Universitat Autònoma de Barcelona

Health-related quality of life and risk factors in hepatitis C patients treated with direct-acting antivirals

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Voor jullie

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List of acronyms

CHC	Chronic hepatitis C
CLDQ	Chronic Liver Disease Questionnaire
DAA	Direct-acting antiviral
QALY	Quality-adjusted life years
EQ-5D	EuroQol 5D questionnaire
EQ-VAS	EuroQol Visual Analog Scale
ER	Endoplasmic reticulum
GT	Genotype
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HCV-PRO	Hepatitis C Virus Patient-Reported Outcomes questionnaire
HIV	Human immunodeficiency virus
HRQL	Health-related quality of life
HUI	Health Utility Index
LDSI	Liver Disease Symptom Index questionnaire
LDQOL	Liver Disease Quality of Life questionnaire
NS	Non-structural
ORF	Open reading fram
IFNα	Interferon-alpha
MCS	Mental Component Scale

MD	Major depression
MELD	Model of end-stage liver disease
NI	Nucleotide inhibitors
NNI	Non-nucleoside inhibitors
PCS	Physical Component Scale
PI	Protease inhibitors
PR	Peginterferon-alpha and ribavirin
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines
PROQOL-HCV	Patient-Reported Outcomes Quality of Life Survey for HCV
PWID	People who inject drugs
QoL	Quality of life
SF-36	MOS Short-Form 36 questionnaire
SF-6D	MOS Short-Form 6 Dimensions questionnaire
ssRNA	Single stranded ribonucleic acid
SUD	Substance use disorder
SVR	Sustained virological response
RBV	Ribavirin
RCT	Randomized Clinical Trial
RNA	Ribonucleic acid
WHO	World Health Organization

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Preface

With recent estimates equating to around 71 million, the hepatitis C virus (HCV) is one of the most important chronic infections worldwide. HCV is also one of the world's leading causes of liver failure. Besides causing liver-related consequences, the virus often causes significant physical, mental, and social impairment. Although different types of antiviral treatment exist to cure this virus, they may exacerbate present or even cause new certain symptoms, further impairing the different aspects of life quality in these persons.

During the realization of my Master Degree in Research Psychology Applied to Health Sciences at the Department of Clinical and Health Psychology at the Universitat Autònoma de Barcelona (2013-2014), the research field of quality of life in chronic illness sparked my interest. In this context, in 2014 I became involved as a predoctoral researcher in a project focussed on quality of life and psychiatric disorders in chronic hepatitis C patients, at the Department of Psychiatry and Psychology at Hospital Clinic de Barcelona.

I have received the support of a predoctoral grant from the Fundació Clínic per a la Recerca Biomédica of Barcelona (2015-2016) to work at the Grup de Recerca en Vulnerabilitat, psicopatología i gènere (SGR2014:1114, IP. RM-S). Part of this research has been realized with the following supports for investigation: Instituto de Carlos III (PSICOCIT-VHC-P110/01827; IP: R. Martin-Santos, and PSIGEN-VHC-EC08/00201; IP: R. Martín-Santos). It was

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During my dissertation period I have realized a research internship at the University Medical Center in Nijmegen, The Netherlands, at the Department of Psychiatry, with Dr. Albert Batalla as my tutor, who gave me the opportunity to improve my methodology and scientific writing skills.

Preliminary results of this thesis have been presented as oral and poster communications on several *national and international congresses*:

Egmond E, Navinés R, Oriolo G, Mariño Z, Pla A, Bartres C, Cavero M, Subirá S, Forns X, Martin-Santos R. “New antiviral treatments for chronic hepatitis C and health-related quality of life: a systematic review and meta-analysis”. Presented as poster at the 5th Annual Scientific Conference of the European Association of Psychosomatic Medicine (EAPM).
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During the time of this dissertation I have co-elaborated several *article publications* in peer-reviewed indexed journals in the same line of research:

Martin-Santos R, **Egmond E**, Cavero M, Marino Z, Subira S, Navines R, Forns X, Valdes M. "Chronic Hepatitis C, depression and gender: a state of art". *Advances in Dual Diagnosis*. 2015; 8:193-210. doi: 10.1108/ADD-05-2015-0009 Citations: 2.

Udina M, Navinés R, **Egmond E**, Oriolo G, Langorh K, Giménez D, …, Martín-Santos R. "Glucocorticoid receptors, brain-derived neurotrophic factor, serotonin and dopamine neurotransmission are associated with interferon-induced depression". *International Journal of Neuropsychopharmacology.* 2015;19:1–12. doi: 10.1093/ijnp/pyv135
Impact Factor: 4.33. Citations: 2.

Furthermore, I have collaborated in the following book chapter publication:

Navinés R, **Egmond E**, Martín-Santos R. (2016). *"Panic disorder and personality disorder comorbidity".* In: Panic Disorder: Neurobiological and Treatment Aspects, pp. 169-184. Switzerland: Springer. ISBN: 978-3-319-12538-1

ABSTRACT

Hepatitis C virus (HCV) affects physical and mental health in 71 million persons worldwide. Classic antiviral treatment with (pegylated) interferon and ribavirin (PR) causes considerable impairment on chronic hepatitis C (CHC) patients' life quality. Recently, direct-acting antivirals (DAAs) have been introduced, which have been associated with high cure rates (over 90%), reduced side effects, and are suggested to have a minimal impact on health-related quality of life (HRQL). However, the amount of evidence is still scarse, as trials on the wide range of these new regimens are ongoing.

In this doctoral thesis, two studies were conducted in order to assess HRQL in HCV patients treated with DAAs: (I) a systematic review and meta-analysis of RCT studies that have assessed HRQL and risk factors, in CHC patients treated with any type or combination of DAAs; (II) a longitudinal naturalistic cohort study assessing HRQL and incidence of depression during antiviral treatment, taking in account possible risk factors that may predict life quality impairment and depression.

Findings from the systematic review suggest that the new antiviral regimens have a minimal impact on life quality, and may even improve in terms of mental wellbeing. With regard to DAAs alone, a slight improvement in patients' mental life quality was observed (MD=2.88; 95%CI=2.24, 3.53). Ribavirin co-administration with DAAs showed impairment on mental HRQL (MD=-1.7; 95%CI=-2.5, -0.91). Any combination of DAAs with PR seemed to impair significantly both mental and physical health quality (MD= -0.13; 95%CI=-0.15, -0.11). At baseline, HRQL is more impaired in CHC patients who are unemployed, have cirrhosis, anemia, or history of depression, anxiety, fatigue, or insomnia than those who do not. Furthermore, female gender, older age, and history of depression may predict HRQL impairment during DAAs plus ribavirin treatment. Also, adverse events and treatment non-response are risk factors for DAAs plus ribavirin or PR.

In the second study, we observed a cumulative incidence of major depression was 13.7% (95%CI: 5.7 to 26.3), and any depressive disorder 51% (95%CI: 36.6 to 65.2) during DAA treatment. Multivariate logistic regression analysis showed that only PHQ-9 score at baseline was a predictive factor for incidence of major depression (p=0.002), with a tendency for family history of depression (p=0.0079). We could not exclude the presence of significant mean (SD) changes in EQ-VAS scores during DAA treatment (67.2±20.3), at treatment end (71.3±19.6), or 12 weeks

after treatment (76.1±18.7) related to baseline, after controlling by age, gender, comorbidity, history of depression, or ribavirin co-administration. No significant changes were detected between those with or without (descompensated) cirrhosis. All patients except one achieved a SVR.

This research has some limitations. Few RCTs in the literature have replicated their findings, and few of them studied HRQL in especific groups such as co-infection, substance use and other psychiatric comorbidity. Limitations of the study included relatively small sample size, inclusion of patients with advanced liver disease and without HIV co-infection, factors that limit the generalization of our results.

In summary, results support that HRQL may improve after successful treatment. It is important to detect those patients with risk factors, especially for those with decompensated cirrhosis or depression, before starting antiviral treatment. Altogether, the findings suggest the use of a holistic, multidisciplinary approach to manage both physical and mental health.

RESUMEN

El virus de la hepatitis C (VHC) causa una de las infecciones crónicas más importantes a nivel mundial, afectando a una población estimada de 71 millones de personas. El tratamiento antiviral clásico con (peg)interferón-alfa y ribavirina (PR) provoca un deterioro significativo en la calidad de vida de los pacientes con hepatitis C crónica (HCC). Recientemente, se han introducido antivirales de acción directa (AAD) que se han asociado a una mayor ratio de respuesta al tratamiento (por encima del 90%), a una reducción de los efectos secundarios y a un impacto mínimo en la calidad de vida relacionada con la salud (CVRS). Sin embargo, las evidencias aún son escasas debido a que los ensayos clínicos investigando los AAD están en desarrollo.

Para esta tesis doctoral, se han llevado a cabo dos estudios, con el fin de evaluar la CVRS en pacientes que reciben AAD: (I) una revisión sistemática y un meta-análisis de ensayos clínicos randomizados (ECR) que han evaluado la CVRS y factores de riesgo en pacientes con HCC tratados con cualquier tipo y combinación de AAD; (II) un estudio de cohorte naturalístico longitudinal con el fin de evaluar la CVRS y la incidencia de depresión durante el tratamiento antiviral, teniendo en cuenta posibles factores de riesgo que podrían predecir un deterioro en la calidad de vida y la aparición de depresión.

Los resultados de la revisión sistemática sugieren que los nuevos regímenes antivirales tienen un impacto mínimo en la calidad de vida, e incluso pueden mejorar el componente de salud mental. Con respecto a los AAD solos, una mejoría ligera en la calidad de vida en el componente mental fue observada (MD=2.88; 95%CI=2.24, 3.53). La co-administración de ribavirina a los AAD mostró un deterioro en la calidad de vida en el componente mental (MD=-1.7; 95%CI=-2.5, -0.91). Cualquier combinación de DAAs con PR empeoró la calidad de vida tanto en el componente mental como físico (MD= -0.13; 95%CI=-0.15, -0.11). A nivel basal, la CVRS fue menor en pacientes con VHC sin empleo, en aquellos con cirrosis, anemia, o con antecedentes de depresión, ansiedad, o con edad avanzada. Además, el género femenino, la edad avanzada, y los antecedentes de depresión pudieron predecir una menor CVRS durante el tratamiento antiviral con AAD. Asimismo, encontramos que los acontecimientos adversos y la no-respuesta al tratamiento con AAD y PR fueron factores de riesgo.

En el segundo estudio, se observó una incidencia acumulada de depresión mayor en el 13.7% (95%CI: 5.7 - 26.3) de los pacientes, y de cualquier trastorno depresivo en el 51% (95%CI: 36.6 - 65.2) durante el tratamiento antiviral con AAD. El análisis de regresión logístico multivariado mostró que el único factor predictivo de incidencia de depresión mayor fue la puntuación a nivel basal del PHQ-9 (p=0.002), y una tendencia sí existía para historia familiar de depresión (p=0.0079). No se pudo descartar la presencia de cambios significativos de la media (DS) en puntuaciones del EQ-VAS durante el tratamiento antiviral con DAA (67.2±20.3), al final de tratamiento (71.3±19.6), o a las 12 semanas de postratamiento comparado a las puntuaciones a nivel basal, después de controlar por edad, género, comorbilidad, antecedentes de depresión, o co-administración con ribavirina. No se detectaron cambios significativos entre pacientes con y sin cirrosis ([des]compensada). Todos los pacientes excepto uno respondieron al tratamiento antiviral.

La presente investigación tiene algunas limitaciones. Pocos ECR en la literatura han replicado los resultados, y pocos de ellos han estudiado la CVRS en grupos específicos, como por ejemplo con coinfección por el VIH, con uso de sustancias o otros trastornos psiquiátricos. Por otro lado, el tamaño de la muestra, la inclusión de pacientes con enfermedad hepática avanzada y sin coinfección con VIH y la no inclusión de un grupo control sin HCC, limitan la generalización de nuestros resultados.

En conclusión, los resultados de la investigación apoyan que la calidad de vida puede mejorar después de un régimen antiviral exitoso. Es importante poder detectar pacientes con factores de riesgo, especialmente ellos con cirrosis hepática decompensada o depresión, antes de empezar el tratamiento antiviral. En general un enfoque multidisciplinar continúa siendo recomendable para mejorar la CVRS de los pacientes infectados por VHC.

RESUM

El virus de l'hepatitis C (VHC) causa una de les infeccions cròniques més importants a nivell mundial, afectant a una població estimada de 71 milions de persones. El tractament antiviral clàssic amb interferó-alfa i ribavirina (PR) provoca un deteriorament significatiu en la qualitat de vida dels pacients amb hepatitis C crònica (HCC). Recentment, s'han introduït antivirals d'acció directa (DAA) que s'han associat a una major ràtio de resposta al tractament (per sobre del 90%), a una reducció dels efectes secundaris i a un impacte mínim en la qualitat de vida relacionada amb la salut (QVRS). No obstant això, les evidències són escasses a causa de que els assaigs clínics investigant els DAA encara estan en desenvolupament.

Per a aquesta tesi doctoral, s'han dut a terme dos estudis, per tal de valorar la QVRS en els pacients reben tractament amb DAA: (I) una revisió sistemàtica i una meta-anàlisi d'assaigs clínics randomitzats (ACR) que han avaluat la QVRS i factors de risc en pacients amb HCC tractats amb qualsevol tipus i combinació de DAA; (II) un estudi de cohort naturalístic longitudinal per tal d'avaluar la QVRS i incidència de depressió durant el tractament antiviral, tenint en compte possibles factors de risc que poguessin predir un deteriorament en la qualitat de vida i l'aparició de depressió.

Els resultats de la revisió sistemàtica suggereixen que els nous règims antivirals tenen un impacte mínim en la qualitat de vida, i fins i tot poden millorar el component de la salut mental. Pel que fa als DAA sols, es va observar una lleugera milloria en el component mental de la QVRS (MD = 2.88; 95% CI = 2.24, 3.53). La co-administració de ribavirina als DAA va mostrar un deteriorament en el component mental de la QVRS (MD = -1.7; 95% CI = -2.5, -0.91). Qualsevol combinació de DAAs amb PR semblava va empitjorar la qualitat de vida tant en el component mental com físic (MD = -0.13; 95% CI = -0.15, -0.11). A nivell basal, la QVRS va ser menor en pacients amb VHC sense ocupació, en els que tenien cirrosi, anèmia, o amb antecednets de trastorn depressiu o ansietat, o amb edat avançada. A més, el gènere femení, l'edat avançada, i els antecedents de depresió van poder predir qualitat de vida alterada durant el tractament antiviral amb DAA. Així mateix, els esdeveniments adversos i la no-resposta al tractament amb DAA i PR foren factors de risc.

En el segon estudi, es va observar una incidència acumulada de depressió major de 13.7% (95% CI: 5.7 - 26.13), i de qualsevol trastorn depressiu de 51%

(95% CI: 36.6 - 65.2) durant el tractament antiviral amb DAAs. L'anàlisi de regressió logística multivariant va mostrar que l'únic factor predictiu d'incidència de depressió major va ser la puntuació basal del PHQ-9 (p = 0.002), i una tendència si existien antecedents familiars de depressió (p = 0.0079). No es va poder descartar la presència de canvis significatius de la mitjana (DS) en puntuacions de l'EQ-VAS durant el tractament antiviral amb DAA (67.2 ± 20.3), al final del tractament (71.3 ± 19.6), a les 12 setmanes de posttractament (76.1 ± 18.7) o a les 48 setmanes de posttractament (76.7 ± 15) comparat amb les puntuacions a nivell basal, després de controlar per edat, gènere, comorbiditat, història de depressió, o co-administració de ribavirina. No es van detectar canvis significatius entre pacients amb i sense cirrosi (descompensada). Tots els pacients tret d'un van respondre al tractament amb DAA.

La present investigació té algunes limitacions. La revisió sistemàtica mostra que pocs ACR han replicat els seus resultats, i pocs d'ells han estudiat la QVRS en grups específics, com per exemple amb coinfecció pel VIH, amb ús de substàncies o amb altres trastorns psiquiàtrics. La mida de la mostra, la inclusió de pacients amb malaltia hepàtica avançada i sense coinfecció i la no inclusió d'un grup control sense HCC limiten la generalització dels nostres resultats.

En conclusió, els resultats de la investigació recolzen que la qualitat de vida dels pacients amb HCC pot millorar després d'un règim antiviral reeixit. És important detectar pacients amb factors de risc, especialment amb la cirrosi decompensada o depressió, abans de començar amb el tractament antiviral. En general, els resultats recolzen que continua sent recomanable un enfocament multidisciplinari per la millora de la salut física i mental d'aquests pacients.

CHAPTER 1

Introduction

"Health is a state of complete physical, mental, and social wellbeing — not merely the absence of disease, or infirmity."

(World Health Organization, 1948)

1.1. Health-related quality of life

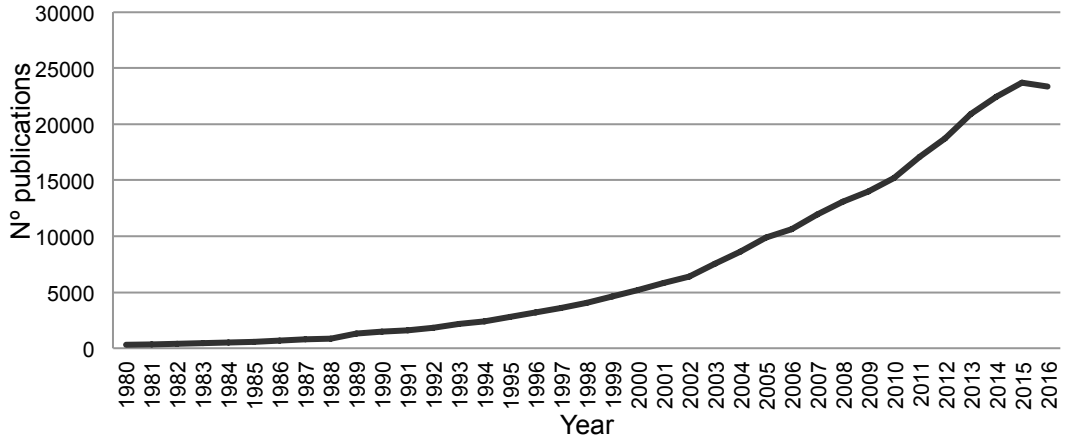
The concept of quality of life (QoL) is an attempt to, in analyzable terms, define the effect of the functional outcome of a disease and its treatment on the patient. What emerges should be a functional definition that is measurable over time. QoL is a social construction that is conceived as composed of several core concepts, domains and indicators that are shared amongst people, as well as characteristics and interests that are unique to individuals (Brown & Brown 2003; Schalock, Gardner, & Bradley, 2007). This conceptualization is based on the World Health Organization (WHO) definition of health as "A state of complete physical, mental, and social wellbeing and not merely the absence of disease or infirmity" (Grad, 2002). This definition is so broad that it includes elements that are beyond the traditional domain of medicine and health caring systems. Opportunity, education, spiritual attitudes, social security, working satisfaction, social relationships, and goods availability, are elements of QoL that are independent of medicine. What we deal with, by using the concept of health-related quality of life (HRQL), is the functional effect of an illness and its therapy on an individual (Amodio et al., 2012).

Although the ancient Greeks were the first to show interest in human health and wellbeing, it was the earliest recognized philosopher of the welfare state, Jeremy Bentham (1748 – 1832) who attempted to measure subjective wellbeing, as he felt that each citizen should be able to achieve their optimal mental wellbeing within the economic and cultural boundaries of society (Bentham, 1834). He defined subjective wellbeing as the difference between the sum of all kinds of pleasure, and the sum of all kinds of pain, experienced by a person in a given period of time, e.g. during a course of treatment lasting for some weeks or months. Physician, philosopher and psychologist William James (1842 – 1910) was the first to introduce the concept of HRQL. He considered human wellbeing to be a subjective, emotional perception, and thus should be measured psychometrically instead of biologically. His essay "Is Life Worth Living" is now regarded as the 'landmark' publication in HRQL (James, 1897). However, the first important study on measurement of HRQL was not performed until the end of the 20th century (Ware and Sherbourne, 1992).

Historically, traditional medical care has focused on the diagnosis and treatment of physiological and anatomical conditions (Wasson et al., 1992), and has tended to overlook global functioning, wellbeing, and life quality. It mostly relied upon measures of morbidity and mortality, where judgements were based on intervention through clinical, radiological and laboratory measures, without giving importance to the self-perceived wellbeing of patients (Blazer & Houpt, 1979; Jenkinson, 1993). However, an important development in the healthcare field was the recognition of the centrality of the

patient's point of view in monitoring the quality of medical care outcomes (Geigle & Jones, 1990) taking into account their needs and expectations. As a result of these developments, since the 1980s the concept of HRQL and its determinants have evolved. Each year, thousands of scientific articles are being published on the subject, emphasizing the increased interest for this theme (see Figure 1.1).

Figure 1.1. Number of publications on quality of life indexed in Pubmed database.



Instead of collecting merely clinical or medical information, practicing physicians and other health providers have increasingly begun to include patient-reported information about functional status, wellbeing, and other health outcomes that are considered important to life quality. HRQL covers the aspects of overall QoL that can be clearly shown to affect either a person's physical or mental health (McHorney, 1999). As the questions that are included in the evaluation of HRQL are drawn from various domains of the experience of the patient, and should therefore represent his/her self-perception in the most complete way, concerning physical, psychological,

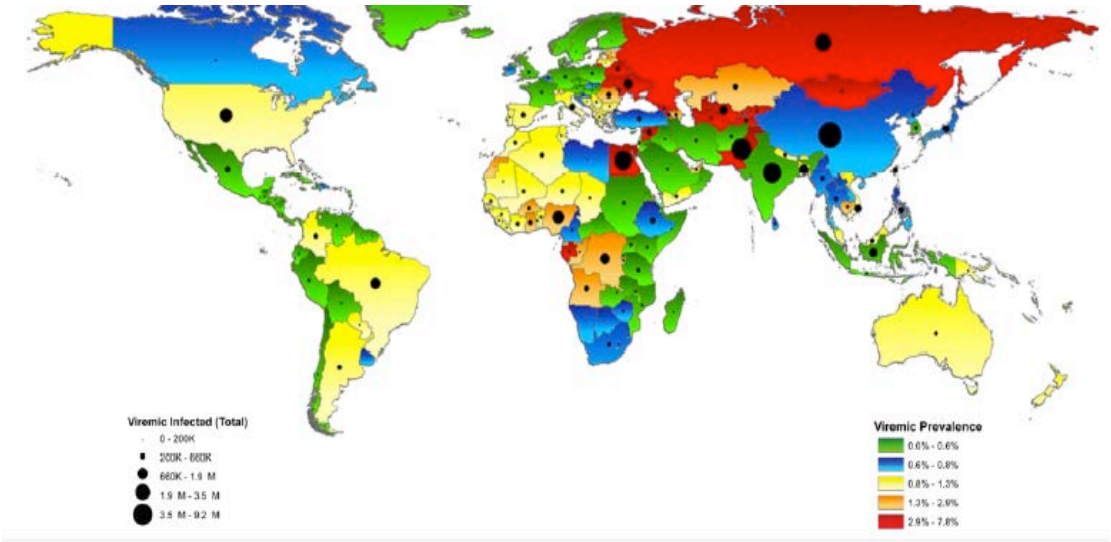
relational, and working experience. Measuring it can help determine the burden of preventable disease, injuries, and disabilities, and it can provide valuable new insights into the relationships between HRQL and risk factors. Policy analysts and managers of healthcare organizations have also started to utilize this information to compare the costs and benefits of competing ways of organizing and financing healthcare services, including for treatment of diseases. Focusing on HRQL as a health standard has given the possibility to bridge between disciplines and social, mental, and medical services (Pope, 1984).

1.2. Illness and quality of life

Persons suffering from illness are known to often have an affected quality of life. The severity of an illness can be expressed in terms of the number and severity of symptoms or associated problems. In healthcare, the primary aim is to improve or maintain the overall functional capacity and general health of patients, as where the general goal of treatment for an illness, when available, is to alleviate symptoms from illness by means of a decrease in physical or psychological symptoms (WHO, 2008). However, some treatments may not always be associated with a decrease, and may even exacerbate existing symptoms. Symptoms may even be more related to the life quality of a patient than direct illness-related variables, such as disease activity and other clinical symptoms. In addition, both individual experience and the perceived impact of an illness play an important role in life quality (Gladman, Urowitz, Ong,

Gough, & MacKinnon, 1996; Reich et al., 2014). This is also the case with the hepatitis C virus (HCV), which is a highly prevalent infectious disease mainly affecting the liver; see Figure 1.2. Besides hepatic manifestations, HCV-infected persons are known to often suffer from a broad range of symptoms that may significantly alter their physical and mental wellbeing, due to complex virological mechanisms in the body and the brain (Bladowska et al., 2014; Solinas, Piras, & Deplano, 2015; Adinolfi et al., 2015).

Figure 1.2. Global distribution of hepatitis C virus infection.



Blach, S., Estes, C., Gamkrelidze, I., Gunter, J., Murphy, K., Nde, H., … Razavi, H. (2015). *Polaris Observatory – Global prevalence of Hepatitis C.* Colorado, USA: Center for Disease Analysis.*

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1.3. Epidemiology, prevalence, and incidence of hepatitis C virus

HCV is a significant human pathogen affecting millions of persons worldwide, and is a leading cause for progressive chronic liver disease, potentially culminating in cirrhosis and hepatocellular carcinoma (Mohd Hanafiah, Groeger, Flaxman, & Wiersma, 2013; Blach et al., 2015; Basnayake & Easterbrook, 2016). HCV is a small enveloped virus, 50–80 nm in diameter, with a positive sense, single stranded ribonucleic genome (ssRNA) of ~9600 nucleotides. The ribonucleic (RNA) molecule contains a single open reading frame (ORF) but lacks a 5' cap. Instead, translation is initiated in the cytoplasm through an internal ribosome entry site (Tsukiyama-Kohara, Iizuka, Kohara, & Nomoto, 1992; Wang, Sarnow, & Siddiqui, 1993). Translation of human HCV-RNA in cultured cells is mediated by an internal ribosome-binding mechanism (Wang et al., 1993). A single amino acid precursor polyprotein is translated at the endoplasmic reticulum (ER) and is then cleaved by host and viral proteases into 10 structural and non-structural (NS) proteins. The structural proteins of HCV are encoded by the 5' terminus of the genome and include the core protein as well as the two glycoproteins, E1 and E2. These are followed by the NS proteins, which include p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B (Lindenbach & Rice, 2005).

The polymerase of HCV, NS5B, exhibits a high mutation rate of approximately 10'4 substitutions per site (Cuevas, Gonzalez-Candelas, Moya, & Sanjuan, 2009; Sanjuan, Nebot, Chirico, Mansky, & Belshaw, 2010). This is combined with a very high rate of virion production in infected individuals (1012 virions

per day) (Neumann et al., 1998). As a result, within host, the HCV genome exists as a heterogeneous RNA population known as quasispecies (Martell et al., 1992). This heterogeneity contributes to a significant evolutionary advantage and provides the virus with the means to adapt to the host immune response and persist as a chronic infection (Vignuzzi, Stone, Arnold, Cameron, & Andino, 2005). At the human population level, HCV has undergone significant evolution resulting in the emergence of seven different genotypes (GT1–GT7) differing by approximately 35% at the nucleotide level (Smith et al., 2014). These genotypes are further classified into “subtypes” (a, b, c, etc.), with about 20% inter-subtype divergence across the genome (Simmonds, 2004; Simmonds et al., 2005).

Before HCV was discovered (Choo et al., 1989), non-HAV non-HBV was identified as a viral hepatitis occurring after transfusion of infected human blood into chimpanzees (Westbrook & Dusheiko, 2014). It soon became known that it involved a new virus, which could be transmitted through blood and bodily fluids from another infected person. Today, the most common routes of HCV transmission include blood transfusion, the use of unsterile needles and other medical equipment, transmission from an infected mother to her unborn or nursing infant in 5% of cases (Reddick, Jhaveri, Gandhi, James, & Swamy, 2011), and unsafe intercourse, occurring mostly between men (van de Laar, Matthew, Prins, & Danta, 2010).

With recent estimates equating to around 71 million, HCV is among the most important chronic infections worldwide (Blach et al., 2015). Around 700.000 deaths occur due to disease-related causes each year (Perz,

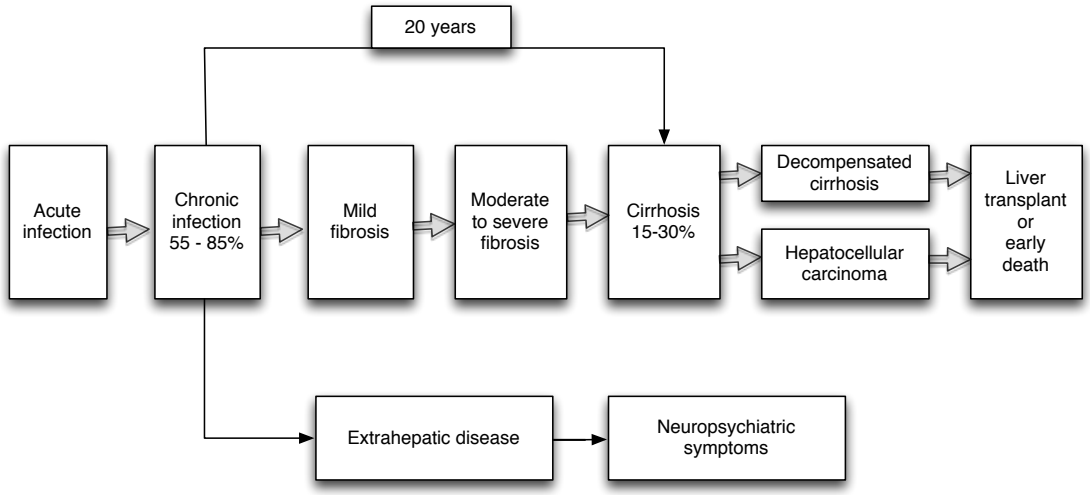
Armstrong, Farrington, Hutin, & Bell, 2006; Lozano et al., 2012). HCV has the greatest impact on morbidity and all-cause mortality in both industrialised and developing countries, along with the chronic hepatitis B virus (HBV). To this day, the associated mortality rate in the United States and Europe surpasses that of human immunodeficiency virus (HIV) infection (Muhlberger et al., 2009; Ly et al., 2012). Seven countries account for 50% of all HCV infections worldwide (i.e. China, followed by Pakistan, India, Egypt, Russia, USA, and Nigeria). Overall, in 2015, the global prevalence of HCV infection was 1%. The Eastern Mediterranean Region had the highest prevalence (2.3%) followed by the European Region (1.5%) (WHO, 2017). Within Europe, the sero-prevalence increases with age, with a peak prevalence occurring in 55–64 year old patients; Southern and Eastern Europeans have the highest peak prevalence (Mohd Hanafiah et al., 2013). Mostly due to common routes of transmission, around 20% of HCV-infected individuals have HIV comorbidity (Soriano Vispo, Labarga, Medrano, & Barreiro, 2010; Basnayake & Easterbrook, 2016). HCV/HIV co-infection is associated with an accelerated course of liver disease and worse treatment outcomes (Koziel & Peters, 2007). Although rates of HCV infection through birth transmission are low, the chance increases significantly when the mother is infected with HIV (Joshi, O'Grady, Dieterich, Gazzard, & Agarwal, 2011; Martin-Santos et al., 2015). However, the most important risk factor for obtaining HCV infection remains through intravenous drug use (Chahua et al., 2015), making people who inject drugs (PWID) an important risk group due to risk-associated behavior (Roncero, Vega, Martinez-Raga, & Torrens, 2017).

After an incubation period ranging from two weeks to six months, HCV may become chronic (Lauer & Walker, 2001). Once chronic hepatitis C (CHC) has developed, the liver normally becomes compromised for years, before gradually becoming more damaged (Youssef, El Kassas, Farag, & Shepherd, 2017). Untreated CHC progresses to chronic liver disease, causing fibrosis, cirrhosis in 20% to 30% of patients within 30 years of initial infection (i.e. scarring of the liver), and hepatocellular carcinoma (i.e. liver cancer) in 3% to 6% of cases, ultimately leading to liver failure and death (Fattovich, Stroffolini, Zagni, & Donato, 2004; Muhlberger et al., 2009). See Figure 1.4. The progression of hepatic fibrosis depends on several co-factors, such as the age at moment of infection, the amount of alcohol consumed, HCV genotype, or viral coinfections (e.g. with HIV) (Bochud et al., 2009; Nkontchou et al., 2011; Webster, 2015). As described in the latter paragraph, in HCV at least six different genotypes exist (HCV-1 to -6, and others) having multiple subtypes (e.g., HCV-1a, 1b). The genetic variability of HCV is high, and varies across countries, regions, and localities (Gower, Estes, Blach, Razavi-Shearer, & Razavi, 2014). Infection with HCV genotype 3 is associated with more rapid progression of fibrosis than infection with other HCV genotypes (Bochud et al., 2009).

As the development of HCV is slow, and most acute infections are asymptomatic (Lavanchy, 2011; Mohd Hanafiah et al., 2013), many patients often remain unaware of the infection for years or even decades. Following initial infection, approximately 80% of people do not exhibit any symptoms. Those who have acute symptoms may exhibit fever, fatigue, decreased

appetite, nausea, vomiting, abdominal pain, dark urine, grey-coloured faeces, joint pain, and jaundice (yellowing of skin and the whites of the eyes). In around 50% to 70% of persons infected with HCV, the virus becomes chronic (Lauer & Walker, 2001). Due to complex mechanisms, CHC has been associated with underlying medical and psychiatric comorbidities, including feelings of anhedonia, depression (Dwight et al., 2000; Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Yarlott, Heald, & Forton, 2017), anxiety, fatigue, sleep alterations (Kallman et al., 2000; Strauss & Teixeira, 2006), increased sensitivity to pain (Monaco, Ferrari, Gajofatto, Zanusso, & Mariotto, 2012), anorexia (Barkhuizen et al., 1999; Lim, Cronkite, Goldstein, & Cheung, 2006; Adinolfi et al., 2015), and loss of appetite (Bull et al., 2009). Furthermore, a significant number of studies have found cognitive functioning to be reduced in HCV patients, including processing speed, verbal fluency, and working memory (Capuron, Lamarque, Dantzer, & Goodall, 1999; Capuron & Miller 2004; Capuron et al., 2005; Forton et al., 2008; Adinolfi et al., 2015; Thames et al., 2015; Fialho et al., 2016). The wide arrange of disease-related manifestations may significantly alter mental and physical life quality of these patients (Younossi, Kallman, & Kincaid, 2007; Hsu et al., 2009).

Figure 1.3. Natural history of HCV infection.



1.4. Treatment of chronic hepatitis C

The chronic hepatitis C virus can be detected through the use of blood tests, which is normally assessed in at-risk populations using screening programs. On the other hand, liver biopsies and ultrasound imaging tests can assess the state of the liver. There is no vaccine available to prevent hepatitis C, although HCV-infected persons should be vaccinated for hepatitis A and B. However, different types of antiviral treatment exist which may cure HCV (Pawlotsky, 2014; Zeuzem, 2017).

The aim of treatment for patients chronically infected with HCV is to achieve a sustained virological response (SVR), defined as the absence of detectable HCV-RNA from the blood, 12 or 24 weeks after treatment is discontinued (Ghany, Strader, Thomas, & Seeff, 2009). The goal of antiviral treatment is to

slow or halt progression of fibrosis and prevent the development of cirrhosis, and partly depends on the virus's genotype the person has contracted. Sustained viral eradication eliminates the risk of individual transmission and is associated with a better quality of life (Spiegel et al., 2005; Younossi et al., 2016[c]). Although the virus may be cured, the classic types of antiviral treatment may exacerbate existing symptoms and even lead to the onset of new symptoms, further affecting the person's mental and physical life quality (Spiegel et al., 2005; Daltro-Oliveira, Morais-de-Jesus, Pettersen, Parana, & Quarantini, 2013).

1.4.1. Antiviral treatment with interferon-alpha

Soon after the discovery of HCV (Choo et al., 1989), antiviral treatment was introduced using the pro-inflammatory cytokine interferon-alpha, a regimen used to treat a number of acute and chronic viral diseases (Hoofnagle & Di Bisceglie, 1989; Hoofnagle & Jones, 1989). The HCV-RNA level of the patient, known as the viral load, is monitored throughout the duration of the treament in order to determine the pattern of response to therapy (Ghany et al., 2009). By a weekly subcutaneous administration of interferon-alpha over a course of 24 weeks, SVR rates of only 6% were achieved which can be determined at 24 weeks of post-treatment. A treatment prolongation to 48 weeks was later found to increase SVR rates to 16%. Subsequently, ribavirin was added (Reichard, Andersson, Schvarcz, & Weiland, 1991) due to the achievement of higher SVR rates of up to 40% to 45% through the accelerated clearance of infected cells (Pawlotsky et al., 2004; Bronowicki et al., 2006). Combination therapy using pegylated interferon-alpha (IFNa) and

oral administration of ribavirin (PR) ultimately showed SVR rates of up to 50% (Manns, Cornberg, & Wedemeyer, 2001; Fried et al., 2002). In general, response to such interferon-based therapy varies greatly amongst patients, and is predominantly affected by the HCV genotype and the presence or absence of cirrhosis. Overall, patients infected with GT2 and GT3 HCV are better respondents to the interferon-based therapy, with SVR rates up to 80% (Feld & Hoofnagle, 2005; Manns, Wedemeyer, & Cornberg, 2006). In contrast, the more prevalent GT1 is associated with a poorer response rate with less than 50% of patients achieving a SVR (Feld & Hoofnagle, 2005).

