Lloyd, A.R., Van Beek, I., Kaldor, J.M., Hellard, M., Dore, G.J., Haber, P.S., 2012. Effect of pegylated interferon- $\alpha$ -2a treatment on mental health during recent hepatitis C virus infection. *J. Gastroenterol. Hepatol.* 27, 957-965. <http://dx.doi.org/10.1111/j.1440-1746.2011.07035.x>
- Archer, J.A., Hutchison, I.L., Dorudi, S., Stansfeld, S.A., Korszun, A., 2012. Interrelationship of depression, stress and inflammation in cancer patients: a preliminary study. *J. Affect. Disord.* 143, 39-46. <http://dx.doi.org/10.1016/j.jad.2012.05.023>
- Banks, W.A., 2005. Blood-brain barrier transport of cytokines: a mechanism for neuropathology. *Curr. Pharm. Des.* 11, 973-984. <http://dx.doi.org/10.2174/1381612053381684>
- Banks, W.A., Erickson, M.A., 2010. The blood-brain barrier and immune function and dysfunction. *Neurobiol. Dis.* 37, 26-32. <http://dx.doi.org/10.1016/j.nbd.2009.07.031>
- Basseri, B., Yamini, D., Chee, G., Enayati, P.D.P., Tran, T., Poordad, F., 2010. Comorbidities associated with the increasing burden of hepatitis C infection. *Liver International* 30, 1012-1018. <http://dx.doi.org/10.1111/j.1478-3231.2010.02235.x>
- Baum, M.K., Jayaweera, D.T., Duan, R., Sales, S., Lai, S., Rafie, C., Regev, A., Page, J.B., Berkman, R., Campa, A., 2008. Quality of life, symptomatology and healthcare utilization in HIV/HCV co-infected drug users in Miami. *J. Addict. Dis.* 27, 37-48. [http://dx.doi.org/10.1300/J069v27n02\\_05](http://dx.doi.org/10.1300/J069v27n02_05)
- Berk, M., Williams, L.J., Jacka, F.N., O'Neil, A., Pasco, J.A., Moylan, S., Allen, N.B., Stuart, A.L., Hayley, A.C., Byrne, M.L., Maes, M., 2013. So depression is an inflammatory disease, but where does the inflammation come from?. *BMC Med.* 11(1), 200. <http://dx.doi.org/10.1186/1741-7015-11-200>
- Bohn, J.-P., Gastl, G., Steurer, M., 2016. Long-term treatment of hairy cell leukemia with interferon- $\alpha$ : still a viable therapeutic option. *Memo.* 9, 63-65. <http://dx.doi.org/10.1007/s12254-016-0269-1>
- Boscarino, J.A., Lu, M., Moorman, A.C., Gordon, S.C., Rupp, L.B., Spradling, P.R., Teshale, E.H., Schmidt, M.A., Vijayadeva, V., Holmberg, S.D., 2015. Predictors of poor mental and physical health status among patients with chronic hepatitis C

- infection: The Chronic Hepatitis Cohort Study (CHeCS). *Hepatology* 61, 802-811.  
<http://dx.doi.org/10.1002/hep.27422>
- Butt, A.A., Justice, A.C., Skanderson, M., Good, C., Kwoh, C. K., 2006. Rates and predictors of hepatitis C virus treatment in HCV–HIV-coinfected subjects. *Aliment. Pharmacol. Ther.* 24, 585-591. <http://dx.doi.org/10.1111/j.1365-2036.2006.03020.x>
- Calabresi, P.A., Kieseier, B.C., Arnold, D.L., Balcer, L.J., Boyko, A., Pelletier, J., Liu, S., Zhu, Y., Seddighzadeh, A., Hung, S., Deykin, A., 2014. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-blind study. *Lancet Neurol.* 13, 657-665.  
[http://dx.doi.org/10.1016/S1474-4422\(14\)70068-7](http://dx.doi.org/10.1016/S1474-4422(14)70068-7)
- Capuron, L., Fornwalt, F.B., Knight, B.T., Harvey, P.D., Ninan, P.T., Miller, A.H., 2009. Does cytokine-induced depression differ from idiopathic major depression in medically healthy individuals?. *J. Affect. Disord.* 119, 181-185.  
<http://dx.doi.org/10.1016/j.jad.2009.02.017>
- Capuron, L., Gumnick, J.F., Musselman, D.L., Lawson, D.H., Reemsnyder, A., Nemeroff, C.B., Miller, A. H., 2002a. Neurobehavioral effects of interferon- $\alpha$  in cancer patients: phenomenology and paroxetine responsiveness of symptom dimensions. *Neuropsychopharmacology* 26, 643-652.  
[http://dx.doi.org/10.1016/S0893-133X\(01\)00407-9](http://dx.doi.org/10.1016/S0893-133X(01)00407-9)
- Capuron, L., Miller, A.H., 2004. Cytokines and psychopathology: lessons from interferon- $\alpha$ . *Biol. Psychiatry* 56, 819-824.  
<http://dx.doi.org/10.1016/j.biopsych.2004.02.009>
- Capuron, L., Neurauter, G., Musselman, D.L., Lawson, D.H., Nemeroff, C.B., Fuchs, D., Miller, A.H., 2003. Interferon-alpha–induced changes in tryptophan metabolism: relationship to depression and paroxetine treatment. *Biol. Psychiatry* 54, 906-914. [http://dx.doi.org/10.1016/S0006-3223\(03\)00173-2](http://dx.doi.org/10.1016/S0006-3223(03)00173-2)
- Capuron, L., Pagnoni, G., Demetrashvili, M.F., Lawson, D.H., Fornwalt, F.B., Woolwine, B., Berns, G.S., Nemeroff, C.B., Miller, A.H., 2007. Basal ganglia hypermetabolism and symptoms of fatigue during interferon- $\alpha$  therapy. *Neuropsychopharmacology* 32, 2384-2392.  
<http://dx.doi.org/10.1038/sj.npp.1301362>
- Capuron, L., Pagnoni, G., Drake, D.F., Woolwine, B.J., Spivey, J.R., Crowe, R.J., Votaw, J.R., Goodman, M.M., Miller, A.H., 2012. Dopaminergic mechanisms of



- reduced basal ganglia responses to hedonic reward during interferon alfa administration. *Arch. Gen. Psychiatry* 69, 1044-1053. <http://dx.doi.org/10.1001/archgenpsychiatry.2011.2094>
- Capuron, L., Ravaud, A., Gualde, N., Bosmans, E., Dantzer, R., Maes, M., Neveu, P.J., 2001. Association between immune activation and early depressive symptoms in cancer patients treated with interleukin-2-based therapy. *Psychoneuroendocrinology* 26, 797-808. [http://dx.doi.org/10.1016/S0306-4530\(01\)00030-0](http://dx.doi.org/10.1016/S0306-4530(01)00030-0)
- Capuron, L., Ravaud, A., Neveu, P.J., Miller, A.H., Maes, M., Dantzer, R., 2002b. Association between decreased serum tryptophan concentrations and depressive symptoms in cancer patients undergoing cytokine therapy. *Mol. Psychiatry* 7, 468-473. <http://dx.doi.org/10.1038/sj.mp.4000995>
- Carta, M. G., Angst, J., Moro, M. F., Mura, G., Hardoy, M. C., Balestrieri, C., Chessa, L., Serra, G., Lai, M.E., Farci, P., 2012. Association of chronic hepatitis C with recurrent brief depression. *J. Affect. Disord.* 141, 361-366. <http://dx.doi.org/10.1016/j.jad.2012.03.020>
- Chasser, Y., Kim, A.Y., Freudenreich, O., 2017. Hepatitis C treatment: clinical issues for psychiatrists in the post-interferon era. *Psychosomatics*. 58, 1-10. <http://dx.doi.org/10.1016/j.psym.2016.09.004>
- Chayama, K., Mitsui, F., Hayes, C.N, 2015. Optimizing triple therapy and IFN/RBV-free regimens for hepatitis C virus infection. *Expert Rev Gastroenterol Hepatol*. 9, 21-30. <http://dx.doi.org/10.1586/17474124.2015.960394>
- Chen, T.Y., Ding, E.L., Seage, G.R., Kim, A.Y., 2009. Meta-analysis: increased mortality associated with hepatitis C in HIV-infected persons is unrelated to HIV disease progression. *Clin. Infect. Dis.* 49, 1605-1615. <http://dx.doi.org/10.1086/644771>
- Cohen, J., 1992. A power primer. *Psychol. Bull.* 112, 155-159. <http://dx.doi.org/10.1037/0033-2909.112.1.155>
- Cunha, E.C., Behrendorf, M.F., Bavaresco, V., Zambrano, D.N., Bellini, J., Kaster, M.P., Spessato, B., Ghisleni, G., 2015. Genotype 1 of hepatitis C virus increases the risk of major depression: a 12-week prospective study. *Gen. Hosp. Psychiatry* 37, 283-287. <http://dx.doi.org/10.1016/j.genhosppsy.2015.03.016>

- Dantzer, R., O'Connor, J.C., Freund, G.G., Johnson, R.W., Kelley, K.W., 2008. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat. Rev. Neurosci.* 9, 46-56. <http://dx.doi.org/10.1038/nrn2297>
- Dowell, N.G., Cooper, E.A., Tibble, J., Voon, V., Critchley, H.D., Cercignani, M., Harrison, N.A., 2016. Acute changes in striatal microstructure predict the development of interferon-alpha induced fatigue. *Biol. Psychiatry* 79, 320-328. <http://dx.doi.org/10.1016/j.biopsych.2015.05.015>
- Eccles, J., Lallemant, C., Mushtaq, F., Greenwood, M., Keller, M., Golding, B., Tibble, J., Haq, I., Whale, R., 2012. Pre-treatment waking cortisol response and vulnerability to interferon  $\alpha$  induced depression. *Eur Neuropsychopharmacol.* 22, 892-896. <http://dx.doi.org/10.1016/j.euroneuro.2012.03.009>
- Fernandes, B.S., Steiner, J., Bernstein, H., Dodd, S., Pasco, J.A., Dean, O.M., Nardin, P., Gonçalves, C.A., Berk, M., 2015. C-reactive protein is increased in schizophrenia but is not altered by antipsychotics: meta-analysis and implications. *Mol. Psychiatry* 21, 554-564. <http://dx.doi.org/10.1038/mp.2015.87>
- Fialho, R., Keller, M., File, A., Woods, C., Pereira, M., Yousseff, E., Tibble, J., Harrison, N., Fisher, M., Rusted, J., Whale, R., 2014. HCV triple therapy in co-infection HIV/HCV is not associated with a different risk of developing major depressive disorder. *J. Int. AIDS Soc.* 17(4). <http://dx.doi.org/10.7448/IAS.17.4.19629>
- First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1996. Structured Clinical Interview for DSM- IV Axis I Disorders, clinician version (SCID-CV). American Psychiatric Press Inc., Washington DC.
- Fritz-French, C., Tyor, W., 2012. Interferon- $\alpha$  (IFN $\alpha$ ) neurotoxicity. *Cytokine Growth Factor Rev.* 23(1-2), 7-14. <http://dx.doi.org/10.1016/j.cytogfr.2012.01.001>
- Fumaz, C.R., Muñoz-Moreno, J.A., Ballesteros, A.L., Paredes, R., Ferrer, M.J., Salas, A., Fuster, D., Masmitjà, E., Pérez-Alvarez, N., Gómez, G., Tural, C., Clotet, B., 2007. Influence of the type of pegylated interferon on the onset of depressive and neuropsychiatric symptoms in HIV-HCV coinfecting patients. *AIDS Care* 19, 138-145. <http://dx.doi.org/10.1080/09540120600645539>
- Harrison, N.A., Brydon, L., Walker, C., Gray, M.A., Steptoe, A., Critchley, H.D., 2009. Inflammation causes mood changes through alterations in subgenual cingulate activity and mesolimbic connectivity. *Biol. Psychiatry* 66, 407-414. <http://dx.doi.org/10.1016/j.biopsych.2009.03.015>

- Hamilton, M., 1960. A rating scale for depression. *J. Neurol. Neurosurg. Psychiatry* 23(1), 56-62.
- Hesamizadeh, K., Sharafi, H., Rezaee-Zavareh, M.S., Behnava, B., Alavian, S.M., 2016. Next steps toward eradication of hepatitis C in the era of direct acting antivirals. *Hepat Mon.* 16(4), e37089. <http://dx.doi.org/10.5812/hepatmon.37089>
- Hilsabeck, R.C., Castellon, S.A., Hinkin, C.H., 2005. Neuropsychological aspects of coinfection with HIV and hepatitis C virus. *Clin. Infect. Dis.* 41(Suppl. 1), S38-S44. <http://dx.doi.org/10.1086/429494>
- Huckans, M., Fuller, B., Wheaton, V., Jaehnert, S., Ellis, C., Kolessar, M., Kriz, D., Anderson, J.R., Berggren, K., Olavarria, H., Sasaki, A.W., Chang, M., Flora, K.D., Loftis, J.M., 2015. A longitudinal study evaluating the effects of interferon-alpha therapy on cognitive and psychiatric function in adults with chronic hepatitis C. *J. Psychosom. Res.* 78, 184-192. <http://dx.doi.org/10.1016/j.jpsychores.2014.07.020>
- Hoyo-Becerra, C., Schlaak, J.F., Hermann, D.M., 2014. Insights from interferon- $\alpha$ -related depression for the pathogenesis of depression associated with inflammation. *Brain Behav. Immun.* 42, 222-231. <http://dx.doi.org/10.1016/j.bbi.2014.06.200>
- Laguno, M., Murillas, J., Blanco, J.L., Martínez, E., Miquel, R., Sánchez-Tapias, J.M., Bargallo, X., García-Criado, A., de Lazzari, E., Larrousse, M., León, A., Loncá, M., Milinkovic, A., Gatell, J.M., Mallolas, J., 2004. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for treatment of HIV/HCV co-infected patients. *AIDS* 18, F27-F36. <http://dx.doi.org/10.1097/00002030-200409030-00003>
- Landau, A., Batisse, D., Piketty, C., Paul, J., Huyen, D. Van, Bloch, F., Belec, L., Bruneval, P., Weiss, L., Jian, R., Kazatchkine, M.D., 2001. Long-term efficacy of combination therapy with interferon- $\alpha$ 2b and ribavirin for severe chronic hepatitis C in HIV-infected patients. *AIDS* 15, 2149-2155. <http://dx.doi.org/10.1097/00002030-200111090-00010>
- Leutscher, P.D.C., Lagging, M., Buhl, M.R., Pedersen, C., Norkrans, G., Langeland, N., Mørch, K., Färkkilä, M., Hjerrild, S., Hellstrand, K., Bech, P., 2010. Evaluation of depression as a risk factor for treatment failure in chronic hepatitis C. *Hepatology* 52, 430-435. <http://dx.doi.org/10.1002/hep.23699>
- Loftis, J.M., Huckans, M., Ruimy, S., Hinrichs, D.J., Hauser, P., 2008. Depressive symptoms in patients with chronic hepatitis C are correlated with elevated plasma

- levels of interleukin-1 $\beta$  and tumor necrosis factor- $\alpha$ . *Neurosci Lett.* 430, 264-268.  
<http://dx.doi.org/10.1016/j.neulet.2007.11.001>
- Loftis, J.M., Patterson, A.L., Wilhelm, C.J., McNett, H., Morasco, B.J., Huckans, M., Morgan, T., Saperstein, S., Asghar, A., Hauser, P., 2013. Vulnerability to somatic symptoms of depression during interferon-alpha therapy for hepatitis C: a 16-week prospective study. *J. Psychosom. Res.* 74, 57-63.  
<http://dx.doi.org/10.1016/j.jpsychores.2012.10.012>
- Lotrich, F.E., 2015. Inflammatory cytokine-associated depression. *Brain Res.* 1617, 113-125. <http://dx.doi.org/10.1016/j.brainres.2014.06.032>
- Maes, M., Ringel, K., Kubera, M., Berk, M., Rybakowski, J., 2012. Increased autoimmune activity against 5-HT: a key component of depression that is associated with inflammation and activation of cell-mediated immunity, and with severity and staging of depression. *J. Affect. Disord.* 136, 386-392.  
<http://dx.doi.org/10.1016/j.jad.2011.11.016>
- Majumdar, A., Kitson, M.T., Roberts, S.K., 2016. Systematic review: current concepts and challenges for the direct-acting antiviral era in hepatitis C cirrhosis. *Aliment Pharmacol Ther.* 43, 1276–1292. <http://dx.doi.org/10.1111/apt.13633>
- Martin, T.C., Martin, N.K., Hickman, M., Vickerman, P., Page, E.E., Everett, R., Gazzard, B.G., Nelson, M., 2013. Hepatitis C virus reinfection incidence and treatment outcome among HIV-positive MSM. *AIDS* 27, 2551-2557.  
<http://dx.doi.org/10.1097/QAD.0b013e32836381cc>
- Martín-Santos R., Diez-Quevedo C., Castellví, P., Navinés, R., Miquel, M., Masnou, H., Soler, A., Ardevol, M., García, F., Galeras, J.A., Planas, R., Solà, R., 2007. De novo depression and anxiety disorders and influence on adherence during peginterferon-alpha-2a and ribavirin treatment in patients with hepatitis C. *Aliment. Pharmacol. Ther.* 27, 257-265. <http://dx.doi.org/10.1111/j.1365-2036.2007.03568.x>
- Martin-Subero, M., Diez-Quevedo, C., 2016. Mental disorders in HIV/HCV coinfecting patients under antiviral treatment for hepatitis C. *Psychiatry Res.* 246, 173-181.  
<http://dx.doi.org/10.1016/j.psychres.2016.09.041>
- Menard, A., Colson, P., Catherine, D., Isabelle, R., Christelle, T., Meddeb, L., Ben Ali, S., Stein, A., 2016. First real life evidence of new direct-acting antivirals (DAA) in co-infected HIV HCV patients: better than ever. *Clin Infect Dis.* 62, 947-949.  
<https://doi.org/10.1093/cid/civ1215>

- Miller, A.H., Haroon, E., Raison, C.L., Felger, J.C., 2013. Cytokine targets in the brain: impact on neurotransmitters and neurocircuits. *Depress. Anxiety* 30, 297-306. <http://dx.doi.org/10.1002/da.22084>
- Miller, A.H., Maletic, V., Raison, C.L., 2009. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biol. Psychiatry* 65, 732-741. <http://dx.doi.org/10.1016/j.biopsych.2008.11.029>
- Miller, A.H., Raison, C.L., 2016. The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat. Rev. Immunol.* 16(1), 22-34. <http://dx.doi.org/10.1038/nri.2015.5>
- Mohd Hanafiah, K., Groeger, J., Flaxman, A.D., Wiersma, S.T., 2013. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. *Hepatology* 57, 1333-1342. <http://dx.doi.org/10.1002/hep.26141>
- Moreno, L., Quereda, C., Moreno, A., Perez-Elías, M.J., Antela, A., Casado, J.L., Dronda, F., Mateos, M.L., Bárcena, R., Moreno, S., 2004. Pegylated interferon alpha2b plus ribavirin for the treatment of chronic hepatitis C in HIV-infected patients. *AIDS* 18, 67-73. <http://dx.doi.org/10.1097/00002030-200401020-00008>
- Myers, R.P., Benhamou, Y., Bochet, M., Thibault, V., Mehri, D., Poynard, T., 2004. Pegylated interferon alpha 2b and ribavirin in HIV/hepatitis C virus-co-infected non-responders and relapsers to IFN-based therapy. *AIDS* 18, 75-79. <http://dx.doi.org/10.1097/00002030-200401020-00009>
- Oxenkrug, G.F., Turski, W.A., Zgrajka, W., Weinstock, J.V., Ruthazer, R., 2014. Increased serum tryptophan but not kynurenine/tryptophan ratio is associated with the risk of interferon-alpha associated depression in hepatitis C virus patients. *J. Res. Dev.* 2, 114. <http://dx.doi.org/10.4172/jrd.1000114>
- Pan, W., Kastin, A.J., 2003. Interactions of cytokines with the blood-brain barrier: implications for feeding. *Curr. Pharm. Des.* 9, 827-834. <http://dx.doi.org/10.2174/1381612033455332>
- Poudel-Tandukar, K., Bertone-Johnson, E.R., Palmer, P.H., Poudel, K.C., 2014. C-reactive protein and depression in persons with human immunodeficiency virus infection: the Positive Living with HIV (POLH) Study. *Brain Behav. Immun.* 42, 89-95. <http://dx.doi.org/10.1016/j.bbi.2014.06.004>
- Poynard, T., McHutchison, J., Manns, M., Trepo, C., Lindsay, K., Goodman, Z., Ling, M.H., Albrecht, J. (2002). Impact of pegylated interferon alfa-2b and ribavirin on

- liver fibrosis in patients with chronic hepatitis C. *Gastroenterology* 122, 1303-1313. <http://dx.doi.org/10.1053/gast.2002.33023>
- Raison, C.L., Dantzer, R., Kelley, K.W., Lawson, M.A., Woolwine, B.J., Vogt, G., Spivey, J.R., Saito, K., Miller, A.H., 2010. CSF concentrations of brain tryptophan and kynurenines during immune stimulation with IFN- $\alpha$ : relationship to CNS immune responses and depression. *Mol. Psychiatry* 15, 393-403. <http://dx.doi.org/10.1038/mp.2009.116>
- Raison, C.L., Demetrasvili, M., Capuron, L., Miller, A.H., 2005. Neuropsychiatric adverse effects of interferon- $\alpha$ . *CNS Drugs* 19, 105-123. <http://dx.doi.org/10.2165/00023210-200519020-00002>
- Réus, G.Z., Jansen, K., Titus, S., Carvalho, A.F., Gabbay, V., Quevedo, J., 2015. Kynurenine pathway dysfunction in the pathophysiology and treatment of depression: evidences from animal and human studies. *J. Psychiatric Res.* 68, 316-328. <http://dx.doi.org/10.1016/j.jpsychires.2015.05.007>
- Reyes-Vázquez, C., Prieto-Gómez, B., Dafny, N., 2012. Interferon modulates central nervous system function. *Brain Res.* 1442, 76-89. <http://dx.doi.org/10.1016/j.brainres.2011.09.061>
- Rockstroh, J.K., Bhagani, S., 2013. Managing HIV/hepatitis C co-infection in the era of direct acting antivirals. *BMC Med.* 11(1), 234. <http://dx.doi.org/10.1186/1741-7015-11-234>
- Rockstroh, J.K., Mudar, M., Lichterfeld, M., Nischalke, H.D., Klausen, G., Götz, J., Dupke, S., Notheis, G., Stein, L., Mauss, S., 2002. Pilot study of interferon alpha high-dose induction therapy in combination with ribavirin for chronic hepatitis C in HIV-co-infected patients. *AIDS* 16, 2083-2085. <http://dx.doi.org/10.1097/00002030-200210180-00016>
- Schaefer, M., Capuron, L., Friebe, A., Diez-Quevedo, C., Robaeys, G., Neri, S., Foster, G.R., Kautz, A., Forton, D., Pariente, C.M., 2012. Hepatitis C infection, antiviral treatment and mental health: a European expert consensus statement. *J Hepatol.* 57, 1379-1390. <http://dx.doi.org/10.1016/j.jhep.2012.07.037>
- Schaefer, M., Engelbrecht, M.A., Gut, O., Fiebich, B.L., Bauer, J., Schmidt, F., Grunze, H., Lieb, K., 2002. Interferon alpha (IFN $\alpha$ ) and psychiatric syndromes: a review. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 26, 731-746. [http://dx.doi.org/10.1016/S0278-5846\(01\)00324-4](http://dx.doi.org/10.1016/S0278-5846(01)00324-4)

- Smith, K.J., Norris, S., O'Farrelly, C., O'Mara, S.M., 2011. Risk factors for the development of depression in patients with hepatitis C taking interferon- $\alpha$ . *Neuropsychiatr. Dis. Treat.* 7, 275-292. <http://dx.doi.org/10.2147/NDT.S13917>
- Sulkowski, M.S., 2008. Viral hepatitis and HIV coinfection. *J Hepatol.* 48, 353-367. <http://dx.doi.org/10.1016/j.jhep.2007.11.009>
- Sulkowski, M.S., 2016. HCV-HIV co-infected patients: no longer a 'special' population?. *Liver Int.* 36, 43-46. doi:10.1111/liv.13021
- Sulkowski, M., Pol, S., Mallolas, J., Fainboim, H., Cooper, C., Slim, J., Rivero, A., Mak, C., Thompson, S., Howe, A.Y., Wenning, L., Sklar, P., Wahl, J., Greaves, W., 2013. Boceprevir versus placebo with pegylated interferon alfa-2b and ribavirin for treatment of hepatitis C virus genotype 1 in patients with HIV: a randomised, double-blind, controlled phase 2 trial. *Lancet Infect Dis.* 13, 597-605. [http://dx.doi.org/10.1016/S1473-3099\(13\)70149-X](http://dx.doi.org/10.1016/S1473-3099(13)70149-X)
- Sun, B., Abadjian, L., Rempel, H., Monto, A., Pulliam, L., 2013. Differential cognitive impairment in HCV coinfecting men with controlled HIV compared to HCV monoinfection. *J. Acquir. Immune Defic. Syndr.* 62, 190-196. <http://dx.doi.org/10.1097/QAI.0b013e31827b61f1>
- Taraz, M., Khatami, M.R., Gharekhani, A., Abdollahi, A., Khalili, H., Dashti-Khavidaki, S., 2012. Relationship between a pro-and anti-inflammatory cytokine imbalance and depression in haemodialysis patients. *Eur. Cytokine Netw.* 23, 179-186. <http://dx.doi.org/10.1684/ecn.2013.0326>
- Tavakkoli, M., Ferrando, S.J., Rabkin, J., Marks, K., Talal, A.H., 2013. Depression and fatigue in chronic hepatitis C patients with and without HIV co-infection. *Psychosomatics* 54, 466-471. <http://dx.doi.org/10.1016/j.psych.2013.02.009>
- Thein, H.-H., Yi, Q., Dore, G.J., Krahn, M.D., 2008. Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis. *AIDS* 22, 1979-1991. <http://dx.doi.org/10.1097/QAD.0b013e32830e6d51>
- Udina, M., Castellví, P., Moreno-España, J., Navinés, R., Valdés, M., Forns, X., Langohr, K., Solà, R., Vieta, E., Martín-Santos, R., 2012. Interferon-induced depression in chronic hepatitis C: a systematic review and meta-analysis. *J. Clin. Psychiatry* 73, 1128-1138. <http://dx.doi.org/10.4088/JCP.12r07694>
- Udina, M., Moreno-España, J., Navinés, R., Giménez, D., Langohr, K., Gratacós, M., Capuron, L., de la Torre, R., Solà R., Martín-Santos, R., 2013. Serotonin and

- interleukin-6: The role of genetic polymorphisms in IFN-induced neuropsychiatric symptoms. *Psychoneuroendocrinology* 38, 1803-1813. <http://dx.doi.org/10.1016/j.psyneuen.2013.03.007>
- Udina, M., Navinés, R., Egmond, E., Oriolo, G., Langorh, K., Giménez, D., Valdés, M., Gómez-Gil, E., Grande, I., Gratacós, M., Kapczinski, F., Artigas, F., Vieta, E., Solà, R., Martín-Santos, R., 2015. Glucocorticoid receptors, brain-derived neurotrophic factor, serotonin and dopamine neurotransmission are associated with interferon-induced depression. *Int. J. Neuropsychopharmacol.* 19(4), 1-12. <http://dx.doi.org/10.1093/ijnp/pyv135>
- Wang, J., Campbell, I.L., Zhang, H., 2008. Systemic interferon- $\alpha$  regulates interferon-stimulated genes in the central nervous system. *Mol. Psychiatry* 13, 293-301. <http://dx.doi.org/10.1038/sj.mp.4002013>
- Webster, D.P., Wojcikiewicz, T., Keller, M., Castelnovo, D., Mistry, H., Gilleece, Y., Tibble, J., Fisher, M., 2013. Spontaneous clearance and treatment of acute hepatitis C infection in HIV-positive men with 48 weeks of interferon-alpha and ribavirin. *Int. J. STD AIDS* 24, 179-183. <http://dx.doi.org/10.1177/0956462412472317>
- Westbrook, R.H., Dusheiko, G., 2014. Natural history of hepatitis C. *J. Hepatol.* 61(Suppl. 1), S58-S68. <http://dx.doi.org/10.1016/j.jhep.2014.07.012>
- Whale, R., Fialho, R., Rolt, M., Eccles, J., Pereira, M., Keller, M., File, A., Haq, I., Tibble, J., 2015. Psychomotor retardation and vulnerability to interferon alpha induced major depressive disorder: prospective study of a chronic hepatitis C cohort. *J. Psychosom. Res.* 79, 640-645. <http://dx.doi.org/10.1016/j.jpsychores.2015.06.003>
- Yeung, M.W., Young, J., Moodie, E., Rollet-Kurhajec, K.C., Schwartzman, K., Greenaway, C., Cooper, C., Cox, J., Gill, J., Hull, M., Walmsley, S., Klein, M.B., 2015. Changes in quality of life, healthcare use, and substance use in HIV/hepatitis C coinfecting patients after hepatitis C therapy: a prospective cohort study. *HIV Clin Trials*. 16, 100-110. <http://dx.doi.org/10.1179/5011000000024>



### **3.2. Major depressive disorder and immune response in HIV/HCV co-infected men during Hepatitis C treatment**

#### **Abstract**

**Objectives:** The aims of this study were to examine the rate of development of major depressive disorder (MDD) during hepatitis C treatment, the incidence of depressive symptoms throughout treatment and the association between the immune response (as assessed by CD4+ T-cell count) and the onset of depression and sustained virological response (SVR) in a sample of HIV men co-infected with HCV.