Both the administration of only IFNa or combined with ribavirin have been associated with severe side effects in around half of patients, including serious rash, hair loss, flu-like symptoms, anxiety, fatigue, and major depression (MD) episodes occurring in around one in four patients (Martin-Santos et al., 2008; Quelhas & Lopez, 2009; Udina et al., 2012). PR treatment has also been associated with significantly lower physical and mental quality of life scores compared to HCV patients receiving placebo (Spiegel et al., 2005; Daltro-Oliveira et al., 2013).

1.4.2. Direct-acting antiviral therapy

The standard of care for HCV genotype 1 was modified with the licensing of the first generation direct-acting antivirals (DAAs) in 2011, i.e. the *protease inhibitors (PI)* telaprevir and boceprevir, administered in combination with PR as triple therapy, with initial results showing increased SVR rates, but similar elongated treatment course, side effect profiles, and quality of life impairment,

as observed in PR therapy. In 2014, the landscape for HCV therapy was significantly shifted with the approval of the first *pan-genotypic* antiviral for HCV, i.e. sofosbuvir, targetting the HCV-RNA-dependent RNA polymerase and opening the door to interferon-free combination DAA therapies (Zeuzem et al., 2014; Lawitz et al., 2013[a,b]; Jacobson et al., 2013; Gane et al., 2013; Pawlotsky, 2014). Different types of DAAs have since been licenced or been put into widespread use (see Figure 1.4.) (European Association for the Study of the Liver [EASL], 2017), and several other regimens are under development.

Figure 1.4. Approved new direct-acting antiviral drugs for treatment of hepatitis C.*

	Patients without hepatic cirrhosis	**Patients with hepatic cirrhosis**
Sofosbuvir/ ledipasvir	HCV-1: 8-12 weeks HCV-4: 12 weeks	HCV-1, -4: 12 weeks*
Sofosbuvir + velpatasvir	HCV-1, -2, -3, -4, -5, -6: 12 weeks	
Paritaprevir/r, ombitasvir, dasabuvir	HCV-1a: 12 weeks* HCV-1b: 8–12 weeks	HCV-1a: 24 weeks* HCV-1b: 12 weeks
Paritaprevir/r, ombitasvir	HCV-4: 12 weeks	HCV-4: 12 weeks*
Grazoprevir + elbasvir	HCV-1a: 12–16 weeks* HCV-1b: 12 weeks HCV-4: 12–16 weeks*	
Sofosbuvir + simeprevir	HCV-1, -4: 12 weeks	HCV-1, -4: 12–24 weeks*
Sofosbuvir + daclatasvir	HCV-1, -2, -3, -4: 12 weeks	HCV-1, -2, -3, -4: 12–24 weeks*

* (Possible) co-administration with ribavirin required.

These new antiviral regimens have shown promising results, such as reduced side effects (Saxena et al., 2016; Desnoyer et al., 2016), higher SVR rates of up to 90% depending on the virus's genotype, easier oral administration, and

a shortened treatment course of 8 to 12 weeks, where SVR can already be determined at 12 weeks after treatment cessation (Jacobson et al., 2013; Younossi et al., 2014[a]; Dusheiko, 2016; Flisiak, Pogorzelska, & Flisiak-Jackiewicz, 2017). However, ribavirin continues to play an important role in various antiviral drug regimens (Hofmann, Hermann, Sarrazin, & Zeuzem, 2008), although limited evidence is available as yet on the possible role of ribavirin as addition to DAAs.

1.4.3. Sustained virological response

As described earlier, the achievement of a SVR involves a molecular demonstration of the absence of HCV-RNA twelve weeks after the end of a course of antiviral treatment, which confirms the sustained eradication of the virus. However, eradication of HCV does not generate protective immunity (Zeuzem, 2017). The likelihood of late recurrence is well under 1%, and most such events are actually not recurrences but re-infections (Grebely et al., 2011). A meta-analysis of 129 studies involving a total of 34.563 patients who had undergone interferon-based treatment, revealed that a sustained virological response was associated with a 62% to 84% reduction of mortality, a 68% to 79% reduction of the risk of hepatocellular carcinoma (HCC), and a 90% reduction of the risk of needing liver transplantation (Zeuzem, 2017). However, new evidence suggests that after clearance of the virus after following antiviral therapy, the virus may persist in the brain, where virus-associated neuropsychiatric symptoms continue to be present or even develop (Dirks et al., 2017), a finding that needs to be confirmed in future studies. As interferon-based treatment was contraindicated in patients with

decompensated cirrhosis, these data are uninformative with respect to any potential clinical benefit, for these patients, of sustained viral eradication with DAAs. Initial studies have yielded clinical and laboratory evidence of improvement mainly for patients with a MELD (i.e. model of end-stage liver disease) score below 16-18 points (Poordad et al., 2016; Charlton et al., 2015; Zimmermann, Beckebaum, & Berg, 2016). In large-scale cohort studies, sustained viral eradication was associated both with lower liver-associated mortality and with substantially lower extrahepatic mortality, although no causal link was demonstrated.

Because of the residual risk of HCC even after successful viral eradication, patients with hepatic cirrhosis (regardless of the possible regression of fibrosis) should undergo lifelong surveillance with hepatic ultrasonography and alpha-fetoprotein measurement every six months (Sarrazin, Berg, & Ross, 2010). Esophageal varices are very unlikely to arise once HCV has been eradicated, because viral eradication is associated with the regression of hepatic fibrosis and portal hypertension (as reflected in the hepatovenous portal pressure gradient) (Zeuzem, 2017).

1.4.4. Mechanisms of direct-acting antiviral regimens

As described in the latter paragraph, today the basis of current treatment involves a combination of direct-acting antiviral drugs, which have shown high efficacy rates, resistance barriers, and different sites of attack (see Figure 1.5).

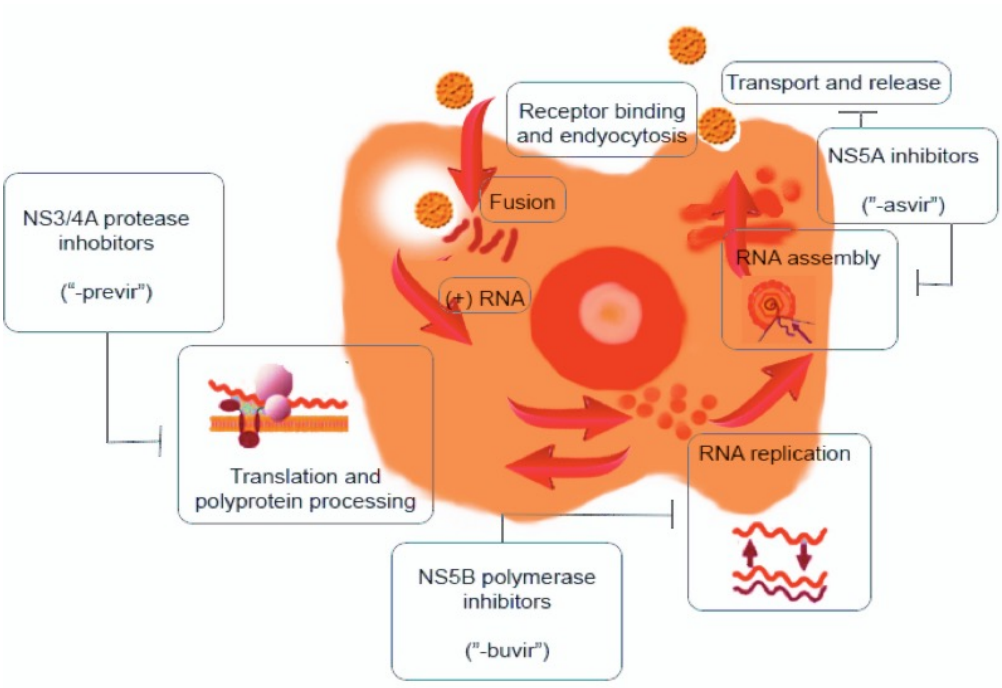
RNA-dependent RNA polymerase inhibitors are categorized as either *nucleotide inhibitors (NI) or non-nucleoside inhibitors (NNI).* NI are

phosphorylated within cells by the activity of cellular kinases, bind as triphosphates to the active center of the HCV-specific NS5B polymerase, and abort the construction of the growing viral RNA chain. NNI cause allosteric inhibition of NS5B polymerase. The generic names of all HCV polymerase inhibitors end in “-buvir.”

Furthermore, protease inhibitors have been developed, which are directed against HCV-NS3/4A serine protease (splitting of the HCV polyprotein); their generic names end in “-previr.” The HCV-NS5A protein plays a role in HCV replication and the modulation of cellular functions.

Moreover, various NS5A inhibitors have been developed; these have generic names ending in “-asvir” (Lange, Jacobson, Rice, & Zeuzem, 2014). Although its antiviral mechanism of action is still incompletely understood, ribavirin continues to play an important role in various antiviral drug regimens.

Figure 1.5. Replication cycle of hepatitis C virus with attack points of antiviral drugs.



1.4.5. Important side effects and drug interactions

With respect to DAAs, since their recent introduction, existing studies have mainly focused on efficacy and safety (Chan et al., 2013; Younossi et al., 2016[a-d]). Despite the good results, certain side effects and drug interactions exist. Sofosbuvir is generally well tolerated; its more common side effects include mild nausea, headache, and insomnia (Ahmed et al., 2017). The combination of sofosbuvir with amiodarone can cause life-threatening bradycardia (Fontaine et al., 2015). The addition of NS5A inhibitors (ledipasvir, daclastasvir, velpatasvir) does not lessen tolerability to any clinically relevant extent (Umar & Akhter, 2016; McCarty & Lim, 2017). Therapeutic elevation of the gastric pH lessens the bioavailability of ledipasvir, and thus the concomitant administration of sofosbuvir/ledipasvir with a proton pump inhibitor in a high dose is not recommended (Afdhal et al., 2014[a]).

The side-effect profile and drug-interaction spectrum of the NS3/4A protease inhibitors are more complex. Simeprevir can evoke both nonspecific side effects (nausea, headache, fatigue) and photosensitivity reactions; patients should be advised to avoid direct exposure to sunlight and to use a topical sunscreen (Gimeno-Ballester et al., 2016). All of the approved NS3/4A protease inhibitors (simeprevir, paritaprevir, grazoprevir) can mildly or moderately elevate bilirubin and transaminase levels (Banerjee & Reddy, 2016). A simultaneous, clinically relevant rise of both the bilirubin concentration and the transaminase concentrations is rare, but presumably reflects hepatoxicity, and must be followed by discontinuation of the protease inhibitor.

The characteristic side effects of ribavirin are (dose-dependent) hemolytic anemia, dyspnea, irritating cough, reduced exercise tolerance, and skin rash (Banerjee & Reddy, 2016). As hemolysis elevates the bilirubin concentration as well, rises in bilirubin levels are more pronounced when ribavirin and NS3/4A protease inhibitors are given simultaneously. All drugs taken for concurrent illnesses should also be checked for possible interactions with antiviral drugs against HCV (see the relevant package inserts and the website maintained by the pharmacology department at the University of Liverpool, www.hepdruginteractions.org) (www.hep-druginteractions.org, 2016).

Particularly critical classes of drugs include anticonvulsants, anti-arrhythmic drugs, antimycobacterial drugs, St. John's wort, and in combination with NS3/4A protease inhibitors-immunosuppressant drugs, antibiotics, antimycotic drugs, antiretroviral drugs, HMG-CoA reductase inhibitors, sedatives, antidepressants, and antipsychotic drugs (www.hep-druginteractions.org, 2016).

Patients with HCV mono-infection and HIV co-infection do not differ with respect to their sustained viral eradication rates or side effect profiles with interferon-free DAA treatment (Naggie et al., 2015; Wyles et al., 2015; Sulkowski et al., 2015; Rockstroh et al., 2015). Prescribing physicians should note potential drug interactions between the various HCV treatment regimens (in particular, those involving NS3/4A protease inhibitors) and the antiretroviral drugs given to treat HIV (www.hep-druginteractions.org, 2016). In HBV/HCV co-infection, the hepatitis virus with the higher viral load is treated with higher priority. The sustained virus eradication rates in the treatment of chronic

hepatitis C are not lessened by the simultaneous presence of hepatitis B (Gane et al., 2016).

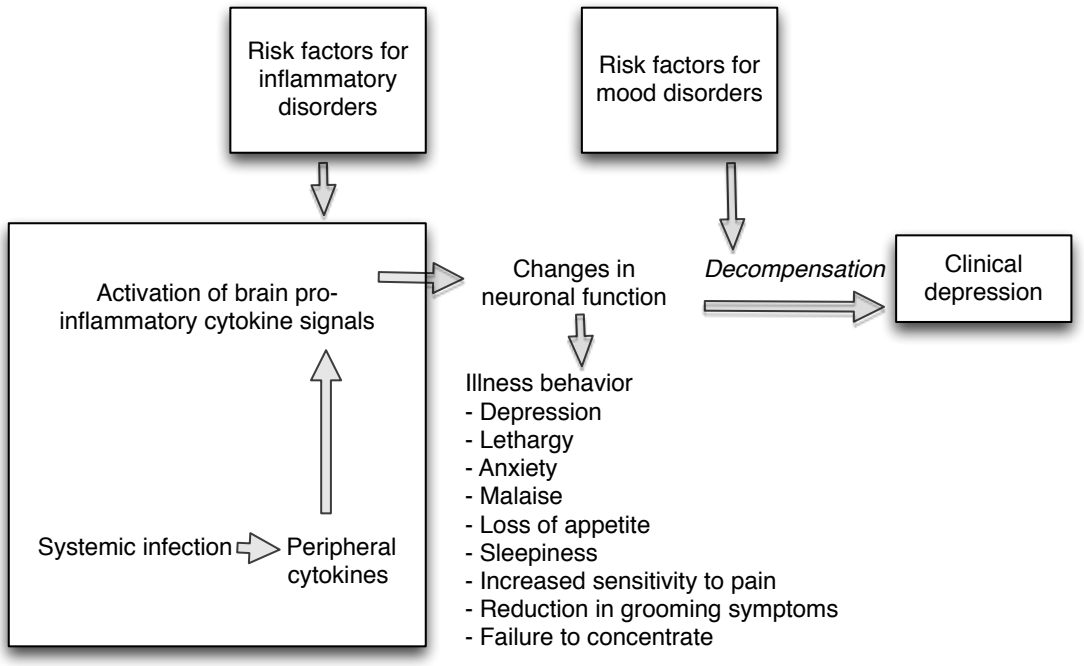
1.5. Neuropsychiatric manifestations of the hepatitis C virus

A number of symptoms observed in HCV patients have not been entirely explained by disease manifestations of the liver. Since the discovery of HCV, knowledge has increased, and several attempts have been made to describe the manifestations of the virus in the body and the brain. HCV is driven by a system of complex mechanisms (Fontana et al, 2001; Bonkovsky et al., 2007), and causes different disfunctions in both the body and the brain (Bladowska et al., 2014; Solinas et al., 2015; Adinolfi et al., 2015), besides affecting the liver. The virus has been found to cross the blood-brain barrier, and is present in both the cerebral spinal fluid and brain tissue, causing a cerebral infection that stimulates the liberation of free radicals, and inflammatory phenomena in the skull (Maggi et al., 1999; Laskus et al., 2002; Raison, Capuron, & Miller, 2006; Murray et al., 2008; Forton et al, 2008), making it a potential neuroinflammatory virus. Inflammation occurs through activation of a number of pathways, resulting in increased cytokine release in the brain (Benveniste, 1998; Rothwell, Luhesi, & Toulmond, 1996), which may result in a wide variety of clinical manifestations worse than those of the physical manifestations of the hepatic infection itself. Cytokines are normally released in the brain as an immune response to disease, damage, infection, or psychosocial stress, in order to favor survival and recovery. Cytokine

release alters the production, metabolism, and transport of neurotransmitters that may affect mood (Capuron & Miller, 2011), and has found to affect the serotonin metabolism and dopamine function, which play an important role in the development of depression and fatigue (Majer et al., 2008; Capuron et al., 2012), and may also contribute to increased anxiety and irritability.

The extrahepatic symptoms described in HCV are similar to those occurring in what has been described as “illness behavior” (Capuron et al., 2005, Raison et al., 2010; Capuron et al., 2012), which is reversible in healthy persons, but in those who are vulnerable including the chronically ill, it may become permanent (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008). It is normally seen in humans and laboratory animals that exhibit behavioral changes due to microbial infections (Hart, 1988), and has been suggested to be relevant to understanding depression (Dantzer, 2009). Other illness behavioral responses include lethargy, anxiety, malaise, loss of appetite (Exton, 1997), sleepiness (Mullington et al., 2000), increased sensitivity to pain (Mitra, 2008), reduction in grooming symptoms (Okuda-Ashitaka et al., 2006), and failure to concentrate (Fu, Zhu, Wang, & Wu, 2007), symptoms similar to those described in HCV infection. See also Figure 1.5.

Figure 1.5. Conceptual model of illness behavior.



1.6. Quality of life in chronic hepatitis C

In the last decades, the assessment of HRQL in CHC patients has become increasingly important (Spiegel et al., 2005; Kallman et al., 2007). CHC is a chronic infection that may affect a person over a course of many years, impacting a person's life on different areas, substantially affecting their wellbeing. Although mental and physical HRQL may differ from person to person, individuals with CHC are known to often have a generally more impaired mental and physical life quality compared to the healthy population, which may be explained by associated symptoms including psychosocial,

physical and mental factors, as well as secondary effects to certain antiviral treatment regimens (Jenkinson, Coulter, & Wright, 1993; Alonso et al., 2004; Helbling et al., 2008; Hsu et al., 2009; Ashrafi et al., 2012; Fabregas et al., 2013; Lowry et al., 2016).

Certain risk factors have been described which may play a role in HRQL impairment in HCV patients, such as low household income (Helbling et al., 2008), awareness of the prognose and diagnose (Rodger, Jolley, Thompson, Lanigan, & Crofts, 1999), intravenous drug use, substance use disorder (Helbling et al., 2008; Dalgard, Egeland, Skaug, Vilimas, & Steen, 2004; Chahua et al., 2015), and alcohol intake (Charlet & Heinz, 2016). Furthermore, HIV exacerbates mechanisms from HCV, such as progression of liver disease and lower SVR rates (Sulkowski & Thomas, 2003; Rockstroh, 2006). However, there has been discussion about whether HIV co-infected patients differ in HRQL compared to CHC mono-infected persons; some authors proposed that HRQL is similar in both patient groups, as they may have improved coping strategies (Fleming et al., 2004; Braitstein et al., 2005; Thein et al., 2007). The symptoms and risk factors associated with HCV infection may have a significant impact on life quality due to their impact on intimate and family relationships, dietary habits, reduced sense of wellbeing because of fear of contagion and prognosis, increase in social marginalization and feelings of anger, hopelessness, and stigma (Helbling et al., 2008; Hsu et al., 2009). On the other hand, symptoms may negatively influence adherence to treatment (Younossi et al., 2007), resulting in the persistence of the virus and associated symptoms, thus remaining a threat for disease spreading.

1.7. Antiviral treatment and quality of life in hepatitis C

Similar to the mechanisms described for HCV involving neural alterations due to proinflammatory cytokine release (Lotrich, 2014; Udina et al., 2016), the antiviral treatment regimen interferon-alpha has been associated with increased cytokine release, resulting in a worsening of several disease-related symptoms and decrease in physical and mental life quality. Although studies on the possible effects of the new DAA regimens on HRQL are still limited, a number of studies have assessed this in patients receiving this type of treatment. Mood and cognitive symptoms develop primarily in vulnerable patients receiving interferon-alpha, including in those with a mood disorder history or higher initial levels of depressive symptoms, or certain genetic polymorphisms associated with risk for depression or inflammation (Capuron & Miller, 2011; Udina et al., 2016). Furthermore, although the co-administration of ribavirin may have clinical advantages, it is known to have a negative impact on other health-related domains (Brok, Gluud, & Gluud, 2005; Bronowicki et al., 2006).

Although the amount of research identifying risk factors for HRQL impairment in HCV patients receiving DAAs is still limited, an important number of studies involving classic therapy using interferon-alpha have detected several factors to be predictive for decreased physical and mental life quality in both HCV mono-infected and HIV co-infected persons. Being female may predict increased reductions in both physical and mental HRQL in HCV/HIV co-infected persons (Dan et al., 2006; Sinakos et al., 2010; Bezemer et al., 2012;

Mandorfer et al., 2014), and being of older age has been found to be an independent predictive factor for lower physical and mental HRQL in both HCV mono-infected and HIV co-infected persons during PR treatment (Bezemer et al., 2012; Mandorfer et al., 2014). Other risk factors include having a lower income (Bezemer et al., 2012), having a BMI of 30 or more (Dan et al., 2006), being infected with HCV through intravenal drug use (Fumaz et al., 2007), and having a history of psychotropic drug use (Sinakos et al., 2010). On the other hand, some clinical and biological risk factors have been found related to decreased physical and mental HRQL, i.e. having a history of depression in both HIV co-infected and HCV mono-infected persons treated with interferon-alpha (Dan et al., 2006; Mandorfer et al., 2014; Martin-Santos et al., 2015), as where the presence of a low viral load may cause further mental health impairment in HCV mono-infected individuals (Dan et al., 2006; Matsushita et al., 2014), and elevated alanine aminotransferase (ALT) levels (i.e. a type of liver enzymes) may alter general HRQL in both HCV mono-infected and HIV co-infected patients (Arora et al., 2006; Mandorfer et al., 2014). Advanced fibrosis and cirrhosis also seem to reduce both mental HRQL in both patient populations receiving PR (Dan et al., 2006; Mandorfer et al., 2014). Moreover, the presence of anemia or low hemoglobin levels might predict lower physical and mental life quality in HCV mono-infected individuals (Dan et al., 2006; Hollander et al., 2006). Lastly, lack of virological erradication of HCV after interferon-alpha treatment appears to be an independent predictor of HRQL impairment in mono-infected persons (Mathew et al., 2006; Smith-Palmer, Cerri, & Valentine, 2015).

Although the evidence on possible effects of DAAs on life quality is still limited, some studies have aimed to describe risk factors for life quality impairment in the use of DAAs. Risk factors include being of older age (Younossi et al., 2014[a,b]), having a present or history of depression or anxiety disorder (Youssef, El Kassas, Farag, & Shepherd, 2017), having treatment-related anemia (Jacobson et al., 2013), and having an elevated number of treatment-related adverse events (Younossi et al., 2014[a,b]). Using triple therapy, some studies have found risk factors including being of female gender (Younossi et al., 2014[a,b]; 2015[b]), being of older age (Vera-Llonch et al., 2013; Younossi et al., 2014[a,b]), having treatment-related anemia, and early treatment discontinuation. These risk factors have also been detected in the administration of classic interferon-alpha treatment (Jacobson et al., 2013).

1.8. Instruments for measuring quality of life

Through the years, sensitive measures have been developed with the aim to capture HRQL from a patient's perspective. HRQL comprises the physical, mental and social effects of a disease, and can be measured by assessing somatic symptoms, psychological status, social interactions, physical, cognitive and psychosocial functioning, sense of wellbeing, and emotional status (Gutteling, de Man, Busschbach, & Darlingston, 2007). Existing tools that measure HRQL may be used both in healthy persons as well as those suffering from an illness. Tools exist that have been specifically developed for

certain patient groups, which have the advantage of successfully capturing data on disease-related symptoms, but with the disadvantage that they cannot be used to compare the effects of different illnesses. On the other hand, generic questionnaires may capture HRQL in a wide range of patient populations. The following questionnaires are adequate for prospective studies, and most have been extensively validated and used in research and clinical practice.

The EuroQol 5 Dimensions (EQ-5D) (EuroQol Group, 1990) is a generic questionnaire, of which the construct validity, reliability, and responsiveness of EQ-5D have been described in general (Lubetkin, Jia, Franks, & Gold, 2005) as well as specific disease populations (Sullivan & Ghushchyan, 2006; Janssen et al., 2013). This has generated useful information of the health status of patients with different characteristics. EQ-5D is a short and concise questionnaire that consists of two parts: a descriptive system each having five levels (from “no problems” to “extreme problems”), which measuring five dimensions (i.e. “mobility”, “self-care”, “anxiety/depression”, “usual activities”, and “pain/discomfort”), with higher scores indicating lower HRQL, and a global health EQ visual analogue scale (EQ-VAS), measuring the current health state from scoring 0 (worst health state possible) to 100 (best health state possible) (Herdman et al., 2011; Sun et al., 2014). In general, the dimension “anxiety/depression” has the greatest impact on overall HRQL (Burström et al., 2014; Rand-Hendriksen, Augestad, Kristiansen, & Stavem, 2012). An overall health state can be calculated from responses to these items, For example, the response set '11111' indicates no problems with any of the five

dimensions, and subsequently perfect overall health. In total there are 243 possible health states, and weighted values have been assigned to each of these on the basis of national and international surveys (van Agt, Essink, Krabbe, & Bonsel, 1994). By applying an algorithm, an index score can be calculated, indicating general quality of life (ranging from 0 indicating worst health, to 100 indicating best health). EQ-5D is also used as a utility measure in cost-effectiveness analyses and medical decision-making studies (Stepanova et al., 2014). With utility measures such as the index score, quality-adjusted life years (QALYs) may be computed, which can provide an indication of the benefits gained from a variety of medical procedures in terms of quality of life and survival of the patient.

The MOS Short-Form-36 (SF-36) (Ware & Sherbourne, 1992) is another often used generic health survey, assessing self-reported functional health and wellbeing. Responses to 35 of the 36 items enable computation of a profile of functional health and wellbeing that consists of eight subscales [i.e. “physical functioning”, role limitations due to physical health (“role-physical”), “bodily pain”, “general health perceptions”, “vitality”, “social functioning”, role limitations due to emotional problems (“role-emotional”), and “mental health”]. The Physical and Mental Health Component Summary (PCS and MCS, respectively) scores may be computed using the eight subscales, to provide a broader metric of physical and mental HRQL. Each scale is scored from 1 to 100, with higher scores indicating better HRQL. A systematic review of 15 studies comparing HRQL in HCV-infected patients versus healthy controls showed that HCV most profoundly impaired vitality, general health, physical

function, and social function. Of these, vitality was considered the most important scale to HCV patients (Spiegel et al., 2005).

Other generic tools in HCV include the Short-Form 6D (SF-6D) (Brazier et al., 2002), which is a shorter questionnaire derived from the SF-36, developed specifically for utility measures. However, as the SF-6D has shown a floor effect, it is not a preferred tool for HCV patients (Younossi, Boparai, McCormick, Price, & Guyatt, 2001). Also, the Health Utility Index (HUI) (Barkhuizen et al., 1999) is a widely used utility measure questionnaire in patients with chronic liver disease (Feeny, Furlong, Boyle, & Torrance, 1995). The utility scores provide a summary index of HRQL on a 0 to 1 scale, covering eight attributes: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain, each with five or six levels.

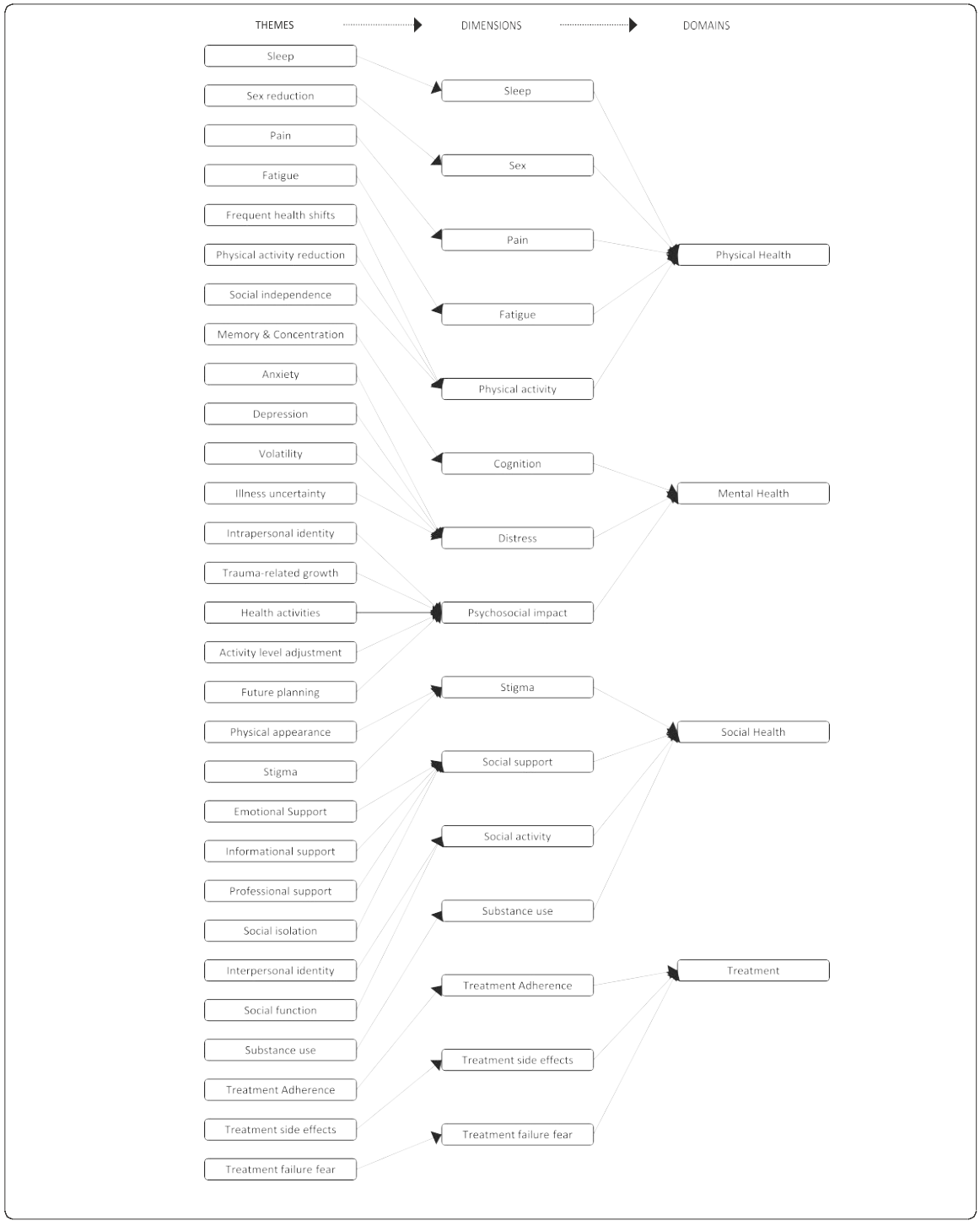
The Chronic Liver Disease Questionnaire (CLDQ) (Younossi, Guyatt, Kiwi, Boparai, & King, 1999) is a disease-specific questionnaire that contains 29 items distributed over six domains (i.e. “abdominal symptoms”, “fatigue”, “systemic symptoms”, “activity”, “emotional function”, and “worry”), of which a general HRQL score may be calculated. However, CLDQ does not discriminate between more advanced stages of liver disease and might not be a preferred tool in patients with severe states of liver damage and may thus not be preferred in these patients. The Liver Disease Quality Of Life questionnaire (LDQOL) was introduced soon after the CLDQ (Gralnek et al., 2000), which addresses a variety of domains containing 101 questions, making it a rather extensive questionnaire measuring HRQL in patients with chronic liver disease, and is therefore mostly used in RCT studies. Furthermore, the Liver Disease Symptom Index 2.0 (LDSI 2.0) (van der Plas

et al., 2004) is another disease-specific questionnaire that measures nine possible symptoms specific for liver disease. It also assesses the burden a patient has from certain symptoms, which is an aspect other disease-specific liver disease questionnaires fail to address.

The Hepatitis C Virus Patient-Reported Outcomes (HCV-PRO) (Anderson et al., 2014[a,b]) is a gathering of several instruments, including SF-36 and EQ-5D questionnaire measuring HRQL and several other related symptoms in CHC patients. HCV-PRO includes 16 items with 5 levels of response ("all of the time" to "none of the time"), and may be converted to a 0 to 100 score scale indicating general HRQL. Moreover, the Patient Reported Outcome Quality of Life survey for HCV (PROQOL-HCV) (Duracinsky et al., 2015; Armstrong et al., 2016) is a recently introduced questionnaire, which is the first to capture both HCV-specific dimensions and possible impact of antiviral treatment. It exists of four domains (i.e physical health, mental health, social health, and treatment) divided over 72 items. See also Figure 1.6. Although the PROQOL-HCV instrument may capture a complete spectrum of symptoms in CHC patients related to HRQL, it has only been assessed in non-cirrhotic, stable patients, and may again not be representable for persons with advanced liver disease.

Lastly, the HCV-specific questionnaire is the Hepatitis Quality of Life Questionnaire (HQLQ) (Bayliss et al., 1998), which is a tool derived from the SF-36, and contributes short HCV-specific sub scales (i.e. "health distress", "positive wellbeing", "limitations owing to hepatitis C", and "distress owing to hepatitis C").

Figure 1.6. Conceptual model of quality of life domains in HCV.



Armstrong, A. R., Herrmann, S. E., Chassany, O., Lalanne, C., Da Silva, M. H., Galano, E., … Duracinsky. (2016). The International development of PROQOL-HCV: An instrument to assess the health-related quality of life of patients treated for Hepatitis C virus. *BMC Infect Dis*, 16(1), 443.*

Finally, after reviewing the different aspects of the topic, two studies related to HRQL of CHC patients treated with the DAA antiviral treatment were designed and performed in the frame of this PhD dissertation.

First, a systematic review and meta-analysis was realized in order to summarize the existing evidence of randomized controlled trial (RCT) studies assessing new DAA regimens and measuring the possible effects on life quality in CHC patients, taking into account risk factors for quality of life impairment.

Second, a prospective longitudinal study was performed in order to assess the possible effects of new DAAs on HRQL and incidence of depression in a real-life cohort of CHC patients, and to evaluate possible associated risk factors.

CHAPTER 2

Objectives & hypothesis

2.1. Objectives

2.1.1. General aim

The general aim of this thesis is to study health-related quality of life (HRQL), depression (PHQ-9) and related risk factors in CHC patients receiving antiviral treatment using DAAs.

2.1.2. Specific objectives

Objectives specifically defined for the **first study** are:

- To perform a systematic revision and meta-analysis of the published literature of RCT studies on HRQL evaluated by using EQ-5D or SF-36 during antiviral DAA treatment;
- To study HRQL of CHC patients in relation to risk factors;
- To study HRQL of CHC patients in relation to treatment response.

Objectives specifically defined for the **second study** are:

- To perform a longitudinal, naturalistic cohort study of CHC patients with advanced liver disease treated with DAA, in order to assess:
- To study HRQL (EQ-5D questionnaire) during antiviral treatment and post-treatment follow-up, and to identify possible risk factors;
- Fatigue and irritability (measured by visual analogue scale: VAS) during antiviral treatment, and post-treatment follow-up and risk factors;
- Cumulative incidence of depression (PHQ-9 questionnaire) and associated risk factors during DAA treatment.

2.2. Hypothesis

2.2.1. General hypothesis

The first study, the systematic review and meta-analysis, would show that the new antiviral agents would have less impact on the health-related quality of life of CHC compared to old treatments [i.e. (pegylated) interferon-alpha and ribavirin]. The systematic review would also identify risk factors related to the impairment of HRQL at baseline, and along the antiviral treatment. The second study, by assessing real-life DAA treatment in CHC patients, would support the results of the systematic review, including the role of several predictive factors such as disease liver severity and incidence of depression.

2.2.2. Specific hypotheses

Hypotheses specifically defined for the **first study** are:

- DAAs would have a smaller impact on HRQL of CHC patients related to classic treatments [(pegylated) interferon-alpha and ribavirin];
- Antiviral regimens with the addition of ribavirin would be associated with a more impaired HRQL;
- The presence of risk factors such as age, gender, comorbidity, liver disease severity, and depressive symptoms, would modulate the impact of antiviral treatment;
- The impact on HRQL would be associated with response to antiviral treatment.

Hypotheses specifically defined for the **second study** are:

- CHC patients with a more advanced level of liver disease naturalistically treated with DAAs would have an impaired HRQL before, during, and after antiviral treatment;
- Included patients receiving co-administration of ribavirin with DAAs would have a more impaired HRQL compared to patients receiving only DAAs;
- The patients with a baseline depressive symptoms, comorbidity, or decompensated cirrhosis, would suffer a higher impact on quality of life along DAA treatment;
- Patients who were euthymic at baseline with personal or family history or depressive symptoms at baseline would have higher risk of incidence of depression during the treatment (PHQ-9 mild depressive symptomatology or major depression);
- The response to antiviral DAA treatment would be associated with improvements in physical and mental life quality.

CHAPTER 3

Study I

New direct-acting antiviral treatments for chronic hepatitis C and health-related quality of life: a systematic review and meta-analysis

Elfi Egmond, Giovanni Oriolo, Ricard Navinés, Myriam Cavero, Zoe Mariño, Susana Subirà, Sabela Lens, Maria Álvarez, Xavier Forns, Rocío Martín-Santos

ABSTRACT

Objectives

Both chronic hepatitis C (CHC) virus and antiviral treatments with pegylated interferon and ribavirin (PR) for CHC often cause considerable impairment in health-related quality of life (HRQL). Recently, new direct-acting antivirals (DAAs) have been introduced, which may have a smaller impact on HRQL. This systematic review and meta-analysis assesses RCT studies that have evaluated HRQL and possible risk factors in CHC patients receiving new DAA regimens.

Methods

Data were collected using PRISMA guidelines. A comprehensive, computerized literature search was conducted. Double blind, randomized, placebo or antiviral treatment-controlled trials of DAAs with or without PR or ribavirin, using EQ-5D or SF-36 questionnaires to assess HRQL for chronic hepatitis C were included. Of 146 studies retrieved, 11 met the inclusion criteria. Outcomes of HRQL scores [mean (SD)] were extracted as measured by both questionnaires, and predictive variables were identified. Meta-analysis was performed when data were available.

Results

6.887 CHC patients were randomly assigned to antiviral treatment or another intervention: DAAs (N=1.782), DAAs plus ribavirin (N=1.936), DAAs plus PR (N=1.006), PR (N=1.849) or placebo (N=187) and placebo with PR (N=127). With regard to DAAs alone, a slight improvement in patients' mental life quality

was observed (MD=2.88; 95%CI=2.24, 3.53). When ribavirin was added to DAAs, impairment was observed on mental HRQL (MD=-1.7; 95%CI=-2.5, -0.91). Any combination of DAAs with PR seemed to impair both mental and physical health quality (MD= -0.13; 95%CI=-0.15, -0.11). At baseline, HRQL is more impaired in CHC patients who are unemployed, have cirrhosis, anemia, or have a history of depression, anxiety, fatigue, or insomnia. Furthermore, female gender, older age, and history of depression may predict HRQL impairment during DAAs plus ribavirin treatment. Also, adverse events and treatment non-response are risk factors for DAAs plus ribavirin or PR.

Conclusions

DAAs alone seem to have a minimal HRQL impact. Any DAA regimen combined with PR appears to significantly reduce mental and physical HRQL, similarly to what has earlier been found for PR treatment. The addition of ribavirin to DAAs may still significantly impair mental life quality. Also, several risk factors may predict HRQL impairment. Individualized management of mental and physical health is needed to optimize the care of CHC patients.

1 BACKGROUND

1.1 Chronic hepatitis C

The hepatitis C virus (HCV) produces an infectious disease, primarily affecting the liver. Four in five persons infected with the virus ultimately develop chronic hepatitis C (CHC) (Lauer et al., 2001). Worldwide, the most recent estimates of disease burden equate to around 71 million, and more than 350.000 persons die annually from liver disease caused by HCV, making it one of the most important global chronic infection diseases (World Health Organization, 2017).

This chronic condition mostly remains asymptomatic for the first years or decades. However, the infection may progress towards the development of severe liver conditions, such as liver cirrhosis and hepatocellular carcinoma, ultimately leading to hepatic failure and death occurring in 20% to 40% of patients (Muhlberger et al., 2009). Like other chronic diseases, CHC has an important effect on the life quality of patients; moreover, the effects of stigma, cognitive impairment, and psychiatric and medical comorbidities, often have a major impact on the patients' mental and physical health (Fábregas et al., 2013; Scalone et al., 2014).

1.2 Antiviral treatment

Unlike other chronic infections, the CHC virus may be cured. Since the discovery of the disease at the end of the 1980s (Hoofnagle et al., 1986), standard therapy to treat CHC involved a combination of pegylated interferon-alpha with ribavirin (PR) during 24 or 48 weeks, depending on the virus's genotype. This therapy has shown efficacy rates of up to 50%, also depending

on the genotype (Messina et al., 2015), but is known to have severe side effects, often significantly altering life quality (Spiegel et al., 2005; Arora et al., 2006). Although the exact mechanisms for the occurrence of adverse events related with this regimen are still incompletely understood (Adinolfi et al., 2015), interferon-alpha has been found to release cytokines in the brain, triggering inflammation and resulting in what has been referred to as illness behavior (fatigue, anhedonia, insomnia, and flu-like symptoms) (Capuron et al., 2012). Indeed, often-reported side effects of interferon-alpha include fatigue, flu-like symptoms, and major depressive episodes that occur in every one out of four patients (Younossi et al., 2007; Udina et al., 2012). The co-administration of ribavirin may have clinical advantages, including higher response rates, but may also have a negative impact on other health-related domains, such as hemolytic anemia and asthenia (Brok et al., 2005; Bronowicki et al., 2006).

Recently, new types of treatment regimen have been introduced, named new direct-acting antivirals (DAAs). These have been associated with higher efficacy rates of more than 90% in almost all patients, have an easier and shorter administration, and have shown better side-effect profiles (Walker et al., 2015). DAAs are more effective than any other combination with PR treatment (Younossi et al., 2014).

1.3 Quality of life

In literature, the term Health-Related Quality of Life (HRQL) is often used as a significant outcome indicator for wellbeing in patients with chronic diseases and treatments (European Association of the Liver, 2014). It is often used to reflect

patients' personal health status, referring to aspects significantly influenced by their mental or physical state (Johnston et al., 2013).

The two mostly used HRQL generic instruments in CHC patients are the validated Short Form-36 Health Survey (*SF-36*) (Ware, 1996; Navines et al., 2012), and the EuroQol Group Questionnaire (*EQ-5D*) (The EuroQol Group, 1990). The *SF-36 questionnaire* is a widely used international standardized tool that consists of 36 items, divided over two summary scales (i.e. physical and mental component scale), and eight sub scales (i.e. physical functioning, role physical, bodily pain, vitality, social functioning, role limits emotional, mental health, and general health) (Alonso et al., 1995; Ren et al., 1998). The *EQ-5D questionnaire* has increasingly been used in quality of life assessment. This tool consists of two parts: a descriptive one, which covers five dimensions (i.e. mobility, self-care, usual activities, pain/discomfort, and anxiety/depression); and *a global health visual analogue scale (EQ-VAS)* scoring self-perceived health, ranging from 0 (worst health state possible) to 100 (best health state possible). The descriptive part can be converted to a single dichotomic *index value*, ranging from 0 (worst health) to 1 (perfect health) (Sullivan & Ghushchyan, 2006). The construct validity, reliability and responsiveness of the *EQ-5D* have been described in general as well as disease populations, including liver disease (van Hout et al., 2012).

1.4 Risk factors

Although a number of risk factors have been suggested to be predictive of life quality impairment in patients with CHC, these have not been yet studied

comprehensively. A review published in 2005 (Spiegel et al.) assessing 15 RCT studies found HRQL to be significantly impaired in patients receiving antiviral treatment involving pegylated interferon-alpha with or without ribavirin, where several of these studies also identified risk factors. On the other hand, studies using new antiviral treatment regimens have mostly focussed on treatment efficacy and side effect profiles. Although the number of studies using new DAA regimens is still limited, these appear to have limited side effects (Rowan et al., 2015), thus likely indicating a reduced effect on the patients' HRQL.

The aim of this systematic review and meta-analysis was to assess RCT studies that have evaluated HRQL (by using *EQ-5D* or *SF-36* questionnaire) and possible risk factors in CHC patients receiving new DAA regimens.

2. METHOD

Data for the systematic review were collected using an advanced document protocol based on the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines (Liberati et al., 2009). It provides a checklist for reporting outcomes of reviews based on evidence-based research. Two clinical researchers (EE and RN) performed each step in this literature search: study identification, study selection, quality assessment, and data extraction. Disagreements were resolved by discussion, and consensus was achieved in the selection of articles for analysis.

2.1. Data sources

A comprehensive, computerized literature search was conducted in MEDLINE, PsycINFO, the Cochrane database, and the US National Institutes of Health database of Clinical Trials. First, databases were searched for relevant studies published in the past in order to identify studies reporting HRQL with HCV treatment. HCV treatments were either interferon-based or all-oral DAA combinations. The considered approved DAA drugs were drugs were: boceprevir, telaprevir, sofosbuvir, simeprevir, ledipasvir, paritaprevir, daclarasvir, and velpatasvir. Additional studies were searched for in the reference lists of the selected articles. Only articles written in English, German, French or Spanish were considered. The titles and abstracts were examined, and full-text articles of potentially relevant studies were retrieved. Subsequently, inclusion and exclusion criteria were applied, and the selected articles were subjected to systematic review and meta-analysis.

2.2. Study selection

Articles were reviewed using the following inclusion criteria: 1) original prospective RCT reporting results of HRQL during antiviral treatment with DAAs (interferon-free and interferon-containing regimens); 2) in adult subjects with CHC of both genders (Martin-Santos et al., 2015); 3) using the self-administered *EQ-5D* or *SF-36* questionnaire at baseline, and when available, at weeks 4, 8, 12, 16, 24 and 48 of treatment, and at 4, 12 and 24 after end of treatment; 4) RCT studies of antiviral treatment with DAAs (interferon-free and interferon-containing regimens) using both *EQ-5D* and *SF-36* will be considered

as separate studies; 5) inclusion of a detailed description of methods and methodological background for assessing HRQL.

The following exclusion criteria were applied: 1) naturalistic, non-randomized controlled studies; 2) sample size < 25 subjects, 3) missing or poor reporting of HRQL scores, and 4) case reports or poster publications.

Quality of sequence generation, allocation concealment, blinding, missing outcome data, selective reporting, and other biases of the RCTs were assessed with the Cochrane risk of bias method (Higgins & Green, 2008).

2.3. Summary measures (outcomes)

Primary outcomes

The primary outcome measure was changes in HRQL scores, using the mean difference (MD) with confidence interval (95% CI), as well as the minimal clinically important difference (MCID) (Ringash et al., 2007) for scores reported by both *EQ-5D* and *SF-36* questionnaires. This was applied from baseline throughout treatment and follow-up.

Secondary outcomes

Secondary outcome measures were changes in HRQL scores, using the mean difference (MD) with confidence interval (95% CI) from baseline taking into account predictive factors of HRQL, such as socio-demographic factors (e.g. age and gender), clinical and biological parameters (i.e. comorbid HIV infection, history of psychiatric disorders or drug abuse, and the presence of cirrhosis),

and sustained virologic response (SVR) (i.e. whether or not treatment had been successful).

2.4. Data extraction

Data from the selected studies were recorded and described. Outcomes in the form of HRQL were extracted, mean differences were calculated from baseline, and potential predictive variables among those analysed in the articles were selected for the risk factor groups.

2.5. Statistical analysis

Mean and standard deviation (SD) with 95% confidence interval (95% CI) were collected when available from all studies. Mean differences (SD) were calculated over treatment course. The minimal clinically important difference (MCID) was calculated in order to identify score changes of clinical significance compared to baseline scores (Guyatt et al., 1993). A MCID of 5% in both the *EQ-5D index score* (a conversion of five dimensions) and in the *EQ-VAS* score (Ringash et al., 2007; Le et al., 2013) was used. For *SF-36* scores, a MCID of the two summary scales score (mental and physical) of at least 4% was set as the minimum cut-off value for this questionnaire (Spiegel et al., 2005).

Meta-analysis was conducted when appropriate. Heterogeneity between trials was assessed using both the chi-square and I-square tests. Between-study heterogeneity was considered to be significant for a p-value < 0.05 on the chi-square test. If there was no heterogeneity, a fixed model was used. In the event of heterogeneity, a random effects model was used.

Publication bias was examined in a funnel plot using the available data. Effect measures were examined on the X-axis and standard error on the Y-axis (anonymous, 1992), and the degree of asymmetry was tested using Begg's test (Begg and Mazumdar, 1994).

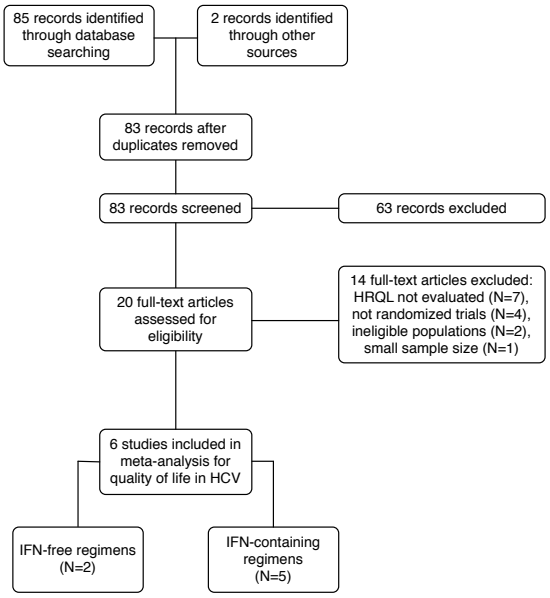
Statistical analysis was performed using Microsoft Excel v. 2010, and Review Manager (RevMan) [Computer program] Version 5.0 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, Oxford, UK, 2008).

3. RESULTS

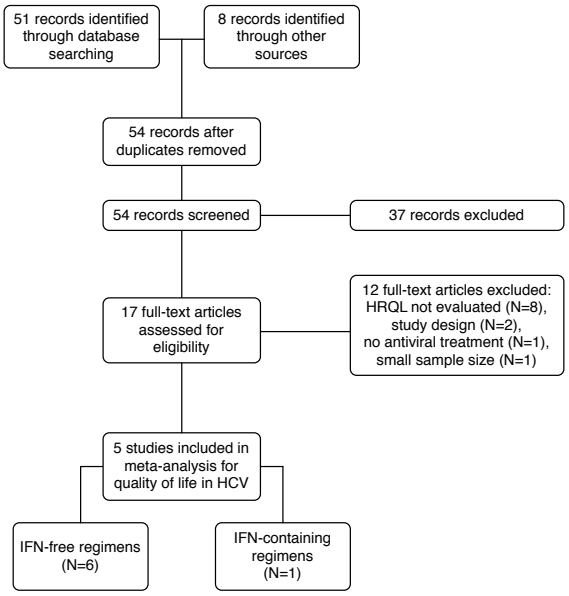
Figure 1 shows the flow charts of study selection of RCTs assessing HRQL, for both *EQ-5D* and *SF-36, questionnaires*. Using keywords and cross-referenced bibliographies searching for the *EQ-5D questionnaire*, 87 articles were identified and examined in depth. Sixty-three articles were rejected because inclusion criteria were not met. Finally, six different articles were selected (Jacobson et al., 2013[a,b], Fried et al., 2013, Vera-Llonch et al., 2013; Zeuzem et al., 2014; Scott et al., 2015). On the other hand, using keywords and cross-referenced bibliographies searching for the *SF-36 questionnaire*, 59 articles were identified and examined in depth. Thirty-seven articles were rejected because inclusion criteria were not met. Finally, five publications using SF-36 were selected for systematic review (Lawitz et al., 2013; Younossi et al., 2014; Younossi et al., 2015; Younossi et al., 2016[a,b]).

Figure 1. Flow charts of selected studies.

A. Using EQ-5D questionnaire:



B. Using SF-36 questionnaire:



The selected studies were published between 2013 and 2016 and all were reported in English. The review includes a total of 6887 CHC patients who were randomly allocated to initiate antiviral treatment with DAAs, comparing to classic treatment using PR or placebo, or a combination of DAA with or without ribavirin or triple therapy with PR.

3.1. Characteristics of the studies

Table 1 shows the characteristics of each of these studies. Most subjects that were included in the RCT studies used DAA and ribavirin (N=1936), followed by PR (N=1849), DAA only (N=1782), and DAA combined with PR (N=1006). Few studies used placebo groups (N=187) or placebo combined with PR (N=127).

Six studies using interferon-free regimens and five studies using regimens that included alpha-interferon. The average age of study subjects was 51 years, included nearly half as much male in ratio to female subjects (N=4224, and N=2663, respectively). None of the studies included patients co-infected with the human immunodeficiency virus (HIV). However, four of the studies did include patients with a history of drug use (Younossi et al., 2014; 2015; 2016[a,b]). Moreover, two studies included patients with a history of psychiatric disorders (Younossi et al., 2016[a]; Jacobson et al., 2013[a]). Six studies included only patients with HCV genotype 1 (Vera-Llonch et al., 2013; Fried et al., 2013; Zeuzem et al., 2014; Scott et al., 2015; Younossi et al., 2015; 2016). Three studies included patients with genotype 2 and 3 (Younossi et al., 2014; Jacobson et al., 2013[a,b]), and two studies also included genotype 4, 5, and 6 patients (Lawitz et al., 2013; Younossi et al., 2016).

In terms of potential bias, all studies were randomized and double blind, although some studies did not have an adequate description of randomization (see eAppendix 1 Section IV). Some studies did not report loss of subjects to follow-up or potential side effects. Other sources of bias were poor reporting of HRQL scores, lack of assessment of risk factors, and incomplete description of sample characteristics (see Table 1).

Table 1. Characteristics of the studies included in the review.

Study	N	Gender	Age (SD/ range)	Genotype	HIV co-infection	Drug abuse	Psychiatric history	HRQL scores	HRQL (week)	Treatment type (dose per week)	Follow-up (wk)	SVR rate post-treatment
IFN-free regimens												
Younossi et al., 2016[a] (ASTRAL-1)	624 116	374♂ 250♀ 68♂ 48♀	54.1 (10.9) 53.2 (10.4)	1, 2, 4, 5, 6	No	Yes	Yes	**SF-36** PCS, MCS	Baseline, 4, 8, 12	Sofosbuvir (400 mg) + Velpatasvir (100 mg) Placebo	16, 20, 24, 28, 32, 36	61.8% *Week 12* 0% *Week 12*
Younossi et al., 2016[b]* (SIRIUS)	78 76	56♂ 22♀ 57♂ 19♀	56.6 (10.7) 56.4 (7.4)	1	No	Yes	NA	**SF-36** PCS, MCS (SD)	Baseline, 12	Sofosbuvir (400 mg) + Ledipasvir (90 mg) Sofosbuvir (400 mg) + Ledipasvir (90 mg) + Ribavirin (1000-1200 mg)	4 , 12	96.1% *Week 12* 97.4% *Week 12*
Younossi et al., 2015*† (ION-1, -2, -3)	1080 872	672♂ 408♀ 503♂ 369♀	53.4 (10) 52.8 (10.5)	1	No	Yes	NA	**SF-36** PCS, MCS (SD)	Baseline, 2, 4, 12	Sofosbuvir (400 mg) + Ledipasvir (90 mg) Sofosbuvir (400 mg) + Ledipasvir (90 mg) + Ribavirin (1000-1200 mg)	4, 12	96.6% *Week 12* 96.8% *Week 12*
Younossi et al., 2014*† (VALENCE)	84 250	46♂ 38♀ 155♂ 95♀	56.7 (10.8) 48 (10.1)	2, 3	No	Yes	NA	**SF-36** All (SD)	Baseline, 4, 12, 24	Sofosbuvir (400 mg) *(12wk)* + Ribavirin (1000-1200 mg) Sofosbuvir (400 mg) *(24wk)* + Ribavirin (1000-1200 mg)	4, 12	NR
Jacobson et al., 2013[a] (POSITRON)	207 71	117♂ 79♀ 34♂ 37♀	52 (21-75) 51 (28-67)	2, 3	No	No	Yes	**SF-36** PCS, MCS (SD) **EQ-5D** index (SD)	Baseline, 12, 48	Sofosbuvir (400 µg) + Ribavirin (1000-1200 µg) Placebo	12	78% *12 weeks* 0% *12 weeks*
Jacobson et al., 2013[b] (FUSION)	103 98	73♂ 30♀ 67♂ 31♀	54 (30-69) 54 (24-70)	2, 3	No	No	No	**SF-36** PCS, MCS (SD) **EQ-5D** index (SD)	Baseline, 12, 48	Sofosbuvir (400 µg) *(12wk)* + Ribavirin (1000-1200 µg Sofosbuvir (400 µg) *(16wk)* + Ribavirin (1000-1200 µg)	4, 12	50% *12 weeks* 73% *12 weeks*
Sub total	3679	2222 1426♀	53.5		No							

Table 1 (continued). Characteristics of the studies included in the review.

Study	N	Gender	Age (SD/ range)	Geno-type	HIV co-infection	Drug abuse	Psychiatric history	HRQL scores	HRQL (week)	Treatment type (dose per week)	Follow up (wk)	SVR rate post-treatment
IFN-containing regimens												
Scott et al., 2015 (QUEST-1, -2, PROM-ISE)	829 444	502♂ 314♀ 265♂ 167♀	49 (18-73) 49 (18-73)	1	No	NA	NA	**EQ-5D** index (SD)	Baseline, 4, 12, 24, 36, 48	Simeprevir (150 mg) + PegIFN-α2a (180 µg) + Ribavirin (1000-1200 µg) PegIFN-α2a (180 µg) + Ribavirin (1000-1200 µg) + Placebo	12	36.1-50% *12 weeks* 79.2-81% *12 weeks*
Zeuzem et al., 2014* (ASPIRE)	344 50	241♂ 103♀ 29♂ 21♀	51 (20-68) 50.5 (22-66)	1	No	NA	No	**EQ-5D** index (SD), VAS (SD)	Baseline, 24, 48	Simeprevir (100/150 mg) + PegIFN-α2a (180 µg) + Ribavirin (1000-1200 µg) PegIFN-α2a (180 µg) + Ribavirin (1000-1200 µg) + Placebo	24	60.6-80% *24 weeks* 23% *24 weeks*
Lawitz et al., 2013† (FISSION)	315 156	196♂ 116♀ 171♂ 85♀	48 (19-77) 48 (20-72)	1, 4, 5, 6	No	No	No	**SF-36** PCS, MCS (SD) **EQ-5D** index (SD)	Baseline, 12, 24	Sofosbuvir (400 µg) + Ribavirin (1000-1200 µg) PegIFN-α (180 µg) + Ribavirin (1000-1200 µg)	12	67% *12 weeks*
Vera-Llonch et al., 2013† (ADVANCE)	428 210 153	211♂ 148♀ 128♂ 82♀ 86♂ 67♀	48.8 (10) 45.9 (10.4) 47.3 (11.2)	1	No	NA	NA	**EQ-5D** index (95% CI)	Baseline, 4, 12, 24, 36, 48	PegIFN-α + RBV (NA) Telaprevir + pegIFN-α + Ribavirin (NR) *(24 weeks)* Telaprevir + pegIFN-α + Ribavirin (NA) *(48 weeks)*	24	36% *24 weeks* 66% *24 weeks* 74% *24 weeks*
Fried et al., 2013† (PILLAR)	299 77	174♂ 125♀ 39♂ 38♀	46.8 (18-69) 45 (21-67)	1	No	NA	NA	**EQ-5D** index (SD), VAS (SD)	Baseline, 48	Simeprevir (75/150 mg) + PegIFN-α2a (180 µg) + Ribavirin (1000-1200 µg) PegIFN-α2a (180 µg) + Ribavirin (1000-1200 µg) + Placebo	24	74.7%-86.1% *24 weeks* 64.9% *24 weeks*
Sub total	3208	2001♂ 1237♀	48.1		No							
Total	6887	4224♂ 2663♀	51		No							

* Sample based on previous treatment non-responders. † Sample based on treatment-naïve patients.

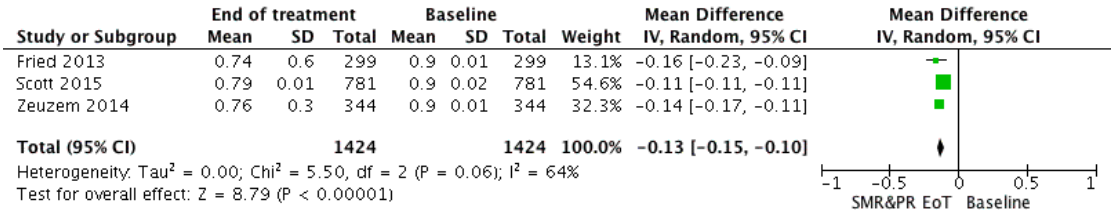
Abbreviations: EQ-5D = EuroQol 5 Dimensions questionnaire; HRQL = health-related quality of life; NR = not available; PegIFN-α = peginterferon-alpha; RBV = ribavirin; SF-36 = Short-Form 36 questionnaire.

3.2. Quality of life

Data from a total of five studies could be included in meta-analysis. Three of these studies could be included in meta-analysis reporting *EQ-5D index scores*, as well as two of these studies also reported *EQ-VAS scores*. Each of the studies included a treatment group receiving simeprevir (SMV) with PR, and a control group receiving PR with placebo (Fried et al., 2013; Zeuzem et al., 2014; Scott et al., 2015). At the end of treatment, in both groups a similar significant decrease from baseline was found in index scores (mean difference = -0.13; 95%CI = -0.15, -0.11; and mean difference = -0.13; 95%CI = -0.16, -0.1, respectively). Furthermore, only in the SMV with PR group, a significant decrease was also found from baseline in *EQ-VAS scores* (mean difference = -8.9; 95%CI = -15.95, -1.84). At follow-up, scores in both groups returned to baseline scores. See Figure 2, and Annex 1 Section VI, for results.

Figure 2. Forest plots from meta-analysis.

A. EQ-5D index score changes at end of treatment from baseline in SMV&PR group.



B. EQ-5D index changes at end of treatment from baseline in PR group.

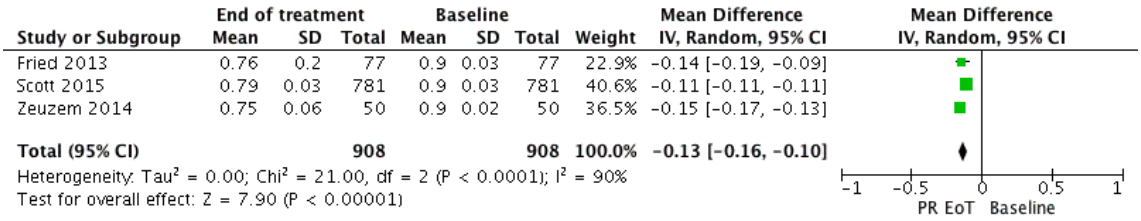
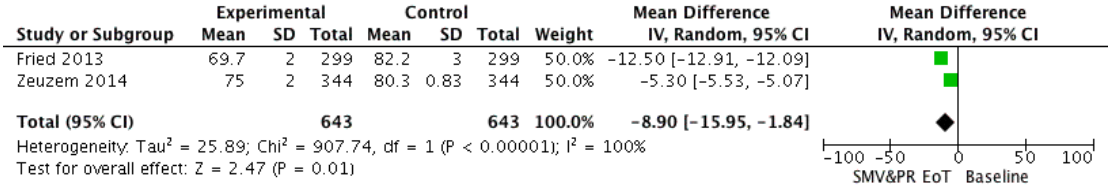
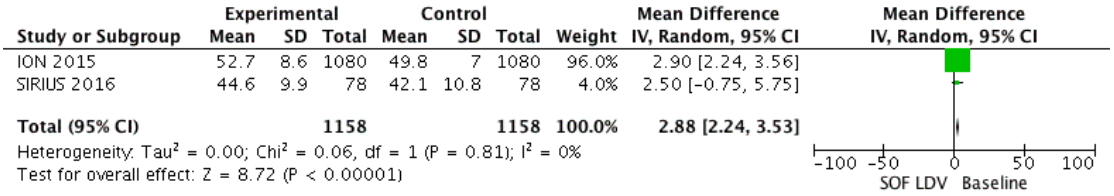


Figure 2 (continued). Forest plots from meta-analysis.

C. EQ-VAS score changes at end of treatment from baseline in SMV&PR group.



D. SF-36 MCS changes at treatment follow-up from baseline in SOF & LDV group.



E. SF-36 MCS changes from baseline at treatment end in SOF&LDV&RBV group.

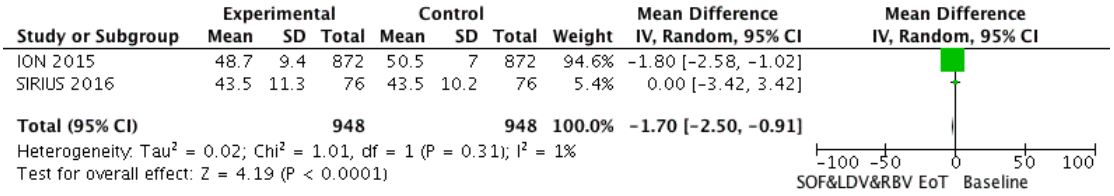


Table 2 shows the individual study results of the four studies not included in the meta-analysis. Of these, a total of three studies used an interferon-free DAA regimen comparison group. The first study (Jacobson et al., 2013[a]) included a group receiving sofosbuvir (SOF) with ribavirin, and a placebo group. Only in the DAA group, compared to baseline [mean (SD) = 0.72 ± 0.21] a significant decrease in *EQ-5D index score* was observed during treatment (mean difference = -0.09). Another RCT from Jacobson et al. (2013[b]) compared two groups receiving the DAA sofosbuvir plus ribavirin, for 12 (plus 4-weeks of placebo) or 16 weeks, respectively. The 12-week arm showed a significant

decrease (mean difference = -0.07) when compared to baseline index score (mean = 0.75 ± 0.23). Regarding the studies, which included IFN-based regimens, Lawitz et al., (2013) study compared sofosbuvir plus ribavirin to PR treatment. Results suggested that only in the PR group, a significant decrease from baseline (mean = 0.77 ± 0.23) was found at 24 weeks of treatment (mean difference = -0.11). Moreover, Vera-Llonch et al. (2013) compared telaprevir plus PR during 24 or 48 weeks, to PR treatment. In each of the three groups, index scores were significantly lower during treatment, returning to baseline again at 24 weeks of post-treatment.

Figure 2 shows the meta-analysis including two studies comparing sofosbuvir plus ledipasvir to sofosbuvir with ledipasvir and ribavirin, both assessing HRQL with *SF-36 questionnaire* (Younossi et al., 2015; 2016[b]). The two studies provided data of the *SF-36* physical component scale (*PCS*) and the mental component scale (*MCS*). In *PCS* no significant differences were observed at baseline, end of treatment, or post-treatment follow-up. However, at the end of treatment, the sofosbuvir and ledipasvir group saw a slight improvement in the *MCS* compared to baseline (mean difference = 2.88; 95%CI = 2.24, 3.53), as where the group receiving the same treatment with ribavirin saw a significant decrease from baseline in *MCS* at 12 weeks after treatment cessation follow-up (mean difference = -1.7; 95%CI = -2.5, -0.91).

Table 2. EuroQol-5D mean index scores (and mean EQ-5D VAS scores) and changes over time.*

Study	Type of treatment	Baseline Mean (SD/95%CI)	4 weeks treatment Mean (SD/95%CI) Δ Mean (SD/95%CI)	12 weeks treatment Mean (SD/95%CI) Δ Mean (SD/95%CI)	24 weeks treatment Mean (SD/95%CI) Δ Mean (SD/95%CI)	36 weeks treatment Mean (SD/95%CI) Δ Mean (SD/95%CI)	48 weeks treatment Mean (SD/95%CI) Δ Mean (SD/95%CI)	4 weeks post-treatment Mean (SD) Δ Mean (SD)	12 weeks post-treatment Mean (SD) Δ Mean (SD)	24 weeks post-treatment Mean (SD/95%CI) Δ Mean (SD/95%CI)
IFN-free regimens										
Jacobson et al., 2013[a] (POSI-TRON)	SOF &RBV	0.72 (0.21)	--	0.66 (0.21)	--	--	--	0.71 (0.23)	--	--
			--	-0.06 (0.0)	--	--	--	**-0.09** (0.02)	--	--
	Placebo	0.67 (0.23)	--	0.67 (0.24)	--	--	--	0.69 (0.24)	--	--
			--	0 (0.01)	--	--	--	0.02 (0.01)	--	--
Jacobson et al.,† 2013[b] (FUSION)	SOF&RBV	0.74 (0.21)	--	0.72 (0.69)	--	--	--	0.74 (0.21)	0.77 (0.22)	--
			--	-0.02 (0.48)	--	--	--	0.0 (0.0)	0.02 (0.01)	--
	SOF&RBV	0.75 (0.23)	--	0.69 (0.23)	--	--	--	0.74 (0.24)	0.79 (0.23)	--
			--	**-0.06** (0.0)	--	--	--	-0.02 (0.01)	0.04 (0.0)	--
DAA- and IFN-based regimens										
Scott et al., 2015 (QUEST-1& 2, PRO-MISE)	SMV& PR	0.9 (0.02)	0.79 (0.01)	0.77 (0.02)	0.79 (0.01)	0.86 (0.01)	0.88 (0.01)	--	0.89 (0.01)	0.9 (0.01)
			-0.11 (--)	**-0.13** (0.01)	**-0.11** (0.0)	**-0.04** (0)	-0.02 (0)	--	-0.01 (0)	0 (0)
	Placebo& PR	0.9 (0.03)	0.8 (0.02)	0.78 (0.03)	0.79 (0.02)	0.78 (0.02)	0.79 (0.03)	--	0.8 (0.03)	0.89 (0.02)
			-0.1 (--)	**-0.12** (0.01)	**-0.11** (0.0)	**-0.12** (0)	**-0.11** (0.01)	--	**-0.1** (0.01)	-0.01 (0)
Zeuzem et al., 2014 ASPIRE)	SMV&PR	0.9 (0.01)	--	--	0.76 (0.03)	--	0.76 (0.04)	--	--	0.87 (0.03)
			--	--	**-0.14** (0.02)	--	**-0.14** (0.03)	--	--	-0.03 (0.02)
		[80.3 (0.83)]	--	--	[69.3 (3.0)]	--	[75 (2.0)]	--	--	[82 (3.0)]
			--	--	[**-11.0** (2.17)]	--	[**-5.3** (1.17)]	--	--	[1.7 (2.17)]
	PR	0.9 (0.02)	--	--	0.74 (0.03)	--	0.75 (0.06)	--	--	0.84 (0.05)
			--	--	**-0.16** (0.01)	--	**-0.15** (0.04)	--	--	**-0.06** (0.03)
		[80.5 (2.22)]	--	--	[69.8 (5.0)]	--	[80.5 (5.0)]	--	--	[82 (4.0)]
			--	--	[**-9.7** (2.78)]	--	[0 (2.78)]	--	--	[1.5 (1.78)]
Lawitz et al., 2013 (FISSION)	SOF&RBV	0.74 (0.23)	--	0.74 (0.25)	--	--	--	--	0.75 (0.23)	--
			--	-0.03 (0.02)	--	--	--	--	0.01 (0)	--
	PR	0.77 (0.24)	--	--	0.65 (0.22)	--	--	--	0.74 (0.22)	--
			--	--	**-0.11** (-0.02)	--	--	--	-0.01 (-0.02)	--
Vera-Llonch et al., 2013 (ADVAN-CE)	PR	0.91 (0.9 to 0.92)	0.84 (0.82 to 0.85)	0.82 (0.81 to 0.84)	0.8 (0.78 to 0.82)	0.83 (0.81 to 0.85)	0.84 (0.82 to 0.86)	--	--	0.89 (0.88 to 0.91)
			-0.07 (-0.09 to -0.06)	**-0.09** (-0.1 to -0.07)	**-0.11** (-0.13 to -0.09)	**-0.08** (-0.1 to -0.06)	**-0.05** (-0.07 to -0.03)	--	--	-0.02 (-0.03 to 0)
	T&PR *24wk*	0.92 (0.91 to 0.94)	0.82 (0.82 to 0.85)	0.8 (0.77 to 0.82)	0.83 (0.81 to 0.85)	0.9 (0.89 to 0.93)	0.93 (0.92 to 0.95)	--	--	0.94 (0.92 to 0.95)
			-0.1 (-0.1 to -0.07)	**-0.12** (-0.15 to -0.1)	**-0.09** (-0.11 to -0.07)	**-0.08** (-0.09 to -0.05)	0.01 (0 to 0.03)	--	--	0.02 (0 to 0.03)

Table 2 (continued). EuroQol-5D mean index scores (and mean EQ-5D VAS scores) and changes over time.*

Study	Type of treatment	Baseline Mean (SD/95%CI)	4 weeks treatment Mean (SD/95%CI) Δ Mean (SD/95%CI)	12 weeks treatment Mean (SD/95%CI) Δ Mean (SD/95%CI)	24 weeks treatment Mean (SD/95%CI) Δ Mean (SD/95%CI)	36 weeks treatment Mean (SD/95%CI) Δ Mean (SD/95%CI)	48 weeks treatment Mean (SD/95%CI) Δ Mean (SD/95%CI)	4 weeks post-treatment Mean (SD) Δ Mean (SD)	12 weeks post-treatment Mean (SD) Δ Mean (SD)	24 weeks post-treatment Mean (SD/95%CI) Δ Mean (SD/95%CI)
DAA- and IFN-based regimens										
Vera-Llonch et al., 2013 (ADVAN-CE)	T&PR *48wk*	0.9 (0.88 to 0.93)	0.81 (0.79 to 0.84) **-0.09** (-0.11 to -0.06)	0.78 (0.75 to 0.82) **-0.12** (-0.15 to -0.08)	0.81 (0.78 to 0.85) **-0.09** (-0.12 to 0.05)	0.85 (0.82 to 0.88) **-0.05** (-0.08 to -0.02)	0.83 (0.79 to 0.86) **-0.07** (-0.11 to -0.04)	-- --	-- --	0.9 (0.88 to 0.93) 0.0 (-0.02 to 0.03)
Fried et al., 2013 (PILLAR)	SMV& PR	0.9 (0.01)	--	--	--	--	0.75 (0.6)	--	0.86 (0.3)	--
			--	--	--	--	**-0.15** (0.59)	--	-0.04 (0.29)	--
		[82.2 (3.0)]	--	--	--	--	[69.7 (2.0)]	--	[82.2 (3.0)]	--
			--	--	--	--	[**-12.5** (-1.0)]	--	[0 (0)]	--
	PR	0.9 (0.03)	--	--	--	--	0.76 (0.2)	--	0.77 (0.5)	--
			--	--	--	--	**-0.14** (-0.01)	--	**-0.13** (0.47)	--
		[83.6 (5.0)]	--	--	--	--	[67.6 (5.0)]	--	[70 (4.0)]	--
			--	--	--	--	[**-16** (0)]	--	[**-13.6** (-1.0)]	--

† Administration of treatment regimen during 16 weeks, or 12 weeks, respectively.

*Numbers in **bold** indicate a minimal clinically important difference (MID) in scores compared to baseline.

Abbreviations: MD = mean difference, PR = peginterferon-alpha plus ribavirin; SMV = simeprevir; SOF = sofosbuvir; T = telaprevir; RBV = ribavirin; SVR = sustained virologic response after treatment cessation.