**Methods:** The sample consisted of 38 MSM HIV/HCV co-infected attending Brighton & Sussex University Hospitals NHS Trust, Brighton (UK). Participants were assessed using the structured clinical assessment for DSM-IV (SCID) and the Hamilton Depression Scale (HAMD) at baseline, during HCV treatment and at SVR endpoint. All participants were treated with interferon-based therapies for 12 weeks. HCV treatment included pegylated interferon, plus ribavirin and the same combination including telaprevir.

**Results:** Ten patients (26.3%) developed MDD during treatment. There was a significant increase in the HAMD total score from baseline to week 4, and a significant decrease between week 24 and SVR endpoint. There was a significant reduction of CD4+ T-cell count between baseline and week 4. No significant correlations were found between immune response (nadir and baseline CD4+ T-cell count) and depression and SVR.

**Conclusions:** The advent of new HCV treatment regimens represents an important opportunity for reducing treatment-associated adverse events in such co-infected patients. However, interferon based therapies remain the only funded treatment for patients with HCV acute infection and emergence of depression is still remain a risk for treatment discontinuation and or HCV (re)infection.

## Introduction

Recent estimates indicate that about 4 to 5 million patients with human immunodeficiency virus (HIV) worldwide are also co-infected with hepatitis C virus (Berenguer et al, 2012; van de Laar, Matthews, Prins, & Danta, 2010; Wandeler et al, 2012). There is evidence that these rates are higher among intravenous drug users (IDU), though an emerging sexual transmission of HCV has been reported, particularly among men who have sex with men, MSM (Urbanus et al., 2009; van de Laar, Matthews, Prins, & Danta, 2010, Winston et al., 2013).

Interferon- $\alpha$  is therapeutically administered to treat hepatitis C infection, however, among HIV/HCV co-infected patients, the neuropsychiatric side-effects, in particular major depressive disorder (MDD), have been reported as an important cause of treatment discontinuation (Butt, Justice, Skanderson, Good, & Kwoh, 2006; Dieperink et al., 2000), impairment in quality of life (Thein et al., 2007) and reduced likelihood of sustained virological response (SVR) (Leutscher et al., 2010). Recently, the advent of direct antiviral agents (DAAs) have changed the direction of the hepatitis C treatment (Feld, 2014), but due to their expense the DAAs may not become available for all patients and interferon- $\alpha$  still represents an important treatment option remaining the only funded treatment for patients with acute HCV (Hoyo-Becerra, Schlaak, & Hermann, 2014).

Exposure of peripheral administration pro-inflammatory cytokines, such as interferon- $\alpha$  increases inflammation response and is a risk factor for developing depression-like behaviour (Capuron & Miller, 2004; Forton et al., 2008). Immune pathways are involved in this inflammatory condition; in particular T cell responses seem to represent a mechanism that affects emergence of depression (Miller & Raison, 2016).

HIV causes an increased production of pro-inflammatory cytokines, such as endogenous interferons (IFNs), at the early stage of infection, and throughout treatment (Nasi, Pinti, Mussini, & Cossarizza, 2014). It has been suggested therefore that HIV is an inflammatory disease (Borges et al., 2015; Nasi et al., 2014). In the acute HIV stage, part of the immune response is activated by IFNs' stimulation, which inhibits HIV replication. In the later stage, the systematic HIV replication leads to an overstimulation of pro-inflammatory cytokines, which has been associated with high levels of HIV RNA (McMichael et al., 2010). As a consequence to high HIV RNA, CD4<sup>+</sup> T-cells are

gradually lost leading to immune dysfunction (Khaitan & Unutmaz, 2011; Picker, 2006) that has been related with symptoms of depression.

A significant association has been found between CD4<sup>+</sup> T-cell count, depression and accelerated spontaneous apoptosis in CD4<sup>+</sup> T-cells (Fallarino et al., 2002; Ivanova et al., 2007) due to an overstimulation of pro-inflammatory cytokines (Miller et al., 2009, 2010; Raison et al., 2006). T-cell apoptosis in depression has been associated with tryptophan depletion (Mellor et al., 2003). Tryptophan (trp) is essential for function of effector T-cells. Therefore, in a tryptophan deprived environment T-cell suppression may occur (Mellor et al., 2003, 2005). Interestingly, in the context of HCV treatment, interferon therapy may also cause tryptophan depletion, boosting an inflammatory response inducing T-cell and indoleamine 2,3-dioxygenase (IDO) enzyme activation (Capuron et al., 2001; Maes et al., 2001a), resulting in accumulation of toxic metabolites (kynurenine). Tryptophan depletion and kynurenine accumulation have been reported as being significantly associated with increased severity of depressive symptoms such as appetite changes, pessimistic thoughts, suicidal ideation and loss of concentration (Bonaccorso et al., 2002; Capuron et al., 2002). It seems that interferon- $\alpha$ , trp metabolism and CD4<sup>+</sup> T cells are part of a complex immune-inflammatory network that contributes to emergence of depression.

CD4<sup>+</sup> cells may potentially affect the outcome of HCV treatment. The impact of baseline CD4<sup>+</sup> count on hepatitis C virological response is not clear however. Previous data showed that the higher CD4<sup>+</sup> cell count was significantly associated with SVR (Mausset et al., 1998; Aviden et al., 2009). In contrast, other reports failed to find this association in co-infected samples (Dazley et al., 2015; Potter et al., 2010). A study by Valerio and colleagues (2008) found that treatment interruption was frequent in HIV/HCV co-infected patients with genotype non-1 and baseline CD4<sup>+</sup>T-cells < 350 cells/mm<sup>3</sup>, and no significant association was found between baseline CD4<sup>+</sup> T cells count and SVR. Another report found no significant differences on SVR in patients with baseline CD4<sup>+</sup> T-cells  $\leq$  250 cells/mm<sup>3</sup> and with CD4<sup>+</sup> T-cells > 250 cells/mm<sup>3</sup> (Mira et al., 2009). CD4<sup>+</sup> T cell count had very little change over course of treatment and were not associated with SVR (Carrat et al., 2004; Mira et al., 2012; Torriani et al., 2014), suggesting that CD4<sup>+</sup> cell is independently associated with SVR.

Despite this, according with the British HIV Association (BHIVA) guidelines for management of HCV in adults infected with HIV, beginning HIV therapy for HIV

control and CD4+ T-cell count optimisation is recommended, ideally with CD4+ T-cells > 350 cells/mm<sup>3</sup>, whether or not HCV therapy is required (Wilkins et al., 2013, BHIVA).

According to the inflammatory paradigm, increased inflammation, induced by interferon- $\alpha$  therapy, activates immune response that can potentially influence the emergence of MDD. Therefore, the aims of this prospective study were to analyse if immune response, as measured by CD4+ T-cell count at baseline and nadir CD4+ T-cell count, was associated with the development of depression and ultimately SVR among patients co-infected with HIV and HCV.

## **Methods**

### **Participants and procedure**

A total of 38 HIV/HCV co-infected patients were consecutively recruited prior to initiating HCV treatment at the outpatient hepatology clinic at Brighton & Sussex University Hospitals NHS Trust, UK. All participants had a diagnosis of HIV infection with acute or chronic hepatitis C infection. Patients receiving IFN $\alpha$  and ribavirin treatment with or without telaprevir were included. All HCV genotypes were eligible to participate. Exclusion criteria were the following: auto-immune disorder or any other cause of liver disease other than HCV, history of neurological disease, being on efavirenz, presence of acute psychiatric illness, MDD at baseline, being on methadone, and active intravenous drug use or alcohol abuse. Ethical approval was obtained through the National Research Ethics Service (NRES) Committee South East Coast [Reference14/LO/0688]. All participants provided written informed consent.

Participants were assessed for depression, using the measures described below, at different time points within the study as follows: baseline, week 4, week 12, week 24, and 6 months after treatment completion (SVR).

### **Hepatitis C treatment**

HCV treatment was defined as the standard combination of PEG-IFN 2  $\alpha$  180  $\mu$ g weekly subcutaneously and oral ribavirin 800-1200mg daily (weight based) for 24 weeks if HCV RNA remained undetectable by this point. When HCV RNA was detectable at week 24, the length of treatment was extended to 48 weeks. However, for

the purposes of our study we considered the patients that required only 24 weeks of treatment. Triple therapy was defined as PEG-IFN  $2 \alpha$  180  $\mu$ g weekly sub-cutaneously and oral ribavirin 800-1200mg daily and protease inhibitor telaprevir orally (750 mg) every 8 hours. The combination of PEG-IFN, ribavirin and telaprevir was administered for 12 weeks. Among patients with undetectable HCV RNA at week 4 and 12, telaprevir was discontinued and PEG-IFN associated with ribavirin was continued until week 24. All patients started PEG-IFN, ribavirin and telaprevir. At week 12 if HCV RNA was undetectable telaprevir was discontinued. All patients continued treatment to week 24. Overall, both treatments had 24 weeks of interferon exposure.

## Measures

Baseline data were gathered during a face-to-face interview, and included collection of sociodemographic, HIV and HCV-related characteristics. Assessment of MDD diagnosis was undertaken with the semi-structured clinical interview for DSM-IV Axis I diagnosis (SCID-I) (First, Spitzer, Gibbon, & Williams, 1996). For the purpose of defining depression threshold, criterion A12D of the SCID-I (excluding other organic aetiologies) was discarded. The severity of depression and sub-syndrome features were assessed with the 21-item Hamilton Depression Rating Scale (HAMD) (Hamilton, 1960). This scale is of particular use in this context due to its detailed rating of both somatic and non-somatic components of depression.

Positive response to treatment was measured by sustained virological response (SVR), defined as negative HCV viral load measured by polymerase chain reaction assay (PCR, HCV RNA < 1.9 log IU/mL) 6 months after the end of treatment.

## Data analysis

Data were analysed using the Statistical Package for Social Sciences (IBM SPSS, version 20.0). Descriptive statistics with means and standard deviations (*SD*) were reported for continuous variables, and frequencies were reported for categorical variables. Changes in depressive symptoms during hepatitis C treatment were analysed using repeated measures multivariate analysis of variance (MANOVA). A Pearson's correlation coefficient was performed to measure the relationship between immune response and depression, and immune response and clearance. The level of significance was two-tailed and set at 0.05.

## Results

### Participants' characteristics

The sample consisted of 38 HIV/HCV co-infected men, with a mean age of 45.66 years ( $SD = 10.78$ ). The majority of participants had college education (60.5%) and were with no regular partner (57.9%). Most participants had HCV genotype 1 (47.4%), followed by genotype 2 (31.6%), and genotype 3/4 (both 10.5%). Mean nadir CD4+ T-cell count was 239.61 cells/mm<sup>3</sup> ( $SD = 101.53$ ; range: 37-494). At baseline, mean CD4+ T-cell count was 639.32 cells/mm<sup>3</sup> ( $SD = 183.16$ ; range: 210-1064). All patients had undetectable HIV RNA viral load ( $< 50$  copies/mL). Most patients (63.2%) were HIV asymptomatic and 30 patients (78.9%) had chronic HCV infection. Regarding HCV and HIV treatments, 22 patients received PEG-IFN 2  $\alpha$  and ribavirin treatment (57.9%) and all patients were on HIV combination anti-retroviral therapy (cART). Sixteen patients (42.1%) indicated a past history of depression and 2 (5.3%) were re-infected, thought to be with HCV.

### Depression measured by SCID

A total of 10 patients (26.3%) developed SCID defined MDD during HCV treatment. Patients who developed depression did so mostly by week 12 ( $n = 6$ ; 60%).

### Depression symptoms total score

At baseline, the mean HAMD score was 3.68 ( $SD = 5.74$ ; range: 0-20). The expression of changes of depressive symptoms indicated that there was a significant increase in HAMD total score from baseline to week 4, and a significant decrease between week 24 and SVR endpoint, Wilks'  $\lambda = .26$ ,  $F(4, 34) = 23.91$ ,  $p < 0.001$  (Figure 1).

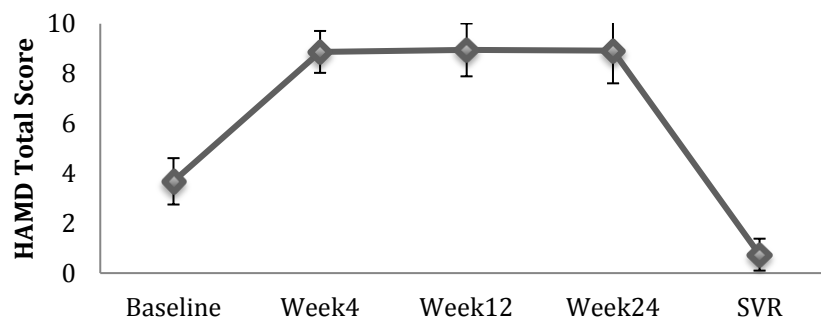


Figure 1 - Time course of HAMD total scores during HCV treatment  
CD4 T-cell count during treatment

During HCV treatment, and adjusting for cART, there was significant effect of time CD4+ T-cell count, Wilks'  $\lambda = .59$ ,  $F(4, 25) = 4.31$ ,  $p = 0.009$  (Figure 2). Follow-up analyses indicated a significant reduction between baseline and week 4 ( $p = 0.006$ ) and a slight increase (non-significant) from week 4 to SVR endpoint.

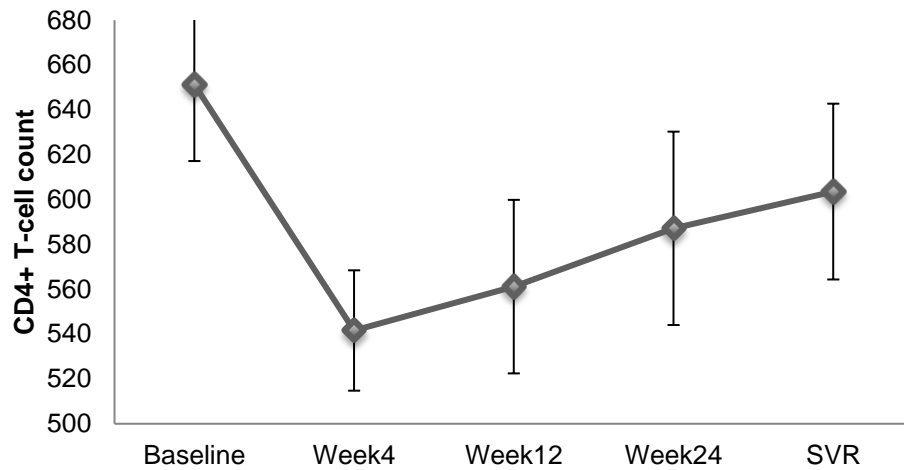


Figure 2 – CD4+ T Cell count during HCV treatment

#### CD4+ T-cell count and development of MDD during HCV treatment

CD4+ T-cell count at baseline was not significantly correlated with the development of MDD during HCV treatment ( $r = .04$ ,  $p = .795$ ). Similarly, the correlation between nadir CD4+ T-cell count and the development of MDD during HCV treatment was not significant ( $r = -.06$ ,  $p = .747$ ). In addition, no significant associations were found with depressive symptoms throughout treatment (all  $p > .142$ ).

#### CD4+ T-cell count and sustained virological response

SVR was achieved in 33 patients (86.8%). No significant correlations were found between nadir and baseline CD4+ T-cell count and SVR ( $r = -.02$ ,  $p = .893$ ;  $r = .24$ ,  $p = .179$ , respectively).

#### Discussion

The main results of this prospective study corroborate prior evidence (Alavi et al., 2012; Udina et al., 2015; Whale et al., 2015) showing a significant increase in depressive symptoms during HCV treatment, in particular at an early stage. No significant association between immune response, measured by CD4+T cell count, and major depressive disorder, measured by SCID-I and SVR was observed. However, a

significant decrease of CD4+ T-cells count between baseline and week 4 ( $p = 0.048$ ) was observed and a slight increase from week 4 to SVR endpoint as reported previously (Arends et al., 2010, Gilleece et al, 2003).

Consistent with prior findings in chronic HCV mono-infection (Udina et al, 2014, 2015; Whale et al., 2015) a significant increase in depressive symptoms was observed early in treatment (Capuron et al., 2002a; Capuron & Miller, 2004). Our results also importantly indicate that depression decreases or remits after the end of treatment, consistent with recent reports (Huckans et al, 2015) supporting a clear role of cytokines and activation of immune factors in the pathophysiology of some depression disorders (Lotrich, 2015; Huckans et al, 2015) with no long-term effect.

Depression has previously been associated with a greater decline in CD4+ T-cell count (Burack et al., 1993; Ickovics et al., 2001; Leserman, 2008). One explanation for T cell alterations in depression is tryptophan depletion. Taking into account the combination of depression, CD4+ T-cell decline and tryptothan as potential mechanisms for the onset of depressive disorders, it was expected that an overstimulation of the inflammatory response via trp mechanisms, as occurs in interferon- $\alpha$  therapy (Capuron et al., 2003; Wichers & Maes, 2004; Zignego et al., 2007), would potentially result in high rates of depression (Capuron et al., 2003, Comai et al., 2011). Interestingly we did not find an association with CD4+ T-cell and MDD during interferon therapy, probably due to the mean of the CD4+ T-cell count being above 500 cells/mm<sup>3</sup> even during HCV treatment. Also, all of our participants had an undetectable HIV viral load and were on anti-retroviral therapy (ARTs).

As mentioned above increased inflammation is a risk factor for developing depression, (Au et al., 2015; Mynt et al., 2013; Duivis et al., 2011; Udina et al., 2015; Harrison et al., 2009). On the other hand, it has been suggested that T cells may be a resilience factor to depression (Brackman et al, 2015; Lewitus et al, 2008). T cells have a role in production of IL-4 within meningeal space and in reducing inflammation, influencing resilience to depression and supporting neural integrity (Loveau et al., 2015; Kim et al., 2012). The mechanisms involved are not clear and the clinical relevance of T cells on depression emergence requires further research. Therefore, it is not surprising that there was a lower rate of depression in a sample that we tend to define as immunologically and inflammatory controlled. It may be that our group of patients with a high mean of CD4+ count and on effective cART suggests that when immune



response, CD4+ T-cells and HIV viral load, are controlled there is a low risk for depression emergence, even under interferon-based therapy.

Additionally, we could consider other potential factors that may explain why HIV/HCV co-infected patients were less vulnerable to developing depression, such as, adherence to treatment and good rate of HCV treatment response.

A significant decrease of CD4+ T cell counts between baseline and week 4 was observed. However, the CD4+ were not equivalent of immunosuppression, they were above >500 cells/ mm<sup>3</sup>. We did not find a correlation between nadir or baseline CD4+ T-cells and SVR. It has been suggested that HCV clearance, measured by SVR, is dependent on the patient's immune status, with a higher CD4+ T-cell count at baseline being associated with a better response to treatment (Caetano et al., 2008; Landau et al., 2001; Mauss et al., 1998; Rosen et al., 2007; Soriano et al., 1996). In contrast, a recent retrospective study with HIV/HCV co-infected patients who were treated for HCV between 2000 and 2008 reported that the baseline CD4+T cell count was not associated with SVR (Aldámiz-Echevarría et al., 2015). Nevertheless, in this large observational study, the median baseline CD4+ T cell count was >500 cells/mm<sup>3</sup>. It seems that having a CD4+ T-cell count >500 cells/ mm<sup>3</sup> is an indicator of SVR, as per our data. Is clear that additional research is needed in order to explore the potential immune and inflammatory mechanisms in HCV infection among HIV/HCV co-infected population.

HCV infection can be transmitted sexually via high-risk behaviour in HIV MSM population (Urbanus et al., 2009; van de Laar et al., 2010, Winston et al., 2013). There is evidence of a significant association between moderate depression and a higher risk of engagement in sexual behaviour in HIV-infected MSM (O'Cleirigh et al., 2013). Additionally, a high rate of HCV re-infection transmitted by sexual risk behaviour in MSM has been reported (van de Laar et al., 2010). Our findings, along with this evidence, highlight the complex association with depression, and subsequently the need for an early screening of depression in order to prevent further HCV infections. Although we did not assess the potential association between depression and risk behaviour, it is possible that changes in depression and well-being over time within this population could explain the difficulty in the diagnosis and treatment of depression (Perdue et al., 2003; Wilson et al., 2014). Overall, in spite of the complex interfaces of depression, our data may facilitate the provision of depression screening and prevent

further HCV infections making it clinically relevant taking into account inflammatory markers.

This study is not without limitations. First, the study was limited by a relatively small sample size, which reduces the power to detect small but potentially important differences. Regarding the paradigm of immune-inflammatory response and depression the use of other HIV markers, such as CD4/CD8 ratio, trp levels and inflammatory markers such as, CRP were not included. A direct link between depression and these parameters was not possible to investigate. It has been suggested that patients with depression may present a poorer anti-inflammatory T cell response. In future studies, it would be relevant to explore the role of T cell as a resilience mechanism to depression in particular within HIV MSM and HCV (re) infection.

This study has however several strengths, including the prospective longitudinal naturalistic design with assessments before, during and after HCV treatment. Additionally, we used well-established depression measures, with well-established psychometric properties and with acknowledged clinical relevance. Therefore, although these findings are novel and potentially important, more research is needed to replicate and extend the results reported herein.

In conclusion, immune response, as measured by nadir and baseline CD4+ T-cells, was not significantly associated with SVR, in HIV/HCV patients. This is an interesting finding and may be associated with the sample size or the high rate of SVR verified in this sample (88%). Additionally, depression was not significantly associated with immune response and SVR, possibly due to the role of T cells as a resilience mechanism. Therefore, given the sample size as well as the substantial gap in the literature, these results must be viewed as preliminary and in need of further replication and extension.

## References

- Aldámiz-Echevarría, T., González-García, J., Von Wichmann, M. A., Crespo, M., López-Aldeguer, J., Quereda, C., ... Guardiola, J. M. (2015). Association of baseline CD4+ cell count and HIV-RNA on sustained virologic response to interferon-ribavirin in HIV/HCV coinfecting patients. *Annals of Hepatology*, 14(4), 464-469.
- Arends, J. E., Claassen, M. A., van den Berg, C. H., Nanlohy, N. M., van Erpecum, K. J., Baak, B. C., ... van Baarle, D. (2010). T-cell responses at baseline and during

- therapy with peginterferon- $\alpha$  and ribavirin are not associated with outcome in chronic hepatitis C infected patients. *Antiviral Research*, 87(3), 353-360.
- Au, B., Smith, K. J., Gariépy, G., & Schmitz, N. (2015). The longitudinal associations between C- reactive protein and depressive symptoms: Evidence from the English Longitudinal Study of Ageing (ELSA). *International Journal of Geriatric Psychiatry*, 30(9), 976-984.
- Berenguer, J., Alejos, B., Hernando, V., Viciana, P., Salavert, M., Santos, I., ... Del Amo, J. (2012). Trends in mortality according to hepatitis C virus serostatus in the era of combination antiretroviral therapy. *AIDS*, 26(17), 2241-2246.
- Bonaccorso, S., Marino, V., Biondi, M., Grimaldi, F., Ippoliti, F., & Maes, M. (2002). Depression induced by treatment with interferon-alpha in patients affected by hepatitis C virus. *Journal of Affective Disorders*, 72(3), 237-241.
- Borges, Á. H., O'Connor, J. L., Phillips, A. N., Rönsholt, F. F., Pett, S., Vjecha, M. J., ... Lundgren, J. D. (2015). Factors associated with plasma IL-6 levels during HIV infection. *Journal of Infectious Diseases*, 212(4), 585-595.
- Brachman, R. A., Lehmann, M. L., Maric, D. & Herkenham, M. (2015) Lymphocytes from chronically stressed mice confer antidepressant-like effects to naive mice. *Journal of Neuroscience*. 35, 1530–1538.
- Burack, J. H., Barrett, D. C., Stall, R. D., Chesney, M. A., Ekstrand, M. L., & Coates, T. J. (1993) Depressive symptoms and CD4 lymphocyte decline among HIV-infected men. *JAMA*, 270, 2568–2573.
- Butt, A. A., Justice, A. C., Skanderson, M., Good, C., & Kwoh, C. K. (2006). Rates and predictors of hepatitis C virus treatment in HCV–HIV-coinfected subjects. *Alimentary Pharmacology & Therapeutics*, 24(4), 585-591.
- Caetano, J., Martinho, A., Paiva, A., Pais, B., Valente, C., & Luxo, C. (2008). Differences in hepatitis C virus (HCV)-specific CD8 T-cell phenotype during pegylated alpha interferon and ribavirin treatment are related to response to antiviral therapy in patients chronically infected with HCV. *Journal of Virology*, 82(15), 7567-7577.
- Capuron, L., Fornwalt, F. B., Knight, B. T., Harvey, P. D., Ninan, P. T., & Miller, A. H. (2009). Does cytokine-induced depression differ from idiopathic major depression in medically healthy individuals? *Journal of Affective Disorders*; 119, 181-185.

- Capuron, L., Hauser, P., Hinze-Selch, D., Miller, A. H., & Neveu, P. J. (2002). Treatment of cytokine-induced depression. *Brain, Behavior and Immunity*, 16, 575-580.
- Capuron, L., & Miller, A. H. (2004). Cytokines and psychopathology: Lessons from interferon- $\alpha$ . *Biological Psychiatry*, 56(11), 819-824.
- Capuron, L., Ravaud, A., & Dantzer, R. (2001). Timing and specificity of the cognitive changes induced by interleukin-2 and interferon-alpha treatments in cancer patients. *Psychosomatic Medicine*, 63(3), 376-386.
- Carrat, F., Bani-Sadr, F., Pol, S., Rosenthal, E., Lunel-Fabiani, F., Benzekri, A., ... Salmon-Céron, D. (2004). Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: A randomized controlled trial. *JAMA*, 292(23), 2839-2848.
- Comai, S., Cavalletto, L., Chemello, L., Bernardinello, E., Ragazzi, E., Costa, C. V. L., & Bertazzo, A. (2011). Effects of PEG-interferon alpha plus ribavirin on tryptophan metabolism in patients with chronic hepatitis C. *Pharmacological Research*, 63(1), 85-92.
- Cunningham, C., Champion, S., Lunnon, K., Murray, C. L., Woods, J. F., Deacon, R. M., ... Perry, V. H. (2009). Systemic inflammation induces acute behavioral and cognitive changes and accelerates neurodegenerative disease. *Biological Psychiatry*, 65(4), 304-312.
- Dieperink, E., Willenbring, M., & Ho, S. B. (2000). Neuropsychiatric symptoms associated with hepatitis C and interferon alpha: A review. *American Journal of Psychiatry*, 157(6), 867-876.
- Duivis, H. E., de Jonge, P., Penninx, B. W., Na, B. Y., Cohen, B. E., & Whooley, M. A. (2011). Depressive symptoms, health behaviors, and subsequent inflammation in patients with coronary heart disease: Prospective findings from the heart and soul study. *American Journal of Psychiatry*, 168(9), 913-920.
- Fallarino, F., Vacca, C., Orabona, C., Belladonna, M. L., Bianchi, R., Marshall, B., ... Puccetti, P. (2002). Functional expression of indoleamine 2, 3-dioxygenase by murine CD8 $\alpha$ <sup>+</sup> dendritic cells. *International Immunology*, 14(1), 65-68.
- Feld, J. J., Kowdley, K. V., Coakley, E., Sigal, S., Nelson, D. R., Crawford, D., ... DaSilva-Tillmann, B. (2014). Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *New England Journal of Medicine*, 370(17), 1594-1603.

- Fialho, R., Keller, M., File, A., Woods, C., Pereira, M., Yousseff, E., ... Whale, R. (2014). HCV triple therapy in co-infection HIV/HCV is not associated with a different risk of developing major depressive disorder. *Journal of the International AIDS Society*, 17(4).
- First MB, Spitzer RL, Gibbon M, Williams JB. *Structured Clinical Interview for DSM-IV Axis I Disorders, clinician version (SCID-CV)*. Washington, DC: American Psychiatric Press, Inc., 1996.
- Forton, D. M., Hamilton, G., Allsop, J. M., Grover, V. P., Wesnes, K., O'Sullivan, C., ... & Taylor-Robinson, S. D. (2008). Cerebral immune activation in chronic hepatitis C infection: A magnetic resonance spectroscopy study. *Journal of Hepatology*, 49(3), 316-322.
- Gilleece, Y. C., Qazi, N. A., Morlese, J. F., Mandalia, S., Gazzard, B. G., Pozniak, A. L., & Nelson, M. R. (2003). The efficacy of lopinavir in individuals experiencing protease inhibitor failure. *Journal of Acquired Immune Deficiency Syndromes*, 32(2), 238-240.
- Hamilton M. (1960). A rating scale for depression. *Journal of Neurology and Neurosurgery Psychiatry*, 23, 56-62.
- Harrison NA, Brydon L, Walker C, Gray MA, Steptoe A, Critchley HD. (2009). Inflammation causes mood changes through alterations in subgenual cingulate activity and mesolimbic connectivity. *Biology Psychiatry*, 66, 407-414.
- Hoyo-Becerra, C., Schlaak, J. F., & Hermann, D. M. (2014). Insights from interferon- $\alpha$ -related depression for the pathogenesis of depression associated with inflammation. *Brain, Behavior, and Immunity*, 42, 222-231.
- Huckans, M., Fuller, B., Wheaton, V., Jaehnert, S., Ellis, C., Kolessar, M., ... Sasaki, A. W. (2015). A longitudinal study evaluating the effects of interferon-alpha therapy on cognitive and psychiatric function in adults with chronic hepatitis C. *Journal of Psychosomatic Research*, 78(2), 184-192.
- Ickovics, J. R., Hamburger, M. E., Vlahov, D., Schoenbaum, E. E., Schuman, P., Boland, R. J., ... & HIV Epidemiology Research Study Group. (2001). Mortality, CD4 cell count decline, and depressive symptoms among HIV-seropositive women: longitudinal analysis from the HIV Epidemiology Research Study. *JAMA*, 285(11), 1466-1474.

- Ingiliz, P., Krznaric, I., Stellbrink, H. J., Knecht, G., Lutz, T., Noah, C., ... Rockstroh, J. K. (2014). Multiple hepatitis C virus (HCV) reinfections in HIV- positive men who have sex with men: No influence of HCV genotype switch or interleukin- 28B genotype on spontaneous clearance. *HIV Medicine*, 15(6), 355-361.
- Ingiliz, P., Steininger, K., Schuetze, M., Dupke, S., Carganico, A., Krznaric, I., ... Baumgarten, A. (2014). Acute hepatitis C virus (HCV) infection in the setting of HIV coinfection: A single-centre 10-year follow-up. *Journal of the International AIDS Society*, 17(4Suppl 3).
- Ivanova, S. A., Semke, V. Y., Vetlugina, T. P., Rakitina, N. M., Kudyakova, T. A., & Simutkin, G. G. (2007). Signs of apoptosis of immunocompetent cells in patients with depression. *Neuroscience and Behavioral Physiology*, 37(5), 527-530.
- Kim, S. J., Lee, H., Lee, G., Oh, S. J., Shin, M. K., Shim, I., & Bae, H. (2012). CD4+ CD25+ regulatory T cell depletion modulates anxiety and depression-like behaviors in mice. *PLoS One*, 7(7), e42054.
- Khaitan, A., & Unutmaz, D. (2011). Revisiting immune exhaustion during HIV infection. *Current HIV/AIDS Reports*, 8(1), 4-11.
- Kuniholm, M. H., Jung, M., Everhart, J. E., Cotler, S., Heiss, G., McQuillan, G., ... Kaplan, R. C. (2014). Prevalence of hepatitis C virus infection in US Hispanic/Latino adults: Results from the NHANES 2007–2010 and HCHS/SOL studies. *Journal of Infectious Diseases*, 209(10), 1585-1590.
- Landau, A., Batisse, D., Piketty, C., Van Huyen, J. P. D., Bloch, F., Belec, L., ... Kazatchkine, M. D. (2001). Long-term efficacy of combination therapy with interferon- $\alpha$ 2b and ribavirin for severe chronic hepatitis C in HIV-infected patients. *AIDS*, 15(16), 2149-2155.
- Lambers, F. A., Prins, M., Thomas, X., Molenkamp, R., Kwa, D., Brinkman, K., ... MOSAIC (MSM Observational Study of Acute Infection with hepatitis C) study group. (2011). Alarming incidence of hepatitis C virus re-infection after treatment of sexually acquired acute hepatitis C virus infection in HIV-infected MSM. *AIDS*, 25(17), F21-F27.
- Leutscher, P. D. C., Lagging, M., Buhl, M. R., Pedersen, C., Norkrans, G., Langeland, N., ... Bech, P. (2010). Evaluation of depression as a risk factor for treatment failure in chronic hepatitis C. *Hepatology*, 52(2), 430-435.

- Lewitus, G. M., Cohen, H., & Schwartz, M. (2008). Reducing post-traumatic anxiety by immunization. *Brain, Behavior and Immunity* 22, 1108–1114.
- Loftis, J. M., Patterson, A. L., Wilhelm, C. J., McNett, H., Morasco, B. J., Huckans, M., ... Hauser, P. (2013). Vulnerability to somatic symptoms of depression during interferon-alpha therapy for hepatitis C: A 16-week prospective study. *Journal of Psychosomatic Research*, 74(1), 57-63.
- Louveau, A., Smirnov, I., Keyes, T. J., Eccles, J. D., Rouhani, S. J., Peske, J. D., ... Harris, T. H. (2015). Structural and functional features of central nervous system lymphatic vessels. *Nature*, 523(7560), 337-341.
- Lotrich, F. E. (2015). Inflammatory cytokine-associated depression. *Brain Research*, 1617, 113-125.
- Luetkemeyer, A. F., Havlir, D. V., & Currier, J. S. (2014). CROI 2014: Viral hepatitis and complications of HIV disease and antiretroviral therapy. *Topics in Antiviral Medicine*, 22, 602-615. Retrieved from <https://www.iasusa.org/tam/may-2014>
- Maes, M., Bonaccorso, S., Marino, V., Puzella, A., Pasquini, M., Biondi, M., Artini, M., Almerighi, C., Meltzer, H. (2001). Treatment with interferon-alpha (IFN alpha) of hepatitis C patients induces lower serum dipeptidyl peptidase IV activity, which is related to IFN alpha-induced depressive and anxiety symptoms and immune activation. *Molecular Psychiatry*, 6, 475-480.
- Maes, M., Capuron, L., Ravaut, A., Gualde, N., Bosmans, E., Egyed, B., ... Neveu, P. J. (2001). Lowered serum dipeptidyl peptidase IV activity is associated with depressive symptoms and cytokine production in cancer patients receiving interleukin-2-based immunotherapy. *Neuropsychopharmacology*, 24(2), 130-140.
- Martin, T. C., Martin, N. K., Hickman, M., Vickerman, P., Page, E. E., Everett, R., ... Nelson, M. (2013). Hepatitis C virus reinfection incidence and treatment outcome among HIV-positive MSM. *AIDS*, 27(16), 2551-2557.
- Mauss, S., Klinker, H., Ulmer, A., Willers, R., Weissbrich, B., Albrecht, H., ... Jablonowski, H. (1998). Response to treatment of chronic hepatitis C with interferon  $\alpha$  in patients infected with HIV-1 is associated with higher CD4+ cell count. *Infection*, 26(1), 16-19.
- McMichael, A. J., Borrow, P., Tomaras, G. D., Goonetilleke, N., & Haynes, B. F. (2010). The immune response during acute HIV-1 infection: Clues for vaccine development. *Nature Reviews Immunology*, 10(1), 11-23.

- Miller, A. H. (2009). Mechanisms of cytokine-induced behavioral changes: Psychoneuroimmunology at the translational interface. *Brain, Behavior, and Immunity*, 23(2), 149-158.
- Miller, A. H. (2010). Depression and immunity: A role for T cells?. *Brain, Behavior, and Immunity*, 24(1), 1-8.
- Miller, A. H., & Raison, C. L. (2016). The role of inflammation in depression: From evolutionary imperative to modern treatment target. *Nature Reviews Immunology*, 16(1), 22-34.
- Mira, J. A., García-Rey, S., Rivero, A., de los Santos-Gil, I., López-Cortés, L. F., Girón-González, J. A., ... Pineda, J. A. (2012). Response to pegylated interferon plus ribavirin among HIV/Hepatitis C virus–coinfected patients with compensated liver cirrhosis. *Clinical Infectious Diseases*, 5(12), 1719-1726.
- Mira, J. A., Gutierrez-Valencia, A., Gil Ide, L., Merino, D., Rivero, A., Rios-Villegas, M. J., ... Pineda, J. A. (2009). Efficacy and safety of pegylated interferon plus ribavirin in HIV and hepatitis C virus–coinfected patients with advanced immunosuppression. *Clinical Infectious Diseases*, 49(8), e84-e91.
- Mellor, A. (2005). Indoleamine 2, 3 dioxygenase and regulation of T cell immunity. *Biochemical and biophysical research communications*, 338(1), 20-24.
- Mellor, A. L., Munn, D., Chandler, P., Keskin, D., Johnson, T., Marshall, B., ... Baban, B. (2003). Tryptophan catabolism and T cell responses. *Advances in Experimental Medicine and Biology*, 527, 27-35.
- Myint, A. M., Bondy, B., Baghai, T. C., Eser, D., Nothdurfter, C., Schüle, C., ... Schwarz, M. J. (2013). Tryptophan metabolism and immunogenetics in major depression: A role for interferon- $\gamma$  gene. *Brain, Behavior, and Immunity*, 31, 128-133
- Nasi, M., Pinti, M., Mussini, C., & Cossarizza, A. (2014). Persistent inflammation in HIV infection: Established concepts, new perspectives. *Immunology Letters*, 161(2), 184-188.
- Neukam, K., Camacho, A., Caruz, A., Rallón, N., Torres-Cornejo, A., Rockstroh, J. K., ... Pineda, J. A. (2012). Prediction of response to pegylated interferon plus ribavirin in HIV/hepatitis C virus (HCV)-coinfected patients using HCV genotype, IL28B variations, and HCV-RNA load. *Journal of Hepatology*, 56(4), 788-794.
- O’Cleirigh, C., Newcomb, M. E., Mayer, K. H., Skeer, M., Traeger, L., & Safren, S. A. (2013). Moderate levels of depression predict sexual transmission risk in HIV-



- infected MSM: A longitudinal analysis of data from six sites involved in a “Prevention for Positives” Study. *AIDS and Behavior*, 17(5), 1764-1769.
- Perry, V. H. (2010). Contribution of systemic inflammation to chronic neurodegeneration. *Acta Neuropathologica*, 120, 277-286.
- Picker, L. J. (2006). Immunopathogenesis of acute AIDS virus infection. *Current Opinion in Immunology*, 18(4), 399-405.
- Patterson, A. L., Morasco, B. J., Fuller, B. E., Indest, D. W., Loftis, J. M., & Hauser, P. (2011). Screening for depression in patients with hepatitis C using the Beck Depression Inventory-II: Do somatic symptoms compromise validity? *General Hospital Psychiatry*, 33, 354-362.
- Soriano, V., Garcia-Samaniego, J., Bravo, R., Gonzalez, J., Castro, A., Castilla, J., ... Rodriguez-Pinero, F. J. (1996). Interferon  $\alpha$  for the treatment of chronic hepatitis C in patients infected with human immunodeficiency virus. *Clinical Infectious Diseases*, 23(3), 585-591.
- Stellbrink, H., Schewe, C., Vogel, M., & Noah, C. (2010). Increasing numbers of acute hepatitis C infections in HIV-infected MSM and high reinfection rates following SVR. *Journal of International AIDS Society*; 13(Suppl. 4): P200.
- Thein, H. H., Maruff, P., Krahn, M., Kaldor, J. M., Koorey, D. J., Brew, B. J., & Dore, G. J. (2007). Cognitive function, mood and health-related quality of life in hepatitis C virus (HCV)-monoinfected and HIV/HCV-coinfected individuals commencing HCV treatment. *HIV Medicine*, 8(3), 192-202.
- Torriani, F. J., Rodriguez-Torres, M., Rockstroh, J. K., Lissen, E., Gonzalez-García, J., Lazzarin, A., ... Sette Jr, H. (2004). Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *New England Journal of Medicine*, 351(5), 438-450.
- Udina, M., Castellví, P., Moreno-España, J., Navinés, R., Valdés, M., Forns, X., ... Martín-Santos, R. (2012). Interferon-induced depression in chronic hepatitis C. *Journal of Clinical Psychiatry*, 73(08), 1128-1138.
- Udina, M., Navinés, R., Egmond, E., Oriolo, G., Langohr, K., Gimenez, D., ... Martín-Santos, R. (2015). Glucocorticoid receptors, brain-derived neurotrophic factor, serotonin and dopamine neurotransmission are associated with interferon-induced depression. *International Journal of Neuropsychopharmacology*, 19(4), pyv135.

- Urbanus, A. T., Van de Laar, T. J., Stolte, I. G., Schinkel, J., Heijman, T., Coutinho, R. A., & Prins, M. (2009). Hepatitis C virus infections among HIV-infected men who have sex with men: an expanding epidemic. *AIDS*, 23(12), F1-F7.
- Urbanus, A. T., Van De Laar, T. J., Geskus, R., Vanhommerig, J. W., Van Rooijen, M. S., Schinkel, J., ... Prins, M. (2014). Trends in hepatitis C virus infections among MSM attending a sexually transmitted infection clinic; 1995–2010. *AIDS*, 28(5), 781-790.
- Valerio, L., Yazdanpanah, Y., Poizot-Martin, I., Rosenthal, E., Marimoutou, C., Gastaut, J., ... Pradier, C. (2008). Baseline CD4 cell count and outcome of pegylated interferon plus ribavirin therapy in HIV/Hepatitis C virus–coinfected patients. *Journal of Acquired Immune Deficiency Syndromes*, 47(1), 50-55.
- Van de Laar, T. J., Matthews, G. V., Prins, M., & Danta, M. (2010). Acute hepatitis C in HIV-infected men who have sex with men: An emerging sexually transmitted infection. *AIDS*, 24(12), 1799-1812.
- Wandeler, G., Gsponer, T., Bregenzer, A., Gunthard, H. F., Clerc, O., & Calmy, A. (2012). Hepatitis C virus infections in the Swiss HIV cohort study: A rapidly evolving epidemic. *Clinical Infectious Diseases*, 55(10), 1408-1416.
- Whale, R., Fialho, R., Rolt, M., Eccles, J., Pereira, M., Keller, M., ... Tibble, J. (2015). Psychomotor retardation and vulnerability to interferon alpha induced major depressive disorder: Prospective study of a chronic hepatitis C cohort. *Journal of Psychosomatic Research*, 79(6), 640-645.
- Winston, A., Arenas-Pinto, A., Stöhr, W., Fisher, M., Orkin, C. M., Aderogba, K., ... Dunn, D. (2013). Neurocognitive function in HIV infected patients on antiretroviral therapy. *PLoS One*, 8(4), e61949.
- Wichers, M. C., & Maes, M. (2004). The role of indoleamine 2, 3-dioxygenase (IDO) in the pathophysiology of interferon-[alpha]-induced depression. *Journal of Psychiatry & Neuroscience*, 29(1), 11-17.
- Zignego, A. L., Ferri, C., Pileri, S. A., Caini, P., & Bianchi, F. B. (2007). Extrahepatic manifestations of Hepatitis C Virus infection: a general overview and guidelines for a clinical approach. *Digestive and Liver Disease*, 39(1), 2-17.

### **3.3. A longitudinal study assessing depression in adults with hepatitis C: Does gender play a role in new-onset depression during interferon-alpha treatment?**

#### **Abstract**

The aim of this prospective study was to examine the differences in new-onset of major depressive disorder (MDD) during interferon-alpha based therapy between men and women infected with hepatitis C virus (HCV). The sample comprised 155 HCV-infected patients (47 women), eligible to receive hepatitis C therapy, including direct acting-antivirals (triple 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. Participants were assessed at baseline, during treatment and six months after treatment completion. In the total sample, the results indicated a significant increase in depressive symptoms from baseline to week 4 and a significant decrease from week 24 to sustained virological response (SVR) endpoint. Women were more likely to present a diagnosis of MDD at end of treatment (week 24). In both men and women, there was a significant increase in neurovegetative and mood-cognitive syndromes at the early stage of treatment, which remitted at the end of the course of HCV therapy. SVR was similar among female and males (91.5% vs. 87%). Under an inflammatory condition, boosted by interferon-based treatments, these results suggest that female gender is not associated with increased vulnerability for development of depression.

## Introduction

There is a high prevalence of hepatitis C virus (HCV) worldwide and HCV infection remains the leading cause of liver disease (Mohd Hanafiah et al. 2013). The transmission of HCV has been consistently associated with intravenous drug use (IDU) and high-risk sexual practices, particularly together with recreational drug use (Ryder 2015). Most studies in this field have been however based on predominantly male samples, leaving HCV-infected women inadequately represented in research. This limits the understanding of potentially important gender differences in response to HCV treatment, and particularly the neuropsychiatric effects associated with interferon-based treatments.

A recent prospective study suggested that women were more likely than men to become infected with HCV, and to report a high risk of injecting behaviours when in a sexual relationship with an IDU partner (Tracy et al. 2014). Among women, substance abuse, HIV infection, and age over 35 years have been identified as risk factors for HCV (Operskalski et al. 2008). These findings highlight the relevance of gender in the context of hepatitis C, which is particularly reinforced by recent meta analytic data indicating that among HCV-infected women the risk of perinatal infection to children was 5.8% [95% confidence interval (CI), 4.2%-15.2%], and that the risk of vertical transmission of HCV is increased among women, with 1 in every 20 children of a mother with chronic HCV infection being infected (Benova et al. 2014; Buchanan and Nash 2015).

Direct-acting antivirals (DAAs) with pegylated-interferon and ribavirin, and interferon-free regimens have emerged as the new treatment options for HCV. Despite the emergence of interferon-free regimens, the pegylated-interferon and ribavirin based treatment is still a valid option, with high cure response rates in acute and chronic HCV infection (Feld 2012). In relation to sex differences, although the research is rather limited, existent evidence about the effectiveness of interferon-based treatment is mixed, with reports of lack of differences between males and females in the response to HCV treatment (Hayashi et al. 1998; McHutchison et al. 2009), but also of lower (Akuta et al. 2007; Villa et al. 2011) and higher (Conjeevaram et al. 2006; Grebely et al. 2014) rates of sustained virological response (SVR) among women. Recent data on DAAs indicated absence of significant differences between men and women in response to treatment with telaprevir and bocepravir (Jacobson et al. 2011; Poordad et al. 2011).

Another study found that women presented a poorer response to treatment (Simoes et al. 2015).

The combination of interferon-alpha (IFN- $\alpha$ ) and ribavirin has been often associated with psychiatric side effects, which have a significant negative impact on patients' quality of life and treatment compliance, and are risk factors for treatment failure. In this context, major depressive disorder (MDD) has been reported as one of the most common psychiatric side effects in the context of interferon-based therapy for HCV (Schaefer et al. 2012). During HCV treatment, increased levels of depressive symptoms have been reported (Udina et al. 2012), particularly at earlier stages of treatment. Moreover, it has been suggested that patients with IFN-induced depression show significantly more symptoms of the neurovegetative syndrome than mood-cognitive symptoms (Capuron et al. 2009). However, if this is true for both men and women with hepatitis C remains to be explored.

It is well-documented that in the the non-iatrogenic model of depression, women present higher rates of depression than men (Kessler et al. 1993; Romans et al. 2007), particularly in bipolar depression (Parker et al. 2014; Piccinelli and Wilkinson 2000). In the general population, there is also evidence that women develop depression at an earlier age and experience more depressive episodes than men (Azorin et al. 2014), which has been related to a multifactorial model, composed of several vulnerability factors, such as childhood sexual abuse, parental loss or disturbed family dynamics, neuroticism traits, early onset of anxiety disorders, substance abuse, low social support and negative life events (Kendler et al. 2002; van Loo et al. 2015). Interestingly, concerning the inflammatory model of depression, such gender vulnerability has not been confirmed. In a recent meta-analysis with 845 patients, although female gender was found to be a weak risk factor for the emergence of IFN-induced depression (Udina et al. 2012), this was not confirmed in a recent study by Whale et al. (2015), which found that gender was not a significant risk factor to the emergence of MDD in a cohort of patients with HCV infection during IFN- $\alpha$  treatment. However, these studies did not focus on the clusters of depressive symptoms (neurovegetative and mood-cognitive), across HCV treatment as described by previous reports (Capuron et al. 2009).

As mentioned, HCV-infected women are an underrepresented population in HCV studies and specific data during hepatitis C treatment are limited. In addition, although a number of studies assessed new-onset depression during treatment, there is still limited

understanding of depression during HCV treatment among women. Understanding the psychiatric side effects during treatment in this population is clinically relevant for carefully planning treatment options and implementing tailored interventions to patients with hepatitis C. Gender sensitive services also need to be considered to address prevention of new HCV infections, mental health comorbidities, as well as unique features of the female population, such as vertical transmission of HCV and menopausal issues. Therefore, the aim of this prospective study was to explore gender differences in the new-onset MDD (defined as the development of depression during treatment among participants who were not depressed prior to the initiation of treatment) during hepatitis C treatment and, additionally, to longitudinally examine the existence of gender differences in the expression of subtypes of depressive symptoms.

## **Methods**

### **Participants and procedure**

A cohort of 231 patients eligible for HCV treatment were prospectively recruited between October 2013 and June 2015 at the outpatient HCV clinic at the Royal Sussex County Hospital, Brighton UK. The following exclusion criteria were considered: being re-infected with HCV, co-infection with HIV, 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. Of the 231 participants enrolled in the study, 15 were excluded from the study analyses because of HCV re-infection episodes, 37 because of HIV co-infection, five due to current drug use and 19 due to baseline MDD. The final sample consisted of 155 participants.

Participants were eligible to start hepatitis C treatment with interferon-based therapies: a combination of PEG-IFN 2 $\alpha$  180  $\mu$ g weekly sub-cutaneously and oral ribavirin 800-1200mg daily (depending on weight and HCV genotype) or PEG-IFN 2 $\alpha$  180  $\mu$ g weekly sub-cutaneously and oral ribavirin 800-1200mg daily and protease inhibitor telaprevir orally (750 mg) every 8 hours. Only those exposed to 24 weeks of treatment were included. All participants were at multiple time points within the study: baseline, week 4, week 12, week 24, and six months after treatment completion (SVR endpoint).

All participants were informed about the aims of the study and gave informed written consent for participation. Ethical approval was obtained through the National Research Ethics Service (NRES) Committee South East Coast.

## **Measures**

At baseline assessment, sociodemographic data (e.g., age, gender, marital status), HCV-related variables (e.g., route of HCV infection, HCV stage, genotype, HCV therapy), and information related to past psychiatric history, and past drug use was collected. Positive response to treatment (viral clearance) was measured by 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 21-item Hamilton Depression Rating Scale (HAM-D) (Hamilton 1960), which consists of 21 items. The total score ranges between 0 and 66, and higher scores denote higher severity of depressive symptoms. This study adopted the factor structure suggested by Capuron et al. (2009): (1) depressive symptoms (depressed mood, feelings of guilt and suicide items); (2) anxiety symptoms (anxiety psychological, hypochondriasis, agitation and anxiety somatic items); (3) impaired activity (work/activities and retardation); (4) sleep alterations (early, middle and late insomnia items); and (5) somatic symptoms (somatic symptoms gastrointestinal, somatic symptoms general, genital symptoms and loss of weight). For the present study, these factors were combined into a biphasic model of depression: the neurovegetative syndrome, which was composed by impaired activity, sleep alterations and somatic symptoms; and the mood-cognitive syndrome, which combined depressive and anxiety symptoms. Alpha reliability in this sample ranged between .82 (Baseline, for men) to .95 (SVR, for men).

## **Data analysis**

Participants were individually coded for either transition to MDD (new-onset depression, defined as development of MDD during treatment among participants who were not depressed prior to the initiation of treatment) or no transition to MDD at any time point during this period. Descriptive statistics with means and standard deviations (*SD*) were reported for continuous variables, and frequencies for categorical variables. Characteristics were compared with Student's *t* tests for continuous variables, and  $\chi^2$  test and Fisher's exact test as appropriate, for testing differences in categorical variables. Repeated-measures multivariate analysis of covariance (MANCOVA) was used to assess changes in depressive symptoms subtypes across groups (between-subjects; female vs. male) and over time (within-subjects). Subsequent univariate analyses of covariance (ANCOVA) were performed to identify the source of the multivariate effects. Bonferroni adjustments were applied to correct for multiple comparisons ( $p < .01$ ). Logistic regression analyses were used to identify factors associated with development of MDD during treatment. Effect sizes were calculated for all analyses (small effects: Cohen's  $d \geq 0.20$ , Cramer's  $V \geq .10$ ; medium effects: Cohen's  $d \geq 0.50$ , Cramer's  $V \geq .30$ ; large effects: Cohen's  $d \geq 0.80$ , Cramer's  $V \geq .50$ ) (Cohen 1992). Data were analysed using the Statistical Package for Social Sciences (IBM SPSS, version 20.0).

## Results

### Participants' characteristics

The final sample consisted of 155 participants (30.3% female;  $n = 47$ ), with a mean age of 46.93 years ( $SD = 10.38$ ; range: 25-71). The majority of participants had HCV chronic infection (84.5%), and were infected with genotype 2 virus (49%). Regarding treatment, most participants received pegylated INF- $\alpha$  and ribavirin ( $n = 107$ ; 69%). Sixty-nine (44.5%) patients reported past psychiatric history, out of which 59 (85.5%) specified prior history of depression. A SVR response was achieved in 88.4% of the sample. No differences were found between male and female patients in the baseline study variables. Table 1 summarizes the sociodemographic and clinical characteristics for the total samples and for the two study groups.

Table 1. Demographic and clinical characteristics of participants receiving HCV treatment ( $N = 155$ )



	Total ( <i>n</i> = 155) <i>n</i> (%)	Female ( <i>n</i> = 47) <i>n</i> (%)	Male ( <i>n</i> = 108) <i>n</i> (%)	$\chi^2$	Cramer's <i>V</i>
Marital status				1.29	.09
Single	70 (45.2)	18 (38.3)	52 (48.1)		
Married/Cohabiting	73 (47.1)	25 (53.2)	48 (44.4)		
Separated/Divorced	12 (7.7)	4 (8.5)	8 (7.4)		
HCV stage				1.73	.11
Acute	24 (15.5)	10 (21.3)	14 (13.0)		
Chronic	131 (84.5)	37 (78.7)	94 (87.0)		
Route of HCV infection				0.00	.001
IDU	99 (63.9)	30 (63.8)	69 (63.9)		
Non-IDU	56 (36.1)	17 (36.2)	39 (36.1)		
Genotype				2.32	.12
1	52 (33.5)	15 (31.9)	37 (34.3)		
2	76 (49.0)	24 (51.1)	52 (48.1)		
3	16 (10.3)	3 (6.4)	13 (12.0)		
4	11 (7.1)	5 (10.6)	6 (5.6)		
HCV treatment				0.35	.05
PEG-IFN 2 $\alpha$ + Ribavirin + Teleprevir	48 (31.0)	13 (27.7)	35 (32.4)		
PEG-IFN 2 $\alpha$ + Ribavirin	107 (69.0)	34 (72.3)	73 (67.6)		
Past psychiatric history				2.06	.12
No	86 (55.5)	22 (46.8)	64 (59.3)		
Yes	69 (44.5)	25 (53.2)	44 (40.7)		
Past drug use				0.04	.01
No	50 (32.3)	15 (31.9)	35 (32.4)		
Yes	105 (67.7)	32 (68.1)	73 (67.6)		
Antidepressant treatment during therapy				0.14	.03
No	99 (63.9)	29 (61.7)	70 (64.8)		
SVR				0.63	.06
Yes	137 (88.4)	43 (91.5)	94 (87.0)		
	<i>M</i> ( <i>SD</i> )	<i>M</i> ( <i>SD</i> )	<i>M</i> ( <i>SD</i> )	<i>t</i>	Cohen's <i>d</i>
Age	46.93 (10.38)	47.66 (9.79)	46.61 (10.66)	-0.58	0.10

\*\*\*  $p < .001$

### Depressive symptoms at baseline

In the total sample, the mean HAMD total score at baseline was 3.17 ( $SD = 4.53$ ; range: 0-22). No significant differences were found between females ( $M = 3.13$ ,  $SD = 4.66$ ) and males ( $M = 3.19$ ,  $SD = 4.50$ ) regarding baseline HAMD total score,  $F(1, 154) = 0.01$ ,  $p = .933$ .

### Development of MDD during treatment

A total of 73 participants (47.1%) developed SCID-I defined MDD during HCV treatment. Of the MDD sample, 35 patients developed MDD by week 4 and by week 12, 55 patients were diagnosed with MDD. These findings represent a cumulative percentage of 75.3% of patients developing MDD within the first 12 weeks of treatment. A higher proportion of women developed MDD during treatment (53.2% vs. 44.4%), although the difference was not statistically significant,  $\chi^2_{(1)} = 1.01$ ,  $p = .316$ , Cramer's  $V = .08$ .

When examining the gender differences in the diagnosis of MDD in each time point, the results indicated that females were not more likely than men to be diagnosed at week 4 (23.4% vs. 22.2%;  $\chi^2_{(1)} = 0.03$ ,  $p = .871$ , Cramer's  $V = .01$ ) or at week 12 (44.7% vs. 31.5%;  $\chi^2_{(1)} = 2.49$ ,  $p = .114$ , Cramer's  $V = .13$ ). However, being female was significantly associated with higher odds of having a MDD diagnosis at week 24 (42.6% vs. 23.6%;  $\chi^2_{(1)} = 5.64$ ,  $p = .018$ , Cramer's  $V = .19$ ).