Table 3 shows the individual study results of the five studies with *SF-36 questionnaire* not included in the meta-analysis. An RCT by Younossi et al. (2016[a]) assessed life quality in CHC patients receiving the combination of sofosbuvir and velpatasvir, versus patients receiving placebo. There was a tendency for increased *PCS* and *MCS scores* in the group receiving DAAs, and a smaller trend in the placebo group. Jacobson et al. (2013[a]) assessed sofosbuvir combined with ribavirin, compared to a placebo group. Results showed an important decrease in the DAA group in *MCS* at 12 weeks, i.e. end of treatment (mean difference = -4.2). Another RCT study by Younossi et al. (2014) compared sofosbuvir plus ribavirin, during 12 or 24 weeks, respectively. Scores indicated only minor changes in *SF-36 scores* during and after treatment compared to baseline. Finally, a study by Lawitz et al. (2013) compared sofosbuvir and ribavirin to PR. Compared to baseline scores, both *MCS* and *PCS* respectively showed a significant decrease during the treatment only in the PR group. However, these scores returned back to baseline scores at post-treatment week 12.

3.3. Risk factors

Table 4 shows a summary of main results with regard to risk factors associated to HRQL impairment at baseline, at the end of antiviral treatment (12, 16, 36 and 48 weeks depending on treatment regimen) and at post-treatment follow-up (12 or 24 weeks after treatment where treatment response is assessed). As no specific HRQL data were given on risk factors, no meta-analysis could be performed.

Table 3. Short-Form 36 quality of life mean scores and changes over time.

Study	Type of treatment	Scale	Baseline	4 weeks treatment	12/16 weeks treatment	24 weeks treatment	4 weeks post-treatment	12 weeks post-treatment
			Mean (SD)	Mean (SD) ΔMean (SD)	Mean (SD) ΔMean (SD)	Mean (SD) ΔMean (SD)	Mean (SD) ΔMean (SD)	Mean (SD) Δ Mean (SD)
IFN-free regimens								
Younossi et al., 2016[a] (ASTRAL-1)	SOF & VEL	PCS	51.0 (8.9)	52.0 (--) 1.0 (--)	-- --	-- --	-- --	54.0 (--) 3.0 (--)
		MCS	49.3 (10.4)	50 .0 (--) 0.7 (--)	-- --	-- --	-- --	52.0 (--) 2.3 (--)
	Placebo	PCS	51.8 (8.5)	50.5 (--) -1.3 (--)	-- --	-- --	-- --	49.0 (--) -2.8 (--)
		MCS	51.0 (8.9)	49.2 (--) -1.9 (--)	-- --	-- --	-- --	49.0 (--) -2.0 (--)
Younossi et al., 2014 (VALENCE)	SOF & RBV *12 weeks*	PCS	51.1 (8.3)	50.2 (8.0) -0.9 (0.3)	49.8 (7.5) -1.3 (-1.8)	-- --	51.5 (7.9) 0.4 (-0.4)	52.6 (6.5) 1.5 (-2.8)
		MCS	47.8 (9.1)	47.6 (9.3) -0.2 (0.2)	45.0 (11.0) -2.8 (1.9)	-- --	47.6 (10.3) -0.2 (1.2)	48.7 (9.4) 0.9 (0.3)
	SOF & RBV *24 weeks*	PCS	52.1 (7.6)	49.9 (8.7) -2.2 (1.1)	-- --	50.4 (8.7) -1.7 (1.1)	51.0 (8.2) -1.1 (0.8)	52.0 (7.2) -0.1 (-0.4)
		MCS	46.5 (11.0)	44.2 (12.0) -2.3 (1.0)	-- --	43.2 (11.6) -3.2 (0.6)	46.2 (11.0) -0.3 (0)	47.5 (11.1) 1 (0.1)
Jacobson et al., 2013 (POSITRON)	SOF & RBV	PCS	48.2 (8.5)	-- --	46.9 (9.5) 1.3 (1.0)	-- --	47.9 (10.0) -0.3 (-0.3)	-- --
		MCS	48.4 (10.4)	-- --	**44.2 (11.6)** **-4.2 (1.2)**	-- --	47.3 (10.9) -1.1 (0.5)	-- --
	Placebo	PCS	46.3 (9.7)	-- --	46.6 (9.5) 0.3 (-0.2)	-- --	47.2 (9.2) 0.9 (-0.5)	-- --
		MCS	45.8 (11.9)	-- --	44.7 (12.6) -1.1 (0.7)	-- --	45.1 (11.3) -0.7 (-0.6)	-- --
Jacobson et al., 2013[b] (FUSION)	SOF & RBV *12 weeks*	PCS	49.2 (9.5)	-- --	47.6 (10.0) -1.6 (0.5)	-- --	-- --	50.4 (9.4) 1.2 (-0.1)
		MCS	49.6 (10.5)	-- --	45.7 (11.6) -3.9 (1.1)	-- --	-- --	51.0 (10.6) 1.4 (0.1)
	SOF & RBV *16 weeks*	PCS	48.5 (9.1)	-- --	48.2 (8.6) -0.3 (-0.5)	-- --	-- --	50.1 (8.5) 1.6 (-0.6)
		MCS	50.3 (10.2)	--	47.9 (11.4) -2.9 (1.2)	--	--	49.0 (11.7) -1.3 (1.5)
Younossi et al., 2016[b] (SIRIUS)	SOF & LDV	PCS	47.5 (6.7)	47.0 (6.9) -0.5 (0.2)	46.6 (8.0) -0.9 (1.3)	47.5 (6.7) 0 (0)	46.7 (7.7) -0.8 (1.0)	49.4 (19.1) 1.9 (12.9)
		MCS	42.1 (10.8)	44.7 (9.7) 2.6 (-1.1)	43.5 (10.7) 1.4 (-0.1)	42.8 (10.7) -0.7 (-0.1)	44.0 (10.4) 1.9 (-0.4)	44.6 (9.9) 2.5 (-0.9)
	SOF & LDV & RBV	PCS	49.2 (7.7)	49.6 (6.7) 0.4 (-1.0)	49.4 (7.4) 0.2 (-0.3)	49.2 (7.7) 0.0 (0)	49.3 (8.4) 0.1 (0.7)	48.8 (7.8) -0.4 (0.1)
		MCS	43.5 (10.2)	44.0 (10.2) 0.5 (0)	43.7 (10.6) 0.2 (0.4)	43.5 (11.3) 0 (1.1)	43.9 (10.0) 0.4 (-0.2)	44.0 (11.0) 0.5 (0.8)
Younossi et al., 2015 (ION-1, -2, -3)	SOF & LDV	PCS	51.5 (5)	52.0 (5.2) 0.5 (0.5)	53.1 (6.1) 1.6 (1.6)	-- --	53.2 (6.2) 1.7 (1.2)	53.2 (6.4) 1.7 (1.4)
		MCS	49.8 (7)	50.6 (7.4) 0.8 (0.8)	51.3 (8.8) 1.5 (1.8)	-- --	51.8 (8.6) 2.0 (1.6)	52.7 (8.6) 2.1 (1.6)
	SOF & LDV & RBV	PCS	50.5 (6)	50.1 (6.1) -0.4 (0.1)	50.4 (6.6) -0.1 (0.6)	-- --	51.5 (6.3) 1.0 (0.3)	52.1 (6.4) 1.6 (0.4)
		MCS	50.5 (7)	49.7 (7.6) -0.8 (0.6)	48.7 (9.4) -1.8 (2.4)	-- --	51.1 (8.6) 0.6 (1.6)	51.9 (8.6) 1.4 (1.6)
DAA- and IFN-based regimens								
Lawitz et al., 2013 (FISSION)	SOF & RBV *12 weeks*	PCS	48.8 (9.3)	-- --	49.1 (10.5) 0.3 (1.2)	-- --	-- --	49.3 (9.6) 0.5 (0.3)
		MCS	50.3 (10.2)	-- --	47.6 (11.8) -2.7 (1.6)	-- --	-- --	49.8 (10.1) -0.5 (-0.1)
	PR *24 weeks*	PCS	50.0 (9.3)	--	--	**45.7 (9.8)**	--	50.4 (8.9)
				--	--	**-4.3 (0.5)**	--	0.4 (-0.4)
		MCS	48.8 (10.2)	--	--	**43.1 (11.9)**	--	48.4 (11.4)
				--	--	**-7.1 (1.7)**	--	-0.4 (1.2)

Numbers in **bold** indicate a minimal clinically important difference (MID) compared to baseline score.
Abbreviations: MCS = mental component scale; PCS = physical component scale; PR = peginterferon-alpha plus ribavirin; SOF = sofosbuvir; RBV = ribavirin; LDV = ledipasvir; MCS = mental component scale; PCS = physical component scale; PR = peginterferon-alpha plus ribavirin; SOF = sofosbuvir.

Five out of seven studies included in this review using *EQ-5D questionnaire* have studied risk factors associated with HRQL impairment. Between them, two studies evaluated DAA plus ribavirin combination only and 3 studies included intereron-alpha as comparison. First, a study using sofosbuvir and ribavirin comparing with placebo (Jacobson et al., 2013[a]) and another study administering sofosbuvir and ribavirin for 12 or 24 weeks (Jacobson et al., 2013[b]), found similar results. Baseline depression, fatigue, anxiety and insomnia were the major predictors of lower *EQ-5D index scores* at the end of treatment. Lawitz et al. (2013) found sofosbuvir plus ribavirin associated with higher end-of-treatment score ($p = 0.002$) when compared to the control group receiving PR. Moreover, Scott et al. (2015) using simeprevir plus PR or PR alone, found cirrhosis to be predictive of general life quality impairment ($p < 0.05$). Finally, a study by Vera-Llonch et al. (2013) included treatment-naïve patients who were randomly assigned to receive triple therapy during 24 or 48 weeks, or PR treatment. At baseline, being unemployed ($p < 0.001$), the number of comorbidities ($p < 0.001$), as well as the presence of bridging fibrosis or cirrhosis ($p = 0.02$), was adversely associated with quality of life scores. At 12 weeks of treatment, a low baseline score ($p < 0.005$), older age ($p = 0.01$), receiving triple treatment ($p = 0.01$), treatment discontinuation ($p < 0.005$), and treatment-related anaemia ($p = 0.04$) were related to lower index scores. At end of treatment, high baseline *EQ-5D index score*, as well as receiving triple treatment for 24 weeks ($p < 0.005$), were positively associated index scores. However, the number of adverse events during treatment had a negative impact ($p < 0.001$). Twenty-four weeks after treatment cessation, response to treatment was associated ($p < 0.001$) with higher index values.

Table 4. Predictive risk factors of HRQL impairment before, during or after antiviral treatment.

Risk factor	Study	Treatment vs. control	Questionnaire [(sub) scale]		SVR		Significance
			Baseline	During treatment	Treatment end	Post-treatment	(*p*)
Clinicodemographic and social factors							
Being male*	Younossi et al., 2015	SOF&LDV&RBV vs. SOF&LDV	--	--	SF-36 (NA)	--	< 0.05
	Younossi et al., 2014	SOF&RBV *(12 or 24wk)*	--	--	SF-36 (PF, RP, BP, VT, PCS)	--	< 0.05
Older age	Vera-Llonch et al., 2013	T&PR *(24 or 48wk)* vs. PR	--	EQ-5D (index)		--	0.01
	Younossi et al., 2014*	SOF&RBV *(12 or 24wk)*	--		SF-36 (PCS)	--	< 0.05
Cirrhosis	Scott et al., 2015	SMV&PR vs. PR&placebo	EQ-5D (index)	--	--	--	< 0.05
	Vera-Llonch et al., 2013	T&PR vs. PR *(24 or 48wk)*	EQ-5D (index)	--	--	--	0.02
Nº comorbidities	Vera-Llonch et al., 2013	T&PR *(24 or 48wk)* vs. PR	EQ-5D (index)	--	--	--	< 0.01
Unemployment	Vera-Llonch et al., 2013	T&PR *(24 or 48wk)* vs. PR	EQ-5D (index)	--	--	--	< 0.005
Psychiatric risk factors							
History of anxiety disorder	Younossi et al., 2016[b]	SOF&LDV&RBV vs. SOF&LDV	--	--	--	SF-36 (NA)	< 0.05
	Younossi et al., 2015	SOF&LDV&RBV vs. SOF&LDV	--	--	--	SF-36 (NA)	< 0.005
	Jacobson et al., 2013[b]	SOF&RBV (*12 or 16wk)*	SF-36 (NA)	SF-36 (NA)	SF-36 (NA)		< 0.05 *(all)*
History of depression	Younossi et al., 2016[b]	SOF&LDV&RBV vs. SOF&LDV	--	--	--	SF-36 (NA)	< 0.05
	Younossi et al., 2015	SOF&LDV&RBV vs. SOF&LDV	--	--	--	SF-36 (NA)	< 0.005
	Jacobson et al., 2013[a]	SOF&RBV vs. placebo	SF-36 (RE)	SF-36 (RE)	SF-36 (RE)	--	0.03 *(all)*
	Jacobson et al., 2013[b]	SOF&RBV (*12 or 16wk)*	SF-36 (NA)	SF-36 (NA)	SF-36 (NA)	--	< 0.05 *(all)*

Table 4 (continued). Predictive risk factors of HRQL impairment before, during or after antiviral treatment.

Risk factor	Study	Treatment vs. control	Questionnaire [(sub) scale]				Significance
			Baseline	During treatment	Treatment end	Post-treatment	*(p)*
Psychiatric risk factors							
History of fatigue disorder	Younossi et al., 2016[b]	SOF&LDV&RBV vs. SOF&LDV	--	--	--	SF-36 (NA)	< 0.05
	Younossi et al., 2015	SOF&LDV&RBV vs. SOF&LDV	--	--	--	SF-36 (NA)	< 0.005
	Jacobson et al., 2013[a]	SOF&RBV vs. placebo	--	--	SF- 36 (PCS)	--	< 0.05
History of insomnia	Younossi et al., 2016[b]	SOF&LDV&RBV vs. SOF&LDV	--	--	--	SF-36 *(NA)*	< 0.05
	Jacobson et al., 2013[a]	SOF&RBV vs. placebo	SF-36 (RE, MH, PCS)	SF-36 (RE, MH, PCS)	SF-36 (RE, MH, PCS)	--	0.03 *(all)*
	Jacobson et al., 2013[b]	SOF&RBV (*12 or 16wk)*	SF-36 (NA)	SF-36 (NA)	SF-36 (NA)	--	< 0.05
Treatment-related risk factors							
RBV co-administration	Younossi et al., 2015	SOF&LDV&RBV vs. SOF&LDV	SF-36 (PCS, MCS)	SF-36 (PF, PCS, MCS)	SF-36 (PCS, MCS)	SF-36 (PCS, MCS)	< 0.005
Treatment discontinuation	Vera-Llonch et al., 2013	T&PR *(24 or 48wk)* vs. PR	--	EQ-5D (index)	--	--	< 0.005
Treatment-related anemia	Vera-Llonch et al., 2013	T&PR *(24 or 48wk)* vs. PR	--	EQ-5D (index)	--	--	0.05
	Jacobson et al., 2013[a]	SOF&RBV vs. placebo	SF-36 (PCS)	SF-36 (PCS)	SF-36 (PCS)	--	< 0.05 *(all)*
	Jacobson et al., 2013[b]	SOF&RBV (*12 or 16wk)*	SF-36 (PCS)	SF-36 (PCS)	SF-36 (PCS)	--	< 0.05 *(all)*
Nº of adverse events	Vera-Llonch et al., 2013	T&PR vs. PR *(24 or 48wk)*	--	--	--	EQ-5D (index)	< 0.001
	Younossi et al., 2014	SOF&RBV (*12 or 24wk)*	--	--	SF-36 *(NA)*	--	< 0.05
SVR*	Vera-Llonch et al., 2013	T&PR *(24 or 48wk)* vs. PR	--	--	--	EQ-5D (index)	< 0.001
	Younossi et al., 2015	SOF&LDV&RBV vs. SOF&LDV	--	--	--	SF-36 *(NA)*	< 0.05
	Younossi et al., 2014	SOF&RBV (*12 or 24wk)*	--	--	--	SF-36 (GH)	< 0.05
	Jacobson et al., 2013[b]	SOF&RBV (*12 or 16wk)*	--	--	--	SF-36 *(NA)*	< 0.05

* Indicates a finding associated with improvement in HRQL.
Abbreviations: BP = bodily pain; EQ-5D = EuroQol 5 Dimension questionnaire; SF-36 = Short-Form 36 questionnaire; GH = general health; LDV = ledipasvir; MH = mental health; MCS = mental component scale; NA = not available; PCS = physical component scale; PR = peginterferon-alpha plus ribavirin; SF = social functioning; SOF = sofosbuvir; T = telaprevir; RBV = ribavirin; RE = role emotional; VI = vitality.

On the other hand, five out of seven studies included in this review using *SF-36 questionnaire* have described data of risk factors associated with quality of life impairment. See Table 4. In this case, four studies included DAA plus ribavirin, whereas one study included IFN-based therapies. Younossi et al. (2014) assessing sofosbuvir plus ribavirin during 12 or 24 weeks, respectively, found male gender related to better life quality (physical functioning, physical role, bodily pain, vitality, and *PCS*, ($p < 0.05$), as well as younger age (below 55 years) (*PCS*, $p < 0.05$), as where adverse events during treatment were adversely related at different time points (all scales, $p < 0.05$). Also, virological response to therapy assessed at 24 weeks of post-treatment was related to decreased general health ($p < 0.05$). Another study by Younossi et al. (2015) using ledipasvir with sofosbuvir and placebo, or ledipasvir with sofosbuvir and ribavirin, found that baseline depression, anxiety, insomnia, and fatigue, the occurrence of gastrointestinal events, as well as cirrhosis and history of treatment non-response, were the most frequently noted independent predictors of lower general HRQL at different time points ($p < 0.05$). Furthermore, the added use of ribavirin was associated with impaired *MCS* ($p < 0.05$). At 24 weeks of post-treatment follow-up, non-response to treatment was related to lower general life quality ($p < 0.001$). Finally, a study by Jacobson et al (2013[b]), comparing sofosbuvir plus ribavirin during 12 weeks or 16 weeks, also found baseline depression, fatigue, anxiety, and anemia as a predictor of decreased life quality over treatment course ($p < 0.05$). At post-treatment follow-up, treatment response was related to higher physical functioning, physical role (both $p < 0.05$), bodily pain, and physical component scale scores (both $p < 0.005$). Furthermore, Lawitz et al. (2013) compared a group receiving DAA to a

group receiving PR, and found that PR was associated with a decrease in *MCS* and *PCS* life quality (p = 0.01). Anemia was also found to be a predictor of lower mental life quality. Moreover, Jacobson et al. (2013[a]) compared a group receiving sofosbuvir and ribavirin versus a placebo group. During treatment, both the mental *(MCS)* and physical *(PCS)* aspects became more decreased in the treatment group (p = 0.015, and p < 0.005, respectively) versus placebo. On the other hand, predictive factors for HRQL impairment included baseline depression (emotional role, p = 0.03), fatigue (physical summary scale, p < 0.05), insomnia (mental summary scale; emotional role; and mental health, all p = 0.03), and anemia (physical summary scale, p < 0.05).

4. PUBLICATION BIAS

Funnel plots revealed no publication bias among the studies analysed, since those included in this systematic review were situated close to the middle axis and were evenly distributed vertically (see Annex 1, Section VII). Studies that allowed for meta-analysis are included in the funnel plots.

5. DISCUSSION

This review systematically gathered RCT studies of the new antiviral treatments, in order to provide an evidence update regarding health-related life quality and risk factors in chronic hepatitis C patients receiving new antiviral treatment regimens. The assessment of HRQL is rather complex, since it

involves both physical and mental aspects, each of which is addressed by several sub scales in the available HRQL tools.

The implosion of the new antiviral treatments for CHC, with a level of efficacy as high as >90% in most patients, has been a complete change on the treatment paradigm of this chronic and impairing disease. In this frame, the results of this review are in part a reflection of this understandable enthusiasm. Although it included only RCTs study designs using DAA, the antiviral regimen and the drug comparison groups were so different that it was only possible to summarize results from 11 studies in two meta-analyses, of two and three studies, respectively. Instead of replicating previous findings, it appears that the objectives of included RCT studies were primarily to investigate a new step on the antiviral treatment response.

As several of the included studies used patients with different characteristics, such as different HCV genotypes, stages of liver disease, co-infection with HIV, and history of psychiatric disorders, our review is not free from heterogeneity. In addition, due to the use of different treatment regimens, or incomplete HRQL data, it was not always possible to perform statistical analysis. However, the use of the MCID should give a reference for statistical significance. With respect to measurement bias, most of the studies often reported limited HRQL data (due to missing sub scales scores) and failed to include disease-specific factors that may play an important role in HRQL impairment in CHC patients during antiviral treatment. The checklist used to assess the quality of RCT studies in the review allowed to identify some flaws of quality in each of the included

studies (Higgins and Green, 2008). Since inclusion criteria were applied for study selection and characteristics of the studies varied, caution must be exercised when generalizing the results of this review to the overall population of CHC patients that could be treated with the new direct antivirals. On the other hand, in the RCTs measuring HRQL, follow-up was until 12 or 24 weeks of post-treatment, perhaps an insufficient period of time to measure longer-term effects on HRQL. As the virus may remain present in the brain after having followed successful treatment (Dirks et al., 2017), it would be interesting to obtain data from a longer follow-up in patients after having receiving antiviral treatment.

In spite of the above comments, this review yields several main important findings. With regard to new antiviral regimens with DAA, results suggest that in the use of interferon-free regimen, no significant impairment occurs in physical and mental life quality, in contrary to what has been found in PR administration (Spiegel et al., 2005; Daltro-Oliveira et al., 2013). At post-treatment follow-up, life quality improvement occurs after antiviral treatment DAA, in contrary to placebo, this being a very encouraging result supporting recent clinical experience (Walker et al., 2015). This is particularly important when considering current antiviral therapy with DAA for HCV patients, usually afraid of being limited in their personal and professional lives. However, there was evidence suggesting that ribavirin added to interferon-free regimens may have a small but significant impairing effect on quality of life, a result also found in interferon-alpha-based regimen when ribavirin is added (Hassanein et al., 2004). Results also showed that the use of triple therapy involving PR and simeprevir, appears to have an equivalent negative impact on mental and physical quality of life to

that observed when administering PR alone. CHC patients indeed appear to experience a reduction in mental and physical quality of life while receiving antiviral treatment involving PR, and the addition of DAAs does not seem to alter these effects (Spiegel et al., 2005).

Evidence flowing from this review also suggests that certain baseline characteristics could predict further impact on life quality, disregarding the type of antiviral treatment regimen. Supporting previous data (Dan et al., 2006; Bezemer et al., 2012; Mandorfer et al., 2014) several baseline factors have been associated to HRQL impairment in CHC patients (i.e. unemployment, number of comorbidities, cirrhosis, and history of depression, anxiety, and fatigue disorder). During DAA plus ribavirin regimens (Vera-Llonch et al., 2013; Jacobson et al., 2013[a,b]; Younossi et al., 2015), being female, older age, and history of depression were associated with lower quality of life scores at baseline; these risk factors were also found in PR-based regimens (Dan et al., 2006; Hollander et al., 2006; Bezemer et al., 2012; Mandorfer et al., 2014). During triple therapy (PR combined with DAA), low baseline scores, older age, anemia, and treatment discontinuation were also identified as risk factors for life quality impairment, findings similar to what has also been described earlier with PR treatment (Sinakos et al., 2010; Bezemer et al., 2012; Udina et al., 2012; Mandorfer et al., 2014). Moreover, at the end of treatment, these triple therapies were related to poor quality of life and significant adverse events. At post-treatment follow-up, treatment non-response was associated with life quality impairment irrespectively of any treatment combinations a finding in line with

earlier research involving classical PR treatment (Spiegel et al., 2005; Brok et al., 2005; Daltro-Oliveira et al., 2013).

With regard to the use of new antiviral treatments, it seems that the assessment of HRQL will still be important for those patients more vulnerable for quality of life impairment, being those with baseline risk factors. Clinicians and researchers are encouraged to assess HRQL in depth in those CHC patients, using a validated tool such as the *EQ-5D* or the *SF-36*. These tools offer the possibility to objectively assess the most important areas in the mental and physical well being from the patients' perspective, and monitor life quality over the course of any antiviral regimen. These tools also would facilitate the interpretation of results and comparison across studies, as was intended in this review (Sullivan et al., 2006).

In summary

The review has found a minimal impact on the quality of life of treatment with DAA in patients with chronic hepatitis. Nevertheless, the relationship between baseline risk factors and quality of life in patients with chronic hepatitis C treated with DAA has not yet been studied in depth. The use of any DAA regimen with ribavirin may decrease mental and physical life quality. Female gender, older age, and history of depression, anxiety, fatigue, or insomnia seem to be baseline risk factors associated to HRQL impairment. Any combination of DAA with PR seems to greatly impair mental and physical life quality of CHC patients similar to what has been observed in PR treatment. Treatment response

remains being an important risk factor for improve quality of live in patients with CHC, supporting the use of new treatments with DAA given its high response rate.

Individualized management of psychological and physical health assessing possible risk factors will provide the best care for CHC patients, regardless whether antiviral treatment is administered.

Conflicts of Interest XF has received grant support from Abbvie and has acted as advisor for Gilead, Jansen and Abbvie. The rest of the authors declare that they have no conflict of interest.

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REFERENCES

* References marked with an asterisk indicate studies included in systematic review.
** References marked with two asterisks indicate studies included in meta-analysis.

[Anonymous]. Cross design synthetis: a new strategy for studying clinical outcomes. *Lancet* 1996;320:944-946.

Adinolfi LE, Nevola R, Lus G, Restivo L, Guerrera B, Romano C, et al. Chronic hepatitis C virus infection and neurological and psychiatric disorders: An overview. *World J Gastroenterol* 2015;21:2269-80.

Alonso J, Prieto L, Antó JM. The Spanish version of the SF-36 Health Survey (the SF-36 health questionnaire): an instrument for measuring clinical results. *Medicina clínica* 1995;104:771–6.

Arora S, O'Brien C, Zeuzem S. Treatment of chronic hepatitis C patients with persistently normal alanine aminotransferase levels with the combination of peginterferon α-2a (40 kDa) plus ribavirin: Impact on health- related quality of life. *J Gastroenterol Hepatol* 2006;21:406–12.

Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50:1088-101.

Bezemer G, Van Gool AR, Verheij-Hart E, Hansen BE, Lurie Y, Esteban JI, Knegt RJ. Long-term effects of treatment and response in patients with chronic hepatitis C on quality of life. An international, multicenter, randomized, controlled study. *BMC Gastroenterology* 2012;12:11.

Brok J, Gluud LL, Gluud C. Effects of Adding Ribavirin to Interferon to Treat Chronic Hepatitis C Infection. A Systematic Review and Meta-analysis of Randomized Trials. *Arch Intern Med* 2005;165:2206-12.

Bronowicki JP, Ouzan D, Asselah T, Desmorat H, Zarski JP, Foucher J, et al. Effect of ribavirin in genotype 1 patients with hepatitis C responding to pegylated interferon alfa-2a plus ribavirin. *Gastroenterology*, 2006;131:1040-8.

Capuron L, Pagnoni G, Drake DF, Woolwine BJ, Spivey JR, Crowe RJ, et al. Dopaminergic mechanisms of reduced basal ganglia responses to hedonic reward during interferon alfa administration. *Arch Gen Psychiatry 2012*;69:1044-53.

Carrión JA, Gonzalez-Colominas E, García-Retortillo M, Cañete N, Cirera I, Coll S, et al. A multidisciplinary support programme increases the efficiency of pegylated interferon alfa-2a and ribavirin in hepatitis C. *J Hepatol* 2013;59:926-33.

Daltro-Oliveira R, Morais-de-Jesus M, Pettersen KM, Paraná R, & Quarantini LC. Impact of sustained virologic response on quality of life in chronic HVC carriers. *Ann Hepatol* 2013;12:399-407.

Dan AA, Martin LM, Crone C. Depression, anemia and health-related quality of life in chronic hepatitis C. *J Hepatol* 2006;4:491-8.

Dirks M, Pflugrad H, Haag K, Tillmann HL, Wedemeyer H, Arvanitis D, et al. Persistent neuropsychiatric impairment in HCV patients despite clearance of the virus?!. *J Viral Hepat* 2017 Jan 24. doi: 10.1111/jvh.12674. [Epub ahead of print]

European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C 2014. *J Hepatol* 2014;61:373–95.

Fabregas BC, Moura AS, Marciano RC, Carmo RA, Teixeira AL. Clinical management of a patient with drug dependence who attempted suicide while receiving peginterferon therapy for chronic hepatitis C. *Braz J Infect Dis* 2009;13:387-90.

**Fried MW, Buti M, Dore GJ, Robert Flisiak R, Ferenci P, Jacobson I, et al. Once-Daily Simeprevir (TMC435) With Pegylated Interferon and Ribavirin in Treatment-Naïve Genotype 1 Hepatitis C: The Randomized PILLAR Study. Hepatology 2013;58:1918-29.

Guyatt GH, Feeny DH, Patrick D. Measuring Health-Related Quality of Life. *Ann Intern Med* 1993;118:622-929.

Hassanein T, Cooksley G, Sulkowski M, Smith C, Marinos G, Lai MY, et al. The impact of peginterferon alfa-2a plus ribavirin combination therapy on health-related quality of life in chronic hepatitis C. *J Hepatol* 2004;40:675–81.

Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1 [updated September 2008].* The Cochrane Collaboration, 2008. http://www.cochrane-handbook.org (accessed Nov 5, 2016)

Hoofnagle JH, Mullen KD, Jones DB, Rustgi V, Di Bisceglie A, Peters M, et al. Treatment of chronic non-A, non-B hepatitis with recombinant human alpha interferon. A preliminary report. *N Engl J Med* 1986;315(25):1575-78.

*Jacobson IM[(a,b)], Gordon SC, Kowdley KV. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Eng J Med* 2013;368:1867-77.

Johnston BC, Patrick DL, Busse JW, da Costa BR, Schünemann JH, Guyatt, GH. Patient-reported outcomes in meta-analyses - Part 1: assessing risk of bias and combining outcomes. *Health Rel Qual Outc* 2013;11:109.

Lauer GM, Walker BD. Hepatitis C virus infection. *N Engl J Med* 2001;345:41-52.

*Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, et al. Sofosbuvir for previously untreated chronic hepatitis c infection. *N Engl J Med* 2013;368:1878-87.

Le, Q. A., Doctor, J. N., Zoellner, L. A., Feeny, N. C. Minimal clinically important differences for the EQ-5D and QWB-SA in post-traumatic stress disorder (PTSD): results from a doubly randomized preference trial (DRPT). *Health Qual Life Outc* 2013;11:1-9.

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009;6:e1000100.

Mandorfer M, Payer BA, Scheiner BA, Breitenecker F, Aichelburg MC, Grabmeier-Pfistershammer K, et al. Health-related quality of life and severity of fatigue in HIV/HCV co-infected patients before, during, and after antiviral therapy with pegylated interferon plus ribavirin. *Liver Int* 2014;34:69-77.

Martin-Santos R, Díez-Quevedo C, Castellví P, Navinés R, Miquel M, Masnou M, et al. De novo depression and anxiety disorders and influence on adherence during peginterferon-alpha-2a and ribavirin treatment in patients with hepatitis C. *Aliment Pharmacol Therapeutics* 2008;27:257-65.

Martin-Santos R, Egmond E, Cavero M, Mariño Z, Subira S, Navines R, Valdes M. Chronic hepatitis C, depression and gender: a state of art. *Advances in Dual Diagnosis*, 2015;8:193-210.

Messina JP, Humphreys I, Flaxman A, Brown A, Cooke GS, Pybus O, et al. Global distribution and prevalence of hepatitis c virus genotypes. *Hepatology* 2015;61:77-87.

Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. *Hepatology* 2013;57,1333-42.

Muhlberger N, Schwarzer R, Lettmeier B, Sroczynski G, Zeuzem S, Siebert U. HCV-related burden of disease in Europe: a systematic assessment of incidence, prevalence, morbidity, and mortality. *BMC Public Health* 2009;9:34.

Navinés R, Castellví P, Moreno-España J, Gimenez D, Udina M, Cañizares S, et al. Depressive and anxiety disorders in chronic hepatitis C patients: reliability and validity of the Patient Health Questionnaire. *J Affect Disord* 2012;138:343-51.

Ren XS, Amick B III, Zhou L, Gandek B. Translation and psychometric evaluation of a Chinese version of the SF-36 Health Survey in the United States. *J Clin Epidemiol* 1998;51:1129–38.

Ringash J, O'Sullivan B, Bezjak A, Redelmeier DA. Interpreting clinically significant changes in patient-reported outcomes. *Cancer* 2007;110:196-202.

Rowan PJ, Bhulani N. Psychosocial assessment and monitoring in the new era of non-interferon-alpha hepatitis C virus treatments. *World J Hepatol* 2015;7:2209-13.

Scalone L, Fagiuoli S, Ciampichini R, Gardini I, Bruno R, Pasulo L, Mantovani LG. The societal burden of chronic liver diseases: results from the COME study. *BMJ Open Gastroenterology* 2014;2:e000025.

**Scott J, Gilles L, Fu M, Brohan E, Panter C, Arbuckle R, et al. Simeprevir added to peginterferon and ribavirin lessens time with fatigue, depressive symptoms and functional limitations in patients with chronic hepatitis C compared with peginterferon and ribavirin: results from 1161 patients in the QUEST-1, QUEST-2 and PROMISE studies. *J Viral Hepat* 2015;22:639–50.

Sinakos E, Gigi E, Lalla T, Bellou A, Sykja A, Orphanou E, et al. Health-related quality of life in Greek chronic hepatitis C patients during pegylated interferon and ribavirin treatment. *Hippokratia* 2010;14:122-5.

Spiegel BM, Younossi ZM, Hays RD, Revicki D, Robbins S, Kanwal F. Impact of hepatitis C on health related quality of life: a systematic review and quantitative assessment. *Hepatology* 2005;41:790-800.

Sullivan PW, Ghushchyan V. Preference-based EQ-5D index scores for chronic conditions in the United States. *Med Decis Making* 2006;26:410-20.

The EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199–208.

Udina M, Castellví P, Moreno-España J, Navinés R, Valdés M, Forns X, et al. Interferon-induced depression in chronic hepatitis C: a systematic review and meta-analysis. *J Clin Psychiatr* 2012;73:1128-38.

Van Hout B, Janssen MF, Feng Y, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value in Health* 2012;15(5):708-15.

*Vera-Llonch M, Martin M, Aggarwal J, Donepudi M, Bayliss M, Goss T, Younossi Z. Health-related quality of life in genotype 1 treatment-naïvechronic hepatitis C patients receiving telaprevir combination treatment in the ADVANCE study. *Aliment Pharmacol Ther* 2013;38:124-133.

Walker DR, Pedrosa MC, Manthena SR, Patel N, & Marx SE. Early view of the effectiveness of new direct-acting antiviral (DAA) regimens in patients with Hepatitis C Virus (HCV). *Adv Ther* 2015;32(11):1117-27.

Ware JE, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): I. Conceptual framework and item selection. *Med Care* 1992;30:473-83.

Younossi ZM, Kallman J, Kincaid J. The effects of HCV infection and management on health-related quality of life. *Hepatology* 2007;45:806-16.

**Younossi ZM[(b)], Stepanova M, Pol S, Bronowicki J, Carrieri MP, Bourlie M. The impact of ledipasvir/sofosbuvir on patient-reported outcomes in cirrhotic patients with chronic hepatitis C: the SIRIUS study. *Liver Int* 2016; 36: 42–8.

*Younossi ZM[(a)], Stepanova M, Feld J, Zeuzem S, Jacobson I, Agarwal K, et al. Sofosbuvir/velpatasvir improves patient-reported outcomes in HCV patients: Results from ASTRAL-1 placebo-controlled trial. *J Hepatol* 2016;65(1):33-9.

**Younossi ZM, Stepanova M, Marcellin P, Afdhal N, Kowdley KV, Zeuzem S, Hunt S. Treatment with ledipasvir and sofosbuvir improves patient-reported outcomes: results from the ION-1, -2, and -3 clinical trials. Hepatology 2015;61:1798-808.

*Younossi ZM, Stepanova M, Zeuzem S, Dusheiko G, Esteban R, Hezode C, Hunt SL. Patient-reported outcomes assessment in chronic hepatitis C treated with sofosbuvir and ribavirin: the VALENCE study. *J Hepatol* 2014;61:228-34.

**Zeuzem S, Berg T, Gane E, Ferenci P, Foster GR, Fried MW, et al. Simeprevir increases rate of sustained virologic response among treatment-experienced patients with HCV genotype-1 infection: a phase IIb trial. *Gastroenterology* 2014;146:430–41.

CHAPTER 4

Study II

Real-life impact of HCV eradication after direct-acting antiviral treatment on quality of life and incidence of psychiatric events during treatment

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ABSTRACT

Objective

To study health-related quality of life (HRQL) and incidence of depression in hepatitis C virus (HCV) patients treated with direct-acting antivirals (DAAs).

Methods

A real-life cohort of HCV patients was eliged to receive DAA regimens. Patients were assessed at baseline, 4 weeks, end of treatment (EOT), and at 12 (12AT) and 48 weeks (48AT) post-treatment, for HRQL (EQ-5D), depression (PHQ-9), and irritability/fatigue (VAS). For longitudinal analysis, linear mixed models were used. Cumulative incidence of depression was calculated during DAA treatment. ANCOVA analysis was performed for associated risk factors.

Results

Ninety-two HCV patients had a mean age of 60.9±10.8, 54.3% were men, 70.7% had genotype 1b, 68.4% presented liver cirrhosis, and 72.8% received ribavirin co-administration. Cumulative incidence during DAA treatment for major depression was 13.7% (95%CI: 5.7-26.3), and any depressive disorder 51% (95%CI: 36.6-65.2). Baseline PHQ-9 score predicted incident major depression (p=0.002). We could not exclude significant changes in EQ-VAS scores during treatment (67.2±20.3), EOT (71.3±19.6), 12AT (76.1±18.7) or 48AT(76.7±15) related to baseline, nor between (de)compensated cirrhotics, after controlling for other variables. EQ-5D pain/discomfort dimension was

lower in decompensated cirrhotic patients (p=0.045). SVR was achieved in 98.9%. Strengths include longitudinal naturalistic cohort design, and blinding to disease progression; limitations are sample size, and non-inclusion of HIV co-infected patients, which did not allow for generalizing results. Also, the HRQL instrument used may fail to include HCV disease-specific factors.