### **Factors associated with development of MDD: Preliminary analyses**

A range of preliminary analyses (univariate logistic regressions) examining the association between baseline factors and new-onset depression during HCV treatment was conducted in the total sample and separately by gender. For the total sample, the results indicated that having past psychiatric history (Odds ratio [OR] 2.47, 95% confidence interval [CI] 1.29-4.73,  $p = .006$ ) was significantly associated with increased odds of developing MDD during treatment. The results also indicated that past drug use was associated with the development of MDD only for women (OR 5.25, 95% CI 1.35-20.40,  $p = .017$ ). Regarding the type of treatment, there was a significant association between being on telaprevir and increased odds of developing MDD only among men (OR 0.37, 95% CI 0.16-0.88,  $p = .024$ ). Thus, in the analyses of the changes in the severity of symptoms of depression during treatment, the results were adjusted for these potential covariates along with anti-depressant treatment, which was defined a priori as a potential confounder.

### **Changes in depressive symptoms during HCV treatment**

Regarding the HAM-D total score, the results of the repeated measures MANCOVA indicated a significant effect of time [Wilk's  $\lambda = .74$ ,  $F(4, 146) = 13.60$ ,  $p < .001$ ,  $\eta_p^2 = .26$ ]. Neither the effect of group [ $F(1, 149) = 0.18$ ,  $p = .666$ ,  $\eta_p^2 = .001$ ]

nor the interaction time x group [Wilk's  $\lambda = .99$ ,  $F(4, 146) = 0.01$ ,  $p = .876$ ,  $\eta_p^2 = .01$ ] were significant. Regarding the effect of time, subsequent analysis indicated that there was a significant increase in HAMD total score from baseline to week 4 (Mean difference = 9.49,  $p < .001$ ), and a significant decrease between week 24 and SVR endpoint (Mean difference = 12.10,  $p < .001$ ). The increase in depressive symptoms from week 4 to week 12, and from week 12 to week 24 was not significant (see Figure 1). No significant differences were found between men and women in the changes of the HAMD total score during treatment.

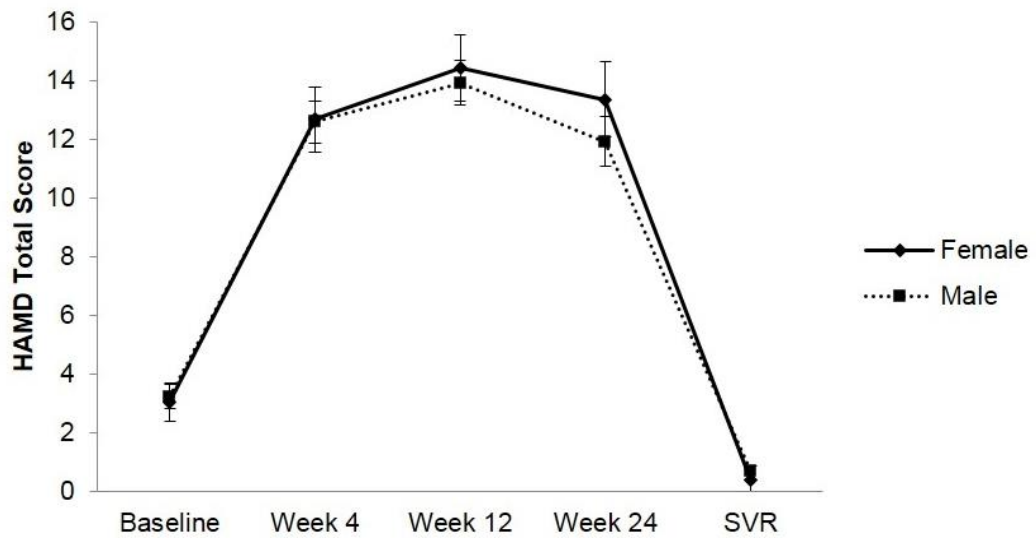


Figure 1. Time course of HAMD total depression score in HCV mono-infected male and female patients during HCV treatment

Regarding the two syndromes of depressive symptoms, the results indicated a significant effect of time [Wilk's  $\lambda = .18$ ,  $F(8, 142) = 79.05$ ,  $p < .001$ ,  $\eta_p^2 = .82$ ]. The effect of group [Wilk's  $\lambda = .98$ ,  $F(2, 148) = 1.88$ ,  $p = .157$ ,  $\eta_p^2 = .03$ ], and the interaction between time and group were not significant [Wilk's  $\lambda = .97$ ,  $F(8, 142) = 1.54$ ,  $p = .766$ ,  $\eta_p^2 = .03$ ]. The descriptive results are summarised in Table 2. Follow-up tests showed a significant increase in both mood-cognitive and neurovegetative syndromes during treatment, most notably between baseline assessment and week 4 ( $p < .001$ ). Additionally, a significant decrease in both syndromes between week 24 and SVR endpoint was found (all  $p < .001$ ) – see Figure 2.

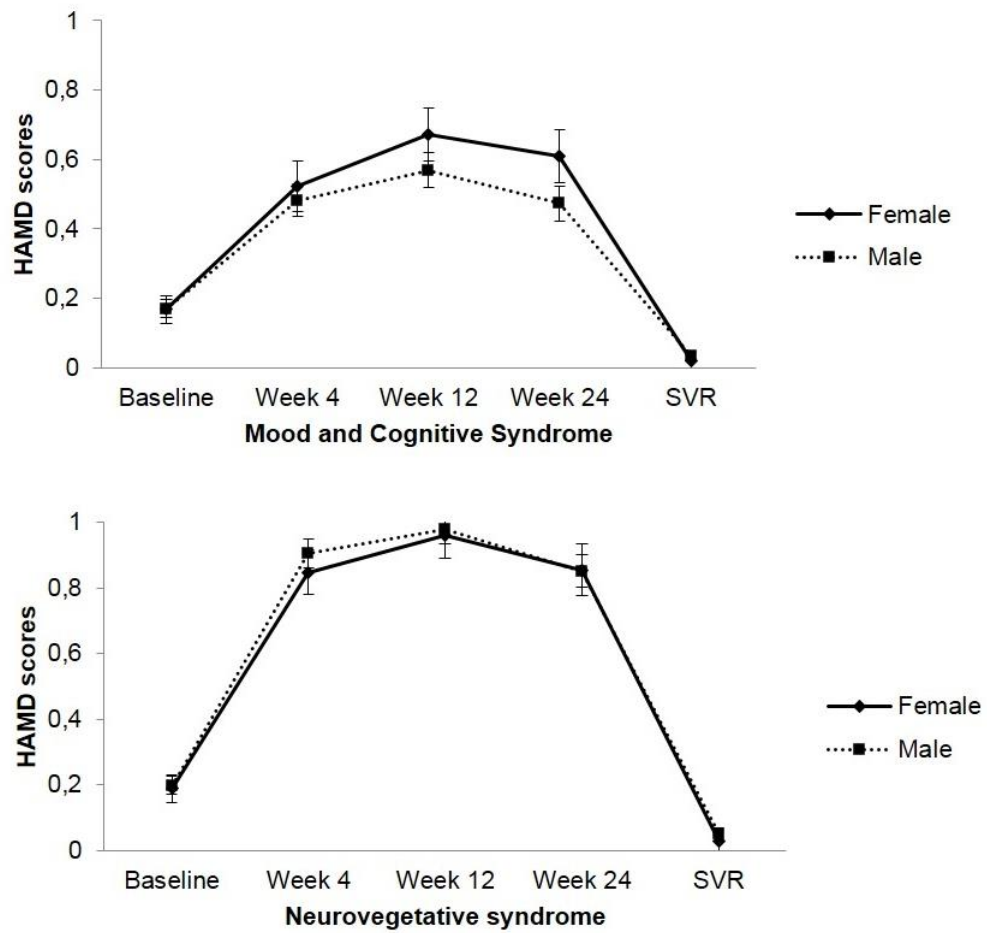


Figure 2. Time course of HAMD clusters of depressive symptoms in HCV-infected men and women during HCV treatment

Table 2. Descriptive statistics in HAMD factors during interferon-based therapy for HCV

	Baseline	Week 4	Week 12	Week 24	SVR	Time (F)	Group (F)	Time X Group (F)
	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>	<i>M (SE)</i>			
Mood-Cognitive syndrome						4.42**	1.41	0.98
Female	0.17 (0.04)	0.52 (0.07)	0.67 (0.07)	0.60 (0.08)	0.02 (0.02)			
Male	0.17 (0.02)	0.48 (0.05)	0.57 (0.05)	0.47 (0.05)	0.03 (0.02)			
Neurovegetative syndrome						19.64***	0.26	0.12
Female	0.19 (0.04)	0.85 (0.07)	0.96 (0.07)	0.86 (0.08)	0.03 (0.03)			
Male	0.20 (0.03)	0.91 (0.05)	0.98 (0.04)	0.85 (0.05)	0.05 (0.02)			

\*\*  $p < .01$ ; \*\*\*  $p < .001$

## Discussion

In this prospective study, we found a significant increase in depressive symptoms from baseline to week 4 and a significant decrease from week 24 to SVR endpoint, a pattern that was similar for both men and women. When examining the association between gender and new-onset MDD in each time point of the study, we found that women were more likely than men to have a diagnosis of MDD at the end of treatment (week 24). During interferon-based therapy, dimensional analyses of depressive symptoms developing during treatment also indicated a similar time course for men and women, that is, a significant increase in neurovegetative and mood-cognitive syndromes at the beginning of the therapy, notably at week 4, and a remission after the end of treatment. The rate of treatment response (SVR) was high in the overall sample (88%), with no differences between men and women.

For both men and women, the severity of depressive symptoms was high at the beginning of treatment and remitted after exposure to treatment, as reported in prior studies (Huckans et al., 2015; Loftis and Hauser, 2004) confirming the transient depressogenic nature of IFN- $\alpha$ . Our findings also indicate that women were more likely to present MDD at week 24 when compared to men (no differences were found in the remaining time points however). Although a recent meta-analysis of ten studies suggested that female gender was a (weak) predictor of new-onset depression during HCV treatment (Udina et al., 2012), all studies included in that meta-analysis did not find evidence of differences between men and women (although there was a trend for women reporting higher odds of occurrence of interferon-alpha-induced depression). To some extent, our findings are consistent with the studies reported in this meta-analysis indicating a lack of differences between men and women in new-onset depression. There is evidence that residual symptoms, early adverse life events and previous episodes of depression are risk factors to recurrence of MDD (Hardeveld et al., 2013; Nanni et al., 2012; van Loo et al., 2015). The presence of MDD at a later stage of HCV treatment in the female sample may relate to the level of residual symptoms that have increased the likelihood of subsequent MDD symptoms, particularly given that more than 50% of women of this sample reported past psychiatric history. Moreover, the kindling hypothesis suggests that the risk of subsequent MDD may depend on the level of stress exposed to (Kendler et al., 2000). Experiencing interferon-based therapy may induce high levels of stress, thus enhancing MDD.

Regarding the dimensional analyses of depressive symptoms developing during treatment, we found that mood-cognitive and neurovegetative syndromes significantly increased at the beginning of treatment, a pattern that was similar for males and females. The neurovegetative syndrome typically occurs within the first month of treatment (Loftis et al., 2013), being less responsive to antidepressant treatment (Capuron and Miller 2004). These symptoms are exhibited preferentially with IFN- $\alpha$  therapy, suggesting that IFN- $\alpha$  causes a dysregulation of the cytokine network that may involve basal ganglia changes and dopamine depletion (Capuron et al., 2007, 2009, 2012; Hayley et al., 2013; Wichers et al., 2007). The emergence of the mood-cognitive syndrome at the early stage of treatment is not consistent with previous findings showing that this syndrome occurs later in treatment (Capuron et al., 2002). There is evidence that IFN-induced mood-cognitive syndrome involves abnormalities in tryptophan/serotonin metabolism (Capuron et al., 2002; Raison et al., 2010). This suggests that IFN- $\alpha$  activates different pathophysiological mechanisms causing two different behavioural syndromes. What is unclear is why the mood-cognitive syndrome develops only in a smaller proportion of patients (Capuron et al., 2007; Musselman et al., 2001). Another explanation might be associated with the overlap effects of emotional adjustment to HCV treatment that often combines symptoms of anxiety and depression, as assessed by the HAMD. The early emergence of these symptoms in treatment suggests that the beginning of treatment is crucial for a comprehensive monitoring and clinical supervision.

This study is not without limitations. The convenience sampling and the relatively small sample size of the female group imply that the generalisation of our results should be undertaken with caution. Despite the inclusion of several sociodemographic and HCV-related variables, we could usefully added other variables (e.g., inflammatory markers, such as IL-6 and CRP) that have been associated with depression (Krogh et al., 2014) and could provide us a better understanding of the nature of IFN-induced depression. Despite these limitations, this study has also important strengths. To our knowledge, this is the first study reporting a detailed assessment of neuropsychiatric side effects in a female sample during HCV treatment. The study design was prospective and longitudinal and all patients were followed in a single centre. In addition, 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 conducted by a trained clinical psychologist.

In summary, in this study, a high rate of MDD was observed during HCV treatment. Women were more likely to present MDD at a later stage of treatment, which may be related to vulnerability factors, such as past psychiatry history and past drug abuse. Neurovegetative and mood-cognitive syndromes stood out as significantly higher at the beginning of the treatment and both remitted at the end of treatment, indicating that these symptoms have a temporary effect caused by the interferon exposure. The persistence of depressive symptoms in the female sample (still present at week 24) may have been attributable to a more severe past history of risk factors. With interferon-free regimens, gender differences are unlikely to be seen, however, because the onset of a MDD episode and recurrence depends on multifactorial model characterized by a complex interplay between biological, psychological and environmental factors (Kendler and Gardner 2014), before starting treatment, it would be valuable to conduct a full assessment of well-established risk factors for new-onset depression. This screening is crucial to decrease the risk of depression and improve treatment compliance and the well-being of this population.

## References

- Akuta, N., F. Suzuki, Y. Kawamura, H. Yatsuji, H. Sezaki, Y. Suzuki, T. Hosaka, M. Kobayashi, M. Kobayashi, Y. Arase, K. Ikeda, and H. Kumada. 2007. Predictors of viral kinetics to peginterferon plus ribavirin combination therapy in Japanese patients infected with hepatitis C virus genotype 1b. *Journal of Medical Virology* 79:1686-95. doi:10.1002/jmv.20979
- Azorin, J. M., R. Belzeaux, E. Fakra, A. Kaladjian, E Hantouche, S. Lancrenon, and M. Adida 2014. Gender differences in a cohort of major depressive patients: Further evidence for the male depression syndrome hypothesis. *Journal of Affective Disorders* 167:85-92. doi:10.1016/j.jad.2014.05.058
- Benova, L., Y. A. Mohamoud, C. Calvert, and L. J. Abu-Raddad. 2014. Vertical transmission of hepatitis C virus: Systematic review and meta-analysis. *Clinical Infectious Diseases* 59:765-73. doi:10.1093/cid/ciu447
- Buchanan, R., and K. L. Nash. 2015. Hepatitis C. *Medicine* 43:607-12. doi:10.1016/j.mpmed.2015.07.008



- Capuron, L., F. B. Fornwalt, B. T. Knight, P. D. Harvey, P. T. Ninan, and A. H. Miller. 2009. Does cytokine-induced depression differ from idiopathic major depression in medically healthy individuals?. *Journal of Affective Disorders* 119:181-5. doi:10.1016/j.jad.2009.02.017
- Capuron, L., J. F. Gummnick, D. L. Musselman, D. H. Lawson, A. Reemsnyder, C. B. Nemeroff, and A. H. Miller. 2002. Neurobehavioral effects of interferon- $\alpha$  in cancer patients: Phenomenology and paroxetine responsiveness of symptom dimensions. *Neuropsychopharmacology* 26:643-52. doi:10.1016/S0893-133X(01)00407-9
- Capuron, L., G. Pagnoni, M. F. Demetrashvili, D. H. Lawson, F. B. Fornwalt, B. Woolwine, G. S. Berns, C. B. Nemeroff, and A. H. Miller. 2007. Basal ganglia hypermetabolism and symptoms of fatigue during interferon- $\alpha$  therapy. *Neuropsychopharmacology* 32:2384-92. doi:10.1038/sj.npp.1301362
- Capuron, L., G. Pagnoni, D. F. Drake, B. J. Woolwine, J. R. Spivey, R. J. Crowe, J. R. Votaw, M. M. Goodman, and A. H. Miller. 2012. Dopaminergic mechanisms of reduced basal ganglia responses to hedonic reward during interferon alfa administration. *Archives of General Psychiatry* 69:1044-53. doi:10.1001/archgenpsychiatry.2011.2094
- Cohen, J. 1992. A power primer. *Psychological Bulletin* 112:155-9. doi:10.1037/0033-2909.112.1.155
- Conjeevaram, H. S., M. W. Fried, L. J. Jeffers, N. A. Terrault, T. E. Wiley-Lucas, N. Afdhal, R. S. Brown, S. H. Belle, J. H. Hoofnagle, D. E. Kleiner, and C. D. Howell. 2006. Peginterferon and ribavirin treatment in African American and Caucasian American patients with hepatitis C genotype 1. *Gastroenterology* 131:470-7. doi:10.1053/j.gastro.2006.06.008
- Feld, J. J. 2012. Treatment indication and response to standard of care with peginterferon and ribavirin in acute and chronic HCV infection. *Best Practice & Research. Clinical Gastroenterology* 26:429-44. doi:10.1016/j.bpg.2012.09.013
- First, M. B., R. L. Spitzer, M. Gibbon, and J. B. W. Williams. 1996. *Structured Clinical Interview for DSM- IV Axis I Disorders, clinician version (SCID-CV)*. Washington DC: American Psychiatric Press Inc.
- Grebely, J., K. Page, R. Sacks-Davis, M. S. Van Der Loeff, T. M. Rice, J. Bruneau, M. D. Morris, B. Hajarizadeh, J. Amin, A. L. Cox, A. Y. Kim, B. H. Mcgovern, J. Schinkel, J. George, N. H. Shoukry, G. M. Lauer, L. Maher, A. R. Lloyd, M.

- Hellard, G. J. Dore, and M. Prins 2014. The effects of female sex, viral genotype, and IL28B genotype on spontaneous clearance of acute hepatitis C virus infection. *Hepatology* 59:109-20. doi:10.1002/hep.26639
- Hamilton, M. 1960. A rating scale for depression. *Journal of Neurology, Neurosurgery & Psychiatry* 23(1):56-62.
- Hardeveld, F., J. Spijker, R. De Graaf, W. A. Nolen, and A. T. F. Beekman. 2013. Recurrence of major depressive disorder and its predictors in the general population: Results from The Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Psychological Medicine* 43, 39-48. doi:10.1017/S0033291712002395
- Hayashi, J., Y. Kishihara, K. Ueno, K. Yamaji, Y. Kawakami, N. Furusyo, Y. Sawayama, and S. Kashiwagi. 1998. Age-related response to interferon alfa treatment in women vs men with chronic hepatitis C virus infection. *Archives of Internal Medicine* 158:177-81. doi:10.1001/archinte.158.2.177
- Hayley, S., J. Scharf, and H. Anisman. 2013. Central administration of murine interferon- $\alpha$  induces depressive-like behavioral, brain cytokine and neurochemical alterations in mice: A mini-review and original experiments. *Brain, Behavior, and Immunity* 31:115-27. doi:10.1016/j.bbi.2012.07.023
- Huckans, M., B. Fuller, V. Wheaton, S. Jaehnert, C. Ellis, M. Kolessar, D. Kriz, J. R. Anderson, K. Berggren, H. Olavarria, A. W. Sasaki, M. Chang, K. D. Flora, and J. M. Loftis. 2015. A longitudinal study evaluating the effects of interferon-alpha therapy on cognitive and psychiatric function in adults with chronic hepatitis C. *Journal of Psychosomatic Research* 78:184-92. doi:10.1016/j.jpsychores.2014.07.020
- Jacobson, I. M., J. G. McHutchison, G. Dusheiko, A. M. Di Bisceglie, K. R. Reddy, N. H. Bzowej, P. Marcellin, A. J. Muir, P. Ferenci, R. Flisiak, J. George, M. Rizzetto, D. Shouval, R. Sola, R. A. Terg, E. M. Yoshida, N. Adda, L. Bengtsson, A. J. Sankoh, T. L. Kieffer, S. George, R. S. Kauffman, and S. Zeuzem. 2011. Telaprevir for previously untreated chronic hepatitis C virus infection. *New England Journal of Medicine* 364:2405-16. doi:10.1056/nejmoa1012912
- Kendler, K. S., C. O. Gardner, and C. A. Prescott. 2002. Toward a comprehensive developmental model for major depression in women. *American Journal of Psychiatry* 159:1133-45. doi:10.1176/appi.ajp.159.7.1133

- Kendler, K. S., and C. O. Gardner. 2014. Sex differences in the pathways to major depression: A study of opposite-sex twin pairs. *American Journal of Psychiatry* 171:426-35. doi:10.1176/appi.ajp.2013.13101375
- Kendler, K. S., L. M. Thornton, and C. O. Gardner. 2000. Stressful Life events and previous episodes in the etiology of major depression in women: An evaluation of the “kindling” hypothesis. *American Journal of Psychiatry* 157:1243-51. doi:10.1176/appi.ajp.157.8.1243
- Kessler, R. C., K. A. McGonagle, M. Swartz, D. G. Blazer, and C. B. Nelson. 1993. Sex and depression in the National Comorbidity Survey I: Lifetime prevalence, chronicity and recurrence. *Journal of Affective Disorders* 29:85-96. doi:10.1016/0165-0327(93)90026-G
- Krogh, J., M. E. Benros, M. B. Jørgensen, L. Vesterager, B. Elfving, and M. Nordentoft. 2014. The association between depressive symptoms, cognitive function, and inflammation in major depression. *Brain, Behavior, and Immunity* 35:70-6. doi:10.1016/j.bbi.2013.08.014
- Loftis, J. M., and P. Hauser 2004. The phenomenology and treatment of interferon-induced depression. *Journal of Affective Disorders* 82:175-90. doi:10.1016/j.jad.2004.04.002
- Loftis, J. M., A. L. Patterson, C. J. Wilhelm, H. McNett, B. J. Morasco, M. Huckans, T. Morgan, S. Saperstein, A. Asghar, and P. Hauser. 2013. Vulnerability to somatic symptoms of depression during interferon-alpha therapy for hepatitis C: A 16-week prospective study. *Journal of Psychosomatic Research* 74:57-63. doi:10.1016/j.jpsychores.2012.10.012
- McHutchison, J. G., E. J. Lawitz, M. L. Shiffman, A. J. Muir, G.W. Galler, J. McCone, L. M. Nyberg, W. M. Lee, R. H. Ghalib, E. R. Schiff, J. S. Galati, B. R. Bacon, M. N. Davis, P. Mukhopadhyay, K. Koury, S. Noviello, L. D. Pedicone, C. A. Brass, J. K. Albrecht, and M. S. Sulkowski. 2009. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *New England Journal of Medicine* 361:580-93. doi:10.1056/NEJMoa0808010
- Mohd Hanafiah, K., J. Groeger, A. D. Flaxman, and S. T. Wiersma. 2013. Global epidemiology of hepatitis C virus infection: New estimates of age-specific antibody to HCV seroprevalence. *Hepatology* 57:1333-42. doi:10.1002/hep.26141.

- Musselman, D. L., D. H. Lawson, J. F. Gumnick, A. K. Manatunga, S. Penna, R. S. Goodkin, K. Greiner, C. B. Nemeroff, and A. H. Miller. 2001. Paroxetine for the prevention of depression induced by high-dose interferon alfa. *New England Journal of Medicine* 344:961-6. doi:10.1056/nejm200103293441303
- Nanni, V. H., R. Uher, and A. Danese. 2012. Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: A meta-analysis. *American Journal of Psychiatry* 169:141-51. doi:10.1176/appi.ajp.2011.11020335
- Operskalski, E. A., W. J. Mack, H. D. Strickler, A. L. French, M. Augenbraun, P. C. Tien, M. C. Villacres, L. Y. Spencer, M. Degiacomo, and A. Kovacs. 2008. Factors associated with hepatitis C viremia in a large cohort of HIV-infected and-uninfected women. *Journal of Clinical Virology* 41:255-63. doi:10.1016/j.jcv.2007.08.021
- Parker, G., K. Fletcher, A. Paterson, J. Anderson, and M. Hong. 2014. Gender differences in depression severity and symptoms across depressive sub-types. *Journal of Affective Disorders* 167:351-7. doi:10.1016/j.jad.2014.06.018
- Piccinelli, M., and G. Wilkison. 2000. Gender differences in depression. *British Journal of Psychiatry* 177:486-92. doi:10.1192/bjp.177.6.486
- Poordad, F., J. McCone, Jr., B. R. Bacon, S. Bruno, M. P. Manns, M. S. Sulkowski, I. M. Jacobson, K. R. Reddy, Z. D. Goodman, N. Boparai, M. J. DiNubile, V. Sniukiene, C. A. Brass, J. K. Albrecht, and J.-P. Bronowicki. 2011. Boceprevir for untreated chronic HCV genotype 1 infection. *New England Journal of Medicine* 364:1195-206. doi:10.1056/nejmoa1010494
- Raison, C. L., R. Dantzer, K. W. Kelley, M. A. Lawson, B. J. Woolwine, G. Vogt, J. R. Spivey, K. Saito, and A. H. Miller. 2010. CSF concentrations of brain tryptophan and kynurenines during immune stimulation with IFN- $\alpha$ : Relationship to CNS immune responses and depression. *Molecular Psychiatry* 15:393-403. doi:10.1038/mp.2009.116
- Ryder, S. D. 2015. Chronic hepatitis C—what do the new drugs offer and who should get them first?. *Clinical Medicine* 15:197-200. doi:10.7861/clinmedicine.15-2-197
- Romans, S. E., J. Tyas, M. M. Cohen, and T. Silverstone. 2007. Gender differences in the symptoms of major depressive disorder. *The Journal of Nervous and Mental Disease* 195:905-11. doi:10.1097/nmd.0b013e3181594cb7

- Simoes, P., A. Asaad, J. Abed, E. S. Engelson, and D. P. Kotler. 2015. Effect of gender on the response to hepatitis C treatment in an inner-city population. *Women's Health Issues* 25:289-93. doi:10.1016/j.whi.2015.02.008
- Schaefer, M., L. Capuron, A. Friebe, C. Diez-Quevedo, G. Robaey, S. Neri, S., G. R. Foster, A. Kautz, D. Forton, and C. M. Pariente. 2012. Hepatitis C infection, antiviral treatment and mental health: A European expert consensus statement. *Journal of Hepatology* 57:1379-90. doi:10.1016/j.jhep.2012.07.037
- Tracy, D., J. A. Hahn, C. F. Lewis, J. Evans, A. Briceño, M. D. Morris, and K. Page. 2014. Higher risk of incident hepatitis C virus among young women who inject drugs compared with young men in association with sexual relationships: A prospective analysis from the UFO Study cohort. *BMJ Open* 4(5):e004988. doi:10.1136/bmjopen-2014-004988
- Udina, M., P. Castellví, J. Moreno-España, R. Navinés, M. Valdés, X. Forns, X., K. Langohr, R. Solà, E. Vieta, and R. Martín-Santos. 2012. Interferon-induced depression in chronic hepatitis C: A systematic review and meta-analysis. *Journal of Clinical Psychiatry* 73:1128-38. doi:10.4088/JCP.12r07694
- Villa, E., A. Karampatou, C. Cammà, A. Di Leo, M. Luongo, A. Ferrari, S. Petta, L. Losi, G. Taliani, P. Trande, B. Lei, A. Graziosi, V. Bernabucci, R. Critelli, P. Pazienza, M. Rendina, A. Antonelli, and A. Francavilla. 2011. Early menopause is associated with lack of response to antiviral therapy in women with chronic hepatitis C. *Gastroenterology* 140:818-29. doi:10.1053/j.gastro.2010.12.027
- van Loo, H. M., S. H. Aggen, C. O. Gardner, and K. S. Kendler. 2015. Multiple risk factors predict recurrence of major depressive disorder in women. *Journal of Affective Disorders* 180:52-61. doi:10.1016/j.jad.2015.03.045
- Whale, R., R. Fialho, M. Rolt, J. Eccles, M. Pereira, M. Keller, A. File, I. Haq, and J. Tibble. 2015. Psychomotor retardation and vulnerability to interferon alpha induced major depressive disorder: Prospective study of a chronic hepatitis C cohort. *Journal of Psychosomatic Research* 79:640-5. doi:10.1016/j.jpsychores.2015.06.003
- Wichers, M. C., G. Kenis, G. H. Koek, G. Robaey, N. A. Nicolson, and M. Maes. 2007. Interferon-alpha-induced depressive symptoms are related to changes in the cytokine network but not to cortisol. *Journal of Psychosomatic Research* 62:207-14. doi:10.1016/j.jpsychores.2006.09.007

#### **4. EXECUTIVE FUNCTIONS AND INTERFERON BASED THERAPY WITH DIRECT ACTING ANTIVIRALS IN HIV ACUTE HCV CO-INFECTION**

#### **4.1. Executive function and interferon based therapy with direct acting antivirals in HIV acute HCV co-infection**

##### **Abstract**

**Background and aims:** Executive function (EF) impairment has been significantly associated with chronic viral conditions such as HIV and hepatitis C (HCV), with implications for overall functioning. As a consequence of interferon-based therapies, changes in cognition have been reported, in particular on EF. The aim of the present study was to analyse the EF performance in an acute HCV/HIV co-infected sample undergoing HCV treatment with direct acting antiviral (DAAs).

**Methods:** Twenty-five HIV infected men who have sex with men (MSM) participants were recruited of which 13 were HCV acute infected and 12 were HIV mono-infected. The groups were matched for age, education and HIV clinical status at baseline, and were assessed prospectively before, during and at the end of treatment using EF measures.

**Results:** The co-infected group showed a significant increase on speed of processing under prospective memory conditions from baseline to week 4. Significant results in speed components on updating, measured by RNG task, and speed of processing measured by TMT part A task, were also observed, which indicated processing speed changes between baseline and week 4. The processing speed impairment was confirmed on between groups analysis, measured by TMT part A, with the co-infected group being more impaired than the HIV group between baseline and week 12.

**Discussion:** In acute HCV co-infection there was an effect of DAAs with IFN- $\alpha$  treatment on EF performance, in particular with the co-infected group presenting a disadvantage on information processing speed. The poor performance on a prospective memory (PM) task also adds another layer to the EF model. However, it is not clear what pathway mediates this cognitive outcome, if it is the inflammatory condition, or HIV itself, or residual effects of both. Clearly more research is needed in a co-infection sample to confer external validity.

## **Introduction**

Executive functions (EF) are high-level cognitive processes that includes several cognitive operations that are thought to guide our behaviour, allowing individuals to behave independently with the ability to make decisions, plan for the future, assess risks, and cope with new situations (Lezak, 2004). The EF performance implies recruiting automatic responses, switching between tasks, planning, ability to inhibit responses in order to control interference to achieve the goal, aspects of verbal fluency and of working memory (Friedman & Miyake, 2016).

It has been proposed that performance of EF is fractionated into sub-processes indicating distinct functions. The three-component model of EF proposes updating, shifting and inhibiting factors (Miyake et al., 2000; Miyake & Friedman, 2012). According to Miyake, updating involves monitoring and coding incoming information, replacing the no longer relevant information with the newer. Shifting is defined as the ability to switch between tasks sets or responses. Finally, inhibition implies suppressing an automatic response in order to make it relevant for the task response (Miyake et al., 2000).

The executive functions (EF) framework has been widely studied, examining concepts of unity and diversity highlighting that EF performance not only presents something common (unity) but also involves specific cognitive features (diversity) (Friedman & Miyake, 2016; Miyake et al., 2000). Classic literature proposed that the correlation between levels of EF argues in favour of the unity paradigm (Friedman et al., 2011; Teuber, 1972; Wiebe, Espy, & Charak, 2008) but at the same time other reports using multivariate statistical analysis confirmed the EF diversity (Miyaki et al., 2000). There is a rich literature on the parcellation of EF, although the findings differ across studies. According to the bifactor model based on correlated factors analysis, unity was considered as a common EF inhibition level and diversity embedded by updating and shifting components (Friedman et al., 2008). However, evidence failed to extract an independent inhibition component questioning the concept on common factor (Banich & Depue, 2015; Friedman et al., 2008; Miyake et al., 2000). Possibly this was due to the nature of the tasks. The association between the EF components is still debatable. The EF component that seems to play a key role in EF performance is inhibition (Hall & Fong, 2015), in particular when task performance requires goal relevant information (Friedman & Miyake, 2016). Some reports suggest that inhibition



and updating are significantly correlated (Klauer, Schmitz, Teige-Mocigemba, & Voss, 2010); others failed to replicate this findings (Hull et al, 2008). Inhibition and shifting were predictors of PM performance, highlighting the correlation between EF components and the influence of other cognitive constructs such as prospective memory (PM) and decision-making (Schnitzspahn et al, 2013). What seems to be consensual is that shifting is separable from inhibition and updating (Brydges et al., 2014).

EF impairment has been strongly associated with HIV neurocognitive disorders-HAND (Reger et al., 2007), which has been linked with sub-cortical pathology (Gongvatana et al., 2007; Thames et al., 2012). In HIV asymptomatic patients on combination antiretroviral therapy (cART) EF impairment is frequent (Heaton et al., 2011) with reports of a significant association between poor performance on executive tasks (Trail Making Test, Grooved Pegboard and Digit symbol) and decrease levels of glutamate and glutamine in frontal white matter (Mohamed et al., 2010). HIV literature describes a significant association between EF impairment and decision-making impairment (Hardy et al., 2006; Iudicello et al., 2013; Martin et al., 2013). EF and decision-making constructs tend to be traditionally assessed due to recruitment of executive functions to select the most advantageous response from a variety of options (Bechara, 2004; Bechara & Damasio, 2005). Also decision-making impairment presents similar symptoms in conditions of frontal lobe lesions (Bechara et al., 1994) and substance use disorders (Duarte et al., 2012; Ludicello et al., 2012; Verdejo-Garcia et al., 2006). The HCV associated neurocognitive disorder (HCV-AND) profile also involves EF impairment, which has been linked with significant brain metabolic changes due to influence on glial cells (Monaco et al., 2015). In HIV/HCV co-infection it is reasonable to hypothesize that EF may be worse than in HIV mono-infection because the presence of both viruses leads to greater cognitive functioning deficits (Letendre et al., 2005; Martin et al., 2004; Webster et al., 2013) due to the viruses' replication in the brain and cerebrospinal fluid (Aronow et al., 2008; Hinkin et al., 2008).

The impact of inflammation on cognitive functions has been widely investigated, most notably the role of cytokines in cognitive processes such as learning and memory (McAfoose et al., 2009) and in particular executive functions (Cohen et al., 2011). Cytokines, such as interferon- $\alpha$  (IFN- $\alpha$ ) are peripheral inflammatory mediators that influence cognition by entry into the central nervous system (CNS) (Rothwell,

1999; Wilson et al., 2002). A strong association has been observed between cytokine concentrations and cognitive performance, with reduced performance on executive EF, measured by the Trial Making Test part A, associated with elevated IL-16 and IP-10 concentrations and reduced levels of IL-10. The Trail Making Test part B was also associated with elevated IL-6 and reduced IL-10 concentrations (Cohen et al., 2011).

The significance of impairment on executive functions via inflammatory mechanisms is not clear; however some empirical evidence for the inflammatory paradigm comes from hepatitis C interferon based treatment. In this context, a significant association with subjective complaints of memory loss, depression, impaired motor activity and executive functioning deficits have been reported (Hilsabeck et al., 2005; Lieb et al., 2006; Wilson, Finch, & Cohen, 2002). In a chronic HCV sample with IFN- $\alpha$  treatment a significant impairment in working memory and executive functions has been observed (Pawelczyk et al., 2008). Another study found that the cognitive decline, including EF performance, during therapy was clinically significant and persistent after treatment ended (Cattie et al., 2014). Similar results revealed reduced verbal learning after 3 months of IFN- $\alpha$  therapy (Juengling et al., 2000).

The literature has not always been consistent. There is evidence that the effects of IFN- $\alpha$  on cognitive performance in HCV patients seem to improve after treatment, associated with a reduction in glia cell inflammation in patients who had a positive treatment outcome (Byrnes et al., 2012). Kraus et al. (2013) investigated neurocognitive performance in 70 chronic HCV patients exposed to IFN- $\alpha$ . Cognitive computer based tasks were performed at pre-treatment, during and at the end of treatment. Cognitive changes on an attentional performance battery during treatment were observed, but significant improvement in executive function and working memory was reported after treatment in patients who achieved a sustained virological response (SVR) over those who failed the treatment. Interferon-based therapy was associated with normal scores in attention and executive function tasks performance, and a significant increase in motor slowing (Majer et al., 2008). A possible explanation for these results is that IFN- $\alpha$  potentially affects motor areas, such as the putamen, substantia nigra and thalamus. These brain areas have some separation from the neuronal network that is related to executive functions performance, which involves the basal ganglia and prefrontal cortex (Majer et al., 2008; Monchi et al., 2001). These findings suggest that EF alterations following IFN- $\alpha$  treatment were related to inflammatory processes itself and are

reversible when associated with eradication of HCV (Byrnes et al., 2012; Forton et al., 2002; Kraus et al., 2013).

A recent study reported that co-infection is a significant risk factor for neurocognitive decline, in particular in memory and global functioning, during HCV treatment with interferon and ribavirin therapy (Miller et al., 2016). Cognitive deficits, and particularly executive functions, are frequently reported as a neuropsychiatric response to interferon-based therapy. Few studies however have examined executive function changes in acute HCV infection in HIV patients undertaking direct acting antivirals (DAAs) IFN- $\alpha$  based therapy. Furthermore, to the best of our knowledge, this is the first study to analyse whether diverse EF latent variables are involved in EF performance under an induced inflammatory condition. Despite the debate about unity and diversity of EF, for the purposes of our study we considered the tripartite model (Miyake, 2000) of EF, measuring inhibition, updating and shifting, to provide more detailed information about the potential cognitive aspects involved in EF performance in co-infected patients. Therefore, the aim of this study was to prospectively explore specifically the effect of DAAs with IFN- $\alpha$  treatment on EF status in a sample of HCV acute infection in HIV patients. We hypothesized that the HIV/HCV co-infected patients would present deterioration in EF performance throughout treatment when exposed to DAAs IFN- $\alpha$  based therapy. We expected treatment related decrements on cognition and to obtain a better understanding of the impact of HCV treatment on EF status. We expected that the co-infected group would present differences on EF performance when compared with HIV control group.

## **Methods**

### **Participants**

A total of 25 HIV men who have sex with men (MSM) were recruited between March 2014 and December 2015, from the outpatient HCV clinic at the Royal Sussex County Hospital, Brighton UK. Of the total sample, 13 were HIV and acute HCV co-infected patients, who were about to initiate HCV treatment with a combination of pegylated INF- $\alpha$ , ribavirin and telaprevir (INF- $\alpha$ +) and 12 were HIV mono-infected patients on cHART (INF- $\alpha$  -).

The inclusion criteria for the co-infected group were as follows: aged 20-60 years old, HIV infection confirmed by an ELISA positive and a Western-blot analysis and HCV infection confirmed by positive HCV RNA based on polymerase chain reaction (PCR) assay, on cART, fulfilled NICE guidelines criteria for initiation of HCV treatment and fluent in English. It is noteworthy that this study includes the hepatitis C new treatments (DAAs) only. Exclusion criteria were: active HIV-related opportunistic infections, concurrent hepatitis B virus (HBV) infection, hepatocellular carcinoma, current treatment for alcohol or drug abuse, major depression disorder (MDD) at baseline and during treatment, history of learning disabilities or neurological illness, and being on Efavirenz (due to clear effect on sleep patterns).

In relation to the HIV mono-infected group, the inclusion criteria were: diagnosis of HIV infection confirmed by an ELISA positive and a Western-blot analysis, patients aged 20-60 years old, and CDC classification system A1 ( $\geq 500$  cells/ $\mu\text{L}$ ), A2 (200-499 cells/ $\mu\text{L}$ ), and symptomatic stage B1 ( $\geq 500$  cells/ $\mu\text{L}$ ), with and without HIV therapy. The exclusion criteria were as follows: active HIV-related opportunistic infections, HBV, current treatment for alcohol and drug abuse, current diagnosis of MDD, history of learning disabilities and neurological illness.

## **Procedure**

All participants gave informed written consent for participation. Ethical approval was obtained through the National Research Ethics Service (NRES) Committee East of England.

Clinical interviews were conducted to collect relevant demographic (e.g., age, marital status, years of education) and clinical data (e.g., route of HIV and HCV infection, HCV genotype, HCV and HIV therapy, HIV and HCV viral load, HIV and HCV clinical stage, prior history of psychiatric illness). A battery of executive function tasks was also administered. The HIV/HCV co-infected group was followed longitudinally before starting HCV treatment (baseline), at the early stage of the treatment approximately at week 4 and at a later stage of the treatment, approximately at week 12 (see Table 1). The HIV group was followed up at equivalent times to the co-infected group before initiation of treatment (baseline) and at week 12 (see Table 1). To control potential influence of major depressive disorder, semi-clinical interview for

DSM-IV (SCID-I; First et al., 1996) was administered in all sessions for all the participants.

Table 1. Time line of EF assessments sessions during HCV treatment

	Baseline	Week 4	Week 12
Assessment Sessions	HIV	HIV HCV	HIV
	HIV HCV	HIV HCV	HIV HCV

## Measures

As previously described the present study considered the three factor model of EF paradigm (Miyaki et al., 2000). For that purpose the EF measures were selected taking into account the specific EF components of inhibition, updating and shifting. Inhibition has been proposed as the common EF factor suggesting being the core EF component with significant associations with updating (Friedman & Miyake, 2016; Hull et al., 2008). The associated EF components are related with significant correlations between diminished control over behaviour (inhibition) and evaluation of positive and negative consequences on decision making (Golub et al., 2012; Martin et al., 2013).

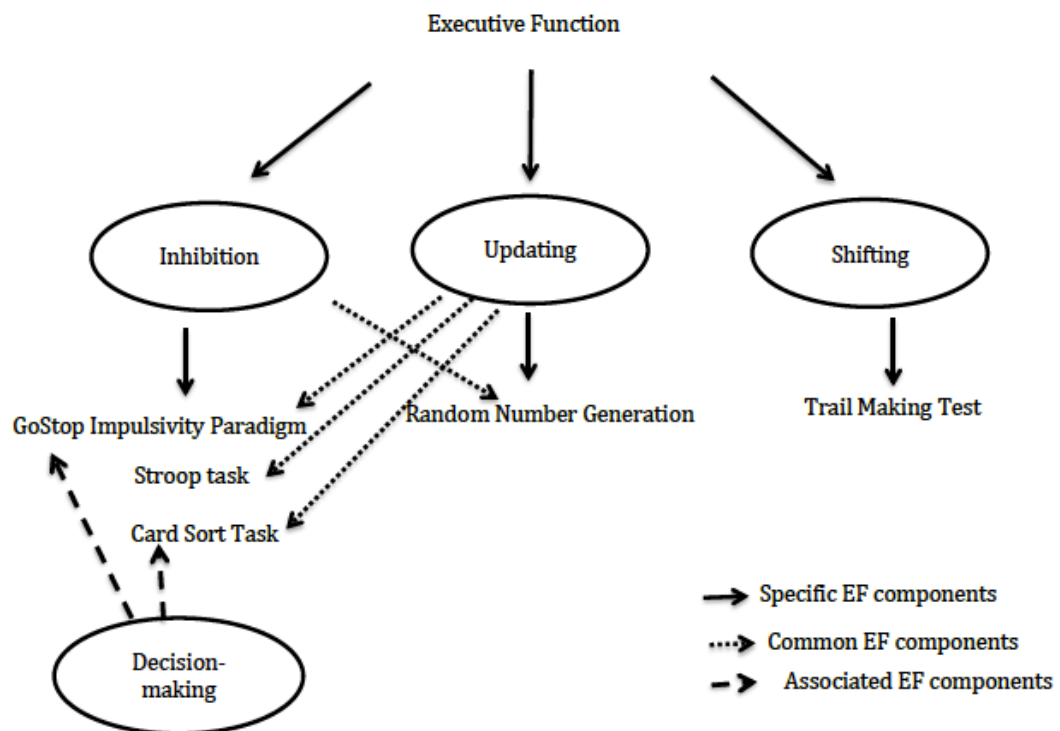


Fig. 1. Executive Function Paradigm based on Miyake model (Miyake et al., 2000)

### **Random Number Generation (RNG)**

The Random Number Generation (RNG) task requires the suppression of stereotyped sequences (inhibition) and tracking and updating responses (updating) (Peters et al., 2007). Participants were told to say out loud a random sequence of digits (1-10), more specifically it was explained that a random sequence is one that does not contain repetition of the same numbers and does not contain sequences or adjacent numbers (Towse & Neil, 1998). Following procedure described in Towse & Neil (1998) participants were asked to generate 30 numbers; their responses and time of performance were annotated on a sheet of paper. To quantify indices of randomisation performance the RNG index was calculated using a computer program (RgCalc) (Evans, 1978; Towse & Neil, 1998).

### **Trail Making Test**

The Trail Making Test requires mental flexibility and motor ability (O'Donnell et al., 1994). Particularly, the Part B performance is indicative of ability to flexibly shift between two elements of the course of an ongoing task (shifting) (Kortte et al., 2002). It is a pen and pencil task consisting of two parts, A and B. In part A, the participants have to connect the numbers 1 to 25 in ascending order; this provides a baseline measure of speed of processing. In part B, the participants must connect two sequences in an ascending order, alternating between numbers (1-25) and letters (A-O) (i.e., 1-A-2B) (Bowie & Harvey, 2006; Corrigan, 1987). A derived score measure was calculated (B-A) based on the difference score of TMT B – TMT A to remove the individual motor speed element from the task. (Corrigan & Hinkeldey, 1987; Lamberty et al., 1994; Lezak, 1995; Misdraju & Gass, 2010).

### **GoStop Impulsivity Paradigm**

The GoStop Impulsivity Paradigm was used to measure response inhibition (Dougherty, 2003). In this task, the participant has to respond to a series of visual stimuli (a 5 digit number) when a target 'go' signal appears and inhibit the response when a 'stop' signal occurs. Participants were instructed to click the mouse when presented with the 'go' (black) stimulus but withhold clicking the mouse if the target changes from black to red, the target 'stop' stimulus (Dougherty & Mathias, 2003). For each trial, a novel stimulus, unseen set of 5 digits, is presented followed by a target stimulus, a set of 5 digits identical to the previous number presented in black. A

proportion of the 'go' signals were unpredictably accompanied by a 'stop' signal, when the target stimuli changed from black (go) to red (stop), to which the participant must withhold their response. The task used fixed stop signal intervals, which remain fixed throughout the session with the changing signals from, go (black) to stop (red) at latency intervals of 50 msec, 150 msec, 250 msec and 350 msec. A lower percentage of inhibited responses reflects the proportion of correctly inhibited responses to the number of stop signals presented out of total responses found in the latency intervals (50 msec, 150 msec, 250 msec and 350 msec). Thus, an increased percentage in failing the inhibition response in this measure reflected greater impulsivity (Marsh et al., 2002).

### **Card Sort Prospective Memory Task**

The Card Sort Prospective Memory Task (Rusted & Trawley, 2006) is a computerised task that measures both decision-making and prospective memory (PM) ability. For the on-going component of the task participants were presented with 52 card stimuli displayed successively on the screen. Each card image remained on the computer screen for 750 ms. In each trial, participants were asked to press the heart key for hearts and spades key for spades; and to inhibit response if presented diamonds or clubs. Participants were allowed 1,750 ms from stimulus onset to respond and received the instruction to respond as quickly and accurately as possible (Marchant et al., 2010; Rusted et al., 2009). Next, the Prospective Memory (PM) instruction was given. Participants were asked to press "space" when any card with the number 7 was presented on the computer screen. Two further decks of the on-going task were presented following the PM rule assignment. Sort accuracy and reaction times were recorded. A PM cost measure was calculated by comparing the performance between these two conditions (sort RT with PM instruction – sort RT with no PM intention) to provide us information regarding the cost of carrying a PM intention on ongoing decision making task (sort task).

### **Stroop Task**

The Stroop task (Hutchison et al., 2010) was used to measure inhibition. In this study, a computerised version was used. Participants were given verbal instructions in which they were cued prior to each trial whether they should name the colour of the word presented on the computer screen or if they should name the word itself (Rogers & Monsell, 1995). Stimuli consisted of four colour words (blue, red, yellow and green)

and four neutral words (poor, legal, bad, deep). Forty trials were congruent when a neutral word appeared in any of the four colours and 48 trials were classified as incongruent when a colour word appeared in a non-matching colour font. Participants completed 24 practice trials and 88 experimental trials. Participants responded verbally, using a microphone, with latency of response being recorded by a serial response box. Accuracy of response was coded for each trial as correct, error or self-corrected error. Taking into account that cognitive slowing is a main feature of HIV associated neurocognitive disorders (Martin et al., 2004) we performed analysis of the Stroop interference effects described when one mental operation degrades the performance of another (Brown 2011) which could give us an indicator of executive inhibition control type and shifting; (Brown 2011). Stroop interference was calculated for correct trials only, by calculating reaction time difference for RT incongruent – RT neutral control (MacLeod, 1991; Monsel, 2003).

### **Data analysis**

Statistical analyses were performed using the Statistical Package of Social Sciences (IBM SPSS version 22.0). For sociodemographic and clinical data, descriptive analysis was performed and reported as means, standard deviations (*SD*) and frequencies. A two-way contingency analysis ( $\chi^2$ ) was conducted to assess whether both groups had statistically different proportions in categorical variables, and Student's *t* tests were performed to compare groups in continuous variables. Across experimental tasks, mixed model repeated-measures analysis of variance (ANOVA) was used to assess changes on EF performance between study groups and over time (within- and between-groups analysis). For assessing changes in EF performance during treatment at baseline, week 4 and week 12, in the co-infected group, repeated-measures analysis of variance (ANOVA) (within group analysis) were performed. All statistical tests were two-tailed with *p* values < .05 as criterion of statistical significance.

## **Results**

### **Participant's characteristics**

The total sample consisted of 25 HIV MSM, with a mean age of 45.60 years (*SD* = 4.28; range: 38-52). The 12 HIV mono-infected interferon free (IFN-) group had a mean age of 45 years (*SD* = 4.20; 38-51) and 13 HIV/HCV co-infected group with



interferon exposure (IFN+) had a mean age of 46.15 years ( $SD = 4.45$ ; 38-52). The majority of participants were single (72%), had college education (76%) and reported no history of intravenous drug use. Nine patients (36.0%) reported other type of drug use, most frequently cocaine. No significant differences were found between the study groups in the baseline characteristics (see Table 2). At baseline all participants were on HIV therapy with HIV negative viral load. Regarding HCV treatment measures, all co-infected patients were seronegative for HCV at week 12.

Table 2. Baseline characteristics for participants

	<b>Total sample</b>	<b>HIV/HCV</b>	<b>HIV</b>
	<i>n (%)</i>	<i>(n = 13)</i>	<i>(n = 12)</i>
	<i>n (%)</i>	<i>n (%)</i>	<i>n (%)</i>
Age	45.60 (4.28)	46.15 (4.45)	45 (4.20)
Single	18 (72.0)	9 (69.2)	9 (75.0)
College education	19 (76.0)	10 (76.9)	9 (75.0)
Recreational drug use	9 (36.0)	5 (38.5)	4 (33.3)
Past history of clinical depression	19 (76.0)	11 (64.6)	8 (66.7)
Family psychiatry history	10 (40.0)	5 (38.5)	5 (41.7)
HCV re-infected	9 (36.0)	9 (69.2)	-

### Within group analysis for HCV treatment over time

#### GoStop Paradigm Task

The means scores ( $SD$ ) of inhibition errors response at each experimental condition (50 msc, 150 msc, 250 msc, 350 msc) and at each time point (baseline, week 4 and week 12) are shown in Table 3. Repeated measures ANOVA did not indicate any significant change in inhibition response across time,  $F(2, 11) = 2.34$ ,  $p = .143$ , but a significant effect of latency intervals was observed,  $F(3, 10) = 30.05$ ,  $p < .001$ . The results indicated a significant decrease of inhibition errors response at increased latency intervals. The interaction between time and interval was not significant,  $F(6, 7) = 2.30$ ,  $p = .150$ .

Table 3. GoStop Paradigm task performance during treatment.

	HIV/HCV		
	Baseline	Week 4	Week 12
	Mean (SD)	Mean (SD)	Mean (SD)
<b>Inhibition errors response (%)</b>			
50 msc	78.46 (24.09)	92.30 (8.80)	84.61 (28.90)
150 msc	63.07 (31.72)	71.92 (21.84)	64.23 (32.45)
250 msc	43.46 (30.37)	60.76 (20.49)	50.76 (27.52)
350 msc	36.15 (24.76)	45.38 (24.27)	33.07 (22.03)

### Card sort Prospective Memory task

The analysis performed on this task were focused on the decision making component based on several performance measures: reaction time (RT) and accuracy to the on-going task of decision making control; RT decision-making card sort task under PM condition and RT cost of the PM intention (the difference in RT to the ongoing decision-making task when there was a concurrent PM requirement). See Table 4 for a summary of performance on this task.

**Decision-making control deck RT and accuracy:** Between baseline and end of treatment, repeated measures ANOVA showed no significant effect of time on reaction time,  $F(2, 11) = 2.99, p = .092$ . Similarly, no significant effect of time was found regarding the levels of accuracy,  $F(1, 12) = 0.06, p = .819$ .

**Decision-making card sort under PM condition:** The results indicated a significant decrease on RT between baseline and end of treatment,  $F(2, 11) = 60.72, p < .001$ . The decrease was however only significant between baseline and week 4 (Mean difference = -21.61,  $p < .001$ ).

**Cost of carrying a PM intention:** Regarding PM cost, there was a significant effect of time,  $F(2, 11) = 46.71, p < .001$ , indicating a significant increase from baseline to week 4 only (Mean difference = -35.82,  $p < .001$ ). There was a decrease on PM cost from week 4 to week 12, which was not statistically significant (Mean difference = -11.22,  $p = .464$ ).

Table 4. Performance on the card sort task during treatment

		HIV/HCV		
		Baseline	Week 4	Week 12
		Mean (SD)	Mean (SD)	Mean (SD)
Decision making control deck	Reaction Time	497.92 (8.59)	512.20 (8.48)	493.44 (8.92)
	Accuracy	25.23 (0.75)	25.21 (0.69)	25.23 (0.72)
Decision making card sort under PM condition	Reaction Time	748.54 (7.15)	726.93 (9.81)	721.46 (5.14)
	PM cost	252.61 (8.90)	269.79 (2.30)	258.01 (10.95)

### Stroop Task

For summary of Stroop Task performance see Table 5. Repeated measures ANOVA were performed on the Stroop incongruent trials and no effect of time was found within HIV/HCV co-infected group throughout treatment,  $F(2,10) = .14$ ,  $p = .865$ . No significant effects were observed on Stroop neutral trials,  $F(2, 10) = .48$ ,  $p = .762$ , and on Stroop interference,  $F(2, 10) = .28$ ,  $p = .913$ , during treatment. Regarding errors, no significant differences were found across time,  $F(6, 40) = 1.19$ ,  $p = .334$ .  $F(6, 40) = .09$ ,  $p = .913$ .

Table 5. Stroop task performance during treatment.

Condition	HIV/HCV		
	Baseline	Week 4	Week 12
	Mean (SD)	Mean (SD)	Mean (SD)
Incongruence	890.052(203.50)	895.87 (201.78)	864.04 (106.83)
Neutral	872.73 (210.28)	857.07 (206.17)	815.60 (155.95)
Stroop interference	17.29 (85.81)	41.86.(90.86)	49,07 (85.58)

### RNG task

Table 6 shows the means scores (and SD) on the RNG task during treatment. The effect of time on the RNG index was not significant during treatment,  $F(2, 11) = 0.50$ ,  $p = .622$ . Overall, there was an increase in the time needed to execute the task (reaction time) among the co-infected group,  $F(2, 11) = 26.12$ ,  $p < .001$ . The results indicated a significant increase from baseline to week 4 (Mean difference = 12.39,  $p <$

.001). The decrease from week 4 to week 12 was not significant (Mean difference = 1.46,  $p = 1.000$ ).

Table 6. RNG task performance during treatment.

		HIV/HCV		
		Baseline	Week 4	Week 12
		Mean (SD)	Mean (SD)	Mean (SD)
RNG task	Reaction Time	42.0 (5.0)	54.38 (4.7)	52.92 (3.81)
	RNG index	0.14 (0.06)	0.14 (0.07)	0.16 (0.07)

### TMT task

For the summary of TMT task performance see Table 7. Regarding the composite TMT B-A, a measure of shifting capacity, the effect of time was not significant,  $F(2, 11) = 1.53$ ,  $p = .259$ . Further analyses on speed processing of the task were performed. During HCV treatment there was a significant effect of time, as measured by TMT part A,  $F(2, 11) = 5.20$ ,  $p = .026$ . Particularly, there was a significant increase from baseline to week 4 on TMT part A (mean difference = 15.15,  $p = .044$ ) and a significant decrease from week 4 to week 12 (Mean difference = 10.69,  $p = .044$ ).