Conclusion

Results suggest that physical and mental health continues to play an important factor in wellbeing of more advanced HCV patients receiving DAAs.

1. INTRODUCTION

With recent estimates equating to around 71 million viremic people (World Health Organization [WHO], 2017), hepatitis C virus (HCV) infection is one of the world's most important chronic illnesses. Known as a major cause of chronic liver disease, it still constitutes one of the main reasons for liver transplantation in most developed countries (Blachier et al., 2013). HCV infection remains as chronic hepatitis C (CHC) in around 80% of cases, and progresses towards liver cirrhosis in one in five patients within 20 to 50 years after initial infection, of which 5% to 10% will develop hepatocellular carcinoma or liver decompensation (Burak & Lee, 2000; Teo & Hayes, 2004; Fischer et al., 2004). Besides affecting the liver, CHC has been recognized as a systemic disease with many extrahepatic manifestations (Cacoub et al., 2016) and increased morbility and mortality. Regarding the psychological-psychiatric dominium, HCV infection has been associated with significant comorbidities, including feelings of anhedonia, depression (Dwight et al., 2000; Dantzer et al., 2008; Navinés et al., 2012; Martin-Santos et al., 2015; Yarlott, Heald, and Forton, 2017), irritability, anxiety, fatigue, and sleep alterations (Kallman et al., 2007), increased sensitivity to pain (Monaco et al., 2012), loss of appetite, or anorexia (Barkhuizen et al., 1999; Lim et al., 2006; Adinolfi et al., 2015). The sum of these disease-related hepatic and extrahepatic symptoms may substantially and deleteriously impact physical and mental health-related quality of life (HRQL) of patients (Younossi et al., 2007; Hsu et al., 2009), and may even be worse in more advanced stages of hepatic disease with physical

deterioration (Younossi et al., 2001; Dan et al., 2006; Younossi et al., 2007; Teuber et al., 2008; Barboza et al., 2016).

HCV may be definitively cured using antiviral treatment. Until some years ago, antiviral treatment involved a weekly injection of pegylated interferon-alpha (IFNa) together with daily weight-based doses of ribavirin (RBV) for 24 to 48 weeks. This regimen was known to cause a wide range of adverse events (AEs) (Younossi et al., 2007) with a secondarily high rate of treatment discontinuations. Among the main AEs, depression was detected in up to 30% of patients (Udina et al., 2012), further affecting physical and mental HRQL (Spiegel et al., 2005; Daltro-Oliveira et al., 2013). The profound knowledge of the HCV viral cycle in the last decade has lead to the development of direct-acting antiviral agents (DAA), with direct inhibitory effect over the viral non-structural proteins. With the use of all-oral DAA combinations, with minimal AEs and high potency, short and long-term prognosis for HCV-infected patients has significantly improved. Besides achieving sustained virological response (SVR) rates over 95% in most patients, and good safety profiles, DAA therapy appears to have a reduced impact on physical and mental HRQL (Dusheiko et al., 2017; Flisiak et al., 2017). Although evidence through naturalistic studies is still sparse, a profound evaluation of the psychiatric sphere is crucial in this population highly susceptible to both physical and mental impairment.

A number of instruments exists that succesfully capture psychiatric symptoms in patient populations. The Patient Health Questionnaire (PHQ) was the first instrument to cover a wide range of psychopathological conditions, and to diagnose specific disorders using the diagnostic criteria from the DSM-IV

(Spitzer et al., 1999). This self-assessment tool measures both threshold disorders (e.g. major depressive disorder), and subthreshold disorders (e.g. other depressive disorder). The PHQ has been validated in primary care (Kroenke et al., 2010; Zuithoff et al., 2010) and in medical and surgical inpatients (Diez-Quevedo et al., 2001), and has shown good diagnostic validity. The depression module has been widely validated across several medical conditions (Dbouk et al., 2008; Kroenke et al., 2010; Sockalingam et al., 2011), including CHC patients (Navinés et al., 2012).

The assessment of quality of life has increased during the last 30 years as a significant outcome indicator for patients with chronic diseases and treatments, as it can quantify the impact of a disease and its treatment on the individual. HRQL is often used to measure self-assessed personal health status that refers to aspects dominated or significantly influenced by mental or physical wellbeing (Johnston et al., 2013). The EuroQol 5 Dimensions (EQ-5D) questionnaire (EuroQol Group, 1990) is a self-assessment tool consisting of five dimension scales assessing different aspects of HRQL on a Likert scale ranging from 1 (e.g. “I am not able to walk”) to 5 (“I have no problems to walk”), and a visual analog scale (EQ-VAS) measuring general HRQL scoring from 0 (“worse than death”) to 100 (“best health state possible”). EQ-5D has increasingly been used to measure HRQL in both the general population (Lubetkin et al., 2005; Sun et al., 2014) and chronic illnesses such as liver disease (Oemar and Janssen, 2013). Its construct validity, reliability, and responsiveness of the have widely been described (Hurst et al., 1997; Szende et al., 2004; Sullivan et al., 2006; van Hout et al., 2012). Furthermore, Visual Analog Scale (VAS) is a common tool which may be used to measure the level

of fatigue or irritability a person experiences, on a scale ranging from 0 ("worse than death") to 100 ("best health state possible)".

Due to the recency of the introduction of DAAs, research assessing HRQL and associated risk factors, using a naturalistic approach, is still limited. Furthermore, current treatment with highly effective DAAs also offers a unique opportunity to evaluate different aspects from depression and quality of life from a multidisciplinary approach in a real-life cohort of HCV patients, and to assess the potential impact on physical and mental dimensions, during and after short and long post-treatment follow-up.

2. PATIENTS AND METHODS

This was a prospective, unicentric study, evaluating the impact of viral eradication by DAAs on quality of life and psychiatric domains. Whenever a psychiatric disorder was detected along the study, an independent specialized intervention by psychiatrists (supportive therapy and/or serotonin selective reuptake inhibitors treatment) was offered. This study was approved by the Ethical Research Committee of the Institution. All patients gave their specific informed written consent before entering the study.

2.1. Patients

All consecutive HCV-infected patients starting all-oral DAA antiviral therapy in the Liver Unit in Hospital Clinic Barcelona from June to December 2015, not enrolled in other clinical studies, were considered for the study. All patients came from the catchment area of the general teaching hospital, and area of

average socio-economic level. Demographic, clinical, and virological data at baseline, treatment, and follow-up were collected. Liver fibrosis was assessed by means of transient elastography (TE) and expressed in kilopascals (KPa): F0-1 (<7.8Kpa), F2 (7.8-9.4Kpa), F3 (9.5-13.9Kpa) and F4 or cirrhosis (≥14kPa). Cirrhosis was also established independently of TE by liver biopsy, clinical evidence (such as presence of esophageal varices or liver decompensation), or the presence of ultrasonographical criteria (liver surface nodularity, enlarged spleen or portal vein diameter>12 mm). Patients with liver cirrhosis were screened for the presence of hepatocellular carcinoma every 6 months as per clinical practice. Three groups of patients were considered for general comparisons: non-cirrhotic patients versus (de)compensated cirrhotic patients.

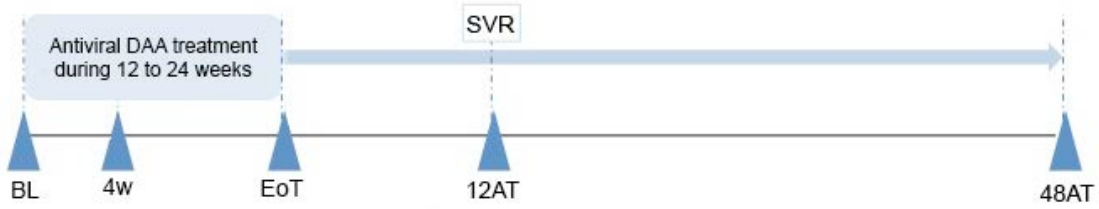
2.2. Antiviral treatment

The DAA combination, duration of therapy (12 or 24 weeks) and the use of RBV was planned at the discretion of the treating physician, in accordance with the national and international recommendations at that time (Burra et al., 2015). RBV was weight-based and considered mainly in those patients with negative predictors for virological failure. Access to oral HCV therapy at that moment in Spain was restricted to patients with advanced liver disease (grade 3 of fibrosis [F3] or cirrhosis) or those with mild liver disease (F0 to 2) but with concomitant extrahepatic manifestations (i.e. cryoglobulinemic vasculitis). Sustained virological response (SVR) was defined as undetectable HCV-RNA 12 weeks after the end of treatment. Moreover, a post-treatment follow-up was extended until 48 weeks after DAA.

2.3. Clinical and psychiatric assessment

At baseline, family and personal history of mood disorders was recorded. All enrolled patients were additionally screened for the presence of current depressive symptoms by means of the self-administered PHQ-9 questionnaire. This questionnaire was again performed along DAA therapy at two points [at four weeks (4w) and end of treatment (EOT)], as well as at 12 (12AT) and 48 (48AT) weeks of post-treatment follow-up. Importantly, all questionnaires (PHQ-9; fatigue and irritability VAS, EQ-VAS, EQ-5D dimension and index scores) were performed before each medical visit and blinded to virological results, in order to avoid any influence of results. See Figure 1 for treatment and post-treatment follow-up course.

Figure 1. Assessment points during and after antiviral DAA treatment.



Abbreviations: 4w = four weeks of treatment; 12AT = 12 weeks after treatment cessation; 48AT = 48 weeks after treatment cessation; BL = baseline, DAA = direct-acting antiviral agents; EoT = end of treatment; SVR = sustained virological response.

The depression module (PHQ-9) (Spitzer et al., 1999) has nine items with four response options rated from 0 to 3 (“Not at all”, “Several days”, “More than half the days” and “Nearly every day”). A total score for the depression module ranging from 0 to 4 indicates no depressive symptoms, a total score of 5 to 9 indicates mild depressive symptoms, and a total score of 9 or more suggests major depression. Furthermore, both the degree of fatigue and irritability were

assessed using a VAS, where scores range from 0 (“not tired” or “not irritated”) to 100 (“extremely tired” or “extremely irritated”), and are measured in millimeters on the 10 cm vertical line.

Independent psychiatric intervention was planned for all patients with positive symptoms of depression (cognitive therapy and/or antidepressant drugs).

2.4. Quality of life assessment

HRQL data were collected using the EQ-5D-5L instrument (EuroQol Group, 1990; Herdman et al., 2011), which is a validated self-assessment tool (Ramos-Goñi, Errea, Rivero-Arias, Cabasés, & Pinto, 2017) comprised by five dimensions (i.e. “Mobility”, “Self-Care”, “Usual Activities”, “Pain/Discomfort”, and “Anxiety/Depression”, each having five levels, on a Likert scale ranging from 1 to 5 (indicating best health, e.g. “I have no problems to walk”, to worst health, e.g. “I am not able to walk”, respectively). The results are expressed as a percentage of each dimension after dichotomizing (i.e. “no symptoms”/“any symptoms”). Also, an index score may be calculated using an algorithm with scores ranging from 0 to 1 (also ranging from “worse than death” to “best health state possible”) (Leidl & Reitmeir, 2011). Moreover, EQ-5D contains a visual analogue scale (EQ-VAS) to self-scoring from 0 (“worse than death”) to 100 (“best health state possible”).

2.5. Statistical analysis

Baseline characteristics of HCV patients are presented using mean and standard deviation (SD) for numeric variables and both absolute and relative

frequencies for categorical variables. In addition, a description of the follow-up data of the PHQ-9, fatigue VAS, irritability VAS, and EQ-5D scores, by means of the mean and SD are given.

The prevalence of major depression (PHQ $\geq$ 10) and mild depressive symptomatology (PHQ $\geq$ 5-9) at baseline was estimated among included patients with and without cirrhosis. On the other hand, the cumulative incidence of major depression and any depression symptomatology (both mild depressive symptoms and major depression) during DAA treatment were estimated in those patients without any depressive symptoms at baseline (PHQ $\leq$ 4). The cumulative incidence of major depression in those patients during the DAA treatment was also studied. The computation of all of the corresponding 95% confidence intervals was based on the binomial distribution. Moreover, multivariate logistic regression models were fitted to study possible risk factors for the incidence of depression.

For the longitudinal analysis of the changes from baseline in PHQ-9 score, fatigue VAS and irritability VAS and EQ-VAS scores, linear mixed models were used that included the variables of interest (cirrhosis and no cirrhosis), time under treatment, gender, age, history of mood disorder, history of alcohol, and comorbidity. All models were adjusted for the respective baseline scores. The same models were replacing the diagnosis of cirrhosis by the type of cirrhosis (non-cirrhotic, compensated cirrhotic, and decompensated cirrhotic group).

The statistical analyses were carried out using the free software environment for statistical computing R (The R Foundation for Statistical

Computing; Vienna, Austria), version 3.2.2. Statistical significance was set at 0.05.

3. RESULTS

3.1. Patient characteristics

Ninety-three subjects were asked to participate in the study and all of them agreed. One patient did not start antiviral treatment and was therefore not evaluable. Baseline characteristics of the final cohort (n=92) are depicted in Table 1. The majority of patients were male (54.3%), with a median age of 60.9, and were infected with HCV subgenotype 1b (70.7%). 68.5% of the cohort presented liver cirrhosis, 23.2% of whom had presented previous or current liver decompensation. Most patients received concomitant administration of RBV (72.8%), and were treated for 12 weeks (81.5%). Table 1 also shows the characteristics of the all sample and divided by the presence (N = 63) or absence (N =29) of liver cirrhosis. Seventy-nine patients (85.9%) were evaluated at 48AT. All 92 patients were assessed at 12AT, and 79 (85.9%) of these patients were again evaluated at 48AT.

Regarding baseline psychiatric symptoms and history, of the total sample, one in four subjects (25%) had a family history of depression and one in three had a personal history of depression (36.6%). Moreover, one in six patients were receiving antidepressant therapy (15.2%) at DAA treatment initiation. Both, family (31% versus 20.3%) and personal history of depression (48.3% versus 31.7%) were higher among non-cirrhotic patients.

Table 1. Baseline characteristics of the cohort sample (N=92).

	Total sample N (%)/mean (SD)(range) N= 92 (100)	**Cirrhotic** N (%)/mean (SD)(range) N= 63 (68.5)	**Non cirrhotic** N (%)/mean (SD)(range) N= 29 (31.5)
Age, years	60.9 (10.8) (53 - 68)	63.1 (9.7) (26 - 80)	56.9 (11.5) 25 - 78
Gender (male)	50 (54.3)	39 (61.9)	11 (37.9)
HCV genotype			
1a	15 (16.3)	8 (12.7)	7 (24.1)
1b	65 (70.7)	46 (73.0)	19 (65.5)
2	3 (3.3)	3 (4.8)	0 (0)
3	4 (4.3)	2 (3.2)	2 (6.9)
4	5 (5.4)	4 (6.3)	1 (3.4)
Previous non-responders	51 (55.4)	36 (61.1)	15 (45.4)
Transient elastrography (TE) (KPa)	14.3 (4.3-75)	19.7 (6-75)	10.5 (4.3-16.9)
TE ≥21 KPa	26 (28.3)	26 (28.3)	0 (0)
Decompensation	21 (33.3)	21 (23.2)	--
Child-Pugh Score (median)	6 (5-9)	6 (5-9)	--
A	--	46 (73)	--
B	--	17 (27)	--
Albumin (g/dL)	42 (30-48)	41 (30 - 48)	44 (34 - 47)
Platelets (10^9/mL)	124 (36-363)	100 (36 - 229)	170 (71 - 363)
MELD score	--	9 (7 - 12)	--
Baseline HB≤10 g/dl	4 (4.3)	3 (75)	1 (25)
DAA therapy			
SOF/LDV	44 (47.8)	38 (86.4)	6 (13.6)
2D/3D	40 (43.5)	20 (50)	20 (50)
SOF/DCV	4 (4.3)	2 (50)	2 (50)
Others	4 (4.3)	3 (75)	1 (25)
Use of RBV	67 (72.8)	55 (82.1)	12 (17.9)
Treatment duration (12 weeks)	75 (81.5)	47 (74.6)	28 (96.6)
Relevant comorbidity*	55 (68.7)	63 (68.5)	29 (31.5)
Family history of depression	23 (25)	14 (20.3)	9 (31.0)
Personal history of depression	34 (36.6)	20 (31.7)	14 (48.3)
Personal history drug/alcohol abuse	25 (26.9)	20 (31.7)	2 (7)
PHQ-9 mild depressive symptoms	19 (20.9)	10 (16.1)	9 (31.0)
PHQ-9 major depression	19 (20.9)	15 (24.2)	4 (13.8)
Fatigue VAS	50 (25.4)	49.5 (24.7)	44.6 (26.9)
Irritability VAS	37.5 (24.1)	37.4 (23.7)	37.7 (25.1)
EQ-VAS	66.7 (19.9)	65.5 (21.1)	69.2 (17.2)
EQ-5D index	0.56	0.5	0.6
EQ-5D dimension			
% reporting “any symptoms”			
Mobility	23 (25)	54 (33.9)	3 (10.3)
Self-care	19 (20.7)	20 (32)	2 (6)
Usual activities	32 (29.4)	21 (33.9)	4 (13.8)
Pain / discomfort	51 (46.9)	33 (52.5)	11 (38)
Anxiety / depression	35 (38)	25 (39.7)	10 (34.5)

Abbreviations: EQ-5D = EuroQol 5 Dimensions questionnaire; EQ-VAS = EuroQol Visual Analog Scale; VAS = Visual Analogue Scale; NA = not available; EH = hepatic encephalopathy; MELD = model for end stage liver disease; HB = haemoglobin; DAA = direct acting antivirals; SOF = sofosbuvir; LDV = ledipasvir ; 2D/3D paritaprevir/ombitasvir/ritonavir with or without dasabuvir; DCV = daclatasvir; RBV = ribavirin.

* Relevant comorbility included: ischemic cardiovascular events and arrithmias, current or previous history of neoplastic disease, cryoglobulinemic vasculitis, EPOC, or any disease potentially impacting daily activities.

Around one in five patients showed major depression (20.9%) at baseline, and a similar number of patients showed mild depressive symptoms (20.9%) (see Figure 2). The baseline prevalence of major depression was higher in the cirrhotic group (24.2%, versus 13.8% in the non-cirrhotic group), whereas non-cirrhotic patients had a higher rate of mild depressive symptoms (31%) compared to cirrhotic patients (16.1%).

Furthermore, scores for fatigue were slightly greater in the non-cirrhotic group. However, irritability scores were similar in both groups. Concerning baseline HRQL scores (EQ-5D questionnaire), results showed a lower general EQ-VAS mean (SD) score (66.7 ± 19.9) compared to the general Spanish population of the same range of age (55-64) (Ramos-Goñi et al., 2017).

EQ-VAS and index scores were slightly lower in the (de)compensated cirrhotic patients, and more of these patients reported having symptoms, indicating more impaired HRQL in this subgroup (Ramos-Goñi et al., 2017). Table 1 shows the percentage of patients experiencing “any symptoms”, being highest in the pain/discomfort dimension, followed by anxiety/depression.

3.2. Antiviral efficacy and safety

All patients but one (91/92) achieved SVR (98.9%) after DAA treatment. Virological failure consisted on a virological relapse at FU4 occurring in a Child C cirrhotic patient treated for 24 weeks with sofobuvir/ledipasvir and RBV; this patient developed a hepatocellular carcinoma. See also Table 1.

No serious adverse events were observed during therapy. Fourteen patients (15.2%) presented anemia (Hb levels ≤ 10 g/dl) during therapy, most of them

receiving RBV as part of the antiviral therapy (9/14, 63.4%). The nadir haemoglobin during therapy was significantly lower among patients with cirrhosis (11.9 vs 12.4 in non-cirrhotics, p=0.003), related with the higher proportion of RBV administration (82% vs 41.3%). Haemoglobin decrease was mainly managed by RBV dose reductions or RBV interruption (46%), with a minority of patients requiring eritrhopoyetin administration (n=12, 13%).

3.3. Depression, fatigue, irritability, and quality of life during treatment

3.3.1. Depressive symptoms (PHQ-9)

Table 2 shows the figures of *PHQ-9 scores* at each assessment during treatment.

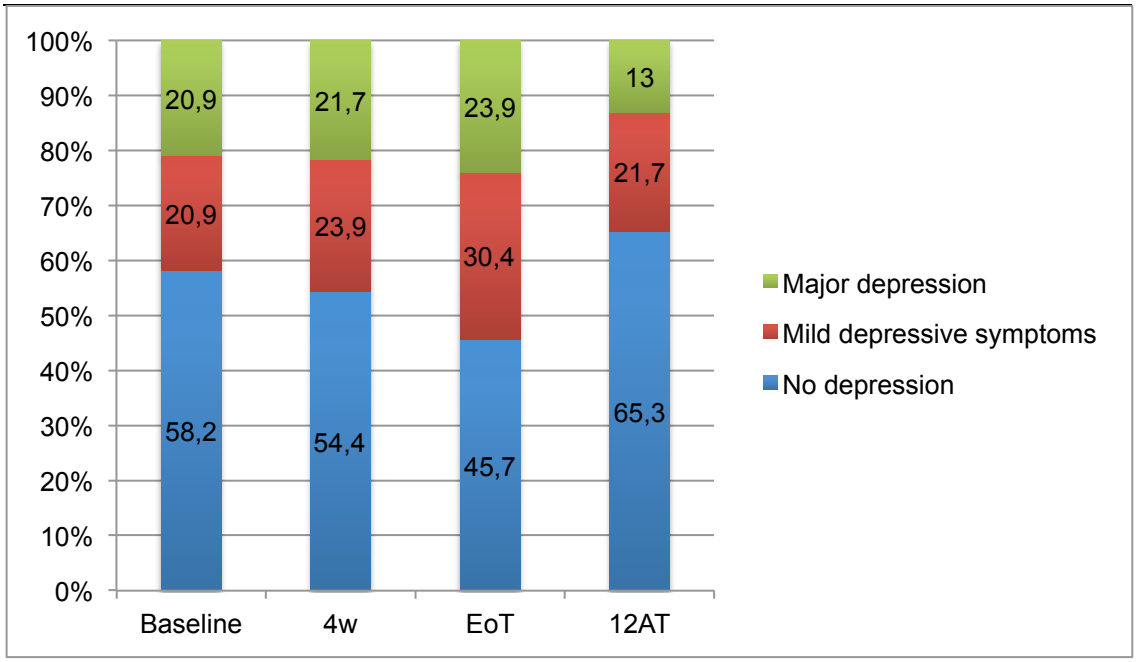
Table 2. Depression, quality of life, fatigue, and irritability, before, during, and at end of treatment, as well as at post-treatment follow-up.

	Baseline N (%)/mean (SD)	**4w** N (%)/mean (SD)	**EoT** N (%)/mean(SD)	**12AT** N (%)/M (SD)
PHQ-9 ≥ 5 to 9	19 (20.9)	22 (23.9)	28 (30.4)	20 (21.7)
PHQ-9 ≥ 10	19 (20.9)	20 (21.7)	22 (23.9)	12 (13)
Any depression	38 (41.8)	42 (45.6)	50 (54.3)	32 (34.7)
Fatigue VAS	47.3 (25.8)	45.1 (26.3)	45.4 (24.8)	36.7 (23.8)
Irritability VAS	37.1 (24.2)	36.5 (26.9)	35 (22.5)	29.8 (22.7)
EQ-5D “any problem”				
- Mobility	23 (25)	22 (23.5)	27 (32.5)	28 (31.1)
- Self-care	10 (10.9)	6 (6.9)	9 (10.8)	9 (10)
- Usual activities	25 (27.2)	27 (31)	24 (38.9)	29 (32.2)
- Pain/discomfort	43 (46.7)	37 (54)	46 (55.4)	43 (47.8)
- Anxiety/ depression	35 (38)	32 (36.8)	34 (39)	30 (34.4)
EQ-VAS	67.2 (20.3)	71.3 (19.6)	75 (15.7)	76.01 (18.7)
EQ-5D index	0.69	0.68	0.67	0.7

Abbreviations: EQ-5D = EuroQol 5 Dimensions questionnaire; EQ-VAS = EuroQol Visual Analog Scale; VAS = Visual Analogue Scale; PHQ-9= Patient Health Questionnaire; 4w= 4 weeks of treatment; EoT = end of treatment; 12AT=12 weeks after end of treatment

Figure 2 describes the prevalence of depression at each assessment time until 12AT, revealing an increase of prevalence in both mild depressive symptoms and major depression at the end of antiviral treatment.

Figure 2. Percentage of depressive symptoms (PHQ-9) before, during, at end of treatment, as well as at post-treatment follow-up.



Abbreviations: PHQ-9 = Patient Health Questionnaire; 4w = 4 weeks of treatment; EoT = end of treatment; 12AT = 12 weeks after end of treatment.

The longitudinal model for PHQ-9 summatory score differences from baseline adjusting for baseline values, age (p=0.995), gender (0.758), history of mood disorders (p=0.219), or alcohol abuse (p=0.561), comorbidity (p=0.689), ribavirin co-administration (p=0.452), and time under DAA treatment (p=0.329) did not show differences of statistical significance along the treatment, or between those patients with and without cirrhosis (p=0.472), nor between compensated (p=0.894) and decompensated cirrhotic patients (p=0.788).

3.3.2. Health-related quality of life

Table 2 shows the figures of EQ-5D scores at each time of assessment during treatment, of each dimension, index, and EQ-VAS scores.

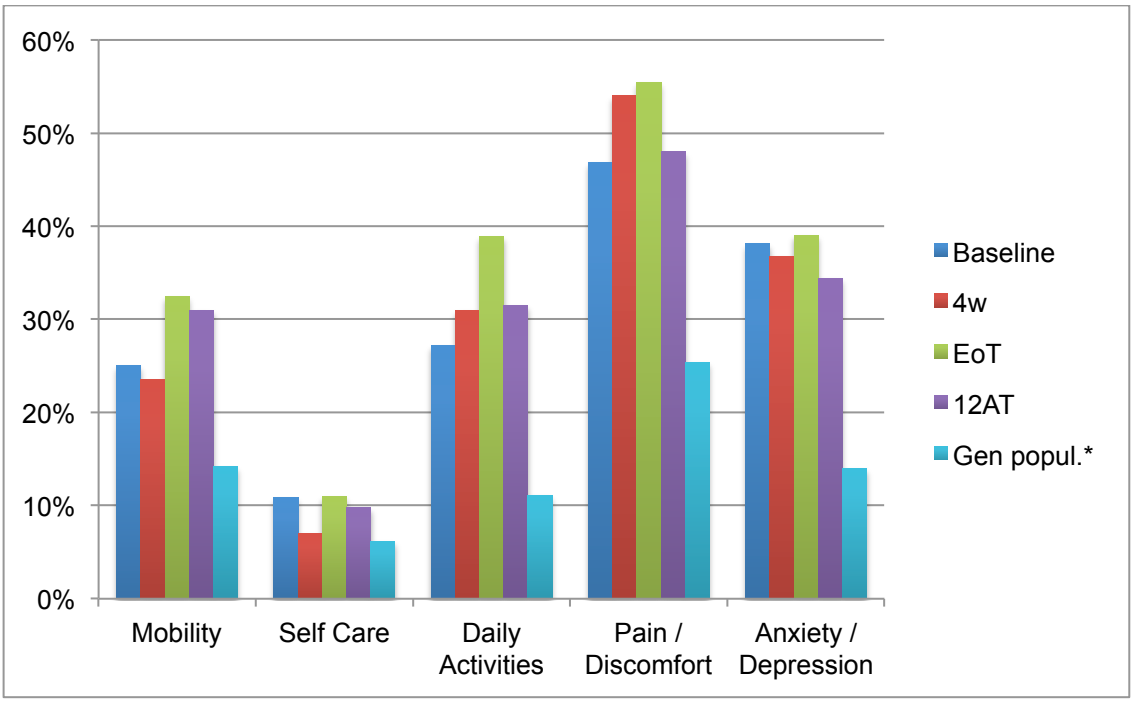
Figure 3 shows the percentage of patients experiencing “any symptoms” on the five dimension scale scores of EQ-5D (mobility”, “self-care”, “usual activities”,

"pain/discomfort", and "anxiety/depression") at the different moments of assessment. With respect to EQ-5D index score, the mean difference (MD) was calculated at 4w and EoT (12 or 24 weeks), with results showing only small changes (MD_{4wk}= -0.1, 95%CI: -0.01 to 0); and MD_{12wk}= -0.02, 95%CI: -0.02 to -0.01), respectively).

The results of the ANOVA models for the five dimension scale scores of EQ-5D over treatment are shown in Table 1 and Table 2 in the Supplementary Material (Annex 2). A significant difference was observed between decompensated cirrhotic and compensated or non-cirrhotic patients in the "pain/discomfort" (p = 0.045) dimension scale.

The longitudinal model for EQ-VAS score mean differences from baseline, adjusting for baseline values, age (p=0.681), gender (p=0.725), history of mood disorders (p=0.785), or alcohol abuse (p=0.461), comorbidity (p=0.945), and ribavirin co-administration (p=0.365), did not show statistically significant differences along the treatment, or between those patients with and without cirrhosis (p=0.472), nor between compensated (p=0.462) and decompensated cirrhotic patients (p=0.58). However, the variable for time under treatment in the linear mixed model showed a tendency for statistical significance (p=0.072).

Figure 3. Percentage of cohort patients experiencing "any problems" in each of the five EQ-5D dimensions during treatment and at 12 weeks of post-treatment follow-up.



Abbreviations: 4w = 4 weeks of treatment; EoT = end of treatment; 12AT = 12 weeks after end of treatment; gen. popul. = general population.
* Ramos-Goñi J, Errea M, Rivero-Arias O, Cabasés JM, Pinto JL. EQ-5D-5L Valuation Project for the Spanish Population 2013; A Descriptive Overview and Preliminary Results. Value in Health. 2017;15(7):A279.

3.3.3. Irritability and fatigue

Table 2 shows the results of VAS irritability and fatigue in each time of assessment during treatment. No difference was observed during the DAA treatment.

In the longitudinal model for *fatigue* scores mean differences from baseline, adjusting for baseline values, age (p=0.843), gender (p=0.451), history of mood disorders (p=0.273), or alcohol abuse (p=0.867), comorbidity (p=0.687), ribavirin co-administration, (p=0.816) and time under treatment (p=0.701), no significant differences were observed between those patients with and without cirrhosis (p=0.286), or between compensated and decompensated cirrhotic patients (p=0.348) along DAA treatment.

The longitudinal model for *irritability* scores differences from baseline, adjusting for baseline values, age (p=0.584), gender (p=0.673), history of mood disorders (p=0.321), or alcohol abuse (p=0.697), comorbidity (p=0.204), co-administration (p=0.322), and time under treatment (p=0.794) did not show statistically significant differences along the treatment, or between those patients with and without cirrhosis (p=0.472) nor between compensated and decompensated cirrhotic patients (p=0.686).

3.4. Incidence of depression during treatment and risk factors

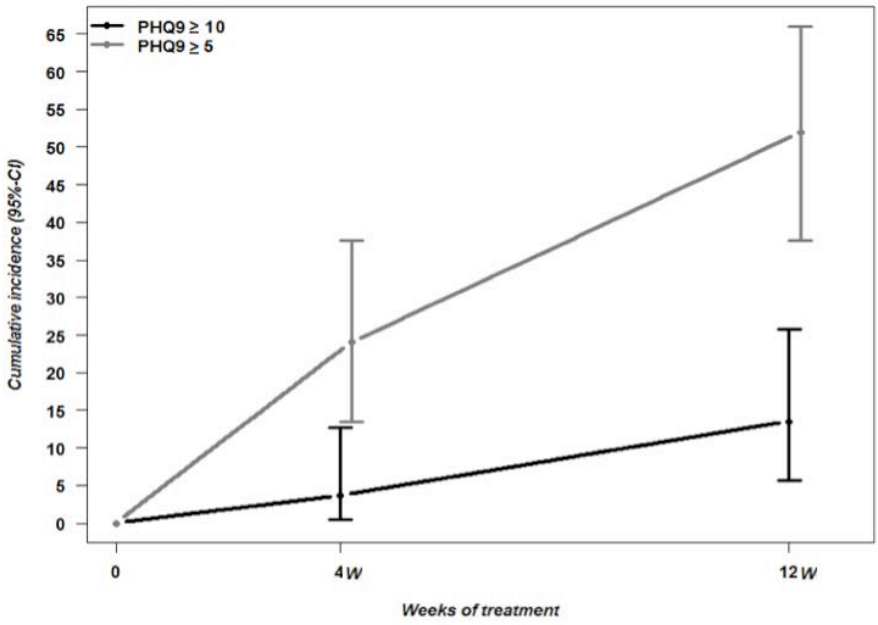
3.4.1. Cumulative incidence of depression during treatment

Figure 4 shows the cumulative incidence of depression measured by PHQ-9 in euthymic (PHQ-9 < 5) HCV patients (N=54) at baseline along the antiviral treatment. In the total sample, the cumulative incidence along the treatment for major depression was 13.7% (95%CI: 5.7 to 26.3), and for any depression (mild depressive symptoms and major depression) was 51% (95%CI: 36.6 to 65.2).

In the cirrhotic group, the cumulative incidence for major depression was 11.4% (95%CI: 3.2 to 26.7), and for any depression was 54.3% (95%CI: 36.6 to 71.2); and in the non-cirrhotic group major depression was 18.8% (95%CI: 4.0 to 45.6), and for any depression, 43.8% (95%CI: 19.8 to 70.1).

In the compensated cirrhotic group, the cumulative incidence of major depression was 11.5% (95%CI: 2.5 to 30.2); for the decompensated cirrhotic group it was 11.1% (95%CI: 0.3 to 48.2). Along the treatment, any depression was studied, in the cirrhotic group being 11.5% (95%CI: 2.4 to 30.2), which was similar in the decompensated cirrhotic group: 11.1% (95%CI: 0.3 to 38.2).

Figure 4. Cumulative incidence of depressive symptoms over course of treatment in euthymic patients at baseline (PHQ-9 score < 5).



Abbreviations: PHQ-9 = Patient Health Questionnaire 9; 4w = 4 weeks of treatment; 12w = end of treatment.

3.4.2. Associated risk factors for incidence of mild depressive symptoms and major depression during treatment

With respect to the incidence of major depression, univariate logistic regression indicated an association with history of family mood disorder (p=0.0140), PHQ-9 score (p=0.0304), and irritability score (p=0.0168). Multivariate logistic regression showed that the only predictive risk factor was PHQ-9 baseline score (p=0.0020). Also, a tendency for history of family mood disorder was observed (p=0.0924), as well as for irritability (p=0.0995).

The results of univariate analysis of the different studied baseline factors (age, gender, family and personal history of depression cirrhosis, comorbidity, RBV, PHQ-9, EQ-VAS, fatigue, and irritability scores) showed no association (p>0.05) with the incidence of any depression.

3.5. Differences in depression, fatigue, and irritability, and quality of life between HCV-infected (baseline) and cured patients (12AT)

Table 2 shows data of the variables from baseline to 12AT. The results of each of the studied models at 12AT for major depression were: Δ mean = 0.43; 95%CI: -1.62 to 2.49, p=0.676; fatigue: Δ mean = -3.25; 95%CI: -13.91 to 7.4, p=0.545; irritability: Δ mean= -7.34; 95%CI: -17.4 to 2.72, p=0.151; and EQ-VAS: Δ mean= -4.4; 95%CI= -13.03% to 4.23, p=0.313. These results showed no statistical significant differences in the total sample, between cirrhotic/non-cirrhotic, or between compensated/decompensated patients.