Table 7. TMT task performance during treatment

		HIV/HCV		
		Baseline	Week 4	Week 12
		Mean (SD)	Mean (SD)	Mean (SD)
TMT task	TMT A	53.77 (15.95)	68.92 (21.30)	58.23 (17.83)
	TMT B-A	84.69 (79.51)	121.53 (86.00)	94.69 (66.99)
	TMT B	138.46 (89.49)	190.46 (87.93)	149.84 (82.59)

### Differences between groups over time

#### GoStop Paradigm task

Table 8 shows the mean scores (SD) of GoStop Paradigm task of both groups at baseline and week 12. Repeated measures ANOVA indicated no significant differences on inhibition performance between study groups,  $F(1, 23) = 1.66$ ,  $p = .210$ , as well as

no significant effect of time between baseline and week 12,  $F(1, 23) = 0.43, p = .519$ . The interaction time x group was not significant,  $F(1, 23) = 0.07, p = .800$ . The effect of latency interval was significant,  $F(3, 21) = 46.24, p < .001$ . No significant effects were found on the interaction latency interval x group,  $F(3, 21) = 0.65, p = .594$ , latency interval x time,  $F(3, 21) = 2.72, p = .070$ , as well as in the interaction time x latency interval x group,  $F(3, 21) = 1.37, p = .279$ .

Table 8. GoStop Paradigm task performance at baseline and week 12

	Baseline		Week 12	
	HIV	HIV/HCV	HIV	HIV/HCV
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Inhibition errors performance (%)				
50msc	86.25 (17.33)	78.46 (24.01)	90.0 (15.37)	84.61 (28.90)
150msc	65.0 (25.67)	63.07 (31.72)	79.16 (17.56)	64.23 (32.45)
250msc	50.75 (29.30)	43.46 (30.37)	63.75 (19.32)	50.76 (27.52)
350msec	40.83 (32.32)	36.15 (24.76)	36.25 (21.43)	33.07 (22.03)

### Card sort Prospective Memory task

See Table 9 for summary of Card sort task performance.

Regarding the on-going decision-making control deck, repeated measures ANOVA indicated no significant differences between groups on RT,  $F(1, 23) = 2.40, p = .135$ . A significant effect of time was found,  $F(1, 23) = 14.64, p = .001$ , which indicated a faster RT at week 12. No difference was found in relation to accuracy. The interaction time x group was not significant,  $F(1, 23) = 3.59, p = .071$ .

**Decision-making card sort under PM condition:** The results indicated a significant effect of time,  $F(1, 23) = 124.79, p < .001$ . No significant differences were found between groups on RT performance,  $F(1, 23) = 2.67, p = .116$ . The interaction time and group was no significant,  $F(1, 23) = 2.90, p = .102$ .

**Cost of carrying a PM intention:** The analysis for PM cost showed that there was a significant effect of time,  $F(1, 23) = 27.92, p < .001$ , indicating a significant decrease in PM cost from baseline to week 12 in both groups. The difference between groups was not significant,  $F(1, 23) = 0.01, p = .914$ . However, the interaction time x group was significant,  $F(1, 23) = 8.95, p = .007$ , showing that the decrease from baseline to week 12 was higher in the co-infected group.

Table 9. Card sort task performance at baseline and week 12

		Baseline		Week 12	
		HIV	HIV/HCV	HIV	HIV/HCV
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Decision making	Reaction Time	497.82 (8.16)	497.92 (8.59)	484.56 (11.20)	493.44 (8.92)
	Accuracy	25.50 (0.67)	25.23 (0.75)	25.43 (0.65)	25.23 (0.72)
Decision making					
card sort under PM	Reaction Time	741.75 (9.86)	748.54 (7.15)	721.83 (5.85)	721.46 (5.14)
condition					
PM cost		243.33 (10.80)	252.61 (8.90)	236.52 (14.44)	228.01 (10.95)

### Stroop Task

Table 10 shows the summary of Stroop Task performance. The results of ANOVA showed no significant differences between groups in incongruent condition across time,  $F(1, 21) = .071$ ,  $p = .792$ , and between groups,  $F(1, 21) = 2.12$ ,  $p = .159$ . The interaction group x time was not significant,  $F(1, 21) = .869$ ,  $p = .362$ .

In neutral condition there were no significant differences across time,  $F(1, 21) = .027$ ,  $p = .872$ ; or between groups  $F(1, 21) = .989$ ,  $p = .331$ . The interaction time x group was not significant  $F(1, 21) = 2.70$ ,  $p = .115$ .

There was no significant difference in Stroop interference across time,  $F(1, 21) = .003$ ,  $p = .957$ , or between groups,  $F(1, 21) = 0.11$ ,  $p = .745$ . The interaction group x time was not significant,  $F(1, 21) = 1.11$ ,  $p = .305$ .

Although participants made fewer errors in all conditions over time, they were not significantly different at baseline and week 12,  $F(3, 19) = 3.08$ ,  $p = .052$ . No significant effect in interaction time x group was found,  $F(3, 19) = 0.35$ ,  $p = .791$ .

Table 10. Stroop Task Performance at baseline and week 12

		Baseline		Week 12	
		HIV	HIV/HCV	HIV	HIV/HCV
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Incongruent		880.21 (178.29)	893.052(203.50)	852.65 (200.01)	864.04 (106.83)
Neutral		765.80 (127.65)	868.21 (201.98)	835.29 (171.04)	811.24 (155.82)
Interference		5.94 (18.94)	16.87 (82.17)	35.55. (48.65)	4.33 (84.48)

### RNG task

The summary of RNG task performance, measured by RNG index and the time to perform the task, measured in seconds, is described in table 11. Repeated measures ANOVA showed no significant differences were found between groups,  $F(1, 23) = 1.09, p = .308$ . The interaction time x group was not statistically significant,  $F(1, 23) = 0.80, p = .381$ . The effect of time on the RNG index was not significant during treatment,  $F(1,23) = 0.50, p = .622$ .

Regarding the time of execution the task, there were no differences between the study groups,  $F(1, 23) = 0.93, p = .346$ . Similarly, the interaction time x group was not significant,  $F(1, 23) = 0.15, p = .700$ . The effect of time was statistically significant,  $F(1, 23) = 47.36, p < .001$ , indicating that both groups took more time to perform the task at week 12.

Table 11. Performance on RNG task (RNG index) and time to performance the task (seconds) at baseline and week 12

	Baseline		Week 12	
	HIV	HIV/HCV	HIV	HIV/HCV
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
RNG index	0.10 (0.05)	0.14 (0.06)	0.16 (0.08)	0.16 (0.07)
RNG time (seconds)	40.83 (8.63)	42.00(5.02)	50.58 (5.28)	53.93 (3.82)

### TMT task

The performance on TMT task is presented in Table 12. In relation to TMT A, the ANOVA showed that the effect of time was not significant,  $F(1, 23) = 0.09, p = .766$ . There was a significant effect of group,  $F(1, 23) = 5.69, p = .026$ , which indicated that HIV/HCV co-infected patients performed significantly worse of TMT A than HIV mono-infected patients. The interaction time x group was not significant,  $F(1, 23) = 3.51, p = .073$ .

The results of the composite TMT B-A indicated no differences over time,  $F(1, 23) = 0.001, p = .981$ . Similarly, no significant effects were found for group,  $F(1, 23) = 0.84, p = .369$ , and interaction time x group,  $F(1, 23) = 0.55, p = .467$ .

Table 12. Performance on TMT A/B task at baseline and week 12.

	Baseline		Week 12	
	HIV	HIV/HCV	HIV	HIV/HCV
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
TMT A	46.33 (13.96)	53.77 (15.96)	40.17 (11.65)	58.23 (17.84)
TMT B-A	73.25 (76.31)	84.69 (79.52)	62.58 (47.08)	94.69 (67.00)
TMT B	119.33 (78.41)	138.46 (89.49)	102.75 (56.22)	149.85 (82.59)

## Discussion

It is well established that HCV INF-  $\alpha$  based treatment potentially induces mood and cognitive changes (Miller et al., 2016; Udina et al., 2014, 2015). The cognitive profile most observed in HCV infection includes EF impairment (Kenelly, 2013; Monaco et al., 2015). The same cognitive deficits have been reported in HIV infection (Thames et al., 2012; Woods et al., 2009), suggesting that the HIV/HCV co-infected population may present a higher risk for EF decline (Garvey et al., 2012; Winston et al., 2010), in particular when exposed to INF-  $\alpha$  treatment (Cattie et al., 2014). Therefore, the aim of this study was to assess the effect of HCV treatment on EF performance in a sample of HCV acute HIV co-infected patients undergoing DAAs treatment with IFN- $\alpha$  based therapy. The main findings indicate that during treatment, the co-infected group showed a significant increase on prospective memory (PM) cost analysis from baseline to week 4. Significant results in speed components on RNG task, and TMT part A task, were also observed, indicating processing speed deficits between baseline and week 4. The processing speed impairment was confirmed on between groups analysis, measured by TMT part A, with the co-infected group being more impaired than the HIV group. Both groups presented significant increased reaction time at week 12. Differences between groups were found on PM cost analysis with a decrease from baseline to week 12, higher in the co-infected group.

The co-infected group showed deficits in PM cost analysis at week 4 of treatment indicating that there is a negative effect of DAAs including IFN- $\alpha$  based treatment on decision making carrying a PM intention. Our results are in accordance with recent reports that considered that inhibition impairment might predispose to difficulties in executing ongoing tasks with prospective intention in a sample of inflammatory chronic condition (Dagenais et al., 2016). It has been suggested that PM



impairment is associated with deficits in sustain and retrieve information (Cona et al., 2015; Kliegel et al., 2002) as part of decision-making processes (Carey et al., 2006; Martin et al., 2007; Woods et al., 2008; 2009). Inhibition has been described as the ability to maintain and manage goals (Friedman & Miyake, 2016) so it seems that when carrying a PM intention in an ongoing decision making task, equivalent of loading prospective memory factors (PM intention), that will cause a cognitive challenge within the co-infected group. The clinical impact of inhibition impairment, measured by PM cost analysis, is related with daily activities that requires processing information to goal directed tasks (taking medication); control of complex cognition (remembering different appointments, diet and controlling side effects of treatment) and non-routine behaviour (Banich, 2009). Our results are pilot data and suggests that DAAS with IFN- $\alpha$  therapy affects cognition . As previously reported exposure to INF- $\alpha$  alone (Cohen et al., 2011; Uchina et al., 2015) might justify these outcomes and also active HCV replication was still present at week 4. Nevertheless, does this PM deficit represent an effect of IFN- $\alpha$  at week 4 of treatment? Or indicate a pattern of deficit that might be present in the course of HIV infection that is not dissociable from the presence of active HCV virus replication? Or is it a combination of both? Clearly, the changes that were observed here on the PM component on the card-sort task indicate an impact on attentional and executive function resources but more research is needed.

Within group analysis of the HIV/HCV co-infected group confirmed the disadvantage on the speed processing components of EF performance during HCV treatment, with significant effect between baseline and week 4. Acute HCV in HIV infection has been associated with significant reduction in certain cerebral metabolites (RBG mL/Cr ratio) suggesting effects of HCV on the central nervous system (CNS) with negative impact on neurocognition (Winston et al., 2010). Acute HCV in HIV-infected patients was independently associated with EF performance impairment (Garvey et al., 2012). These results indicate that a neurological compromise involves prefrontal cortex and fronto-striatal regions even in samples without HCV treatment. It is reasonable to hypothesize that in the presence of DAAs with IFN- $\alpha$  the co-infected group presents cognitive deficits. A recent study suggested that IFN- $\alpha$  at week 4 causes changes in striatal molecular structure (Dowell et al., 2015). In addition, it was reported that after peripheral IFN- $\alpha$  administration the whole brain presented functional network changes, translated by a reduction in mean number of network connections that were

significantly associated with mood and cognitive impairments (Dipasquale et al., 2016). It seems that the presence of IFN- $\alpha$  causes changes in the brain that would explain the decline on information processing speed level of EF performance and the preference of IFN- $\alpha$  acting in brain areas that affect motor behaviour as described above (Monchi et al., 2001).

The frontal lobe hypothesis was often linked to executive function deterioration, information processing speed impairment being significantly associated with structural changes in the prefrontal cortex (Kerchner et al., 2012). However, recent studies found that EF are not exclusively based on prefrontal contributions resulting in a complex interplay of frontal-parietal brain areas (Bettcher et al., 2016; Miyake & Friedman, 2014; Niendam et al., 2012). Factor analysis using a two factor model considering shifting/inhibition and updating/working memory provided evidence that cortical grey matter was significantly associated with updating performance and cortical grey matter and corpus callosum contribute to shifting/inhibition performance (Bettcher et al., 2016). Another report demonstrated that updating tasks were associated with activation on anterior and posterior brain areas, while shifting performance activated parietal lobe and inhibition performance was associated with right orbitofrontal gyrus areas (Collette et al., 2005). It is clear that a broad network of brain structures are involved in EF performance.

The data indicated an improvement in PM cost in both groups between baseline and week 12, however that improvement was higher in the co-infected group. As previously reported being co-infected is a risk factor for cognitive impairment, with studies reporting a significant decline on EF status (Garvey et al., 2012; Winston et al., 2010). A study aimed to clarify the effect of HCV on cognitive dysfunction. The cross-sectional study enrolled 53 participants, 19 HCV mono infected, 14 HIV mono infected, 17 co infected with HIV/HCV, and 28 controls. All participants were free of substance abuse, without clinical depression, and had undetectable HIV viral load. Neuropsychological assessment covered seven cognitive domains. The co-infected HIV HCV group performed more poorly on attention, executive function, fine motor function and visual and verbal learning/memory tests compared with a HCV mono infected group (Sun et al., 2013). This research group pointed out that co infection with HIV and HCV significantly increases the risk of cognitive impairment in subjects with controlled HIV viral loads (Sun et al., 2013). Therefore, our results are not surprising,

because at week 12 the co-infected group was clear for HCV virus, which means that when treated for HCV an improvement on cognition was expected. Nevertheless, our results must be interpreted carefully due to the nature of our sample, acute HCV infection in HIV MSM group, and the type of treatment, DAAs. There is a research gap on evidence of neuropsychiatric side effects of DAAs and our sample size is small leading us to look at our data as potential arguments that need to be replicated. Additionally, variability in the literature could be accounted for, by inconsistency in neuropsychological batteries and methodologies.

Both groups presented higher reaction time on the RNG task at week 12, however with no disadvantage on updating performance, measured by RNG index. Recently, changes in the striatum after 4 weeks peripheral administration of IFN- $\alpha$  in HCV mono-infection was observed, that has been significantly associated with fatigue (Dowell et al., 2015). The higher reaction time on RNG task, as observed in both groups, could be explained by fatigue. In the co-infection group it is reasonable to associate fatigue with residual effects of IFN- $\alpha$  but it remains unclear why the same effect was found in the HIV group. Another hypothesis could be related to the effect of HIV itself on the information processing speed component. Although due to HIV therapy efficacy the severity of HIV associated neurocognitive disorders reduced the less severe forms of HIV-associated cognitive impairment is reported (Heaton et al., 2011). The reasons for high rates of minor and mild HIV-associated cognitive disorders are unclear, but several hypotheses have been suggested; such as incomplete HIV viral suppression in the CNS, drug resistance, prolonged exposure to inflammatory responses and cART neurotoxicity (Heaton et al., 2011).

We found significant differences between groups on TMT part A indicating that the co-infected group performed worse than the mono-infected group. The TMT part A has been linked with pure motor skills that was significantly associated with mental processing speed (Misdraji & Gass, 2010). These findings highlight that the co-infected group performance was consistent with information processing speed impairment probably because of the influence of IFN- $\alpha$  on motor control mechanism of EF. EF relies heavily on prefrontal cortex (PFC) recruiting several neural substrates (Collette et al., 2005). Neuroimaging studies reported that updating and inhibition were more associated with anterior prefrontal areas than shifting (Wager & Smith, 2003). However, it seems that IFN- $\alpha$  affects brain areas, which primarily influence motor behaviour (Monchi et al., 2001). It is noteworthy to clarify that at week 12 the co-

infected group was seronegative for HCV RNA being less likely to have HCV replication in the CNS. We must interpret our results very carefully considering that processing information impairment in co-infection might be associated with a cumulative effect of IFN- $\alpha$ , or the influence of HIV itself or both.

### **Strengths and limitations**

Our results were not consistent across the cognitive tasks as previously described with evidence of EF impairment during IFN- $\alpha$  based treatment (Hilsabeck et al., 2005; Lieb et al., 2006) and other studies failing to find those changes (Fontana et al., 2007; Majer et al., 2008). Potential explanations are associated with the time and dose of IFN- $\alpha$  (Fontana et al., 2007), suggesting that short period of exposure, as 12 weeks, will not affect EF performance. Another explanation might be related with the characteristics of our total sample with undetectable HIV viral load, acute HCV infection, no history of injection drug use (IDU) and no major depressive disorder (MDD), matched by age and education. It is worth highlighting that our total sample presented HIV viral load suppression and CD4 counts > 500, suggestive of cART efficacy, as previous reported (Letendre et al., 2008) that has greatly contributed to reduce severity cognitive impairment (Ferrando et al., 2003; Letendre et al., 2004; Sacktor et al., 1999). It is also important to note that the sample of this study was not depressed as measured by SCID-I in all sessions. Major depressive disorder and EF appear to share similar neurological networks. MDD is associated with changes in prefrontal cortex (PFC) function (Levin et al., 2007) as has been posited in EF (Davidson et al., 2002). Meta-analytic data suggested that increased severity of depression was significantly associated with EF impairment (Marazzitti et al., 2010; McDermott et al., 2009; Snyder et al., 2012). It is therefore not surprising that in a non-depressed cohort there were no EF performance impairment differences on all tasks between groups. Nevertheless, reports on cognitive impairment in HIV/HCV co-infection are limited and more research is needed in order to clarify in what way both viruses actually affect the CNS, with and without HCV treatment exposure. Regarding treatment with interferon-based therapies, acute infection is strongly associated with high rates of SVR, with studies reporting a 98% rate of cure (Jaeckel et al., 2001; Mangia et al., 2013). DAAs have been associated with significant improvement in SVR (Bansal et al., 2015). In our study, participants were acute HCV infected and presented a high rate of SVR with DAAs regimens being HCV seronegative at week 12, which

represents an absence of HCV RNA on the CNS and consequently no significant impact on cognitive status measured by EF tasks performance.

Our data shows that EF tasks present a variability, which may be due to task impurity and individual differences, as previously described in the literature (Friedman & Miyake, 2016; Miyake & Friedman, 2012). Nevertheless, the strengths of this study include the use of multiple measures of EF to obtain a purer outcome of EF performance during hepatitis C treatment and use of a prospective design.

This study is not without limitations. These limitations include the small sample size, which emphasize that our findings need to be interpreted carefully. We could also have included the HCV mono-infection group or an untreated HIV HCV group to analyse the HCV EF associated impairment. Another limitation is the absence of a time point of assessment after treatment ended; this would be relevant to explore the residual effects of treatment on cognition. Nevertheless, we controlled bias factors, such as depression and chronic HCV stage (in our sample all the patients were acute HCV), which have been identified as risk factors for cognitive impairment.

## **Conclusions and Future directions**

Overall in acute HCV and HIV MSM co-infected patients undergoing DAAs with IFN- $\alpha$  based therapy the between and withinsubject-analysis confirmed that in EF composite there is a cost to processing information speed. This outcome has implications in terms of ability to adhere to complex treatment regimes, such as HCV and HIV therapy and it might be a cognitive marker for progression of neurocognitive infection diseases that needs to be routinely included in psychological assessment routine. In this study, nine participants were HCV-reinfected. The rate of HCV reinfection in positive HIV MSM is increasing and the costs associated with repeated treatments are worth taking into account (Ingiliz et al., 2016; Martin et al., 2013). For future research a careful assessment of EF should be performed in co-infected patients with HCV reinfection receiving HCV treatment and exploration of whether reinfection is a consequence of EF impairment.

## References

- Aronow, H. A., Weston, A. J., Pezeshki, B. B., & Lazarus, T. S. (2008). Effects of coinfection with HIV and hepatitis C virus on the nervous system. *The AIDS Reader*, 18(1), 43-43.
- Banich, M. T. (2009). Executive function: The search for an integrated account. *Current Directions in Psychological Science*, 18(2), 89-94.
- Banich, M. T., & Depue, B. E. (2015). Recent advances in understanding neural systems that support inhibitory control. *Current Opinion in Behavioral Sciences*, 1, 17-22.
- Bansal, S., Singal, A. K., McGuire, B. M., & Anand, B. S. (2015). Impact of all oral anti-hepatitis C virus therapy: A meta-analysis. *World Journal of Hepatology*, 7(5), 806-813.
- Bechara, A. (2004). The role of emotion in decision-making: Evidence from neurological patients with orbitofrontal damage. *Brain and Cognition*, 55(1), 30–40.
- Bechara, A., & Damasio, A. R. (2005). The somatic marker hypothesis: A neural theory of economic decision. *Games and Economic Behavior*, 52(2), 336–372
- Bechara, A., Damasio, A. R., Damasio, H., & Anderson, S. W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition*, 50(1), 7-15.
- Bettcher, B. M., Mungas, D., Patel, N., Eloffson, J., Dutt, S., Wynn, M., ... Kramer, J. H. (2016). Neuroanatomical substrates of executive functions: Beyond prefrontal structures. *Neuropsychologia*, 85, 100-109.
- Brown, T. L. (2011). The relationship between Stroop interference and facilitation effects: statistical artifacts, baselines, and a reassessment. *Journal of Experimental Psychology: Human Perception and Performance*, 37(1), 85.
- Brydges, C. R., Fox, A. M., Reid, C. L., & Anderson, M. (2014). The differentiation of executive functions in middle and late childhood: A longitudinal latent-variable analysis. *Intelligence*, 47, 34-43.
- Byrnes, V., Lowry, D., Alsop, D., & Afdhal, N. H. (2012). Reply to: “Neuroinflammation in HCV-infection—Peril or protection?”: Effects of anti-viral therapy and HCV clearance on cerebral metabolism and cognition. *Journal of Hepatology*, 57(4), 923-924.

- Carey, C. L., Paul Woods, S., Rippeth, J. D., Heaton, R. K., Grant, I., & HIV Neurobehavioral Research Center (HNRC) Group. (2006). Prospective memory in HIV-1 infection. *Journal of Clinical and Experimental Neuropsychology*, 28(4), 536-548.
- Cattie, J. E., Letendre, S. L., Woods, S. P., Barakat, F., Perry, W., Cherner, M., ... Grant, I. (2014). Persistent neurocognitive decline in a clinic sample of hepatitis C virus-infected persons receiving interferon and ribavirin treatment. *Journal of Neurovirology*, 20(6), 561-570.
- Cohen, R. A., de la Monte, S., Gongvatana, A., Ombao, H., Gonzalez, B., Devlin, K. N., ... Tashima, K. T. (2011). Plasma cytokine concentrations associated with HIV/hepatitis C coinfection are related to attention, executive and psychomotor functioning. *Journal of Neuroimmunology*, 233(1), 204-210.
- Collette, F., Van der Linden, M., Laureys, S., Delfiore, G., Degueldre, C., Luxen, A., & Salmon, E. (2005). Exploring the unity and diversity of the neural substrates of executive function. *Human Brain Mapping*, 25, 409–423.
- Cona, G., Scarpazza, C., Sartori, G., Moscovitch, M., & Bisiacchi, P. S. (2015). Neural bases of prospective memory: A meta-analysis and the “Attention to Delayed Intention” (AtoDI) model. *Neuroscience & Biobehavioral Reviews*, 52, 21-37
- Dagenais, E., Rouleau, I., Tremblay, A., Demers, M., Roger, É., Jobin, C., & Duquette, P. (2016). Prospective memory in multiple sclerosis: The impact of cue distinctiveness and executive functioning. *Brain and Cognition*, 109, 66-74.
- Davidson, R. J., Pizzagalli, D., Nitschke, J. B., & Putnam, K. (2002). Depression: Perspectives from affective neuroscience. *Annual Review of Psychology*, 53, 545–574.
- Dipasquale, O., Cooper, E. A., Tibble, J., Voon, V., Baglio, F., Baselli, G., ... Harrison, N. A. (2016). Interferon- $\alpha$  acutely impairs whole-brain functional connectivity network architecture – A preliminary study. *Brain, Behavior, and Immunity*, 58, 31-39.
- Dougherty, D. D., Mathias, C. W., & Marsh, D. M. (2003). *GoStop Impulsivity Paradigm (Versio 1.0) [Manual]*. Neurobehavioral Research Laboratory and Clinic, University of Texas Health Science Centre at Houston, Houston, Texas.
- Dowell, N. G., Cooper, E. A., Tibble, J., Voon, V., Critchley, H. D., Cercignani, M., & Harrison, N. A. (2016). Acute changes in striatal microstructure predict the

- development of interferon-alpha induced fatigue. *Biological Psychiatry*, 79(4), 320-328.
- Duarte, N. A., Woods, S. P., Rooney, A., Atkinson, J. H., Grant, I., & Translational Methamphetamine AIDS Research Center (TMARC) Group. (2012). Working memory deficits affect risky decision-making in methamphetamine users with attention-deficit/hyperactivity disorder. *Journal of Psychiatric Research*, 46(4), 492-499.
- errando, S. J., Rabkin, J. G., Van Gorp, W., Lin, S., & McElhiney, M. (2003). Longitudinal improvement in psychomotor processing speed is associated with potent combination antiretroviral therapy in HIV-1 infection. *The Journal of Neuropsychiatry and Clinical Neurosciences*, 15(2), 208-214.
- Fialho, R., Pereira, M., Bucur, M., Fisher, M., Whale, R., & Rusted, J. (2016). Cognitive impairment in HIV and HCV co-infected patients: A systematic review and meta-analysis. *AIDS Care*, 28(12), 1481-1494.
- Fontana, R. J., Bieliauskas, L. A., Lindsay, K. L., Back- Madruga, C., Wright, E. C., Snow, K. K., ... Padmanabhan, L. (2007). Cognitive function does not worsen during pegylated interferon and ribavirin retreatment of chronic hepatitis C. *Hepatology*, 45(5), 1154-1163.
- Forton, D. M., Thomas, H. C., Murphy, C. A., Allsop, J. M., Foster, G. R., Main, J., ... Taylor-Robinson, S. D. (2002). Hepatitis C and cognitive impairment in a cohort of patients with mild liver disease. *Hepatology*, 35(2), 433-439.
- Friedman, N. P., & Miyake, A. (2016). Unity and diversity of executive functions: Individual differences as a window on cognitive structure. *Cortex*.
- Friedman, N. P., Miyake, A., Altamirano, L. J., Corley, R. P., Young, S. E., Rhea, S. A., Hewitt, J. K. (2016). Stability and change in executive function abilities from late adolescence to early adulthood: A longitudinal twin study. *Developmental Psychology*, 52(2), 326-340.
- Friedman, N. P., Miyake, A., Robinson, J. L., & Hewitt, J. K. (2011). Developmental trajectories in toddlers' self-restraint predict individual differences in executive functions 14 years later: A behavioral genetic analysis. *Developmental Psychology*, 47, 1410-1430.
- Friedman, N. P., Miyake, A., Young, S. E., DeFries, J. C., Corley, R. P., & Hewitt, J. K. (2008). Individual differences in executive functions are almost entirely genetic in origin. *Journal of Experiment Psychology: General*, 137, 201-225.



- Garvey, L. J., Pavese, N., Ramlackhansingh, A., Thomson, E., Allsop, J. M., Politis, M., ... Winston, A. (2012). Acute HCV/HIV coinfection is associated with cognitive dysfunction and cerebral metabolite disturbance, but not increased microglial cell activation. *PloS One*, 7(7), e38980.
- Gongvatana, A., Schweinsburg, B. C., Taylor, M. J., Theilmann, R. J., Letendre, S. L., Alhassoon, O. M., ... Ellis, R. J. (2009). White matter tract injury and cognitive impairment in human immunodeficiency virus-infected individuals. *Journal of Neurovirology*, 15, 187–195.
- Hall, P. A., & Fong, G. T. (2015). Temporal self-regulation theory: A neurobiologically informed model for physical activity behavior. *Frontiers in Human Neuroscience*, 9(117).
- Hardy, D. J., Hinkin, C. H., Levine, A. J., Castellon, S. A., & Lam, M. N. (2006). Risky decision making assessed with the gambling task in adults with HIV. *Neuropsychology*, 20, 355–360.
- Heaton, R. K., Franklin, D. R., Ellis, R. J., McCutchan, J. A., Letendre, S. L., LeBlanc, S., ... Collier, A. C. (2011). HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: Differences in rates, nature, and predictors. *Journal of Neurovirology*, 17(1), 3-16.
- Hilsabeck, R. C., Castellon, S. A., & Hinkin, C. H. (2005). Neuropsychological aspects of coinfection with HIV and hepatitis C virus. *Clinical Infectious Diseases*, 41(Supplement 1), S38-S44.
- Hinkin, C. H., Castellon, S. A., Levine, A. J., Barclay, T. R., & Singer, E. J. (2008). Neurocognition in individuals co-infected with HIV and hepatitis C. *Journal of Addictive Diseases*, 27(2), 11-17.
- Hull, R., Martin, R. C., Beier, M. E., Lane, D., & Hamilton, A. C. (2008). Executive function in older adults: A structural equation modeling approach. *Neuropsychology*, 22, 508e522.
- Hutchison, K. A., Balota, D. A., & Ducheck, J. M. (2010). The utility of Stroop task switching as a marker for early-stage Alzheimer's disease. *Psychology and Aging*, 25(3), 545-559.
- Ingiliz, P., Martin, T. C., Rodger, A., Stellbrink, H. J., Mauss, S., Boesecke, C., ... Lacombe, K. (2016). HCV reinfection incidence and spontaneous clearance rates in HIV-positive men who have sex with men in Western Europe. *Journal of Hepatology*.