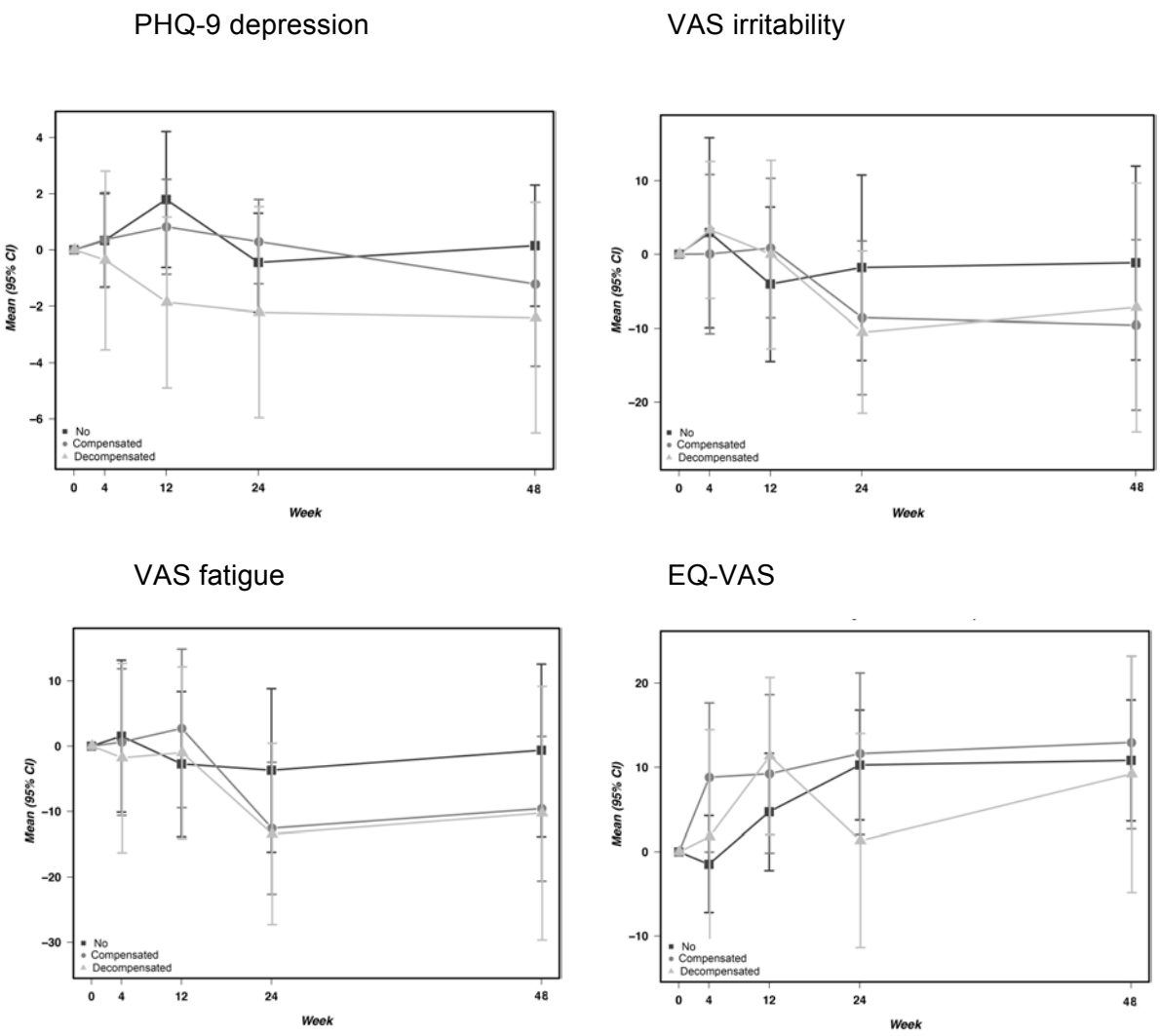
3.6. Differences in depression, fatigue, and irritability, and quality of life between HCV-infected (baseline) and long-term cured patients (48AT)

From the initial 92 HCV patients of the cohort, 79 (85.9%) were followed up until 48 weeks after end of treatment (48AT). The results of each of the studied models at 48AT for major depression were similar of those observed at 12AT, being: Δ mean = 0.06, 95%CI: -2.32 to 2.43, p=0.961; for fatigue: Δ mean = 0.38, 95%CI: -12.06 to 12.81, p=0.952; for irritability: Δ mean = -5.09, 95%CI: -15.74 to 5.57, p=0.344; and EQ-VAS score: Δ mean= -4.15; 95%CI = -11.53 to 3.24, p=0.267. No differences between (de)compensated cirrhotic and non-cirrhotic patients were observed.

Figure 5 shows the results of the ANCOVA models of the differences from baseline, and at post-treatment follow-up of the 79 patients until 48 weeks after end of treatment, for PHQ-9 (major depression and mild depressive symptoms), fatigue, irritability, and EQ-VAS (general HRQL) scores, after adjusting for baseline values, history of mood disorder, gender, and age.

Table 3 in the Supplementary Material (Annex 2) shows the data on depression, fatigue, irritability, and HRQL at baseline and 12AT as well as 48AT, in the 79 patients assessed at 48AT.

Figure 5. Differences* between (de)compensated cirrhotic and non-cirrhotic patients over DAA treatment course, and 48 weeks after treatment cessation.



Abbreviations: EQ-VAS = EuroGroup Quality of Life Questionnaire visual analogue scale; PHQ-9 = Patient Health Questionnaire 9; VAS = visual analogue scale.
* ANCOVA model adjusting for baseline values, history of mood disorder, gender, and age, including the 79 HCV patients that were assessed from baseline until 48 weeks after end of treatment.
P > 0.05 in all models.

DISCUSSION

This observational study included a real-life cohort of HCV patients receiving direct-acting antiviral therapy. Due to their novelty, no studies have been yet published that assess mood disorders in HCV patients receiving DAAs. On the other hand, current knowledge on quality of life, fatigue, and irritability outcomes mainly relies on clinical trial data (Marcellin et al., 2017). Furthermore, no real-life cohort studies up to date have assessed possible long-term effects of DAA regimens on depression, fatigue, irritability, or HRQL.

The most important findings from the present study show that depressive disorders may occur during DAA treatment in HCV patients with advanced liver disease. Nearly 14% of euthymic patients at baseline developed a major depression during DAA treatment, and 51% developed depressive symptoms. On the other hand, even though our cohort showed at baseline major impairment in general HRQL, both physical and mental life quality aspects compared to the general population, we could not discard statistical significant changes along the treatment. However, quality of life, as well as depressive symptoms, fatigue, and irritability, showed a tendency to improve after virological eradication with DAA therapy.

The classic antiviral treatment with interferon-alpha with ribavirin, a pro-inflammatory cytokine, is associated with an incidence close to 40% of major depression (Udina et al., 2016). Pro-inflammatory cytokines may change brain function function in several ways, such as altering serotonin and dopaminergic neurotransmission, and glucocorticoids and neurotrophic factors. DAAs are no

pro-inflammatory cytokines. DAAs have directly an inhibitory effect over the different replication steps of the VHC. Thus, a direct neuropsychiatric effect would not be expected. Several reasons might explain the elevated incidence of major depression and depressive symptoms during the DAA treatment. First, four in five patients included in our study received ribavirin, an antiviral co-agent with unclear mechanisms of action, is known to have impairing effects on mental health (Brok et al., 2005; Bronowicki et al., 2006; Egmond et al., 2017). In the present cohort, ribavirin co-administration with DAAs was not identified as a confounding factor. Second, the incidence of depression may be due to the advanced liver disease of the cohort sample, as these patients often suffer more from symptoms related to the disease (Younossi et al., 2015). However, when we controlled for the presence of decompensated cirrhosis, no statistically significant differences were found. The same was observed with the presence of other medical comorbid diseases.

With respect to the incidence of major depression during DAA treatment, some factors seem to be associated with history of family depression, the PHQ-9 and the irritability baseline score. However, none of the studied factors were associated with the incidence of depressive symptoms during DAA treatment. In the frame of allostatic load, the subgroup of HCV patients with an underlying low degree of chronic inflammation may be more vulnerable to depression (Rubinow & Rubinow, 2017). Large future cohort studies will be needed to confirm these results.

Considering the prevalence of depression over treatment course, a slight increase in mainly major depression was observed, with a decrease rate at viral eradication point (12AT). As nearly all patients achieved a sustained

virological response, it is possible that this tendency for post-treatment improvement is associated to successful HCV eradication, suggesting a role of the virus in the brain and its possible relationship with neuropsychiatric symptoms (Forton et al, 2008; Capuron & Miller, 2011). Furthermore, although a tendency for improvement occurred in fatigue and irritability over treatment course, changes were not of statistical significance.

With respect to general health-related quality of life, although no statistically significant changes were detected over DAA treatment from baseline, an improvement in general life quality was observed at both short-term and long-term follow-up after treatment cessation. However, compared to EQ-5D VAS scores observed in the general Spanish population of the same age range and from the same community area, our sample showed a major HRQL burden at each assessment (Ministerio de Sanidad, Servicios Sociales e Igualdad, Encuesta Nacional de Salud 2011/12, 2014). The two mostly affected dimensions of EQ-5D during DAA treatment were “pain or discomfort”, especially in the decompensated cirrhosis patient group, followed by “anxiety or depression”. These two dimensions are the mostly scored EQ-5D dimensions in the general Spanish population (over to 25%), being higher in women (Ministerio de Sanidad, Servicios Sociales e Igualdad, Encuesta Nacional de Salud 2011/12, 2014). This gender difference was not observed in our cohort. However, depression is the third illnesses found to mostly affect life quality scores (Szende, Janssen, and Cabases, 2014; Ministerio de Sanidad, Servicios Sociales e Igualdad, Encuesta Nacional de Salud 2011/12, 2014; WHO, 2017). Moreover, as expected cirrhotic patients in the cohort reported

slightly more problems in all dimensions than the non-cirrhotic patients (Dan et al., 2006; Mandorfer et al., 2014; Younossi et al., 2015).

On the other hand, as our sample had advanced stages of liver disease, and as liver disease progression may be halted but not reversed, a less pronounced improvement in general life quality was expected in our cohort. However, results from the study suggest that eradication of HCV with DAAs may be related to a slight improvement in life quality. Similarly, short-term post-treatment improvements have also been found in RCT studies using both interferon-alpha (Spiegel et al., 2005; Mathew et al., 2006; Bonkovsky et al., 2007) and DAAs (Younossi et al., 2014[b]; Smith-Palmer et al., 2015; Younossi et al., 2016).

This study is not free from limitations. Due to the relatively small sample size, the advanced liver disease stage of the patients, and non-inclusion of HIV co-infected patients, caution must be exercised in the generalization of our results. Because of the naturalistic cohort design, the study was lacking a control group, and patients were included in the study consecutively. On the other hand, the relatively small amount of subjects included in this cohort limited the study of other covariables that could be included in longitudinal analysis, and may also explain the dispersed confidence intervals.

With respect to measurement bias, a generic instrument was used to measure general quality of life, EQ-5D, possibly failing to include disease-specific factors that may play an important role in HRQL impairment in patients with CHC and during antiviral treatment. However, EQ-5D has been validated for measuring a complete spectrum of life quality, physical and mental health,

and has often been used in chronic illnesses including hepatitis C (Szende et al., 2004; Lubetkin et al., 2005; Sullivan et al., 2006; van Hout et al., 2012; Oemar & Janssen, 2013; Ministerio de Sanidad, Servicios Sociales e Igualdad, Encuesta Nacional de Salud 2011-12, 2014).

A strong point of the study is the fact that each participant filled in the questionnaires before every medical visit, thus avoiding prior knowledge of patient of the disease state and progression. In this manner, results could not be biased with knowledge on virus eradication. The longitudinal design of this study should further avoid measurement bias. Furthermore, the use of multivariate analysis allowed for controlling possible confounding variables, and permitted the assessment of possible important risk factors.

In conclusion, although physical health is normally monitorized in CHC patients in clinical settings during antiviral treatment, our findings on quality of life outcomes and incidence of depression underline the importance of the assessment of possible risk factors that may interfere with mental life quality during DAA treatment, and support a multidisciplinary, and holistic clinical approach. This will improve the wellbeing and individual level management of CHC patients. Future researchers are encouraged to study physical and mental health and their risk factors in HCV patients receiving direct-acting antiviral therapy, including any of the several comorbidities that are highly prevalent, such as HIV co-infection, psychiatric or substance use disorders.

REFERENCES

Adinolfi LE, Nevola R, Lus G, Restivo L, Guerrera B, Romano C, ... Marrone A. Chronic hepatitis C virus infection and neurological and psychiatric disorders: an overview. *World J Gastroenterol* 2015;21(8):2269-80.

Barboza KC, Salinas LM, Arun FS, Jesudian B, Weisberg IL, Sigal SH. Impact of depressive symptoms and hepatic encephalopathy on health-related quality of life in cirrhotic hepatitis C patients. *Metabol Brain Dis* 2016;31(4):869–80.

Barkhuizen A, Rosen HR, Wolf S, Flora K, Benner K, Bennett RM. Musculoskeletal pain and fatigue are associated with chronic hepatitis C: a report of 239 hepatology clinic patients. *Am J Gastroenterol* 1999;94(5):1355-60.

Blachier M, Leleu G, Peck-Radosavljevic M, Valla D, Roudot-Thoraval F. The burden of liver disease in Europe: A review of available epidemiological data. *J Hepat* 2013;58:593–608.

Bonkovsky HL, Snow KK, Malet PF, Back-Madruga C, Fontana RJ, Sterling RK, Kulig CC, Di Bisceglie AM, Morgan TR, Dienstag JL, Ghany MG, Gretch DR; HALT-C Trial Group. Health-related quality of life in patients with chronic hepatitis C and advanced fibrosis. *J Hepatol* 2007;46:420-31.

Brok J, Gluud LL, Gluud C. Effects of adding ribavirin to interferon to treat chronic hepatitis C infection: a systematic review and meta-analysis of randomized trials. *Arch Intern Med* 2005;165(19):2206-12.

Bronowicki JP, Ouzan D, Asselah T, Desmorat H, Zarski JP, Foucher J, ... Pawlotsky JM. Effect of ribavirin in genotype 1 patients with hepatitis C

responding to pegylated interferon alfa-2a plus ribavirin. *Gastroenterology* 2006;131(4):1040-8.

Burak KW, Lee SS. Treatment options in patients with chronic hepatitis C. *Can J Public Health* 2000;91(S1):S22-6–S24-8.

Burra P, Burroughs A, Graziadei I, Pirenne J, Valdecasas JC, Muiesan P, Samuel D, Forns X; European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Liver transplantation. *J Hepatol* 2016;64(2):433-85.

Burström K, Sun S, Gerdtham UG, Henriksson M, Johannesson M, Levin LA Zethraeus N. Swedish experience-based value sets for EQ-5D health states. *Quality Life Res* 2014;23(2):431–42.

Cacoub P, Comarmond C, Domont F, Savey L, Desbois AC, Saadoun D. Extrahepatic manifestations of chronic hepatitis C virus infection. *Ther Adv Infect Dis* 2016;3(1):3-14.

Capuron L, Miller AH. Immune system to brain signaling: neuropsychopharmacological implications. *Pharmacol Ther* 2011;130(2):226-38.

Capuron L, Pagnoni G, Drake DF, Woolwine BJ, Spivey JR, Crowe RJ, ... Miller AH. Dopaminergic mechanisms of reduced basal ganglia responses to hedonic reward during interferon alfa administration. *Arch Gen Psychiatry* 2012;69(10):1044-53.

Corfield EC, Yang Y, Martin NG, Nyholt DR. A continuum of genetic liability for minor and major depression. *Transl Psychiatry* 2017;7(5):e1131.

Daltro-Oliveira R, Morais-de-Jesus M, Pettersen KM, Paraná R, Quarantini LC. Impact of sustained virologic response on quality of life in chronic HVC carriers. *Ann Hepatol* 2013;12:399-407.

Dan, A. A., Martin, L. M., Crone, C., Ong, J. P., Farmer, D. W., Wise, T., ... Younossi, Z. M. (2006). Depression, anemia and health-related quality of life in chronic hepatitis C. *J Hepatol 2006;*44(3):491-8.

Dantzer R, O'Connor JC, Freund GG, Johnson RW, & Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci* 2008;9(1):46-56.

Dbouk N, Arguedas MR, Sheikh A. Assessment of the PHQ-9 as a screening tool for depression in patients with chronic hepatitis C. *Dig Dis Sci* 2008;53:1100–06.

Diez-Quevedo C, Rangil T, Sanchez-Planell L, Kroenke K, Spitzer RL. Validation and utility of the patient health questionnaire in diagnosing mental disorders in 1003 general hospital Spanish inpatients. *Psychosom Med* 2001;6:679–86.

Dusheiko, G. (2017). The impact of antiviral therapy for hepatitis C on the quality of life: a perspective. *Liver Int* 2017;37S1:7-12.

Dwight MM, Kowdley KV, Russo JE, Ciechanowski PS, Larson AM, Katon JW. Depression, fatigue, and functional disability in patients with chronic hepatitis C. *J Psychosom Res* 2000;49(5):311-7.

EuroQol Group. EuroQol - a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199-208.

Fischer B, Haydon E, Rehm J, Krajden M, Reimer J. Injection drug use and the hepatitis C virus: considerations for a targeted treatment approach – the case study of Canada. *J Urban Health* 2004;81:428–47.

Flisiak R, Pogorzelska J, Flisiak-Jackiewicz M. Hepatitis C: efficacy and safety in real life. *Liver Int* 2017;37(S1):26-32.

Forton DM, Hamilton G, Allsop JM, Grover VP, Wesnes K, O'Sullivan C, ... Taylor-Robinson SD. Cerebral immune activation in chronic hepatitis C infection: a magnetic resonance spectroscopy study. *J Hepatol* 2008;49(3):316-22.

Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, Bonsel G, Badia X. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20(10);1727–36.

Hsu PC, Krajden M, Yoshida EM, Anderson FH, Tomlinson GA, Krahn MD. Does cirrhosis affect quality of life in hepatitis C virus-infected patients? *Liver Int* 2009;29(3):449-58.

Hurst NP, Kind P, Ruta D, Hunter M, Stubbings A. Measuring health-related quality of life in rheumatoid arthritis: Validity, responsiveness and reliability of EuroQol (EQ-5D). *Br J Rheumatol* 1997;36(5):551-9.

Johnston BC, Patrick DL, Busse JW, da Costa BR, Schünemann HJ, Guyatt GH. Patient-reported outcomes in meta-analyses - Part 1: assessing risk of bias and combining outcomes. *Health Rel Qual Life Outcomes* 2013;11:109.

Kallman J, O'Neil MM, Larive B, Boparai N, Calabrese L, Younossi ZM. Fatigue and health-related quality of life (HRQL) in chronic hepatitis C virus infection. *Dig Dis Sci 2007;*52(10):2531-39.

Kroenke K, Spitzer RL, Williams JB, Löwe B. The Patient Health Questionnaire somatic, anxiety, and depressive symptom scales: a systematic review. *Gen Hosp Psychiatr* 2010;32:345–59.

Leidl R, Reitmeir P. A value set for the EQ-5D based on experienced health states. *PharmacoEconomics* 2011;29(6):521–34.

Lim JK, Cronkite R, Goldstein MK, Cheung RC. The impact of chronic hepatitis C and comorbid psychiatric illnesses on health-related quality of life. *J Clin Gastroenterol* 2006;40(6):528-34.

Lubetkin EI, Jia H, Franks P, Gold MR. Relationship among sociodemographic factors, clinical conditions, and health-related quality of life: Examining the EQ-5D in the US general population. *Qual Life Res* 2005;14(10):2187–96.

Mandorfer M, Payer BA, Scheiner B, Breitenecker F, Aichelburg MC, Grabmeier-Pfistershammer K, ... Reiberger T. Health-related quality of life and severity of fatigue in HIV/HCV co-infected patients before, during, and after antiviral therapy with pegylated interferon plus ribavirin. *Liver Int* 2014;34(1):69-77.

Martin-Santos R, Egmond E, Cavero M, Mariño Z, Subira S, Navines R, Forns X, Valdes M. Chronic hepatitis C, depression and gender: a state of art. *Adv Dual Diagn* 2015;8(4):193-210.

Mathew A, Peiffer LP, Rhoades K, McGarrity TJ. Improvement in quality of life measures in patients with refractory hepatitis C, responding to re-treatment with pegylated interferon alpha-2b and ribavirin. *Health Qual Life Outcomes* 2006;4:30.

Ministerio de Sanidad, Servicios Sociales e Igualdad. Encuesta Nacional de Salud. España 2011/12. *Calidad de vida relacionada con la salud en adultos: EQ-5D-5L. Serie Informes monográficos nº 3.* Madrid: Ministerio de Sanidad, Servicios Sociales e Igualdad, 2014.

Monaco S, Ferrari S, Gajofatto A, Zanusso G, Mariotto S. HCV-related nervous system disorders. *Clin Dev Immunol* 2012;236148.

Navinés R, Castellvi P, Moreno-Espana J, Gimenez, D, Udina, M, Canizares S, … Martin-Santos R. Depressive and anxiety disorders in chronic hepatitis C patients: reliability and validity of the Patient Health Questionnaire. *J Affect Disord* 2012;138(3):343-51.

Oemar M, Janssen B. *EQ-5D-5L user guide.* Rotterdam: EuroQol Group; 2013.

Ramos-Goñi J, Errea M, Rivero-Arias O, Cabasés JM, Pinto JL. EQ-5D-5L Valuation Project for the Spanish Population 2013; A Descriptive Overview and Preliminary Results. *Value in Health* 2017;*15*(7):A279.

Sockalingam S, Blank D, Al Jarad A, Alosaimi F, Hirschfield G, Abbey, SE. A comparison of depression screening instruments in hepatitis C and the impact of depression on somatic symptoms. *Psychosomatics* 2011;52:433–40.

Smith-Palmer J, Cerri K, Valentine W. Achieving sustained virologic response in hepatitis C: a systematic review of the clinical, economic and quality of life benefits. *BMC Infect Dis* 2015;15:19.

Spiegel BM, Younossi ZM, Hays RD, Revicki D, Robbins S, Kanwal F. Impact of Hepatitis C on Health Related Quality of Life: A Systematic Review and Quantitative Assessment. *Hepatology* 2005;41:790-800.

Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. *JAMA* 1999;282:1737–44.

Sullivan PW, Ghushchyan V. Preference-Based EQ-5D Index Scores for Chronic Conditions in the United States. *Med Decis Making* 2006;26:410-20.

Sun S, Chen J, Kind P, Xu L, Zhang Y, Burström K. Experience-based VAS values for EQ-5D-3L health states in a national general population health survey in China. *Qual Life Res* 2014;24(3):693–703.

Szende A, Janssen B, Cabases J. (2014). *Self-reported population health: an international perspective based on EQ-5D*. Berlin: Springer.

Szende A, Williams A. (2004). *Measuring self-reported population health: An international perspective based on EQ-5D*. Rotterdam: SpringMed Publishing.

Teo M, Hayes P. Management of hepatitis C. *Br Med Bull* 2004;70:51–69.

Teuber G, Schäfer A, Rimpel J, Paul K, Keicher C, Scheurlen M, … Kraus MR. Deterioration of health-related quality of life and fatigue in patients with chronic hepatitis C: Association with demographic factors, inflammatory activity, and degree of fibrosis. *J Hepatol* 2008;49(6):923-9.

Udina M, Castellví P, Moreno-España J, Navinés R, Valdés M, Forns X, … Martín-Santos R. Interferon-induced depression in chronic hepatitis C: A systematic review and meta-analysis. *J Clin Psychiatry* 2012:73(8);1128-38.

Van Hout B, Janssen MF, Feng Y, Kohlmann T, Busschbach J, Golicki D, ... Pickard S. (Interim scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value in Health* 2012;15(5):708-15.

World Health Organization (WHO). (2017). *Global Hepatitis Report 2017.* Geneva: World Health Organization.

Younossi ZM, Boparai N, McCormick M, Price LL, & Guyatt G. Assessment of utilities and health-related quality of life in patients with chronic liver disease. *Am J Gastroenterol* 2001;96(2):579-83.

Younossi ZM, Kallman J, Kincaid J. The effects of HCV infection and management on health-related quality of life. *Hepatology* 2007;45:806-16.

Youssef NF, El Kassas M, Farag A, Shepherd A. Health-related quality of life in patients with chronic hepatitis C receiving Sofosbuvir-based treatment, with and without Interferon: a prospective observational study in Egypt. *BMC Gastroenterol* 2017;17(1):18.

Younossi ZM, Stepanova M, Afdhal N, Kowdley KV, Zeuzem S, Henry L, Hunt SL, Marcellin P. Improvement of health-related quality of life and work productivity in chronic hepatitis C patients with early and advanced fibrosis treated with ledipasvir and sofosbuvir. *J Hepatol* 2015;63(2):337-45.

Younossi ZM[a], Stepanova M, Zeuzem S, Dusheiko G, Esteban R, Hezode C, ... Hunt S. Patient-reported outcomes assessment in chronic hepatitis C treated with sofosbuvir and ribavirin: the VALENCE study. *J Hepatol* 2014;61(2):228-34.

Younossi ZM[b], Stepanova M, Henry L, Gane E, Jacobson IM, Lawitz E, ... Hunt S. Minimal impact of sofosbuvir and ribavirin on health related quality of life in chronic hepatitis C (CH-C). *J Hepatol* 2014;60(4):741-7.

Younossi ZM, Stepanova M, Pol S, Bronowicki JP, Carrieri MP, Bourliere M. The impact of ledipasvir/sofosbuvir on patient-reported outcomes in cirrhotic patients with chronic hepatitis C: the SIRIUS study. *Liver Int* 2016;36(1):42-8.

Zuithoff NP, Vergouwe Y, King M, Nazareth I, van Wezep MJ, Moons KG, Geerlings MI. The Patient Health Questionnaire-9 for detection of major depressive disorder in primary care: consequences of current thresholds in a cross sectional study. *BMC Family Practice* 2010;11:98.

CHAPTER 5

Discussion

5.1. Main findings

This dissertation offers an attempt into studying health-related quality of life and mood disorders in persons infected with the hepatitis C virus, with respect to the new antiviral regimens that are soon expected to become the standard of care, but of which few data are yet available due to their novelty. Two studies on the subject were carried out from different perspectives: (I) through systematically gathering the evidences from analyzing existing RCTs studies on chronic hepatitis C patients receiving new direct-acting antiviral regimens, and (II) by prospectively studying a real-life cohort of chronic hepatitic C patients with advanced liver disease receiving DAAs. A number of important data flow from results of the studies that were carried out, which revealed interesting evidence in addition to the frame of existing literature. Although a detailed discussion has been included in each of the studies, subsequently the most relevant aspects of each of the manuscripts are summarized, and the implications of these findings on the existing literature are discussed.

Moving towards the *specific hypotheses* of **Study 1** (Chapter 3), the systematic review and meta-analysis provides new evidence for the minimal impact on life quality in chronic hepatitis C patients using direct-acting treatments. In fact, mental life quality may improve after achieving a SVR after having received successful DAA treatment. DAAs also seem to transcend possible combination treatments involving both ribavirin and interferon-alpha in terms of physical and mental health. On the other hand, several risk factors for decreased life quality remain to exist for HCV-infected individuals, also in

the absence of treatment, suggesting the use of an integrated approach in a multidisciplinary care setting for HCV patients.

With regard to the *specific hypotheses* of **Study 2** (Chapter 4), the role of quality of life and de novo presentation of depressive disorders was assessed in a cohort of chronic hepatitis C patients receiving DAAs. Results showed that an incidence of major depression (13.7%) and depressive symptoms (51%) might occur over DAA treatment course. Although no statistically significant differences on general life quality were observed during treatment, a slight improvement occurred up to 48 weeks of post-treatment. However, around half of all patients indicated to experience symptoms related to the pain or discomfort subscale, followed by 35% for the depression or anxiety subscale. The percentage of each of the five dimension scales was twice as high compared to the general population (Ramos-Goñi et al., 2013). HCV patients with decompensated cirrhosis had a significantly greater burden on the area of pain and discomfort during treatment. At 12 of post-treatment follow-up, depressive symptoms and general life quality scores tended to improve, as well as scores of irritability and fatigue. These findings suggest that, although HCV patients with advanced liver disease have a more impaired physical and mental life quality, successful DAA treatment is associated with a possible improvement in both aspects.

5.2. Effects of antiviral treatment regimens on life quality

The **first study**, a systematic review and meta-analysis of HRQL in patients included in RCTs using new antiviral regimens to treat HCV, revealed several interesting findings that are in support, and offer an update, of existing evidence concerning DAAs. Results from our study confirm that the new antiviral regimens may have a minimal impact on the patient's life quality, and in fact, may even produce an improvement in terms of mental wellbeing. Supporting recent clinical experience (Walker et al., 2015), these results reflect the excitement that has recently arisen with the arrival of the new antiviral therapies. Due to their improved safety profiles and efficacy levels of over 90% (Dusheiko, 2017), DAAs offer a realistic possibility of global disease erradication which has been set as target by WHO for the year 2030 (WHO, 2017).

On the other hand, results from this study suggest that co-administration of ribavirin to new direct acting antiviral regimens may significantly alter mental life quality in chronic hepatitis C patients. This is in line with what earlier has been found with the addition of ribavirin to interferon-alpha compared to interferon-alpha alone, where adverse events decreased (Brok et al., 2005), and quality of life was slightly better in the treatment without ribavirin (Hassanein et al., 2004). Although these findings support the use of only new antiviral regimens, as the co-administration of ribavirin to DAAs significantly increases the possibility of treatment response in patients with certain characteristics, ribavirin co-administration may be still be preferred for some patients (AASLD-IDSA, 2016).

In relation to triple therapy (i.e. combining new antiviral regimens with (peg)interferon-alpha and ribavirin), this the combination of classic and new antiviral regimens may cause a significant impairment in physical and mental life quality. Not surprisingly, similar reductions in life quality have been observed in the administration of classic treatment involving interferon-alpha and ribavirin (Spiegel et al., 2005; Daltro-Oliveira et al., 2013). Although an advantage of triple therapy above classic interferon-alpha and ribavirin treatment would include increased treatment response rates, the addition of these regimens to DAAs appears to offer no clinical advantages, as the SVR rates are excellent in the use of these new regimens. Conclusively, our systematic review supports evidence suggesting that antiviral therapy with interferon-alpha seems to become increasingly obsolete (Younossi et al., 2015[a]). Although our study suggested the mental impairing effects of ribavirin, in terms of quality of life, the administration of DAAs alone would be preferred.

Moreover, the study has revealed important improvements in physical and mental life quality at post-treatment follow-up, using both interferon-free and interferon-containing regimens, between patients responding to antiviral treatment compared to their own baseline, i.e. when infected with HCV. This supports previous findings where treatment response has been related to improved life quality after responding to interferon-alpha treatment (Spiegel et al., 2005; Mathew et al., 2006; Daltro-Oliveira et al., 2013; Smith-Palmer et al., 2015), and suggests that persistence of the virus is related to a decreased life quality. As new antiviral regimens have been associated with response rates almost twice as high (Younossi et al., 2015[b]), the possibilities of quality of life improvement will likely increase.

Irrespective of antiviral therapy, certain predictive baseline factors continue to exist for physical and mental quality of life impairment in HCV patients. History of anxiety, fatigue, insomnia, and depressive disorders, as well as baseline depression and anemia, appear to be the most common baseline predictors for decreased life quality in studies assessing only DAAs or combined with interferon-alpha and ribavirin. Similar predictive baseline factors have been found in earlier studies using classic interferon-alpha and ribavirin treatment (Dan et al., 2006; Hollander et al., 2006; Bezemer et al., 2012; Udina et al., 2012; Mandorfer et al., 2014). Despite improved safety profiles and reduced side effects in the use of DAAs, a number of risk factors have been identified in our study for life quality impairment during treatment. With respect to the administration of DAAs combined with ribavirin, associated risk factors for physical health include female gender, older age, anemia, lower socio-economic status, cirrhosis; for mental health, associated risk factors include history of anxiety, fatigue, insomnia and depressive disorders.

Similar predictive factors seem to continue present at post-treatment follow-up when treatment efficacy is assessed. Some of these risk factors have also been identified during and after following classic therapy using interferon-alpha and ribavirin (Hollander et al. 2006; Bezemer et al., 2012; Mandorfer et al., 2014). In addition to the risk factors found in studies using DAA plus ribavirin treatment, the systematic review suggests that adverse events and treatment discontinuation are predictive for reduced life quality over triple treatment course and at post-treatment follow-up. These factors have been identified in both HCV mono-infected and HIV co-infected patients receiving interferon-alpha with ribavirin treatment (Sinakos et al., 2010;

Mandorfer et al., 2014), and might be due to the persistence of the virus in the body and in the brain (Dirks et al., 2017).

Evidence from the study supports the increasing belief about the improvement these new regimens offer patients on different areas of wellbeing, in contrary to classic treatment involving interferon-alpha and ribavirin. This knowledge is particularly important when considering new antiviral regimens for these patients, who are usually afraid of becoming limited in physical, mental, and social aspects that may affect their wellbeing, also due to previous experience with treatment involving interferon-alpha. When considering antiviral treatment using new direct-acting therapies, quality of life seems to be most optimal in the absence of interferon-alpha or ribavirin co-administration. However, even though the new antiviral regimens have been associated with high response rates, good safety profiles, and reduced side effects, several risk factors for decreased physical and mental life quality as described above continue to be present in this vulnerable group of persons. Especially since several comorbidities are frequent in HCV patients (i.e. HIV co-infection, psychiatric and substance abuse disorders) (Quelhas & Lopes, 2009; Soriano et al., 2010; Udina et al., 2012; Basnayake et al., 2016), a thorough assessment of both physical and mental health in HCV patients is of high importance when considering and administering any type of antiviral therapy. As this population as known have a risk to present dual diagnoses and higher psychiatric prevalence, it is important to include these patient groups in study trials in order to assess physical and mental health during and after antiviral HCV treatment.

5.3. Life quality and depression in a naturalistic advanced liver disease cohort receiving direct-acting antivirals

The **second study** included a real-life cohort existing of HCV patients receiving DAA with or without ribavirin. The most important findings from the second study showed that CHC patients with advanced liver disease have a generally impaired physical and mental life quality compared to the general population, and mood disorders may occur during DAA treatment in those HCV patients euthymic at baseline. However, mental and physical life quality aspects, depressive symptoms, fatigue, and irritability, may improve sustainably after having successfully completed DAA therapy.

Compared to the Spanish general population with similar range of age, our cohort presented symptoms at least twice as often related to physical and mental quality of life (Ministerio de Sanidad, Servicios Sociales e Igualdad, 2014), especially in the dimensions reflecting pain, discomfort, anxiety, and depression, after controlling for other possible confounding factors. These findings may be explained by the severity of liver disease of the cohort included in the study, as progressed liver disease often significantly affects physical aspects, which has been found in previous studies using interferon-alpha and ribavirin (Dan et al., 2006; Mandorfer et al., 2014). On the other hand, depression is the third of all illnesses found to mostly affect life quality scores (Szende, Janssen, and Cabases, 2014; Ministerio de Sanidad, Servicios Sociales e Igualdad, 2014), and the dimension anxiety and depression of EQ-5D has been found to have the greatest impact on overall

life quality (Burström et al., 2014; Rand-Hendriksen et al., 2012). Results also suggest that patients with decompensated cirrhosis may have a significantly worse physical life quality in terms of pain and discomfort, compared to patients with less advanced liver disease. A study assessing life quality in the use of DAAs has also found advanced stage of liver disease related to worse life quality (Dan et al., 2006; Mandorfer et al., 2014; Younossi et al., 2015[a]).

With regard to incidence of depression during DAA treatment observed in the study, fourteen percent of euthymic patients at baseline showed a major depression during DAA treatment, and 51% developed depressive symptoms. Cumulative incidence rate was lower than that observed during interferon treatment (Udina et al, 2016). However, it was higher compared to that found in the general population (Angst et al, 2007). On the other hand, PHQ-9 baseline score and history of family depression were found predictive factors for the incidence of major depression during DAA treatment, similar to depression induced by interferon-alpha (Udina et al, 2012). As DAAs are no pro-inflammatory cytokines, as is the case with interferon-alpha, neuropsychiatric effects were not expected during treatment. However, several factors might explain the elevated incidence of major depression and depressive symptoms during the DAA treatment. The observed incidence during DAA administration may be due to the more advanced liver disease stages of the participants, as these patients often suffer more from symptoms related to the disease (Younossi et al., 2015[a]). Also, four in five patients included in our study received ribavirin, a regimen that is known to have impairing effects on mental health (Brok et al., 2005; Bronowicki et al., 2006;

Egmond et al., 2017). However, in the present cohort ribavirin co-administration could not be identified as confounding factor. It seems that the subgroup of HCV patients, with an underlying low degree of chronic inflammation, and higher vulnerability (family history and baseline depressive symptomatology), are more probable to develop a major depression during DAA treatment. Moreover, 12 weeks after treatment cessation, when all patients but one were cured from HCV, a positive change in major depression was observed. This tendency for decrease in symptoms sustained at 48 weeks of post-treatment. The sum of these findings might suggest a possible role of the virus in the brain and a relationship with major depression (Forton et al, 2008; Miller, Maletic, & Raison, 2009).

Our findings underline the importance of thorough management of physical and mental care, especially for those with advanced liver disease. On the other hand, the post-treatment improvements on the areas of depression, general life quality, irritability, and fatigue observed in this study, may be in part attributable to the treatment response. Several studies have found the achievement of a SVR using both interferon-alpha (Spiegel et al., 2005; Mathew et al., 2006; Bonkovsky et al., 2007) and DAAs (Younossi et al., 2014[b]; Smith-Palmer et al., 2015; Younossi et al., 2016) predictive of better life quality. The results point out the interest of prospectively studying brain activation and connectivity, and of metabolism related to cognitive and psychopatological and inflammatory markers, which may increase our understanding of the role of treatment in the central nervous system.

5.4. Limitations

The research from the two studies included in this dissertation has some points that need to be addressed.

The systematic review and meta-analysis revealed that the objectives of the RCT studies included in the review were primarily to focus on the efficacy of the new antiviral treatment response. Instead of replicating previous findings, these RCTs studies tried to respond to new questions on the treatment response, such as efficacy related to placebo, differences between DAAs, addition of ribavirin or interferon-alpha. This was noticed through insufficient reporting of HRQL data (see also Chapter 3, Table 1), as most of the included studies did not publish HRQL sub scale scores, and did not study the different physical and mental domains. The possibility to compile data was limited due to the fact that each RCT was different from the other (see Chapter 3, Table 1). On the other hand, as quality of life involves a wide range of psychological, physical, and social domains, the systematic review may not capture all the important factors that are involved in life quality in CHC patients, as data were included using a generic HRQL instrument. In this frame, we tried to use the minimal clinically important difference from results that could not be included in meta-analysis, as it should give an indication for clinical significance. Also, the use of a quality checklist may be used as reference to assess some flaws included in a systematic review (Higgins & Green, 2008).

Although the use of pre-determined criteria for article selection and PRISMA guidelines were determinant to diminish heterogeneity, the patients

included in each of the studies showed a wide range of characteristics and disease states. None of these studies reported specific quality of life data on common risk groups in hepatitis C [e.g. age, gender, (non) cirrhosis, (history of) psychiatric comorbidities or drug abuse, or HIV co-infection]. Furthermore, not all studies described the complete characteristics of the included sample, and of those that did, all failed to include HIV co-infected patients, and only few studies included treatment naïve patients (Lawitz et al., 2013; Fried et al., 2013; Vera-Llonch et al., 2013; Younossi et al., 2014[b], 2015[b]), history of substance abuse (Lazarus, Sperle, Maticic, & Wiessing, 2014; Younossi et al., 2014; 2015[b]; 2016[a,b]) or other psychiatric disorders (Younossi et al., 2013[a]; Younossi et al., 2016[a]). None of the RCTs included HIV co-infected patients. This is an important fact, as the prevalence of these comorbidities is high in HCV patients. Another aspect to note is that post-treatment follow-up of patients was no longer than 24 weeks, a perhaps too brief period to assess long-term effects on HRQL of the new antiviral treatments.

The second study also has some points that need consideration. Due to the relatively small sample size, the lack of control group due to the naturalistic design, the advanced liver disease stage of the included patients, and exclusion of HIV co-infected patients, caution must be exercised in the generalization of the study results. However, the inclusion of a cohort sample of HCV patients with more advanced liver disease and the real-life longitudinal design instills confidence in our data, and increases its generalizability. Although few studies of naturalistic design have yet investigated life quality and depressive disorders in DAAs, findings from existing literature stroke with

our findings (Younossi & Henry, 2014; Walker et al., 2015). In addition, as HCV is known to have an impact on a broad range of aspects with respect to life quality, as generic questionnaires were used to assess physical and mental life quality, several areas that may play an important role in life quality were not considered in the analyses. Thus, our results may not completely capture each domain that encompasses the wellbeing of these patients. However, the employed questionnaires have been widely validated and used in chronic illnesses including HCV (Szende et al., 2004; Lubetkin et al., 2005; Sullivan et al., 2006; van Hout et al., 2012; Oemar & Janssen, 2013; Ministerio de Sanidad, Servicios Sociales e Igualdad, Encuesta Nacional de Salud 2011-12, 2014). Strengths of the study include the blinding to results on disease state and progression, so that the responses of each participant could not be biased with prior knowledge on virological development. Furthermore, the use of multivariate analysis allowed for controlling possible confounding variables, and permitted the assessment of possible important risk factors.

In summary, due to a limited amount of research up to date, findings from this study remain to be replicated in future studies, where possible associated risk factors for HRQL impairment should be assessed in depth. These studies should also consider the broad range of antiviral treatment regimens and combinations, as well as common comorbidities such as HIV co-infection, current and past psychiatric disorders, or substance use disorder.

5.5. Future considerations

Since the arrival of the new antiviral regimens for HCV, there has been a complete change on the treatment paradigm of this chronic and impairing disease, as DAAs offer patients improvement on important areas such as higher efficacy rates, shorter treatment course, and good side effect profiles. The findings from both studies herein support the understandable initial enthusiasm reflected in a number of articles assessing these new regimens. Although the results are promising and support the availability and use of new antiviral treatments, the physical and mental quality of life remains more impaired compared to the general population, and psychiatric disorders including depression and substance use disorder are more prevalent. As both comorbidities and disease states may have a negative impact on the patients' physical and mental wellbeing, it seems that the assessment of life quality will remain important, especially for patients with a higher vulnerability. Besides halting liver disease progression, both studies in this dissertation suggested a significant improvement in physical and mental health after curing from HCV, findings that underlines the importance of antiviral treatment for all patients. Future researchers are encouraged to study possible risk groups in these subgroups, including any of the comorbidities that are highly prevalent and are associated with risk behavior, i.e. HIV co-infection or substance use disorders (Roncero, Vega, Martinez-Vaga, & Torrens, 2017).

There is a recognized gap between treatment guidelines and current practice for chronic care (Younossi & Henry, 2014), as the true public health

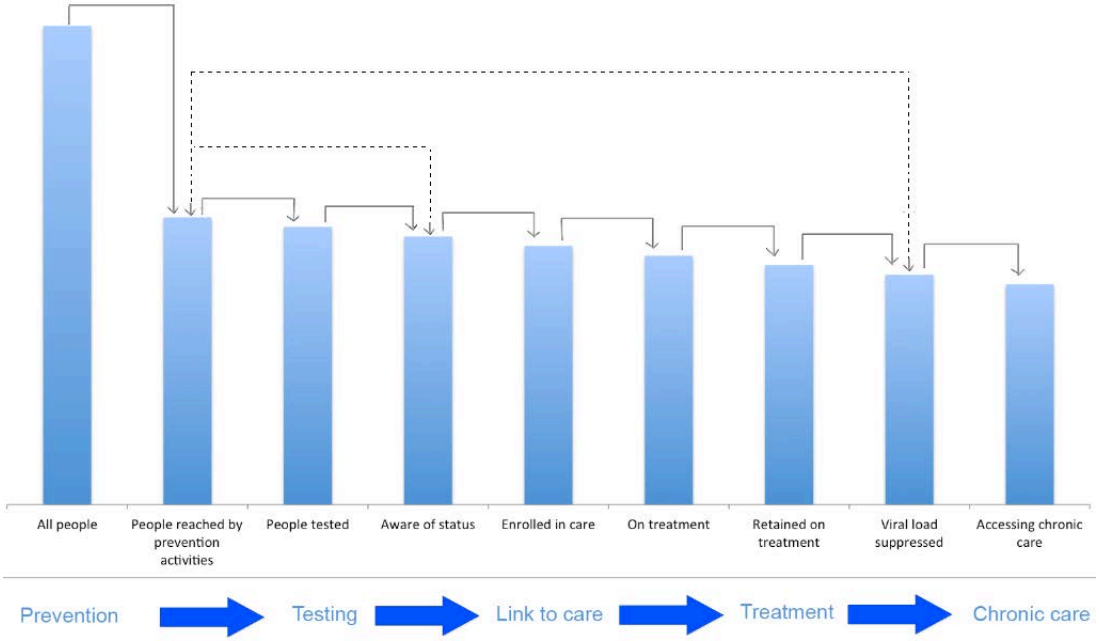
dimensions and impact of hepatitis epidemics are poorly understood in many countries, making it difficult to plan for focused action and prioritize the allocation of resources. Recent estimates (WHO, 2016) suggest that worldwide less than 1% of HCV patients have accessed effective antiviral therapy, partly due to high prices and reduced coverage of these new medicines in many countries. Only 5% of infected patients are aware of their illness, mainly due to weak surveillance and lacking prevention programmes (Reau & Jensen, 2014; WHO, 2016). Although HCV has been associated with a great clinical, economic, and social burden, antiviral treatment is often delayed in patients with initial disease severity, ultimately increasing care costs up to three times (Younossi & Henry, 2014). Also, the presence of certain comorbidities (e.g. HIV co-infection, substance use disorder, or psychiatric disorders) in HCV patients often leads to the exclusion of such patients from antiviral treatment, despite the high prevalence, in some cases causing faster progression of liver disease (Quelhas & Lopes, 2009; Younossi & Henry, 2014; EASL, 2017). However, a significant amount of evidence suggests that HCV-infected individuals with mental health and/or substance abuse issues can safely and effectively undergo antiviral treatment when delivered through multidisciplinary care settings (Martin-Santos et al., 2010; Bonner, Barritt, Fried, & Evon, 2012; Smith et al., 2015).

Although physical health is normally monitorized during antiviral treatment in HCV patients, our findings on quality of life outcomes and incidence of depression underline the mental vulnerability of at least a part of these patients, and support the need of integrating psychopathological assessment

before and during any antiviral treatment regimen. Our findings underline the importance of the assessment of possible risk factors that may interfere with mental life quality of these patients during DAA treatment. Future clinicians and researchers are encouraged to study the HCV patients using a more holistic approach, as many aspects affect not only physical but also mental wellbeing and other aspects important in the wellbeing of hepatitis C patients. Evidence on efficacy, side effect profiles, quality of life, and cost-effectiveness using new antiviral regimens, should increase awareness on the necessity of global availability for DAAs for CHC patients with different characteristics and comorbidities (Yu, 2017; Bruno et al., 2017). In order to have the highest impact, effective interventions should be combined and tailored for the specific population, location and setting (WHO, 2016). See Figure 5.1.

Furthermore, findings from this dissertation support the need for studying long-term quality of life in HCV patients after finishing antiviral DAA treatment (WHO, 2017). Although physical and mental wellbeing may improve after successfully having followed antiviral treatment, we cannot forget that HCV patients that already developed advanced liver disease, including cirrhosis, will continue to be severely ill. Some studies suggested that the virus might remain present in the brain after having followed successful classic treatment using interferon-alpha and ribavirin (Pham et al., 2004; Chen et al., 2013), or direct-acting antiviral treatments (Dirks et al., 2017). Multimodal neuroimaging studies, combined with cognitive assessment, inflammatory, and brain damage markers, would be useful in order to confirm these findings.

Figure 5.1. Scheme of care services and possible barriers for viral hepatitis.

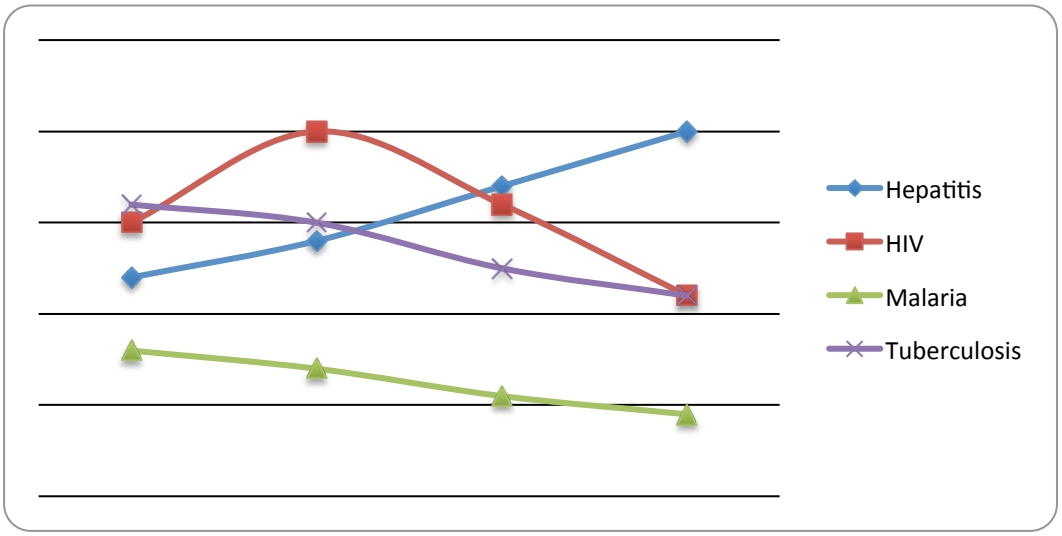


5.6. Final considerations

In a world with new emerging treatments for illnesses such as HCV, disease eradication is increasingly becoming a reality (WHO, 2017). However, several factors still limit this possibility, as described earlier. Future clinical research will hopefully shed more light on the necessity of availability of these treatments, considering not only a global cure but also significant improvements in quality of life of millions of people. Despite the high costs of new DAA regimens (Petta & Craxí, 2015), several studies have shown their cost-effectiveness (Chan et al., 2013). It is critical that health care providers

learn the impact of disease on individuals, if treatments are not only to improve health, but also function and unexpected treatment outcomes (Younossi & Henry, 2014), also considering the fact that hepatitis-related deaths are on the rise, in contrary to most other important infections worldwide (see Figure 5.2).

Figure 5.2. Estimated global number of deaths (in millions) due to diseases.



Source: *Global Burden of Disease and WHO/UNAIDS estimates*. Accessed on 2 April 2017, http://ihmeuw.org/3pms, http://ihmeuw.org/3pmt.

Preventive screening, and multidisciplinary and self-management interventions can educate HCV-infected persons, improve their quality of life, prepare them for treatment (Groessl et al., 2017), and support them during treatment (Younossi & Henry, 2014; Gallach et al., 2016). Individual approaches that combine HCV treatment providers with mental health evaluation and support, detecting those at higher risk, i.e. psychiatric and substance use disorder, can facilitate successful treatment of these persons.

CHAPTER 6

Conclusions

This chapter describes the conclusions in relation to the objectives defined in preparation for the studies included in this dissertation.

Objective 1: *To perform a systematic review and meta-analysis of the published literature of RCT studies on self-perceived health-related quality of life evaluated using EQ-5D or SF-36 over the course of antiviral treatment with DAAs.*

Results from the first study conclude that:

- The number of RCT studies assessing health-related quality of life in HCV patients over the course of DAA administration is still limited.

- Eleven out of 148 RCT studies were finally included in the systematic review and meta-analysis; most reported incomplete quality of life data (missing dimension scores), and none of the studies reported specific quality of life data on risk groups, as where only few studies included patients with frequent comorbidities.

- It appeared that new direct-acting antiviral regimens to treat HCV have a minimal impact on health-related quality of life, and may even cause a slight improvement on mental aspects.

- Co-administration with ribavirin to DAAs may significantly decreased mental life quality as opposed to DAAs alone.

- The antiviral treatment combination involving the classic treatment (pegylated) interferon-alpha greatly impairs physical and mental life quality, to the same extent as observed with classic interferon-alpha treatment.

- A number of risk factors exist that may be predictive for decreased life quality in HCV patients, i.e. history of anxiety, fatigue, insomnia, and depressive disorders, as well as baseline depression and anemia.

- During DAA treatment combined with ribavirin, risk factors included female gender, older age, anemia, lower socio-economic status, cirrhosis, and for mental health associated risk factors included history of anxiety, fatigue, insomnia and depressive disorders.

- In triple treatment combining DAAs with interferon-alpha and ribavirin, the same risk factors as mentioned in the previous point, and also adverse events and treatment discontinuation, may predict altered life quality during treatment.

- After successful treatment using both DAAs with ribavirin and triple treatment (DAAs, ribavirin, and pegylated interferon-alpha), physical and mental life quality significantly improves compared to before starting antiviral treatment, i.e. when being infected with HCV.

Objective 2: *To study health-related quality (EQ-5D questionnaire) of life and incidence of depression (PHQ-9 questionnaire) in a naturalistic prospective cohort of CHC patients receiving DAAs with or without ribavirin.*

Results flowing from the second study conclude that advanced liver disease HCV patients:

- Fourteen percent of baseline euthymic HCV patients developed major depression, and 51% depressive symptomatology, during the administration of direct-acting antiviral regimens.

- PHQ-9 baseline score predicted the development of major depression during DAA treatment; having a history of family depression and irritability baseline score showed a tendency for major depression incidence during DAA treatment.

- None of the baseline factors studied (age, gender, ribavirin, comorbidity, history of family depression, alcohol use) appeared to be risk factors for incidence of depressive symptomatology in baseline euthymic HCV patients during DAA treatment.

- We were not able to discard statistical significant changes from baseline during DAA treatment related to irritability and fatigue scores.

- Physical and mental HRQL was more impaired in our cohort of HCV patients with advanced liver disease compared to the general population.

- Most patients reported symptoms for pain or discomfort, and anxiety or depression EQ-5D dimension scores, during DAA treatment.

- The pain or discomfort dimension scale showed significantly more impairment in decompensated cirrhotic patients at all moments of assessment.

- Cirrhotic patients had a slightly more impaired physical, mental, and general quality of life compared to non-cirrhotic patients.

- Treatment eradication at 12 weeks of DAA post-treatment was associated with a tendency for improvement in depressive symptoms, general health-related quality of life, irritability, and fatigue.

In summary, both studies suggest that virological eradication of the hepatitis C virus may contribute to a better life quality, although both possible risk factors and highly prevalent risk groups should be finvestigated in depth, especially with regard to DAAs, as studies assessing the new regimens are still ongoing.

References

Adinolfi, L. E., Nevola, R., Lus, G., Restivo, L., Guerrera, B., Romano, C., ... Marrone, A. (2015). Chronic hepatitis C virus infection and neurological and psychiatric disorders: an overview. *World Journal of Gastroenterology,* 21(8), 2269-2280.

Afdhal, N., Reddy, K. R., Nelson, D. R., Lawitz, E., Gordon, S. C., Schiff, E., ... Investigators, I. O. N. (2014[a]). Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *New England Journal of Medicine*, 370(16), 1483-1493.

Afdhal, N., Zeuzem, S., Kwo, P., Chojkier, M., Gitlin, N., Puoti, M., ... Investigators, I. O. N. (2014[b]). Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *New England Journal of Medicine*, 370(20), 1889-1898.

Ahmed, O. A., Kaisar, H. H., Hawash, N., Samir, H., Shabana, S. S. T., Fouad, M. H. A., … Abd-Elsalam, S. (2017). Efficacy of sofosbuvir plus ribavirin with or without peginterferon-alfa in treatment of a cohort of Egyptian patients with hepatitis C virus infection. *Infectious Disorders Drug Targets*. doi: 10.2174/1871526517666170417143216

Alonso, J., Ferrer, M., Gandek, B., Ware, J. E., Jr., Aaronson, N. K., Mosconi, P., ... Group, I. P. (2004). Health-related quality of life associated with chronic conditions in eight countries: results from the International Quality of Life Assessment (IQOLA) Project. *Quality of Life Research*, 13(2), 283-298.

American Association for the Study of Liver Diseases-Infectious Diseases Society of America (AASLD-IDSA). *Recommendations for testing, managing, and treating hepatitis C*. www.hcvguidelines.org. Accessed on May 2, 2017.

Amodio, P., Salari, L., Montagnese, S., Schiff, S., Neri, D., Bianco, T., & Minazzato, L. (2012). Hepatitis C virus infection and health-related quality of life. *World Journal of Gastroenterology,* 18(19), 2295-2299.

Anderson, R. T., Baran, R. W., Dietz, B., Kallwitz, E., Erickson, P., & Revicki, D. A. (2014[a]). Development and initial psychometric evaluation of the hepatitis C virus-patient-reported outcomes (HCV-PRO) instrument. *Quality of Life Research*, 23(2), 561-570.

Anderson, R. T., Baran, R. W., Erickson, P., Revicki, D. A., Dietz, B., & Gooch, K. (2014[b]). Psychometric evaluation of the hepatitis C virus patient-reported outcomes (HCV-PRO) instrument: validity, responsiveness, and identification of

the minimally important difference in a phase 2 clinical trial. *Quality of Life Research*, 23(3), 877-886.

Angst, J., Gamma, A., Pezawas, L., Ajdacic-Gross, V., Eich, D., Rössler, W., & Altamura, C. (2007). Parsing the clinical phenotype of depression: the need to integrate brief depressive episodes. Acta Psychiatrica Scandinavica, 1154(3), 221-8.

Arora, S., O'Brien, C., & Zeuzem, S. (2006). Treatment of chronic hepatitis C patients with persistently normal alanine aminotransferase levels with the combination of peginterferon α-2a (40 kDa) plus ribavirin: Impact on health-related quality of life. *Journal of Gastroenterology and Hepatology*, 21, 406–412.

Armstrong, A. R., Herrmann, S. E., Chassany, O., Lalanne, C., Da Silva, M. H., Galano, E., ... Duracinsky, M. (2016). The International development of PROQOL-HCV: An instrument to assess the health-related quality of life of patients treated for Hepatitis C virus. *BMC Infectious Diseases*, 16(1), 443.

Ashrafi, M., Modabbernia, A., Dalir, M., Taslimi, S., Karami, M., Ostovaneh, M. R., ... Poustchi, H. (2012). Predictors of mental and physical health in non-cirrhotic patients with viral hepatitis: a case control study. *Journal of Psychosomatic Research*, 73(3), 218-224.

Banerjee, D., Reddy, K. R. (2016). Review article: safety and tolerability of direct-acting anti-viral agents in the new era of hepatitis C therapy. *Alimentary Pharmacology and Therapeutics*, 43(6), 674-696.

Barkhuizen, A., Rosen, H. R., Wolf, S., Flora, K., Benner, K., & Bennett, R. M. (1999). Musculoskeletal pain and fatigue are associated with chronic hepatitis C: a report of 239 hepatology clinic patients. *American Journal of Gastroenterology*, 94(5), 1355-1360.

Basnayake, S. K., & Easterbrook, P. J. (2016). Wide variation in estimates of global prevalence and burden of chronic hepatitis B and C infection cited in published literature. *Journal of Viral Hepatitis*, 23(7), 545-559.

Bayliss, M. S., Gandek, B., Bungay, K. M., Sugano, D., Hsu, M. A., & Ware, J. E., Jr. (1998). A questionnaire to assess the generic and disease-specific health outcomes of patients with chronic hepatitis C. *Quality of Life Research*, 7(1), 39-55.

Bentham, J. (1834). *Deontology or the science of morality*. London: University of London.

Benveniste, E. N. (1998). Cytokine actions in the central nervous system. *Cytokine Growth Factor Reviews*, 9(3-4), 259-275.

Bezemer, G., Van Gool, A. R., Verheij-Hart, E., Hansen, B. E., Lurie, Y., Esteban, J. I., ... Group, D. H. S. (2012). Long-term effects of treatment and response in patients with chronic hepatitis C on quality of life. An international, multicenter, randomized, controlled study. *BMC Gastroenterology*, 12, 11.

Blach, S., Estes, C., Gamkrelidze, I., Gunter, J., Murphy, K., Nde, H., … & Razavi, H. (2015). *Polaris Observatory – Global prevalence of Hepatitis C.* Colorado, USA: Center for Disease Analysis.

Bladowska, J., Zimny, A., Knysz, B., Malyszczak, K., Koltowska, A., Szewczyk, P., ... Sasiadek, M. J. (2013). Evaluation of early cerebral metabolic, perfusion and microstructural changes in HCV-positive patients: a pilot study. *Journal of Hepatology*, 59(4), 651-657.

Blazer, D., & Houpt, J. (1979). Perception of poor health in the healthy older adult. *Journal of American Geriatric Society,* 27, 330-334.

Bochud, P. Y., Cai, T., Overbeck, K., Bochud, M., Dufour, J. F., Mullhaupt, B., ... Swiss Hepatitis, C. C. S. G. (2009). Genotype 3 is associated with accelerated fibrosis progression in chronic hepatitis C. *Journal of Hepatology*, 51(4), 655-666.

Bonkovsky, Snow, Malet, Back-Madruga, Fontana, Sterling, … HALT-C Trial Group. (2007). Health-related quality of life in patients with chronic hepatitis C and advanced fibrosis. *Journal of Hepatology*, 46(3), 420-431.

Bonner, J. E., Barritt, A. S. t., Fried, M. W., & Evon, D. M. (2012). Time to rethink antiviral treatment for hepatitis C in patients with coexisting mental health/substance abuse issues. *Digestive Diseases and Sciences*, 57(6), 1469-1474.

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(4), 505-515.

Brazier, J., Roberts, J., & Deverill, M. (2002). The estimation of a preference-based measure of health from the SF-36. *Journal of Health Economics*, 21(2), 271-292.

Brok, J., Gluud, L. L., & Gluud, C. (2005). Effects of adding ribavirin to interferon to treat chronic hepatitis C infection: a systematic review and meta-analysis of randomized trials. *Archives of Internal Medicine*, 165(19), 2206-2212.

Bronowicki, J. P., Ouzan, D., Asselah, T., Desmorat, H., Zarski, J. P., Foucher, J., ... Pawlotsky, J. M. (2006). Effect of ribavirin in genotype 1 patients with hepatitis

C responding to pegylated interferon alfa-2a plus ribavirin. *Gastroenterology*, 131(4), 1040-1048.

Brown, I., & Brown, R. (2003). *Quality of Life and Disability: An Approach for Community Practitioners*. London: Jessica Kingsley Publishers.

Bruno, G., Saracino, A., Fabrizio, C., Scudeller, L., Milano, E., Dell'Acqua, R., ... Angarano, G. (2017). Safety and effectiveness of a 12-week course of sofosbuvir and simeprevir +/- ribavirin in HCV-infected patients with or without HIV infection: a multicentre observational study. *International Journal of Antimicrobial Agents*, 49(3), 296-301.

Bull, S. J., Huezo-Diaz, P., Binder, E. B., Cubells, J. F., Ranjith, G., Maddock, C., ... Pariante, C. M. (2009). Functional polymorphisms in the interleukin-6 and serotonin transporter genes, and depression and fatigue induced by interferon-alpha and ribavirin treatment. *Molecular Psychiatry*, 14(12), 1095-1104.

Burström, K., Sun, S., Gerdtham, U. G., Henriksson, M., Johannesson, M., Levin, L. A., & Zethraeus, N. (2014). Swedish experience-based value sets for EQ-5D health states. *Quality of Life Research,* 23(2), 431-442.

Capuron, L., Lamarque, D., Dantzer, R., & Goodall, G. (1999). Attentional and mnemonic deficits associated with infectious disease in humans. *Psychological Medicine*, 29(2), 291-297.

Capuron, L., & Miller, A. H. (2004). Cytokines and psychopathology: lessons from interferon-alpha. *Biological Psychiatry,* 56(11), 819-824.

Capuron, L., Pagnoni, G., Demetrashvili, M., Woolwine, B. J., Nemeroff, C. B., Berns, G. S., & Miller, A. H. (2005). Anterior cingulate activation and error processing during interferon-alpha treatment. *Biological Psychiatry,* 58(3), 190-196.

Capuron, L., & Miller, A. H. (2011). Immune system to brain signaling: neuropsychopharmacological implications. *Pharmacology and Therapeutics,* 130(2), 226-238.

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.

Chahua, M., Sanchez-Niubo, A., Torrens, M., Sordo, L., Bravo, M. J., Brugal, M. T., ... Group, I. P. (2015). Quality of life in a community sample of young cocaine and/or heroin users: the role of mental disorders. *Quality of Life Research,* 24(9), 2129-2137.

Chan, K., Lai, M. N., Groessl, E., Lorig, K., Ganiats, T. G., Ho, S. B. (2013). Cost-effectiveness of direct-acting antiviral therapy. *Clinical Gastroenterology and Hepatology*, 11, 1503-1510.

Charlet, K., & Heinz, A. (2016). Harm reduction-a systematic review on effects of alcohol reduction on physical and mental symptoms. *Addiction Biology.* doi: 10.1111/adb.12414

Charlton, M., Everson, G. T., Flamm, S. L., Kumar, P., Landis, C., Brown, R. S., ... Afdhal, N. (2015). Ledipasvir and Sofosbuvir Plus Ribavirin for Treatment of HCV Infection in Patients with Advanced Liver Disease. *Gastroenterology*, *149*(3), 649-665.

Chen, A. Y., Zeremski, M., Chauhan, R., Jacobson, I. M., Talal, A. H., & Michalak, T. I. (2013). Persistence of Hepatitis C Virus during and after Otherwise Clinically Successful Treatment of Chronic Hepatitis C with Standard Pegylated Interferon α-2b and Ribavirin Therapy. *PLoS ONE,* 8(11): e80078.

Choo, Q. L., Kuo, G., Weiner, A. J., Overby, L. R., Bradley, D. W., & Houghton, M. (1989). Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science*, 244(4902), 359-362.

Chung, R. T., Evans, S. R., Yang, Y., Theodore, D., Valdez, H., Clark, R., ... Team, A. C. T. G. S. (2002). Immune recovery is associated with persistent rise in hepatitis C virus RNA, infrequent liver test flares, and is not impaired by hepatitis C virus in co-infected subjects. *Aids*, 16(14), 1915-1923.

Combellick, J., Smith, D. J., Jordan, A. E., & Hagan, H. (2015). Hepatitis C Virus Disease Progression in People Who Inject Drugs: Protocol for a Systematic Review and Meta-Analysis. *JMIR Research Protocols,* 4(2), e68.

Corfield, E. C., Yang, Y., Martin, N. G., Nyholt, D. R. (2017). A continuum of genetic liability for minor and major depression. *Translation Psychiatry*, 7(5), e1131.

Cuevas, J. M., Gonzalez-Candelas, F., Moya, A., Sanjuan, R. (2009). Effect of ribavirin on the mutation rate and spectrum of hepatitis C virus in vivo. *Journal of Virology,* 83, 5760–5764.

Dalgard, O., Egeland, A., Skaug, K., Vilimas, K., & Steen, T. (2004). Health-related quality of life in active injecting drug users with and without chronic hepatitis C virus infection. *Hepatology*, 39(1), 74-80.

Daltro-Oliveira, R., Morais-de-Jesus, M., Pettersen, K. M., Parana, R., & Quarantini, L. C. (2013). Impact of sustained virologic response on quality of life in chronic HVC carriers. *Annals of Hepatology,* 12(3), 399-407.

Dan, A. A., Martin, L. M., Crone, C., Ong, J. P., Farmer, D. W., Wise, T., ... Younossi, Z. M. (2006). Depression, anemia and health-related quality of life in chronic hepatitis C. *Journal of Hepatology,* 44(3), 491-498.

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. (2009). Cytokine, sickness behavior, and depression. *Immunology And Allergy Clinics of North America,* 29(2), 247-264.

Desnoyer, A., Pospai, D., Lê, M. P., Gervais, A., Heurgué-Berlot, A., Laradi, A., … Peytavin, G. (2016). Pharmacokinetics, safety and efficacy of a full dose sofosbuvir-based regimen given daily in hemo-dialysis patients with chronic hepatitis C. *Journal of Hepatology,* 65, 40-47.

Di Bisceglie, A. M. (1997). Hepatitis C and hepatocellular carcinoma. *Hepatology,* 26(3 Suppl 1), 34S-38S.

Dirks, M., Pflugrad, H., Haag, K., Tillmann, H. L., Wedemeyer, H., Arvanitis, D., ... Weissenborn, K. (2017). Persistent neuropsychiatric impairment in HCV patients despite clearance of the virus?!. *Journal of Viral Hepatitis*. doi: 10.1111/jvh.12674

Duracinsky, M., Armstrong, A., Herrmann, S., Lalanne, C., Galano, E., Da Silva, M. H., ... Chassany, O. (2015). Psychometric Validation of the New International Questionnaire to Assess Health-Related Quality of Life (Hrql) Specific to Viral Hepatitis C: Proqol-Hcv. *Value Health*, 18(7), A591-592.

Dusheiko, G. (2017). The impact of antiviral therapy for hepatitis C on the quality of life: a perspective. *Liver International*, 37 Suppl 1, 7-12.

Dwight, M. M., Kowdley, K. V., Russo, J. E., Ciechanowski, P. S., Larson, A. M., & Katon, W. J. (2000). Depression, fatigue, and functional disability in patients with chronic hepatitis C. *Journal of Psychosomatic Research,* 49(5), 311-317.

Egmond, E., Oriolo, G., Navinés, N., Cavero, M., Mariño, M., Subirà, S., … Martín-Santos, R. (2017). *New direct-acting antiviral treatments for chronic hepatitis C and health-related quality of life: a systematic review and meta-analysis.* Manuscript submitted for publication.

European Association for the Study of the Liver (EASL). EASL Recommendations on Treatment of Hepatitis C 2016. *Journal of Hepatology*, 66(1), 153-194.

EuroQol, G. (1990). EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy,* 16(3), 199-208.

Exton, M. S. (1997). Infection-induced anorexia: active host defence strategy. *Appetite*, 29(3), 369-383.

Fabregas, B. C., de Avila, R. E., Faria, M. N., Moura, A. S., Carmo, R. A., & Teixeira, A. L. (2013). Health related quality of life among patients with chronic hepatitis C: a cross-sectional study of sociodemographic, psychopathological and psychiatric determinants. *Brazilian Journal Infective Diseases,* 17(6), 633-639.

Fattovich, G., Stroffolini, T., Zagni, I., & Donato, F. (2004). Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology,* 127(5 Suppl 1), S35-50.

Feeny, D., Furlong, W., Boyle, M., & Torrance, G. W. (1995). Multi-attribute health status classification systems. Health Utilities Index. *Pharmacoeconomics,* 7(6), 490-502.

Feld, J.J., Hoofnagle, J.H. (2005). Mechanism of action of interferon and ribavirin in treatment of hepatitis C. *Nature,* 436, 967–972.

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.

Fleming, C. A., Christiansen, D., Nunes, D., Heeren, T., Thornton, D., Horsburgh, C. R., Jr., ... Craven, D. E. (2004). Health-related quality of life of patients with HIV disease: impact of hepatitis C coinfection. *Clinical Infectious Diseases*, 38(4), 572-578.

Flisiak, R., Pogorzelska, J., & Flisiak-Jackiewicz, M. (2017). Hepatitis C: efficacy and safety in real life. *Liver International*, 37 Suppl 1, 26-32.

Fontaine, H., Lazarus, A., Pol, S., Pecriaux, C., Bagate, F., Sultanik, P., … Cochin Hepatology and Cardiology Group. (2015). Bradyarrhythmias Associated with Sofosbuvir Treatment. *New England Journal of Medicine,* 373(19), 1886-1888.

Fontana, R. J., Moyer, C. A., Sonnad, S., Lok, A. S. F., Sneed-Pee, N., Walsh, J., … Webster, S. (2001.) Comorbidities and quality of life in patients with interferon-refractory chronic hepatitis C. *American Journal Gastroenterology*, 96(1), 170-178.

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.

Fried, M. W., Peter, J., Hoots, K., Gaglio, P. J., Talbut, D., Davis, P. C., ... Abshire, T. C. (2002). Hepatitis C in adults and adolescents with hemophilia: a randomized, controlled trial of interferon alfa-2b and ribavirin. *Hepatology*, 36(4 Pt 1), 967-972.

Fu, X., Zhu, Z. H., Wang, Y. Q., & Wu, G. C. (2007). Regulation of proinflammatory cytokines gene expression by nociceptin/orphanin FQ in the spinal cord and the cultured astrocytes. *Neuroscience*, 144(1), 275-285.

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 coinfected patients. *AIDS Care*, 19(1), 138-145.

Gallach, M., Vergara, M., Miquel, M., Casas, M., Sanchez-Delgado, J., Dalmau, B., ... Calvet, X. (2016). Effects of a multidisciplinary approach on the effectiveness of antiviral treatment for chronic hepatitis C. *Annals of Hepatology*, 15(4), 524-531.

Gane, E. J., Stedman, C. A., Hyland, R. H., Ding, X., Svarovskaia, E., Symonds, W. T., … Berrey, M.M. (2013). Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C*. New England Journal of Medicine*, 368, 34–44.

Gane, E. J., Hyland, R. H., An, D., Svarovskaia, E. S., Brainard, D., & McHutchison, J. G. (2016). Ledipasvir and sofosbuvir for HCV-infection in patients coinfected with HBV. *Antiviral Therapy,* 21(7), 605-609.

Geigle, R., & Jones, S. B. (1990). Outcomes measurement: a report from the front. *Inquiry*, 27(1), 7-13.

Ghany, M.G., Strader, D.B., Thomas, D.L., & Seeff, L.B. (2009). Diagnosis, management, and treatment of hepatitis C: An update. *Hepatology*, 49, 1335–1374.

Gimeno-Ballester, V., Simón, M. Á., Trigo, C., Mar, J., & San Miguel, R. (2016). Sofosbuvir plus simeprevir for the treatment of genotype 1 chronic hepatitis C: a review of evidence. *Expert Review of Gastroenterology and Hepatology,* 10(11), 1289-1303.

Gladman, D. D., Urowitz, M. B., Ong, A., Gough, J., & MacKinnon, A. (1996). A comparison of five health status instruments in patients with systemic lupus erythematosus (SLE). *Lupus*, 5(3), 190-195.

Gower, E., Estes, C., Blach, S., Razavi-Shearer, K., & Razavi, H. (2014). Global epidemiology and genotype distribution of the hepatitis C virus infection. *Journal of Hepatology*, 61(1 Suppl), S45-57.

Grad, F. P. (2016). The Preamble of the Constitution of the World Health Organization. *Bulletin WHO.* http://www.who.int/bulletin/archives/ 80(12)981.pdf (accessed Dec 20, 2016)

Gralnek, I. M., Hays, R. D., Kilbourne, A., Rosen, H. R., Keeffe, E. B., Artinian, L., ... Martin, P. (2000). Development and evaluation of the Liver Disease Quality of

Life instrument in persons with advanced, chronic liver disease--the LDQOL 1.0. *American Journal of Gastroenterology,* 95(12), 3552-3565.

Grebely, J., Prins, M., Hellard, M., Cox, A. L., Osburn, W. O., Lauer, G., … Dore, G. J. (2012). Hepatitis C virus clearance, reinfection, and persistence, with insights from studies of inject- ing drug users: towards a vaccine. *Lancet Infectious Diseases,* 12, 408-414.

Groessl, E. J., Sklar, M., Laurent, D. D., Lorig, K., Ganiats, T. G., & Ho, S. B. (2017). Cost-Effectiveness of the Hepatitis C Self-Management Program. *Health Educative Behavior*, 44(1), 113-122.

Gutteling, J. J., de Man, R. A., Busschbach, J. J., & Darlington, A. S. (2007). Overview of research on health-related quality of life in patients with chronic liver disease. *Netherlands Journal of Medicine,* 65(7), 227-234.

Hart, B. L. (1988). Biological basis of the behavior of sick animals. *Neuroscience and Biobehavioral Reviews,* 12(2), 123-137.

Hassanein, T., Cooksley, G., Sulkowski, M., Smith, C., Marinos, G., Lai, M. Y., ... Green, J. (2004). The impact of peginterferon alfa-2a plus ribavirin combination therapy on health-related quality of life in chronic hepatitis C. *Journal of Hepatology,* 40(4), 675-681.

Helbling, B., Overbeck, K., Gonvers, J. J., Malinverni, R., Dufour, J. F., Borovicka, J., ... Swiss Hepatitis, C. C. S. (2008). Host- rather than virus-related factors reduce health-related quality of life in hepatitis C virus infection. *Gut,* 57(11), 1597-1603.

Herdman, M., Gudex, C., Lloyd, A., Janssen, M., Kind, P., Parkin, D., ... Badia, X. (2011). Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Quality of Life Research,* 20(10), 1727-1736.

Higgins, J. P. T., & Green, S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1 [updated September 2008].* The Cochrane Collaboration, 2008. http://www.cochrane-handbook.org (accessed Nov 5, 2016)

Hofmann, W. P., Herrmann, E., Sarrazin, C., & Zeuzem, S. (2008). Ribavirin mode of action in chronic hepatitis C: from clinical use back to molecular mechanisms. *Liver International*, 28, 1332–1343.