- Iudicello, J. E., Woods, S. P., Cattie, J. E., Doyle, K., Grant, I., & HIV Neurobehavioral Research Program (HNRP) Group. (2013). Risky decision-making in HIV-associated neurocognitive disorders (HAND). *The Clinical Neuropsychologist*, 27(2), 256-275.
- Iudicello, J. E., Woods, S. P., Deutsch, R., Grant, I., & HIV Neurobehavioral Research Program (HNRP) Group. (2012). Combined effects of aging and HIV infection on semantic verbal fluency: A view of the cortical hypothesis through the lens of clustering and switching. *Journal of Clinical and Experimental Neuropsychology*, 34(5), 476-488.
- Jaeckel, E., Cornberg, M., Wedemeyer, H., Santantonio, T., Mayer, J., Zankel, M., ... Manns, M. P. (2001). Treatment of acute hepatitis C with interferon alfa-2b. *New England Journal of Medicine*, 345(20), 1452-1457.
- Juengling, F. D., Ebert, D., Gut, O., Engelbrecht, M. A., Rasenack, J., Nitzsche, E. U., ... Lieb, K. (2000). Prefrontal cortical hypometabolism during low-dose interferon alpha treatment. *Psychopharmacology*, 152(4), 383-389.
- Kerchner, G. A., Racine, C. A., Hale, S., Wilhelm, R., Laluz, V., Miller, B. L., & Kramer, J. H. (2012). Cognitive processing speed in older adults: Relationship with white matter integrity. *PLoS ONE*, 7(11), e50425.
- Klauer, K. C., Schmitz, F., Teige-Mocigemba, S., & Voss, A. (2010). Understanding the role of executive control in the Implicit Association Test: Why flexible people have small IAT effects. *The Quarterly Journal of Experimental Psychology*, 63(3), 595-619.
- Kliegel, M., Martin, M., McDaniel, M.A., & Einstein, G.O. (2002). Complex prospective memory and executive control of working memory: A process model. *Psychologische Beiträge*, 44, 303–318.
- Kraus, M. R., Schäfer, A., Teuber, G., Porst, H., Sprinzel, K., Wollschläger, S., ... Scheurlen, M. (2013). Improvement of neurocognitive function in responders to an antiviral therapy for chronic hepatitis C. *Hepatology*, 58(2), 497-504.
- Letendre, S. L., Cherner, M., Ellis, R. J., Marquie-Beck, J., Gragg, B., Marcotte, T., ... Grant, I. (2005). The effects of hepatitis C, HIV, and methamphetamine dependence on neuropsychological performance: Biological correlates of disease. *AIDS*, 19(Suppl 3), S72-8.
- Letendre, S. L., McCutchan, J. A., Childers, M. E., Woods, S. P., Lazzaretto, D., Heaton, R. K., ... Ellis, R. J. (2004). Enhancing antiretroviral therapy for human

- immunodeficiency virus cognitive disorders. *Annals of Neurology*, 56(3), 416-423.
- Letendre, S., Marquie-Beck, J., Capparelli, E., Best, B., Clifford, D., Collier, A. C., ... Simpson, D. (2008). Validation of the CNS Penetration-Effectiveness rank for quantifying antiretroviral penetration into the central nervous system. *Archives of Neurology*, 65(1), 65-70.
- Levin, R. L., Heller, W., Mohanty, A., Herrington, J. D., & Miller, G. A. (2007). Cognitive deficits in depression and functional specificity of regional brain activity. *Cognitive Therapy and Research*, 31, 211–233.
- Lezak, M. D. (2004). *Neuropsychological assessment*. 4. New York: Oxford UnivERSITY Press.
- Lieb, K., Engelbrecht, M.A., Gut, O., Fiebich, B.L., Bauer, J., Janssen, G., Schaefer, M. (2006). Cognitive impairment in patients with chronic hepatitis treated with interferon alpha (IFNalpha): Results from a prospective study. *European Psychiatry*, 21, 204–210.
- MacLeod, C. M. (1991). Half a century of research on the Stroop effect: An integrative review. *Psychological Bulletin*, 109, 163-203.
- Majer, M., Welberg, L. A., Capuron, L., Pagnoni, G., Raison, C. L., & Miller, A. H. (2008). IFN-alpha-induced motor slowing is associated with increased depression and fatigue in patients with chronic hepatitis C. *Brain, Behavior, and Immunity*, 22(6), 870-880.
- Mangia, A., Santoro, R., Copetti, M., Massari, M., Piazzolla, V., Spada, E., ... di Mauro, L. (2013). Treatment optimization and prediction of HCV clearance in patients with acute HCV infection. *Journal of Hepatology*, 59(2), 221-228.
- Marazziti, D., Consoli, G., Picchetti, M., Carlini, M., & Faravelli, L. (2010). Cognitive impairment in major depression. *European Journal of Pharmacology*, 626(1), 83-86.
- Marchant, N. L., King, S. L., Tabet, N., & Rusted, J. M. (2010). Positive effects of cholinergic stimulation favor young APOE ε4 carriers. *Neuropsychopharmacology*, 35(5), 1090-1096
- Martin, E. M., DeHaan, S., Vassileva, J., Gonzalez, R., Weller, J., & Bechara, A. (2013). Decision making among HIV+ drug using men who have sex with men: A preliminary report from the Chicago Multicenter AIDS Cohort Study. *Journal of Clinical and Experimental Neuropsychology*, 35(6), 573-583.

- Martin, E. M., Nixon, H., Pitrak, D. L., Weddington, W., Rains, N. A., Nunnally, G., ... Bechara, A. (2007). Characteristics of prospective memory deficits in HIV-seropositive substance-dependent individuals: Preliminary observations. *Journal of Clinical and Experimental Neuropsychology*, 29(5), 496-504.
- Martin, E. M., Novak, R. M., Fendrich, M., Vassileva, J., Gonzalez, R., Grbesic, S., ... Sworowski, L. (2004). Stroop performance in drug users classified by HIV and hepatitis C virus serostatus. *Journal of the International Neuropsychological Society*, 10(2), 298–300.
- McDermott, L. M., & Ebmeier, K. P. (2009). A meta-analysis of depression severity and cognitive function. *Journal of Affective Disorders*, 119, 1–8.
- Mendelsohn, D., Riedel, W. J., & Sambeth, A. (2009). Effects of acute tryptophan depletion on memory, attention and executive functions: A systematic review. *Neuroscience & Biobehavioral Reviews*, 33(6), 926-952
- Miller, A. H., Maletic, V., & Raison, C. L. (2009). Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biological Psychiatry*, 65(9), 732-741.
- Miller, T. R., Weiss, J. J., Bräu, N., Dieterich, D. T., Stivala, A., & Rivera-Mindt, M. (2016). Greater decline in memory and global neurocognitive function in HIV/hepatitis C co-infected than in hepatitis C mono-infected patients treated with pegylated interferon and ribavirin. *Journal of NeuroVirology*, 1-13.
- Misdraju, E.L & Gass, C.S (2010). The Trail Making Test and its neurobehavioral components. *Journal of Clinical Experimental Neuropsychology*, 32, 159-163.
- Miyake, A., & Friedman, N. P. (2012). The nature and organization of individual differences in executive functions four general conclusions. *Current Directions in Psychological Science*, 21(1), 8-14.
- Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex “frontal lobe” tasks: A latent variable analysis. *Cognitive Psychology*, 41(1), 49-100.
- Mohamed, M. A., Barker, P. B., Skolasky, R. L., Selnes, O. A., Moxley, R. T., Pomper, M. G., & Sacktor, N. C. (2010). Brain metabolism and cognitive impairment in HIV infection: A 3-T magnetic resonance spectroscopy study. *Magnetic Resonance Imaging*, 28(9), 1251-1257.

- Monaco, S., Mariotto, S., Ferrari, S., Calabrese, M., Zanusso, G., Gajofatto, A., ... Dammacco, F. (2015). Hepatitis C virus-associated neurocognitive and neuropsychiatric disorders: Advances in 2015. *World Journal of Gastroenterol*, 21(42), 11974-11983.
- Monchi, O., Petrides, M., Petre, V., Worsley, K., & Dagher, A. (2001). Wisconsin card sorting revisited: distinct neural circuits participating in different stages of the task identified by event-related functional magnetic resonance imaging. *Journal of Neuroscience*, 21, 7733–7741.
- Monsell, S. (2003). Task switching. *Trends in Cognitive Sciences*, 7(3), 134–140.
- Niendam, T. A., Laird, A. R., Ray, K. L., Dean, Y. M., Glahn, D. C., & Carter, C. S. (2012). Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. *Cognitive, Affective, & Behavioral Neuroscience*, 12, 241e268
- Pawelczyk, T., Pawelczyk, A., Strzelecki, D., & Rabe-Jablonska, J. (2008). Pegylated interferon  $\alpha$  and ribavirin therapy may induce working memory disturbances in chronic hepatitis C patients. *General Hospital Psychiatry*, 30(6), 501-508.
- Reger, M., Welsh, R., Razani, J., Martin, D. J., & Boone, K. B. (2002). A meta-analysis of the neuropsychological sequelae of HIV infection. *Journal of the International Neuropsychological Society*, 8, 410–424.
- Rogers, R. D., & Monsell, S. (1995). Costs of a predictable switch between simple cognitive tasks. *Journal of Experimental Psychology: General*, 124(2), 207.
- Rothwell, N. J. (1999). Annual review prize lecture cytokines. *Journals of Physiology*, 514, 3-17.
- Rusted, J. M., Sawyer, R., Jones, C., Trawley, S. L., & Marchant, N. L. (2009). Positive effects of nicotine on cognition: The deployment of attention for prospective memory. *Psychopharmacology*, 202(1-3), 93-102.
- Rusted, J. M., & Trawley, S. (2005). Comparable effects of nicotine in smokers and nonsmokers on a prospective memory task. *Neuropsychopharmacology*, 31(7), 1545-1549.
- Sacktor, N. C., Lyles, R. H., Skolasky, R. L., Anderson, D. E., McArthur, J. C., McFarlane, G., ... Miller, E. N. (1999). Combination antiretroviral therapy improves psychomotor speed performance in HIV-seropositive homosexual men. *Neurology*, 52(8), 1640-1640.

- Schnitzspahn, K. M., Stahl, C., Zeintl, M., Kaller, C. P., & Kliegel, M. (2013). The role of shifting, updating, and inhibition in prospective memory performance in young and older adults. *Developmental Psychology*, 49(8), 1544.
- Snyder, H. R. (2013). Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: A meta-analysis and review. *Psychological Bulletin*, 139(1), 81.
- Sun, B., Abadjian, L., Rempel, H., Monto, A., & Pulliam, L. (2013). Differential cognitive impairment in HCV coinfecting men with controlled HIV compared to HCV mono-infection. *Journal of Acquired Immune Deficiency Syndromes*, 62, 190-196.
- Teuber, H.-L. (1972). Unity and diversity of frontal lobe functions. *Acta Neurobiologiae Experimentalis*, 32, 615–656.
- Thames, A. D., Foley, J. M., Wright, M. J., Panos, S. E., Ettenhofer, M., Ramezani, A., ... Hinkin, C. H. (2012). Basal ganglia structures differentially contribute to verbal fluency: Evidence from Human Immunodeficiency Virus (HIV)-infected adults. *Neuropsychologia*, 50(3), 390-395.
- Udina, M., Hidalgo, D., Navinés, R., Forns, X., Solà, R., Farré, M., ... Martín-Santos, R. (2014). Prophylactic antidepressant treatment of interferon-induced depression in chronic hepatitis C. *The Journal of Clinical Psychiatry*, e1113-e1121.
- Udina, M., Navinés, R., Egmond, E., Oriolo, G., Langohr, K., Gimenez, D., ... Martín-Santos, R. (2015). Glucocorticoid Receptors, Brain-Derived Neurotrophic Factor, Serotonin and Dopamine Neurotransmission are Associated with Interferon-Induced Depression. *International Journal of Neuropsychopharmacology*, 19(4), pyv135.
- Verdejo-García, A., Bechara, A., Recknor, E. C., & Perez-Garcia, M. (2006). Executive dysfunction in substance dependent individuals during drug use and abstinence: An examination of the behavioral, cognitive and emotional correlates of addiction. *Journal of the International Neuropsychological Society*, 12(03), 405-415.
- Wager, T. D., & Smith, E. E. (2003). Neuroimaging studies of working memory: A meta-analysis. *Cognitive, Affective, & Behavioral Neuroscience*, 3, 255–274.
- Webster, D. P., Wojcikiewicz, T., Keller, M., Castelnovo, D., Mistry, H., Gilleece, Y., ... Fisher, M. (2013). Spontaneous clearance and treatment of acute hepatitis C infection in HIV-positive men with 48 weeks of interferon-alpha and ribavirin. *International Journal of STD & AIDS*, 24(3), 179-183.

- Wiebe, S. A., Espy, K. A., & Charak, D. (2008). Using confirmatory factor analysis to understand executive control in preschool children: I. Latent structure. *Developmental Psychology*, 44, 573–587.
- Wilson, C. J., Finch, C. E., & Cohen, H. J. (2002). Cytokines and cognition—the case for a head- to- toe inflammatory paradigm. *Journal of the American Geriatrics Society*, 50(12), 2041-2056.
- Winston, A., Garvey, L., Scotney, E., Yerrakalva, D., Allsop, J. M., Thomson, E. C., ... Taylor-Robinson, S. D. (2010). Does acute hepatitis C infection affect the central nervous system in HIV- 1 infected individuals?. *Journal of Viral Hepatitis*, 17(6), 419-426.
- Woods, S. P., Dawson, M. S., Weber, E., Gibson, S., Grant, I., & Atkinson, J. H. (2009). Timing is everything: Antiretroviral nonadherence is associated with impairment in time-based prospective memory. *Journal of the International Neuropsychological Society*, 15(01), 42-52.
- Woods, S. P., Iudicello, J. E., Moran, L. M., Carey, C. L., Dawson, M. S., & Grant, I. (2008). HIV-associated prospective memory impairment increases risk of dependence in everyday functioning. *Neuropsychology*, 22(1), 110.
- Woods, S. P., Moore, D. J., Weber, E., & Grant, I. (2009). Cognitive neuropsychology of HIV-associated neurocognitive disorders. *Neuropsychology Review*, 19(2), 152-168.

## **5. DISCUSSION AND FINAL CONCLUSIONS**



Infection with Hepatitis C virus has a devastating impact with about 20% to 85% of the infected patients progressing to HCV chronic condition mainly due to unawareness of their infection (Mah'moud, 2016). Historically, the treatment of HCV in HIV/HCV coinfection has been more complex when compared with HCV mono-infection due to longer treatment and less response to treatment (Bidell et al., 2016). When sexual transmission of HCV emerged as the main cause of the HCV epidemic in MSM at the turn of the century (Browne et al., 2004) the importance of routine HCV testing became a priority, especially in HIV infected individuals (Platt et al., 2016).

A solid body of research showed that HIV/HCV co-infection group is more likely to present with psychiatric disorders than HCV or HIV mono-infection (Baillargeon et al., 2008; Hilsabeck et al., 2005; Operskalski & Kovacs, 2011). In addition, there is a higher risk of HCV reinfection in HIV positive MSM (Martin et al., 2013; Simons et al., 2016), and these individuals are also more at risk of developing neuropsychiatric side effects during HCV IFN- $\alpha$  based treatment (Laguno et al., 2004; Landau et al., 2001; Myers et al., 2004; Moreno et al., 2004; Rockstroh et al., 2002).

The model of inflammation induced psychiatric disorders comes from evidence of cytokine immune therapy and has included studies of patients with chronic HCV infection (Capuron et al, 2002, 2004, 2006, 2007; Eccles et al, 2012; Schaefer et al., 2012; Udina et al, 2014; Whale et al, 2015). Powerful empirical data supports an IFN- $\alpha$  induced neuropsychiatric syndrome in hepatitis C treatment (Capuron & Castanon, 2017; Harrison, 2017) via an inflammatory response that has been associated with a complex relationship between the immune system and the brain, mediated by cytokines (Dantzer et al., 2008; Hoyo-Becerra et 2014; Miller, 2010; Raison & Miller, 2006; Swardfager et al., 2016). The IFN- $\alpha$  based behavioral syndrome is characterized by a combination of mood depression and cognitive changes (Barbosa et al., 2014; Capuron & Miller, 2004; Dowell et al., 2015; Fialho et al., 2017; Goldsmith et al., 2016; Miller & Raison, 2016, Whale et al., 2015).

The neuropsychiatric side effects of hepatitis C interferon based therapy had been significantly associated with emergence of MDD and cognitive impairment with implications on achieving sustained virological response due to high rates of withdrawing from treatment and non remittance of neuropsychiatric symptoms (Udina et al., 2012; Udina et al., 2015; Cattie et al., 2014). Potential inflammatory mechanisms boosted by HCV infection itself (Forton et al., 2008) and the effect of HCV interferon

based therapy (Whale et al., 2015) might explain these behavioural outcomes. Inflammation may play a role in the pathogenesis of psychiatric disorders and therapeutic options are needed to reduce neuropsychiatric symptoms

The lack of studies of HIV HCV co-infection was clear, which lead me initially to synthesise empirical questions about differences in neuropsychiatric syndromes between co-infection and HIV and HCV mono-infection groups. Furthermore, it was crucial to understand what type of depression-like behaviour is associated with HCV treatment, with the aim of reducing the risk of treatment attrition by optimising the screening and treatment of this specific depressive disorder.

Cognitive impairment had been broadly described as a side effect of HCV treatment but the literature was not consistent. The need was identified to assess the nature of this cognitive impairment profile and explore to what extent it may have an impact on treatment outcome such as adherence or dropout from therapy.

The research gap in HIV/HCV co-infection was clear, which led me initially to synthesise empirical evidence on neuropsychiatric syndromes, such as depression and cognitive impairment. Meta-analyses in this thesis more conclusively showed that the co-infected group had higher rates of depression symptoms and were more globally cognitively impaired when compared with HIV or HCV mono-infection respectively (Fialho et al., 2016; Fialho et al., 2017).

There are several possible explanations for why the co-infected group was more likely to report depressive symptoms when compared with HIV or HCV mono-infected groups. One possible explanation is related with the baseline characteristics of the participants, who had high rates of historical injecting drug use (Backus et al., 2005; Clifford et al., 2005) as confirmed by a meta-analysis that the prevalence of co-infection in HIV was 82% in people who injected drugs (Platt et al., 2016). The influence of well described psychosocial factors, such as stress, hopelessness, social disadvantage that have been significantly associated with this population (Pantalone et al., 2012; Pereira et al., 2014) might also contribute to a higher risk profile for the emergence of depression. In patients undergoing HCV treatment the side effects could also increase the risk of depression (Laguno et al., 2004; Landau et al., 2001; Myers et al., 2004; Rockstroch et al., 2002). My results add weight to the evidence that a high rate of depression is associated with co-infection. However, I also showed that data on HCV treatment in co-infection is suboptimal, with studies that were not recent, small in sample size and co-infected HIV MSM were understudied.

In the systematic review and meta-analysis on cognitive aspect in HIV/HCV co-infection, the co-infected group had a significantly higher global deficit score and information processing speed impairment than the HIV mono-infected patients. The greater cognitive impairment among co-infection appears associated with HCV replication in the brain (Sun et al., 2013) monocyte activation (Rempel et al., 2013), plasma inflammatory cytokine levels (Cohen et al., 2011), and the combination of HIV and HCV replication on specific brain sites (Hilsabeck et al., 2005). The greater neurotoxicity as a result of infection by both viruses may explain the global cognitive deficit and in particular the information processing speed impairment. No significant differences in cognition between co-infection and HCV mono-infected group were reported, which may be related to HCV specific mechanisms that are not yet established. Methodological issues might also explain this lack of difference between co-infection and HCV mono-infection, in particular heterogeneity on cognitive measures and samples characteristics. Furthermore, in the included studies sufficient explanations regarding the specific aspects of cognition in coinfection patients undergoing hepatitis C treatment was not provided. Nevertheless, the relevance of the findings is an association with the patient's difficulties in overall functioning, including adherence to treatment.

The systematic review and meta-analyses chapter demonstrated that the co-infected injected drug use (IDU) group is more at risk of developing depression and cognitive impairment, but most importantly reveals that the co-infected group is an understudied population, in particular during HCV interferon based treatment.

As stated above HCV is a major health burden, with increasing cases of HCV infection in HIV infected patients that has been associated with poorer treatment response (Weber et al., 2006) than in HCV monoinfected populations. Therefore, I designed several prospective studies within clinical populations, aiming to explore potential behavioral and clinical markers of the effect of HCV treatment, including direct acting antivirals (DAAs) therapy.

### **Is interferon-induced depression a sub-type of major depressive disorder in hepatitis C treatment?**

Data showed a high rate of major depressive disorder (MDD) during HCV interferon based therapy in a sample of HCV infected patients, including HIV/HCV co-

infection. Both groups had significantly increased depressive symptoms at the beginning of the treatment in comparison to pretreatment and showed remittance of depressive symptoms after treatment ended as previously reported (Fialho et al., 2014, 2015; Huckans et al., 2015; Whale et al., 2015; Udina et al., 2014, 2015). This suggests that IFN- $\alpha$  is directly associated with depressive like behavior (Capuron et al., 2001, 2003; Cattie et al., 2014; Loftis, 2013). However, in contrast with established literature (Laguno et al., 2004; Landau et al., 2001; Moreno et al., 2004; Myers et al., 2004; Rockstroh et al., 2002) my findings indicated that the HCV group is most vulnerable to develop depression when compared with the co-infected group. Potential explanations may be associated with the sample characteristics however; the HCV group were more likely to present risk factors to develop MDD, such as previous history of mental health and past history of drug abuse (Boscarino et al., 2015; Carta et al., 2012; Hilsabeck et al., 2005; Udina et al., 2015).

The HCV mono-infected group was more likely to present with MDD at the beginning of treatment and presented with significantly more neurovegetative depressive symptoms than the HIV/HCV co-infected group. Several studies on hepatitis C treatment reported that interferon activates different mechanisms that are significantly associated with different behavioral syndromes (Capuron et al., 2002, 2003; Eccles et al., 2012; Loftis 2013). In particular, the diversion of tryptophan metabolism (Capuron et al., 2003; Reus et al., 2015) has been significantly associated with the emergence of neurovegetative symptoms such as fatigue (Dowell et al., 2015), impaired activity (Whale et al., 2015) and sleep alterations (Raison et al., 2010). This result is particularly relevant for interferon induced depression treatment because as previously reported a neurovegetative syndrome has been described as more resistant to anti-depressant treatment (Capuron et al., 2004).

Overall it seems that there is a subtype of MDD that emerges at the beginning of IFN- $\alpha$  treatment and tends to present a neurovegetative symptom profile, as previously reported (Whale et al., 2015). These symptoms appeared more prevalent within the mono-infection group than the co-infected group, possibly because the HCV group had a higher rate of past psychiatric history and IDU.

**Does gender play a role in the emergence of interferon-induced depression?**

The neuropsychiatric syndrome induced by inflammation is well studied, however the described results must be interpreted carefully because not all MDD cases are inflammation based. MDD can occur without increased inflammatory cytokine activation (Marques-Deak et al., 2007) and equally patients can have increased inflammatory markers but do not present MDD symptoms (Lotrich et al., 2007). The lack of overall consensus regarding the inflammatory model of depression suggests need for clarification of a specific type of inflammatory induced depression behavior.

In the non-iatrogenic model of depression, being female is a well-established vulnerability factor (Azorin et al., 2014; Parker et al., 2014) for the development of depression. In the inflammatory model of depression, however, female gender as a vulnerability marker was not confirmed (Whale et al., 2015; Udina et al., 2012). I aimed to examine the prevalence of MDD and explore differences between genders in a mono-infected HCV sample undergoing hepatitis C DAAs with interferon based treatment. The findings confirmed the depressogenic nature of interferon with a significant increase in MDD at the beginning of treatment and a significant decrease in MDD at the end of treatment. It seems that interferon induced depression causes a severe depressive reaction that should be treated to avoid HCV treatment disruption (Fialho et al., 2016; Whale et al., 2015). Women were more likely to experience MDD at the end of treatment when compared with men. These results could be explained by a cumulative effect of symptoms that was confirmed by the high rate of neurovegetative and mood-cognitive syndromes as measured by the Hamilton Depression Rating Scale (HAMD), or could be associated with residual symptoms and risk factors such as past drug use and previous history of psychiatric disorders.

I failed to replicate the biphasic depression paradigm with both of the syndromes (neurovegetative and mood-cognitive) being significant at the beginning of the treatment and that could be associated with as yet unidentified mechanisms induced by protease inhibitor (DAAs). HCV triple therapy, composed of IFN- $\alpha$ ; ribavirin and a protease inhibitor (telaprevir) appears to reduce the likelihood of MDD in women only. Adding a protease inhibitor, the rates of sustained virological response (SVR) are high and the time of treatment can be reduced (Hullegie et al., 2015), but if it inhibits depression emergence, then the mechanisms involved require further exploration.

### **Does the immune response act to prevent interferon-induced depression in co-infection?**

Another route to explore interferon-induced depression was to examine the role of the immune system. IFN- $\alpha$ , tryptophan metabolism and CD4 cells count are part of a complex immune inflammatory network that has been associated with depression like behaviour (Capuron et al., 2001; Maes et al., 2001). An association between high rates of depression and a poor immune response during interferon treatment was expected. I confirmed a significant increase of depressive symptoms at an early stage of treatment but no significant association with immune response, as measured by CD4 cell count. Although a significant decrease of CD4 cell count was observed at the beginning of treatment there was no significant association with depression score. My findings can be justified by the high baseline CD4 cell count (>500 cells/mm<sup>3</sup>) before the start of treatment and well controlled HIV as represented by HIV RNA below the level of detectability (<40c/ml). Chronic inflammatory conditions are risk factors for the development and/or exacerbation of depression conditions. Thus, these inflammatory states may contribute to neuroimmune changes that underlie depressive like behavior (Wohleb et al., 2016). Interestingly, neuroendocrine activation can promote a beneficial immune response. In particular, recent evidence found that CD4 cells might induce resistance to depression by reducing inflammation (Kim et al., 2016; Loveau et al., 2015). The mechanisms involved in the role of the immune system fighting the emergence of depression have not been explored in this study, but our findings seem to indicate that a high CD4 cells count is associated with a reduced likelihood of presenting depression symptoms. Clearly more research is needed to clarify the specific mechanism activated by CD4 cells and how they influence depression, however it has been suggested that CD4 cells have anti-inflammatory effects that may actually contribute to the treatment of depression (Felger et al., 2015; Miller, 2010).

### **Does interferon-based treatment with DAAs confer a specific cognitive profile in co-infected samples?**

Neuropsychiatric side effects of HCV INF-  $\alpha$  based treatment are composed of depression and cognitive impairment (Sarkar et al., 2014; Cattie et al., 2014). Interferon

induced cognitive impairment has been commonly described but poorly explored in the literature. Subjective memory complaints, attention deficits and executive function impairment have been reported (Hilsabeck et al., 2005; Lieb et al., 2006; Pawelczyk et al., 2008; Monaco et al., 2015; Wilson, Finch, & Cohen, 2002). In particular, executive function impairment has been frequently reported in chronic viral conditions (Monaco et al., 2015; Thames et al., 2012). Main cognitive findings indicated that during DAAs interferon based treatment, in acute HCV in an HIV men who have sex with men (MSM) sample there was a cost to processing speed information. A significant increase on prospective memory cost analysis was observed from baseline to week 4. These cognitive outcomes were observed at the time of treatment where there was a clear effect of interferon (at week 4), indicating that there is an influence of an inflammatory condition on processing speed performance. Data indicated that in acute HIV/HCV co-infection there is a possible effect on cognition that, as in depression, seems to remit after treatment ended (week 12). The between group analysis confirmed a disadvantage on the speed components in the con-infected group when compared with the HIV group. Overall, there was an effect of DAAs IFN- $\alpha$  based therapy on executive function performance, with a disadvantage on information processing speed components with potential influence on attentional prospective memory layers. The implications of my findings are relevant for HIV/HCV co-infected patients due to impact on daily tasks such as medication adherence (Banich, 2009). At the best of our knowledge we are the first research group looking at the cognitive side effects of DAAs in HIV/HCV co-infection, nevertheless, our sample size is small and we interpret our results as an indicator of potential cognitive changes in the new era of HCV therapy.

HCV treatment has dramatically changed with the advent of interferon free therapy in recent years (Mah'moud, 2016). Recent clinical trials have demonstrated high efficacy of these treatments in HCV infected patients but the utility and efficacy in co-infected groups is unclear due to poorly representative samples (Ingiliz et al., 2016), HCV reinfection in HIV patients, drug interactions, and the effect of short term treatment on the efficacy of DAA treatment in co-infection (Hesamizadeh et al., 2016; Majumdar et al., 2016; Sulkowski, 2016). It appears that the DAAs reduce the prevalence of advanced liver disease but their high cost may constitute a barrier to their use worldwide (Chayama et al., 2015). It is likely that therapies including interferon will need to continue to be a treatment option therefore in the foreseeable future.

My findings have an important clinical impact. Firstly, recognition of the distinct profile of neuropsychiatric side effects of HCV in co-infection and HCV mono-infection will allow for the screening and treatment of these conditions accordingly, increasing the overall HCV therapy efficacy. Secondly, the co-infected population studied was mainly HIV MSM. According to recent reports there is an increasing HCV epidemic in HIV MSM in the UK (Martin et al., 2016). HCV has been considered as a sexually transmitted infection (STI) due to an outbreak of acute HCV infection among the HIV MSM population (Browne et al., 2004; Page & Nelson, 2016). Additionally, MSM with moderate to low levels of depression appear more at risk to engage in risky sexual behavior (O’Cleirigh et al., 2013), increasing the likelihood of HCV infections. The study sample was not severely depressed, indicating that they may be more likely to be at risk of HCV (re) infections. My findings highlight that regular screening and treatment of lower to moderate depression symptoms and assessment of sexual health should be risk-reducing strategies for the acute HCV HIV MSM population.

The effect of HCV treatment on cognitive status appears to be a specific impact on processing speed that remits when treatment ends, as confirmed by meta-analysis in populations without HCV treatment (Fialho et al., 2016). The clinical impact is based on the nature of this specific cognitive outcome, which has been considered a cognitive marker for developing severe HIV associated neurocognitive disorders (Becker & Salthouse, 1999). Although I present pilot data, it appears that the co-infected group have a disadvantage in information processing speed. These patients could therefore benefit from cognitive assessment before, during and after treatment to monitor and identify impairments with the aim of reducing impact on overall functioning, including ability to adhere to treatment (Arentsen et al., 2016; Huerta et al., 2016).

The limitations of my studies are detailed in each report, however during the research process what stood out, as a main barrier was the constant need to translate the research outcomes into real clinical benefits. It was a challenge to manage some factors that are out of the scope of this thesis but they are worthy of mention. Tasks such as recruitment, testing and providing feedback for a non academic audience were the main difficulties.

There is evidence suggesting that clinical practices improved when based on clinical research outcomes (Doyle et al., 2016; Ishida et al., 2016). My perspective is that optimal assessment and clarification of neuropsychiatric symptoms, including depressive disorders and cognitive functioning, at baseline is essential to enable early



detection versus late detection of neuropsychiatric interferon induced syndromes. However, from my experience the impact of conducting clinical studies in this clinically complex population is challenging.

The nature of this research was focused on clinical benefit to patients, on a dynamic platform between School of Psychology (UoS), Sussex Partnership Foundation Trust (SPT) and Brighton and Sussex University Hospitals (BSUH). BSUH was selected as a National Hepatitis Treatment Centre, which allowed me to work closely with this population and apply research outcomes to inform improved clinical care. My findings replicated the depressogenic nature of interferon treatment and identified a sub-type of depression composed of neurovegetative symptoms. I also clarified a specific cognitive impairment profile, specifically of processing speed in acute HCV HIV MSM population during DAA treatment. Regarding vulnerability factors, it appears that being female does not confer specific risk for developing depression and we were unable to identify an association with mood disorders and the biological marker CD4 cell count. For future research it is important to explore how cytokine induced depressive disorder differs from non-iatrogenic depressive disorder. Also, it is crucial to flag the reinfection group and explore what are the particular risk factors associated with it. Taking into account my findings, hypothetically the information processing speed impairment and mild depression symptoms may boost decision-making deficits and contribute to the (re)infection behavior. Further exploration of IFN- $\alpha$  free regimes and associated neuropsychiatric side effects it still needed.. My findings suggest that somatic features are predominant in interferon- $\alpha$  induced depression. The identification of an inflammatory influence on mood disorder may be further explored in HIV alone, particularly examining association between inflammatory markers and somatic depressive features.

As previously reported there is poverty of studies exploring the co-infected HIV HCV group. Interestingly this clinical group appears to have a high rate of HCV reinfection following treatment (Martin et al., 2013) that has been associated with sexual risk behaviours and depressive disorder (O’Cleirigh et al., 2013). It would be valuable to develop an epidemiologic analysis of reinfection patterns and associations with risk behaviour. Additionally the findings of this thesis suggest that information processing speed is impaired in the co-infected group. This processing change may be a factor which contributes to reduced adherence to medication, for example difficulties in

remembering times to take medication and dietary requirements (Huerta et al., 2016). Future research in the post interferon era would validly focus on how to reduce reinfection, which may be achieved through interventions to improve cognition and reduce depressive symptoms. This may include more proactive screening and specific cognitive interventions for those with identified changes. A Cognitive Behavioural Therapy integrative model using cognitive restructuring, behavioural activation techniques and proactive depression treatment would validly be explored in a feasibility study to explore effect on reinfection rates.

## References

- Arends, J. E., Lieveld, F. I., Boeijen, L. L., De Kanter, C. T., van Erpecum, K. J., Salmon, D., ... Ustianowski, A. (2015). Natural history and treatment of HCV/HIV coinfection: Is it time to change paradigms?. *Journal of Hepatology*, 63(5), 1254-1262
- Arentsen, T. J., Panos, S., Thames, A. D., Arbid, J. N., Castellon, S. A., & Hinkin, C. H. (2016). Psychosocial correlates of medication adherence among HIV-positive, cognitively impaired individuals. *Journal of HIV/AIDS & Social Services*, 15(4), 404-416.
- Azorin, J. M., Belzeaux, R., Fakra, E., Kaladjian, A., Hantouche, E., Lancrenon, S., & Adida, M. (2014). Gender differences in a cohort of major depressive patients: Further evidence for the male depression syndrome hypothesis. *Journal of Affective Disorders*, 167, 85-92.
- Backus, L. I., Boothroyd, D., & Deyton, L. R. (2005). HIV, hepatitis C and HIV/Hepatitis C virus co-infection in vulnerable populations. *AIDS*, 19(Suppl. 3), S13-S19.
- Baillargeon, J. G., Paar, D. P., Wu, H., Giordano, T. P., Murray, O., Raimer, B. G., ... Pulvino, J. S. (2008). Psychiatric disorders, HIV infection and HIV/hepatitis co-infection in the correctional setting. *AIDS Care*, 20(1), 124-129.
- Barbosa, I. G., Bauer, M. E., Machado-Vieira, R., & Teixeira, A. L. (2014). Cytokines in bipolar disorder: Paving the way for neuroprogression. *Neural Plasticity*, 2014, 1-9.
- Becker, J. T., & Salthouse, T. A. (1999). Neuropsychological test performance in the acquired immunodeficiency syndrome: Independent effects of diagnostic group on functioning. *Journal of the International Neuropsychological Society*, 5, 41-47.

- Bidell, M. R., McLaughlin, M., Faragon, J., Morse, C., & Patel, N. (2016). Desirable characteristics of hepatitis C treatment regimens: A review of what we have and what we need. *Infectious Diseases and Therapy*, 5(3), 299-312.
- Boscarino, J. A., Lu, M., Moorman, A. C., Gordon, S. C., Rupp, L. B., Spradling, P. R., ... Holmberg, S. D. (2015). Predictors of poor mental and physical health status among patients with chronic hepatitis C infection: the Chronic Hepatitis Cohort Study (CHeCS). *Hepatology*, 61(3), 802-811.
- Browne, R., Asboe, D., Gilleece, Y., Atkins, M., Mandalia, S., Gazzard, B., & Nelson, M. (2004). Increased numbers of acute hepatitis C infections in HIV positive homosexual men: Is sexual transmission feeding the increase?. *Sexually Transmitted Infections*, 80(4), 326-327.
- Capuron, L., & Castanon, N. (2017). Role of inflammation in the development of neuropsychiatric symptom domains: Evidence and mechanisms. *Current Topics in Behavioral Neurosciences*, 31, 31-44.
- Capuron, L., Fornwalt, F. B., Knight, B. T., Harvey, P. D., Ninan, P. T., & Miller, A. H. (2009). Does cytokine-induced depression differ from idiopathic major depression in medically healthy individuals? *Journal of Affective Disorders*; 119, 181-185.
- Capuron, L., Gumnick, J. F., Musselman, D. L., Lawson, D. H., Reemsnyder, A., Nemeroff, C. B., & Miller, A. H. (2002). Neurobehavioral effects of interferon- $\alpha$  in cancer patients: Phenomenology and paroxetine responsiveness of symptom dimensions. *Neuropsychopharmacology* 26, 643-652.
- Capuron, L., & Miller, A. H. (2004). Cytokines and psychopathology: Lessons from interferon- $\alpha$ . *Biological Psychiatry*, 56(11), 819-824.
- Capuron, L., Neurauter, G., Musselman, D. L., Lawson, D. H., Nemeroff, C. B., Fuchs, D., & Miller, A. H. (2003). Interferon-alpha-induced changes in tryptophan metabolism: Relationship to depression and paroxetine treatment. *Biological Psychiatry*, 54, 906-914.
- Capuron, L., Pagnoni, G., Demetrashvili, M. F., Lawson, D. H., Fornwalt, F. B., Woolwine, B., ... Miller, A. H. (2007). Basal ganglia hypermetabolism and symptoms of fatigue during interferon- $\alpha$  therapy. *Neuropsychopharmacology*, 32(11), 2384-2392.
- Capuron, L., Pagnoni, G., Drake, D. F., Woolwine, B. J., Spivey, J. R., Crowe, R. J., ... Miller, A. H. (2012). Dopaminergic mechanisms of reduced basal ganglia

- responses to hedonic reward during interferon alfa administration. *Archives of General Psychiatry*, 69(10), 1044-1053.
- Capuron, L., Ravaud, A., Gualde, N., Bosmans, E., Dantzer, R., Maes, M., Neveu, P.J. (2001). Association between immune activation and early depressive symptoms in cancer patients treated with interleukin-2-based therapy. *Psychoneuroendocrinology* 26, 797-808.
- Capuron, L., Ravaud, A., Neveu, P. J., Miller, A. H., Maes, M., & Dantzer, R. (2002). Association between decreased serum tryptophan concentrations and depressive symptoms in cancer patients undergoing cytokine therapy. *Molecular Psychiatry*, 7(5), 468-473.
- Carta, M. G., Angst, J., Moro, M. F., Mura, G., Hardoy, M. C., Balestrieri, C., ... Farci, P. (2012). Association of chronic hepatitis C with recurrent brief depression. *Journal of Affective Disorders*, 141(2), 361-366.
- Cattie, J. E., Letendre, S. L., Woods, S. P., Barakat, F., Perry, W., Cherner, M., ... Grant, I. (2014). Persistent neurocognitive decline in a clinic sample of hepatitis C virus-infected persons receiving interferon and ribavirin treatment. *Journal of Neurovirology*, 20(6), 561-570.
- Chayama, K., Mitsui, F., & Hayes, C. N. (2014). Optimizing triple therapy and IFN/RBV-free regimens for hepatitis C virus infection. *Expert Review of Gastroenterology & Hepatology*, 9(1), 21-30.
- Cohen, R. A., de la Monte, S., Gongvatana, A., Ombao, H., Gonzalez, B., Devlin, K. N., ... Tashima, K. T. (2011). Plasma cytokine concentrations associated with HIV/hepatitis C coinfection are related to attention, executive and psychomotor functioning. *Journal of Neuroimmunology*, 233(1-2), 204-210.
- Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W., & Kelley, K. W. (2008). From inflammation to sickness and depression: When the immune system subjugates the brain. *Nature Reviews Neuroscience*, 9(1), 46-56.
- Deterding, K., Grüner, N., Buggisch, P., Wiegand, J., Galle, P. R., Spengler, U., ... Großhennig, A. (2013). Delayed versus immediate treatment for patients with acute hepatitis C: a randomised controlled non-inferiority trial. *The Lancet Infectious Diseases*, 13(6), 497-506.
- Dowell, N. G., Cooper, E. A., Tibble, J., Voon, V., Critchley, H. D., Cercignani, M., & Harrison, N. A. (2016). Acute changes in striatal microstructure predict the development of interferon-alpha induced fatigue. *Biological Psychiatry*, 79(4),

320-328.

- Doyle, K. L., Woods, S. P., Morgan, E. E., Iudicello, J. E., Cameron, M. V., Gilbert, P. E., ... & HIV Neurobehavioral Research Program (HNRP) Group. (2016). Health-related decision-making in HIV disease. *Journal of Clinical Psychology in Medical Settings*, 23(2), 135-146.
- Eccles, J., Lallemant, C., Mushtaq, F., Greenwood, M., Keller, M., Golding, B., ... Whale, R. (2012). Pre-treatment waking cortisol response and vulnerability to interferon  $\alpha$  induced depression. *European Neuropsychopharmacology*, 22(12), 892-896.
- Felger, J. C., Haroon, E., & Miller, A. H. (2015). Risk and resilience: Animal models shed light on the pivotal role of inflammation in individual differences in stress-induced depression. *Biological Psychiatry*, 78(1), 7-9.
- Fialho, R., Burridge, A., Pereira, M., Keller, M., File, A., Tibble, J., & Whale, R. (2016). Norepinephrine-enhancing antidepressant exposure associated with reduced antiviral effect of interferon alpha on hepatitis C. *Psychopharmacology*, 233(9), 1689-1694.
- Fialho, R., Pereira, M., Bucur, M., Fisher, M., Whale, R., & Rusted, J. (2016). Cognitive impairment in HIV and HCV co-infected patients: A systematic review and meta-analysis. *AIDS Care*, 28(12), 1481-1494.
- Goldsmith, D. R., Haroon, E., Woolwine, B. J., Jung, M. Y., Wommack, E. C., Harvey, P. D., ... Miller, A. H. (2016). Inflammatory markers are associated with decreased psychomotor speed in patients with major depressive disorder. *Brain, Behavior, and Immunity*, 56, 281-288.
- Harrison, N. A. (2017) Brain Structures implicated in inflammation associated depression. *Current Topics in Behavioural Neuroscience*, 31, 221-248.
- Harrison, N. A., Dowell, N., Cooper, E., Tibble, J., Voon, V., Cercignani, M., & Critchley, H. (2015). Interferon- $\alpha$  induced fatigue is predicted by acute changes in stratal magnetisation transfer (qMT). *Brain, Behavior, and Immunity*, 49, e40.
- Hepgul, N., Pariante, C. M., Baraldi, S., Borsini, A., Bufalino, C., Russell, A., ... Mondelli, V. (2016). Depression and anxiety in patients receiving interferon-alpha: The role of illness perceptions. *Journal of Health Psychology*, doi:10.1177/1359105316658967

- Hesamizadeh, K., Sharafi, H., Rezaee-Zavareh, M. S., Behnava, B., & Alavian, S. M. (2016). Next steps toward eradication of hepatitis C in the era of direct acting antivirals. *Hepatitis Monthly*, 16(4), e37089.
- Hilsabeck, R. C., Castellon, S. A., & Hinkin, C. H. (2005). Neuropsychological aspects of coinfection with HIV and hepatitis C virus. *Clinical Infectious Diseases*, 41(Supplement 1), S38-S44.
- Hoyo-Becerra, C., Schlaak, J. F., & Hermann, D. M. (2014). Insights from interferon- $\alpha$ -related depression for the pathogenesis of depression associated with inflammation. *Brain, Behavior, and Immunity*, 42, 222-231.
- Huckans, M., Fuller, B., Wheaton, V., Jaehnert, S., Ellis, C., Kolessar, M., ... Sasaki, A. W. (2015). A longitudinal study evaluating the effects of interferon-alpha therapy on cognitive and psychiatric function in adults with chronic hepatitis C. *Journal of Psychosomatic Research*, 78(2), 184-192.
- Huerta, D. H., Torres, C. P., Gúrpide, A. M., Mangado, E. O., & Elias, M. P. (2016). Relationship between executive functions and adherence to antiretroviral therapy in HIV-infected patients. *European Psychiatry*, 33, S368-S369.
- Hullegie, S. J., Claassen, M. A., van den Berk, G. E., van der Meer, J. T., Posthouwer, D., Lauw, F. N., ... Bierman, W. F. (2016). Boceprevir, peginterferon and ribavirin for acute hepatitis C in HIV infected patients. *Journal of Hepatology*, 64(4), 807-812.
- Ingiliz, P., Christensen, S., Kimhofer, T., Hueppe, D., Lutz, T., Schewe, K., ... Simon, K. G. (2016). Sofosbuvir and ledipasvir for 8 weeks for the treatment of chronic hepatitis C virus (HCV) infection in HCV-monoinfected and HIV-HCV-coinfected individuals: Results from the German Hepatitis C Cohort (GECCO-01). *Clinical Infectious Diseases*, 63(10), 1320-1324.
- Ingiliz, P., Martin, T. C., Rodger, A., Stellbrink, H. J., Mauss, S., Boesecke, C., ... Lacombe, K. (2016). HCV reinfection incidence and spontaneous clearance rates in HIV-positive men who have sex with men in Western Europe. *Journal of Hepatology*. doi:10.1016/j.jhep.2016.09.004
- Ishida, H., Ikai, H., Suenaga, R., Suka, M., & Hirao, T. (2016). The impact of the difference in natural history models on the cost-effectiveness of antiviral agents for patients with genotype 1 chronic hepatitis C. *Value in Health*, 19(7), A374.
- Kim, Y. K., Na, K. S., Myint, A. M., & Leonard, B. E. (2016). The role of pro-inflammatory cytokines in neuroinflammation, neurogenesis and the

- neuroendocrine system in major depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 64, 277-284.
- Laguno, M., Murillas, J., Blanco, J. L., Martínez, E., Miquel, R., Sánchez-Tapias, J. M., ... León, A. (2004). Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for treatment of HIV/HCV co-infected patients. *AIDS*, 18(13), 27-36.
- Landau, A., Batisse, D., Piketty, C., Van Huyen, J. P. D., Bloch, F., Belec, L., ... Kazatchkine, M. D. (2001). Long-term efficacy of combination therapy with interferon- $\alpha$ 2b and ribavirin for severe chronic hepatitis C in HIV-infected patients. *AIDS*, 15(16), 2149-2155.
- Lieb, K., Engelbrecht, M.A., Gut, O., Fiebich, B.L., Bauer, J., Janssen, G., & Schaefer, M. (2006). Cognitive impairment in patients with chronic hepatitis treated with interferon alpha (IFNalpha): results from a prospective study. *European Psychiatry*, 21, 204-210.
- Loftis, J. M., Patterson, A. L., Wilhelm, C. J., McNett, H., Morasco, B. J., Huckans, M., ... Hauser, P. (2013). Vulnerability to somatic symptoms of depression during interferon-alpha therapy for hepatitis C: A 16-week prospective study. *Journal of Psychosomatic Research*, 74(1), 57-63.
- Lotrich, F. E., Rabinovitz, F., Gironde, P., & Pollock, B. G. (2007). Depression following pegylated interferon-alpha: Characteristics and vulnerability. *Journal of Psychosomatic Research*, 63(2), 131-135.
- Louveau, A., Smirnov, I., Keyes, T. J., Eccles, J. D., Rouhani, S. J., Peske, J. D., ... Harris, T. H. (2015). Structural and functional features of central nervous system lymphatic vessels. *Nature*, 523(7560), 337-341.
- Maes M, Capuron L, Ravaut A, Gualde N, Bosmans E, Egyed B, Dantzer R, Neveu PJ. (2001 a) Lowered serum dipeptidyl peptidase IV activity is associated with depressive symptoms and cytokine production in cancer patients receiving interleukin-2- based immunotherapy. *Neuropsychopharmacology*, 24(2), 130-140.
- Mah'moud, M. A. (2016). Current management of hepatitis C virus infection. *North Carolina Medical Journal*, 77(3), 188-193.
- Majumdar, A., Kitson, M.T., & Roberts, S.K. (2016). Systematic review: Current concepts and challenges for the direct-acting antiviral era in hepatitis C cirrhosis. *Aliment Pharmacol Ther.* 43, 1276-1292.

- Marques-Deak, A. H., Neto, F. L., Dominguez, W. V., Solis, A. C., Kurcgant, D., Sato, F., ... Prado, E. B. A. (2007). Cytokine profiles in women with different subtypes of major depressive disorder. *Journal of Psychiatric Research*, 41(1), 152-159.
- Martin, E. M., DeHaan, S., Vassileva, J., Gonzalez, R., Weller, J., & Bechara, A. (2013). Decision making among HIV+ drug using men who have sex with men: A preliminary report from the Chicago Multicenter AIDS Cohort Study. *Journal of Clinical and Experimental Neuropsychology*, 35(6), 573-583.
- Martin-Subero, M., & Diez-Quevedo, C. (2016). Mental disorders in HIV/HCV coinfectd patients under antiviral treatment for hepatitis C. *Psychiatry Research*, 246, 173-181.
- Miller, A. H. (2010). Depression and immunity: A role for T cells?. *Brain, Behavior, and Immunity*, 24(1), 1-8.
- Miller, A. H., & Raison, C. L. (2016). The role of inflammation in depression: From evolutionary imperative to modern treatment target. *Nature Reviews Immunology*, 16(1), 22-34.
- Monaco, S., Mariotto, S., Ferrari, S., Calabrese, M., Zanusso, G., Gajofatto, A., ... Dammacco, F. (2015). Hepatitis C virus-associated neurocognitive and neuropsychiatric disorders: Advances in 2015. *World Journal of Gastroenterol*, 21(42), 11974-11983.
- Moreno, L., Quereda, C., Moreno, A., Perez-Elías, M. J., Antela, A., Casado, J. L., ... Moreno, S. (2004). Pegylated interferon alpha2b plus ribavirin for the treatment of chronic hepatitis C in HIV-infected patients. *AIDS*, 18, 67-73.
- Musselman, D. L., Lawson, D. H., Gumnick, J. F., Manatunga, A. K., Penna, S., Goodkin, R. S., ... Miller, A. H. (2001). Paroxetine for the prevention of depression induced by high-dose interferon alfa. *New England Journal of Medicine*, 344(13), 961-966
- Myers, R. P., Benhamou, Y., Bochet, M., Thibault, V., Mehri, D., & Poynard, T. (2004). Pegylated interferon alpha 2b and ribavirin in HIV/hepatitis C virus-co-infected non-responders and relapsers to IFN-based therapy. *AIDS*, 18, 75-79.
- O'Cleirigh, C., Newcomb, M. E., Mayer, K. H., Skeer, M., Traeger, L., & Safren, S. A. (2013). Moderate levels of depression predict sexual transmission risk in HIV-infected MSM: a longitudinal analysis of data from six sites involved in a "prevention for positives" study. *AIDS and Behavior*, 17(5), 1764-1769.
- Operskalski, E. A., & Kovacs, A. (2011). HIV/HCV co-infection: pathogenesis, clinical



- complications, treatment, and new therapeutic technologies. *Current HIV/AIDS Reports*, 8(1), 12-22.
- Pantalone, D. W., Hessler, D. M., Barkoff, S. M., & Shah, B. J. (2012). Psychosocial correlates of HIV-monoinfection and HIV/HCV-coinfection among men who have sex with men. *Journal of Behavioral Medicine*, 35, 520-528.
- Parker, G., Fletcher, K., Paterson, A., Anderson, J., & Hong, M. (2014). Gender differences in depression severity and symptoms across depressive sub-types. *Journal of Affective Disorders*, 167, 351-357.
- Pearlman, B. L., & Traub, N. (2011). Sustained virologic response to antiviral therapy for chronic hepatitis C virus infection: A cure and so much more. *Clinical Infectious Diseases*, 52(7), 889-900.
- Pereira, M., Fialho, R., & Canavarro, M. C. (2014). Prevalence and correlates of emotional distress in HIV/HCV co-infection. *AIDS Care*, 26(Suppl.1), S56-S64.
- Platt, L., Easterbrook, P., Gower, E., McDonald, B., Sabin, K., McGowan, C., ... Vickerman, P. (2016). Prevalence and burden of HCV co-infection in people living with HIV: A global systematic review and meta-analysis. *The Lancet infectious diseases*, 16(7), 797-808.
- Raison, C. L., Capuron, L., & Miller, A. H. (2006). Cytokines sing the blues: Inflammation and the pathogenesis of depression. *Trends in Immunology*, 27(1), 24-31.
- Raison, C.L., Dantzer, R., Kelley, K.W., Lawson, M.A., Woolwine, B.J., Vogt, G., Spivey, J.R., Saito, K., & Miller, A.H. (2010). CSF concentrations of brain tryptophan and kynurenines during immune stimulation with IFN- $\alpha$ : Relationship to CNS immune responses and depression. *Molecular Psychiatry*, 15, 393-403.
- Rempel, H., Sun, B., Calosing, C., Abadjian, L., Monto, A., & Pulliam, L. (2013). Monocyte activation in HIV/HCV coinfection correlates with cognitive impairment. *PloS One*, 8(2), e55776.
- Rockstroh, J. K., Mudar, M., Lichterfeld, M., Nischalke, H. D., Klausen, G., Götz, J., ... Mauss, S. (2002). Pilot study of interferon alpha high-dose induction therapy in combination with ribavirin for chronic hepatitis C in HIV-co-infected patients. *AIDS*, 16, 2083-2085.
- Sarkar, S., & Schaefer, M. (2014). Antidepressant pretreatment for the prevention of interferon alfa-associated depression: A systematic review and meta-analysis.

*Psychosomatics*, 55(3), 221-234.

- Schaefer, M., Capuron, L., Friebe, A., Diez-Quevedo, C., Robaeys, G., Neri, S.,...  
Pariente, C.M. (2012). Hepatitis C infection, antiviral treatment and mental health: a European expert consensus statement. *Journal of Hepatology*, 57, 1379-1390.
- Simmons, B., Saleem, J., Heath, K., Cooke, G. S., & Hill, A. (2015). Long-term treatment outcomes of patients infected with hepatitis C virus: A systematic review and meta-analysis of the survival benefit of achieving a sustained virological response. *Clinical Infectious Diseases*, 61(5), 730-740.
- Simmons, B., Saleem, J., Hill, A., Riley, R. D., & Cooke, G. S. (2016). Risk of late relapse or reinfection with hepatitis C virus after achieving a sustained virological response: A systematic review and meta-analysis. *Clinical Infectious Diseases*, 62(6), 683-694.
- Sulkowski, M. S. (2016). HCV-HIV co-infected patients: No longer a 'special' population?. *Liver International*, 36, 43-46.
- Sun, B., Abadjian, L., Rempel, H., Monto, A., & Pulliam, L. (2013). Differential cognitive impairment in HCV coinfecting men with controlled HIV compared to HCV monoinfection. *Journal of Acquired Immune Deficiency Syndromes*, 62, 190-196.
- Swardfager, W., Rosenblat, J. D., Benlamri, M., & McIntyre, R. S. (2016). Mapping inflammation onto mood: Inflammatory mediators of anhedonia. *Neuroscience & Biobehavioral Reviews*, 64, 148-166.
- Thames, A. D., Foley, J. M., Wright, M. J., Panos, S. E., Ettenhofer, M., Ramezani, A., ... Hinkin, C. H. (2012). Basal ganglia structures differentially contribute to verbal fluency: Evidence from Human Immunodeficiency Virus (HIV)-infected adults. *Neuropsychologia*, 50(3), 390-395.
- Udina, M., Castellví, P., Moreno-España, J., Navinés, R., Valdés, M., Forns, X., ... Martín-Santos, R. (2012). Interferon-induced depression in chronic hepatitis C: A systematic review and meta-analysis. *Journal of Clinical Psychiatry*, 73, 1128-1238.
- Udina, M., Hidalgo, D., Navinés, R., Forns, X., Solà, R., Farré, M., ... Martín-Santos, R. (2014). Prophylactic antidepressant treatment of interferon-induced depression in chronic hepatitis C. *The Journal of Clinical Psychiatry*, e1113-e1121.

- Udina, M., Navinés, R., Egmond, E., Oriolo, G., Langohr, K., Gimenez, D., ... Martín-Santos, R. (2015). Glucocorticoid receptors, brain-derived neurotrophic factor, serotonin and dopamine neurotransmission are associated with interferon-induced depression. *International Journal of Neuropsychopharmacology*, 19(4), pyv135.
- Weber, R., Sabin, C. A., Friis-Moller, N., Reiss, P., El-Sadr, W. M., Kirk, O., ... Akerlund, B. (2006). Liver-related deaths in persons infected with the human immunodeficiency virus: the D: A: D study. *Archives of Internal Medicine*, 166(15), 1632-1641.
- Whale, R., Fialho, R., Rolt, M., Eccles, J., Pereira, M., Keller, M., ... Tibble, J. (2015). Psychomotor retardation and vulnerability to interferon alpha induced major depressive disorder: Prospective study of a chronic hepatitis C cohort. *Journal of Psychosomatic Research*, 79(6), 640-645.
- Wilson, C. J., Finch, C. E., & Cohen, H. J. (2002). Cytokines and cognition—the case for a head-to-toe inflammatory paradigm. *Journal of the American Geriatrics Society*, 50(12), 2041-2056.
- Wohleb, E. S., Franklin, T., Iwata, M., & Duman, R. S. (2016). Integrating neuroimmune systems in the neurobiology of depression. *Nature Reviews Neuroscience*, 17(8), 497-511.