Hollander, A., Foster, G. R., & Weiland, O. (2006). Health-related quality of life before, during and after combination therapy with interferon and ribavirin in unselected Swedish patients with chronic hepatitis C. *Scandinavian Journal of Gastroenterology,* 41(5), 577-585.

Hoofnagle, J. H., & Di Bisceglie, A. M. (1989). Treatment of chronic type C hepatitis with alpha interferon. *Seminars in Liver Disease,* 9(4), 259-263.

Hoofnagle, J. H., & Jones, E. A. (1989). Therapy of chronic viral hepatitis: past, present, and future. . *Seminars in Liver Disease,* 9(4), 231-234.

Hsu, P. C., Krajden, M., Yoshida, E. M., Anderson, F. H., Tomlinson, G. A., & Krahn, M. D. (2009). Does cirrhosis affect quality of life in hepatitis C virus-infected patients? *Liver International,* 29(3), 449-458.

Jacobson, I. M., Gordon, S. C., Kowdley, K. V., Yoshida, E. M., Rodriguez-Torres, M., Sulkowski, … Bennett, M. (2013). Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *New England Journal of Medicine*, 368, 1867–1877.

James, W. (1987). *The will to believe.* London, Longmans, Green & Co.

Janssen, M. F., Pickard, A. S., Golicki, D., Gudex, C., Niewada, M., Scalone, L., ... Busschbach, J. (2013). Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Quality of Life Research,* 22(7), 1717-1727.

Jenkinson, C., Coulter, A., & Wright, L. (1993). Short form 36 (SF36) health survey questionnaire: normative data for adults of working age. *Biomedical Journal,* 306(6890), 1437-1440.

Jenkinson, C. (1994). *Measuring health and medical outcomes: an overview, in Jenkinson, C. (ed)* Measuring Health and Medical Outcomes. London: UCL Press.

Joshi, D., O'Grady, J., Dieterich, D., Gazzard, B., & Agarwal, K. (2011). Increasing burden of liver disease in patients with HIV infection. *Lancet,* 377(9772), 1198-1209.

Kallman, J., O'Neil, M. M., Larive, B., Boparai, N., Calabrese, L., & Younossi, Z. M. (2007). Fatigue and health-related quality of life (HRQL) in chronic hepatitis C virus infection. *Digestive Disease Sciences,* 52(10), 2531-2539.

Kent, C., Sugaya, K., Bryan, D., Personett, D., & McKinney, M. (1999). Expression of superoxide dismutase messenger RNA in adult rat brain cholinergic neurons. *Journal of Molecular Neuroscience,* 12(1), 1-10.

Koziel, M. J., & Peters, M. G. (2007). Viral hepatitis in HIV infection. *New England Journal of Medicine*, 356(14), 1445-1454.

Lange, C. M., Jacobson, I. M., Rice, C. M., Zeuzem, S. (2014). Emerging therapies for the treatment of hepatitis C. *EMBO Molecular Medicine*, 6: 4–15.

Laskus, T., Radkowski, M., Bednarska, A., Wilkinson, J., Adair, D., Nowicki, M., ... Rakela, J. (2002). Detection and analysis of hepatitis C virus sequences in cerebrospinal fluid. *Journal of Virology,* 76(19), 10064-10068.

Lauer, G. M., & Walker, B. D. (2001). Hepatitis C virus infection. *New England Journal of Medicine*, 345(1), 41-52.

Lavanchy, D. (2011). Evolving epidemiology of hepatitis C virus. *Clinical Microbiology and Infection,* 17(2), 107-115.

Lawitz, E., Lalezari, J.P., Hassanein, T., Kowdley, K.V., Poordad, F.F., Sheikh, A.M., … Freilich, B. (2013[a]). Sofosbuvir in combination with peginterferon alfa-2a and ribavirin for non-cirrhotic, treatment-naive patients with genotypes 1, 2, and 3 hepatitis C infection: A randomised, double-blind, phase 2 trial. *Lancet Infectious Diseases*, 13, 401–408.

Lawitz, E., Mangia, A., Wyles, D., Rodriguez-Torres, M., Hassanein, T., Gordon, S. C., Schultz, M., Davis, M. N., Kayali, Z., Reddy, K. R. (2013[b]). Sofosbuvir for previously untreated chronic hepatitis C infection. *New England Journal of Medicine*, 368, 1878–1887.

Lazarus, J. V., Sperle, I., Maticic, M., & Wiessing, L. (2014). A systematic review of Hepatitis C virus treatment uptake among people who inject drugs in the European Region. *BMC Infectious Diseases*, 14 Suppl S6, S16.

Lazarus JV, Sperle I, Maticic M, Wiessing L, Lim, J. K., Cronkite, R., ... Cheung, R. C. (2006). The impact of chronic hepatitis C and comorbid psychiatric illnesses on health-related quality of life. *Journal of Clinical Gastroenterology,* 40(6), 528-534.

Lindenbach, B.D., & Rice, C.M. (2005). Unravelling hepatitis C virus replication from genome to function. *Nature,* 436, 933–938.

Loria, A., Escheik, C., Gerber, N. L., & Younossi, Z. M. (2013). Quality of life in cirrhosis. *Current Gastroenterology Reports*, 15(1), 301.

Lotrich, F.E. (2014). Inflammatory cytokine-associated depression. *Brain Research*, 1617, 113-125.

Lowry, D., Burke, T., Galvin, Z., Ryan, J. D., Russell, J., Murphy, A., ... Crowe, J. (2016). Is psychosocial and cognitive dysfunction misattributed to the virus in hepatitis C infection? Select psychosocial contributors identified. *Journal of Viral Hepatitis*, 23(8), 584-595.

Lozano, R., Naghavi, M., Foreman, K., Lim, S., Shibuya, K., Aboyans, V., ... Memish, Z. A. (2012). Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet,* 380(9859), 2095-2128.

Lubetkin, E. I., Jia, H., Franks, P., & Gold, M. R. (2005). Relationship among sociodemographic factors, clinical conditions, and health-related quality of life: examining the EQ-5D in the U.S. general population. *Quality of Life Research,* 14(10), 2187-2196.

Ly, K. N., Xing, J., Klevens, R. M., Jiles, R. B., Ward, J. W., & Holmberg, S. D. (2012). The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. *Annals of Intern Medicine,* 156(4), 271-278.

Maggi, F., Giorgi, M., Fornai, C., Morrica, A., Vatteroni, M. L., Pistello, M., ... Bendinelli, M. (1999). Detection and quasispecies analysis of hepatitis C virus in the cerebrospinal fluid of infected patients. *Journal of Neurovirology,* 5(3), 319-323.

Maier, S. F., Wiertelak, E. P., Martin, D., & Watkins, L. R. (1993). Interleukin-1 mediates the behavioral hyperalgesia produced by lithium chloride and endotoxin. *Brain Research,* 623(2), 321-324.

Majer, M., Welberg, L. A., Capuron, L., Miller, A. H., Pagnoni, G., & Reeves, W. C. (2008). Neuropsychological performance in persons with chronic fatigue syndrome: results from a population-based study. *Psychosomatic Medicine,* 70(7), 829-836.

Mandorfer, M., Payer, B. A., Scheiner, B., Breitenecker, F., Aichelburg, M. C., Grabmeier-Pfistershammer, K., ... Reiberger, T. (2014). Health-related quality of life and severity of fatigue in HIV/HCV co-infected patients before, during, and after antiviral therapy with pegylated interferon plus ribavirin. *Liver International,* 34(1), 69-77.

Manns, M. P., Cornberg, M., & Wedemeyer, H. (2001). Current and future treatment of hepatitis C. *Indian Journal of Gastroenterology*, 20 Suppl 1, C47-51.

Manns, M.P., Wedemeyer, H., & Cornberg, M. (2006). Treating viral hepatitis C: Efficacy, side effects, and complications. *Gut*, 55, 1350–1359.

Mariotto, S., Ferrari, S., & Monaco, S. (2014). HCV-related central and peripheral nervous system demyelinating disorders. *Inflammation and Allergy Drug Targets,* 13(5), 299-304.

Martell, M., Esteban, J., Quer, J., Genesca, J., Weiner, A., Esteban, R., … Gomez, J. (1992). Hepatitis C virus (HCV) circulates as a population of different but closely related genomes: Quasispecies nature of HCV genome distribution. *Journal of Virology,* 66, 3225–3229.

Martín-Santos, R., Díez-Quevedo, C., Castellví, P., Navinés, R., Miquel, M., Masnou, H., … Solà, R. (2008), De novo depression and anxiety disorders and influence

on adherence during peginterferon-alpha-2a and ribavirin treatment in patients with hepatitis C. *Alimentary Pharmacology and Therapeutics*, 27, 257–265.

Martín-Santos, R., Egmond, E., Cavero, M., Mariño, Z., Subirà, S., Navinés, R., … Valdes, M. (2015). Chronic Hepatitis C, depression and gender: a state of art. *Advances in Dual Diagnosis*, 8, 193-210.

Mathew, A., Peiffer, L. P., Rhoades, K., & McGarrity, T. J. (2006). Improvement in quality of life measures in patients with refractory hepatitis C, responding to re-treatment with Pegylated interferon alpha -2b and ribavirin. *Health Quality of Life Outcomes*, 4, 30.

Matsushita, H., Ikeda, F., Iwasaki, Y., Seki, H., Nanba, S., Takeuchi, Y., … Yamamoto, K. (2013). Assessment of health-related quality of life and how it predicts the outcome of pegylatedinterferon and ribavirin therapy for chronic hepatitis C. *Journal of Gastroenterology and Hepatology*, 29(2), 337-343.

McCarty, T. R., & Lim, J. K. (2017). Developing therapies to treat hepatitis C infection in post-liver transplant recipients. *Expert Opinion on Pharmacotherapy,* 18(2), 165-174.

McHorney, C. A. (1999). Health status assessment methods for adults: past accomplishments and future challenges. *Annual Review of Public Health*, 20, 309-335.

Messina, J. P., Humphreys, I., Flaxman, A., Brown, A., Cooke, G. S., Pybus, O. G., & Barnes, E. (2015). Global distribution and prevalence of hepatitis C virus genotypes. *Hepatology*, 61(1), 77-87.

Ministerio de Sanidad, Servicios Sociales e Igualdad. (2014). *Encuesta Nacional de Salud. España 2011/12. Calidad de vida relacionada con la salud en adultos: EQ-5D-5L. Serie Informes monográficos no 3.* Madrid: Ministerio de Sanidad, Servicios Sociales e Igualdad.

Mitra, S. (2008). Opioid-induced hyperalgesia: pathophysiology and clinical implications. *Journal of Opioid Management*, 4(3), 123-130.

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(4), 1333-1342.

Monaco, S., Ferrari, S., Gajofatto, A., Zanusso, G., & Mariotto, S. (2012). HCV-related nervous system disorders. *Clinical and Developmental Immunology,* 2012, 236148.

Muhlberger, N., Schwarzer, R., Lettmeier, B., Sroczynski, G., Zeuzem, S., & Siebert, U. (2009). HCV-related burden of disease in Europe: a systematic assessment of incidence, prevalence, morbidity, and mortality. *BMC Public Health*, 9, 34.

Mullington, J., Korth, C., Hermann, D. M., Orth, A., Galanos, C., Holsboer, F., & Pollmacher, T. (2000). Dose-dependent effects of endotoxin on human sleep. *American Journal Physiology Regulatory Integrative and Comparative Physiology*, 278(4), R947-955.

Murray, J., Fishman, S. L., Ryan, E., Eng, F. J., Walewski, J. L., Branch, A. D., & Morgello, S. (2008). Clinicopathologic correlates of hepatitis C virus in brain: a pilot study. *Journal of Neurovirology*, 14(1), 17-27.

Naggie, S., Cooper, C., Saag, M., Workowski, K., Ruane, P., Towner, W. J., … ION-4 Investigators. (2015). Ledipasvir and Sofosbuvir for HCV in patients coinfected with HIV-1. *New England Journal of Medicine*, 373, 705-713.

Navines, R., Castellvi, P., Moreno-Espana, J., Gimenez, D., Udina, M., Canizares, S., ... Martin-Santos, R. (2012). Depressive and anxiety disorders in chronic hepatitis C patients: reliability and validity of the Patient Health Questionnaire. *Journal of Affective Disorders*, 138(3), 343-351.

Neumann, A. U., Lam, N. P., Dahari, H., Gretch, D.R., Wiley, T.E., Layden, T.J., Perelson, A.S. (1998). Hepatitis C viral dynamics in vivo and the antiviral efficacy of interferon-α therapy. *Science*, 282, 103–107.

Nkontchou, G., Ziol, M., Aout, M., Lhabadie, M., Baazia, Y., Mahmoudi, A., ... Beaugrand, M. (2011). HCV genotype 3 is associated with a higher hepatocellular carcinoma incidence in patients with ongoing viral C cirrhosis. *Journal of Viral Hepatitis,* 18(10), e516-522.

Okuda-Ashitaka, E., Minami, T., Matsumura, S., Takeshima, H., Reinscheid, R. K., Civelli, O., & Ito, S. (2006). The opioid peptide nociceptin/orphanin FQ mediates prostaglandin E2-induced allodynia, tactile pain associated with nerve injury. *European Journal of Neuroscience*, 23(4), 995-1004.

Pawlotsky, J. M., Dahari, H., Neumann, A. U., Hezode, C., Germanidis, G., Lonjon, I., ... Dhumeaux, D. (2004). Antiviral action of ribavirin in chronic hepatitis C. *Gastroenterology,* 126(3), 703-714.

Pawlotsky, J. M. (2014). New hepatitis C virus (HCV) drugs and the hope for a cure: concepts in anti-HCV drug development. *Seminars on Liver Disease*, 34(1), 22-29.

Perz, J. F., Armstrong, G. L., Farrington, L. A., Hutin, Y. J., & Bell, B. P. (2006). The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. *Journal of Hepatology*, 45(4), 529-538.

Petta, S., & Craxi, A. (2015). Current and future HCV therapy: do we still need other anti-HCV drugs? *Liver International,* 35 Suppl 1, 4-10.

Pham, T. N., MacParland, S. A., Mulrooney, P. M., Cooksley, H., Naoumov, N. V., & Tomasz I. Michalak, T. I. (2004). Hepatitis C Virus Persistence after Spontaneous or Treatment-Induced Resolution of Hepatitis C. *Journal of Virology*, 5867-5874.

Poordad, F., Schiff, E. R., Vierling, J. M., Landis C., Fontana, R. J., Yang, R., … Swenson, E. S. (2016). Daclatasvir with sofosbuvir and ribavirin for hepatitis C virus infection with advanced cirrhosis or postliver transplantation recurrence. *Hepatology*, 2016; 63: 1493–1505.

Pope, C. R. (1984). Disability and health status: the importance of longitudinal studies. *Social Science and Medicine*, 19(6), 589-593.

Quelhas, R., & Lopes, A. (2009). Psychiatric problems in patients infected with hepatitis C before and during antiviral treatment with interferon-alpha: a review. *Journal of Psychiatric Practince,* 15(4), 262-281.

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.

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.

Raison, C. L., Rye, D. B., Woolwine, B. J., Vogt, G. J., Bautista, B. M., Spivey, J. R., & Miller, A. H. (2010). Chronic interferon-alpha administration disrupts sleep continuity and depth in patients with hepatitis C: association with fatigue, motor slowing, and increased evening cortisol. *Biological Psychiatry,* 68(10), 942-949.

Rand-Hendriksen, K., Augestad, L. A., Kristiansen, I. S., & Stavem, K. (2012). Comparison of hypothetical and experienced EQ-5D valuations: relative weights of the five dimensions. *Quality of Life Research,* 21(6), 1005-1012.

Reau, N. S., & Jensen, D. M. (2014). Sticker shock and the price of new therapies for hepatitis C: is it worth it? *Hepatology,* 59(4), 1246-1249.

Reddick, K. L., Jhaveri, R., Gandhi, M., James, A. H., & Swamy, G. K. (2011). Pregnancy outcomes associated with viral hepatitis. *J Viral Hepatitis,* 18(7), e394-e398.

Reich, S., Kovermann, M., Lilie, H., Knick, P., Geissler, R., Golbik, R. P., ... Behrens, S. E. (2014). Initiation of RNA synthesis by the hepatitis C virus RNA-dependent RNA polymerase is affected by the structure of the RNA template. *Biochemistry*, 53(44), 7002-7012.

Reichard, O., Andersson, J., Schvarcz, R., & Weiland, O. (1991). Ribavirin treatment for chronic hepatitis C. *Lancet*, 337(8749), 1058-1061.

Rockstroh, J. K. (2006). Influence of viral hepatitis on HIV infection. *Journal of Hepatology,* 44(1 Suppl), S25-27.

Rockstroh, J. K., Nelson, M., Katlama, C., Lalezari, J., Mallolas, J., Bloch, M., … Sulkowski, M. (2015). Efficacy and safety of grazoprevir (MK-5172) and elbasvir (MK-8742) in patients with hepatitis C virus and HIV co-infection (C-EDGE CO-INFECTION): a non-randomised, open-label trial. *Lancet HIV*, 2, e319–327.

Rodger, A. J., Jolley, D., Thompson, S. C., Lanigan, A., & Crofts, N. (1999). The impact of diagnosis of hepatitis C virus on quality of life. *Hepatology*, 30(5), 1299-1301.

Roncero, C., Vega, P., Martinez-Raga, J., & Torrens, M. (2017). Chronic Hepatitis C and people with a history of injecting drugs in Spain: population assessment, challenges for effective treatment. *Adicciones,* 29(2), 71-73.

Rothwell, N. J., Luheshi, G., & Toulmond, S. (1996). Cytokines and their receptors in the central nervous system: physiology, pharmacology, and pathology. *Pharmacology and Therapeutics*, 69(2), 85-95.

Rubinow, K. B., & Rubinow, D. R. (2017). In immune defense: redefining the role of the immune system in chronic disease. *Dialogues in Clinical Neuroscience*, 19(1), 19-26.

Sanjuan, R., Nebot, M.R., Chirico, N., Mansky, L.M., & Belshaw, R. (2010). Viral mutation rates. *Journal of Virology*, 84, 9733–9748.

Sarrazin, C., Berg, T., & Ross, R. S. (2010). Prophylaxe, Diagnostik und Therapie der Hepatitis C Virus (HCV) Infektion: German guidelines on the management of HCV infection. *Zeitschrift für Gastroenterologie,* 2010; 48: 289–351.

Saxena, V., Koraishy, F. M., Sise, M. E., Lim, J. K., Schmidt, M., Chung, R. T., … HCV-TARGET. (2016). Safety and efficacy of sofosbuvir-containing regimens in hepatitis C-infected patients with impaired renal function. *Liver International,* 36, 807–816.

Schalock, R. L., Gardner, J. F., & Bradley, V. J. (2007). *Quality of Life of Persons with Intellectual and Other Developmental Disabilities: Applications across Individuals, Organizations, Systems, and Communities*. Washington, DC: American Association on Intellectual and Developmental Disabilities.

Simmonds, P. (2004). Genetic diversity and evolution of hepatitis C virus—15 Years on. *Journal of Genetic Virology,* 85, 3173–3188.

Simmonds, P., Bukh, J., Combet, C., Deleage, G., Enomoto, N., Feinstone, S., … Maertens, G. (2005). Consensus proposals for a unified system of nomenclature of hepatitis C virus genotypes. *Hepatology,* 42, 962–973.

Sinakos, E., Gigi, E., Lalla, T., Bellou, A. L., Sykja, A., Orphanou, E., ... Raptopoulou, M. (2010). Health-related quality of life in Greek chronic hepatitis C patients during pegylated interferon and ribavirin treatment. *Hippokratia*, 14(2), 122-125.

Smith, D.B., Bukh, J., Kuiken, C., Muerhoff, A.S., Rice, C.M., Stapleton, J.T., & Simmonds, P. (2014). Expanded classification of hepatitis C virus into 7 genotypes and 67 subtypes: Updated criteria and genotype assignment web resource. *Hepatology*, 59, 318–327.

Smith, D. J., Combellick, J., Jordan, A. E., & Hagan, H. (2015). Hepatitis C virus (HCV) disease progression in people who inject drugs (PWID): A systematic review and meta-analysis. *International Journal of Drug Policy,* 26(10), 911-921.

Smith-Palmer, J., Cerri, K., & Valentine, W. (2015). Achieving sustained virologic response in hepatitis C: a systematic review of the clinical, economic and quality of life benefits. *BMC Infectious Diseases*, 15, 19.

Solinas, A., Piras, M. R., & Deplano, A. (2015). Cognitive dysfunction and hepatitis C virus infection. *World Journal of Hepatology,* 7(7), 922-925.

Soriano, V., Vispo, E., Labarga, P., Medrano, J., & Barreiro, P. (2010). Viral hepatitis and HIV co-infection. *Antiviral Research,* 85(1), 303-315.

Spiegel, B. M., Younossi, Z. M., Hays, R. D., Revicki, D., Robbins, S., & Kanwal, F. (2005). Impact of hepatitis C on health related quality of life: a systematic review and quantitative assessment. *Hepatology,* 41(4), 790-800.

Stepanova, M., Nader, F., Cure, S., Bourhis, F., Hunt, S., & Younossi, Z. M. (2014). Patients' preferences and health utility assessment with SF-6D and EQ-5D in patients with chronic hepatitis C treated with sofosbuvir regimens. *Alimentary Pharmacology and Therapeutics,* 40(6), 676-685.

Strauss, E., & Dias Teixeira, M. C. (2006). Quality of life in hepatitis C. *Liver International,* 26(7), 755-765.

Sulkowski, M. S., Eron, J. J., Wyles, D., Trinh, R., Lalezari, J., Wang, C., … Podsadecki, T. (2015). Ombitasvir, paritaprevir co-dosed with ritonavir, dasabuvir, and ribavirin for hepatitis C in patients co-infected with HIV-1: a randomized trial. *Journal of the American Medical Association,* 313, 1223-1231.

Sulkowski, M. S., & Thomas, D. L. (2003). Hepatitis C in the HIV-Infected Person. *Annals of Intern Medicne,* 138(3), 197-207.

Sullivan, P. W., & Ghushchyan, V. (2006). Preference-Based EQ-5D index scores for chronic conditions in the United States. *Medical Decision Making,* 26(4), 410-420.

Sun, S., Chen, J., Kind, P., Xu, L., Zhang, Y., & Burstrom, K. (2015). Experience-based VAS values for EQ-5D-3L health states in a national general population health survey in China. *Quality of Life Research*, 24(3), 693-703.

Szende, A., & Williams, A. (2004). *Measuring self-reported population health: An international perspective based on EQ-5D.* Rotterdam: SpringMed Publishing.

Szende, A., Janssen, B., & Cabases, J. (2014). *Self-reported population health: an international perspective based on EQ-5D.* Berlin: Springer.

Thames, A. D., Castellon, S. A., Singer, E. J., Nagarajan, R., Sarma, M. K., Smith, J., ... Hinkin, C. H. (2015). Neuroimaging abnormalities, neurocognitive function, and fatigue in patients with hepatitis C. *Neurology Neuroimmunology and Neuroinflammation*, 2(1), e59.

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(3), 192-202.

Tsukiyama-Kohara, K. Iizuka, N. Kohara, M., & Nomoto, A. (1992). Internal ribosome entry site within hepatitis C virus RNA. *Journal of Virology,* 66, 1476–1483.

Udina, M., Castellvi, P., Moreno-Espana, J., Navines, R., Valdes, M., Forns, X., ... Martin-Santos, R. (2012). Interferon-induced depression in chronic hepatitis C: a systematic review and meta-analysis. *Journal of Clinical Psychiatry,* 73(8), 1128-1138.

Udina, M., Navines, R., Egmond, E., Oriolo, G., Langohr, K., Gimenez, D., ... Martin-Santos, R. (2016). Glucocorticoid Receptors, Brain-Derived Neurotrophic Factor, Serotonin and Dopamine Neurotransmission are Associated with Interferon-Induced Depression. *International Journal of Neuropsychopharmacology*, 19(4).

Umar, M., Akhter, T. S. (2016). New Direct Acting Antiviral Agents for the Treatment of Hepatitis C: 2016 and Beyond. *Journal of College of Physicians and Surgeons Pakistan,* 26(10), 843-850.

University of Liverpool: HEP drug interaction. *www.hep-druginteractions.org* (last accessed on 20 August 2016).

Van Agt, H. M., Essink-Bot, M. L., Krabbe, P. F., & Bonsel, G. J. (1994). Test-retest reliability of health state valuations collected with the EuroQol questionnaire. *Social Science and Medicine*, 39(11), 1537-1544.

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.

Van der Plas, S. M., Hansen, B. E., de Boer, J. B., Stijnen, T., Passchier, J., de Man, R. A., & Schalm, S. W. (2004). The Liver Disease Symptom Index 2.0, validation of a disease-specific questionnaire. *Qual Life Res,* 13(8), 1469-1481.

Vera-Llonch, M., Martin, M., Aggarwal, J., Donepudi, M., Bayliss, M., Goss, T., & Younossi, Z. (2013). Health-related quality of life in genotype 1 treatment-naive chronic hepatitis C patients receiving telaprevir combination treatment in the ADVANCE study. *Alimentary Pharmacology and Therapeutics,* 38(2), 124-133.

Vignuzzi, M., Stone, J.K., Arnold, J.J., Cameron, C.E., & Andino, R. (2005). Quasispecies diversity determines pathogenesis through cooperative interactions in a viral population. *Nature*, 439, 344–348.

Walker, D. R., Pedrosa, M. C., Manthena, S. R., Patel, N., & Marx, S. E. (2015). Early View of the Effectiveness of New Direct-Acting Antiviral (DAA) Regimens in Patients with Hepatitis C Virus (HCV). *Advances in Therapy*, 32(11), 1117-1127.

Wang, C., Sarnow, P., Siddiqui, A. (1993). Translation of human hepatitis C virus RNA in cultured cells is mediated by an internal ribosome-binding mechanism. *Journal of Virology,* 67, 3338–3344.

Ware, J. E., Jr., & Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical Care*, 30(6), 473-483.

Wasson, J., Keller, A., Rubenstein, L., Hays, R., Nelson, E., Johnson, D. & the Dartmouth Primary Care COOP Project. (1992). Benefits and obstacles of health status assessment in ambulatory settings: the clinician's point of view. *Medical Care*, 30, MS42-MS49.

Webster, D. P., Klenerman, P., & Dusheiko, G. M. (2015). Hepatitis C. *Lancet*, 385(9973), 1124-1135.

Westbrook, R. H., & Dusheiko, G. (2014). Natural history of hepatitis C. *Journal of Hepatology*, 61(1 Suppl), S58-68.

World Health Organization (WHO). (2008). *Primary health care: Now more than ever. World health report 2008.* Geneva: World Health Organization.

World Health Organization (WHO). (2016). *Draft global health sector strategies: viral hepatitis, 2016-2021. Sixty-ninth World Health Assembly.* Geneva: World Health Organization.

World Health Organization (WHO). (2017). *Global Hepatitis Report 2017.* Geneva: World Health Organization.

Wyles, D. L., Ruane, P. J., Sulkowski, M. S., Dieterich, D., Luetkemeyer, A., Morgan, T. R., … ALLY-2 Investigators. (2015). Daclatasvir plus Sofosbuvir for HCV in patients coinfected with HIV-1. *New England Journal of Medicine,* 373, 714-725.

Yarlott, L., Heald, E., & Forton, D. (2017). Hepatitis C virus infection, and neurological and psychiatric disorders - A review. *Journal of Advance in Research*, 8(2), 139-148.

Younossi, Z. M., Guyatt, G., Kiwi, M., Boparai, N., & King, D. (1999). Development of a disease specific questionnaire to measure health related quality of life in patients with chronic liver disease. *Gut*, 45(2), 295-300.

Younossi, Z. M., Boparai, N., McCormick, M., Price, L. L., & Guyatt, G. (2001). Assessment of utilities and health-related quality of life in patients with chronic liver disease. *American Journal of Gastroenterology*, 96(2), 579-583.

Younossi, Z., Kallman, J., & Kincaid, J. (2007). The effects of HCV infection and management on health-related quality of life. *Hepatology*, 45(3), 806-816.

Younossi, Z., & Henry, L. (2014). The impact of the new antiviral regimens on patient reported outcomes and health economics of patients with chronic hepatitis C. *Digestive Liver Diseases*, 46 Suppl 5, S186-196.

Younossi, Z. M., Stepanova, M., Henry, L., Gane, E., Jacobson, I. M., Lawitz, E., ... Hunt, S. (2014[a]). Minimal impact of sofosbuvir and ribavirin on health related quality of life in chronic hepatitis C (CH-C). *Journal of Hepatology,* 60(4), 741-747.

Younossi, Z. M., Stepanova, M., Zeuzem, S., Dusheiko, G., Esteban, R., Hezode, C., ... Hunt, S. L. (2014[b]). Patient-reported outcomes assessment in chronic hepatitis C treated with sofosbuvir and ribavirin: the VALENCE study. *Journal of Hepatology*, 61(2), 228-234.

Younossi, Z. M, Kanwal, F., Saab, S., Brown, K. A., El-Serag, H. B., Kim, W. R., … Gordon, S. C. (2015[a]). The impact of hepatitis C burden: an evidence-based approach. *Alimentary Pharmacology and Therapeutics,* 42, 286–295.

Younossi, Z. M., Stepanova, M., Marcellin, P., Afdhal, N., Kowdley, K. V., Zeuzem, S., & Hunt, S. L. (2015[b]). Treatment with ledipasvir and sofosbuvir improves patient-reported outcomes: Results from the ION-1, -2, and -3 clinical trials. *Hepatology,* 61(6), 1798-1808.

Younossi, Z. M., Stepanova, M., Feld, J., Zeuzem, S., Jacobson, I., Agarwal, K., ... Hunt, S. (2016[a]). Sofosbuvir/velpatasvir improves patient-reported outcomes in

HCV patients: Results from ASTRAL-1 placebo-controlled trial. *Journal of Hepatology,* 65(1), 33-39.

Younossi, Z. M., Stepanova, M., Nader, F., & Henry, L. (2016[b]). Patient-Reported Outcomes of Elderly Adults with Chronic Hepatitis C Treated with Interferon- and Ribavirin-Free Regimens. *Journal of American Geriatric Society*, 64(2), 386-393.

Younossi, Z. M., Stepanova, M., Pol, S., Bronowicki, J. P., Carrieri, M. P., & Bourliere, M. (2016[c]). The impact of ledipasvir/sofosbuvir on patient-reported outcomes in cirrhotic patients with chronic hepatitis C: the SIRIUS study. *Liver International,* 36(1), 42-48.

Younossi, Z. M., Stepanova, M., Sulkowski, M., Foster, G. R., Reau, N., Mangia, A., ... Hunt, S. (2016[d]). Ribavirin-Free Regimen With Sofosbuvir and Velpatasvir Is Associated With High Efficacy and Improvement of Patient-Reported Outcomes in Patients With Genotypes 2 and 3 Chronic Hepatitis C: Results From Astral-2 and -3 Clinical Trials. *Clinical Infectious Diseases,* 63(8), 1042-1048.

Youssef, N. F., El Kassas, M., Farag, A., & Shepherd, A. (2017). Health-related quality of Life in patients with chronic hepatitis C receiving Sofosbuvir-based treatment, with and without Interferon: a prospective observational study in Egypt. *BMC Gastroenterology*, 17(1), 18.

Yu, M. L. (2017). Hepatitis C Treatment From "Response-guided" to "Resource-guided" therapy in the transition era from IFN-containing to IFN-free regimens. *Journal of Gastroenterology and Hepatology. doi:* 10.1111/jgh.13747

Zeuzem, S., Dusheiko, G.M., Salupere, R., Mangia, A., Flisiak, R., Hyland, …, Symonds, W.T. (2014). Sofosbuvir and ribavirin in HCV genotypes 2 and 3. *England Journal of Medicine*, 370, 1993–2001.

Zeuzem, S. (2017). Treatment Options in Hepatitis C. *Deutsch Arzteblat International*, 9, 114(1-02), 11-21.

Zimmermann, T., Beckebaum, S., & Berg, C. (2016). The combination of sofosbuvir with amiodarone can cause life-threatening bradycardia. *Gastroenterology,* 54, 665–684.

Annex I. Supplementary Material Study I

Title: New antiviral treatments for chronic hepatitis C and health-related quality of life: a systematic review and meta-analysis

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List of Supplementary Material for the article

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I. Protocol

Background

Description of the condition

Quality of life is often significantly impaired in patients with chronic illnesses compared to the general population, including in those infected with chronic hepatitis C (CHC). The virus may initiate the development of severe liver conditions, such as liver cirrhosis and hepatocellular carcinoma, ultimately leading to hepatic failure and death occurring in 20 to 40% of patients (Muhlberger et al., 2009). Furthermore, associated extra-hepatic symptoms, such as cognitive impairment, psychiatric and medical comorbidities, but also the effects of stigma, often have a major impact on the patients' life quality (Scalone et al., 2015).

Unlike most chronic illnesses, CHC may be treated. Since the discovery of the virus at the end of the 1980s, standard therapy to treat CHC involved a combination of pegylated interferon-alpha with ribavirin (PR). PR has shown efficacy rates of up to 50% (Messina et al., 2015), but is known to have several side effects altering life quality (Arora et al., 2006). Recently, new types of therapy have been introduced, named new direct-acting antivirals (DAA). These offer higher efficacy rates of up to 90%, easier and shorter administration, and better side-effect profiles (Walker et al., 2015). However, knowledge of the possible impact of these new regimens on health-related quality of life (HRQL) is still limited.

Description of the intervention

Antiviral treatment using interferon-alpha has shown to significantly alter patient's mental and physical quality of life. Although new antiviral treatments using direct-acting antiviral agents show improved results, such as increased response rates and reduced side effects, the effect of these different regimens on quality of life is not yet widely studied.

How the intervention might work

CHC patients are known to have a reduced mental and physical life quality compared to the general population. Antiviral treatment involving interferon-alpha may further decrease life quality (Spiegel et al., 2005; Capuron et al., 2012). Although research is still limited, new DAA regimen may have less pronounced altering effects on the life quality of CHC patients.

Why it is important to do this review

To summarize the evidence of RCT studies assessing HRQL in CHC patients receiving DAA alone or in combination with PR, or ribavirin, and related risk factors

Objectives

To carry out a systematic review and meta-analysis of data that could help to assess whether HRQL is significantly better in patients receiving DAA compared to those receiving PR, or combination therapy involving PR or ribavirin. Moreover, to study risk factors associated to HRQL in CHC patients before and during antiviral treatment.

Methods

Types of studies

Randomized clinical trials assessing HRQL in patients receiving antiviral therapy involving DAA for CHC.

Types of participants

We included patients with CHC, inititating antiviral treatment with DAA, or using a combination of DAA plus PR or plus ribavirin.

Types of interventions

2. Direct-acting antiviral agents. Any dose. 1. Direct-acting antiviral agents and Peginterferon-alpha and/or Ribavirin. Any dose. 3. Placebo with or

without PR or ribavirin. Any dose.

Primary outcomes

The primary outcome measure was change in HRQL scores, using the mean difference (MD) with standard deviation (SD) or confidence interval (95% CI), as well as the minimal clinically important difference (MCID) (Ringash et al., 2007) for scores reported by both EQ-5D and SF-36 questionnaires. This was applied from baseline throughout treatment and follow-up.

Secondary outcomes

Secondary outcome measures were changes from baseline in the predictive factors of HRQL, using OR and confidence interval of 95% or mean differences (MD) with SD, for sociodemographic factors (e.g. age and gender), clinical and biological parameters (i.e. comorbid HIV infection, history of psychiatric disorders or drug abuse, and the presence of cirrhosis), and sustained virologic response (SVR) (i.e. whether or not treatment had been successful).

Searches

Databases: MEDLINE, PsycINFO, the Cochrane Library, Clinicaltrials.gov, and manual searches.

Keywords:

1) hepatitis AND c AND (interferon-alpha OR peginterferon OR (pegylated AND interferon) OR direct-acting antiviral OR DAA OR telaprevir OR boceprevir OR simeprevir OR sofosbuvir OR velpatasvir OR ledipasvir OR daclatasvir OR paritaprevir) AND (HRQL OR HRQoL OR quality of life) AND (randomized controlled trial OR RCT) AND (EuroQol-5D OR EQ-5D OR HCV-PRO).

2) hepatitis AND c AND (interferon-alpha OR peginterferon OR (pegylated AND interferon) OR direct-acting antiviral OR DAA OR telaprevir OR boceprevir OR simeprevir OR sofosbuvir OR velpatasvir OR ledipasvir OR

daclatasvir OR paritaprevir) AND (HRQL OR HRQoL OR quality of life) AND (randomized controlled trial OR RCT) AND (Short-Form-36 SF-36 OR HCV-PRO).

Date: No limit. Language: English, German, French or Spanish

Selection of studies

Study selection was independently performed by two clinical researchers (EE and RN). Disagreements were resolved by discussion, and consensus was achieved in the selection of articles for analysis.

Data extraction and management

Extraction: Data were independently abstracted by both reviewers (EE and RN), who recorded the author, year of publication, design, characteristics of the study population, viral co-infection, history of drug use, history of psychiatric disorders, and dose and type of antiviral treatment. Also, outcomes of HRQL scores and potential risk factors were abstracted for each study group.

Management: Data were extracted in simple forms.

Data: Numerical data was obtained using the EQ-5D and SF-36 questionnaires, instruments that have been validated and used in chronic illnesses.

Assessment of risk of bias in included studies

Two authors assessed risk of bias using the tool described in the Cochrane Library.

This tool recommends evaluation of: Sequence generation, allocation concealment, blinding, and completeness of outcome data, selective reporting, and other biases.

The risk of bias in each domain and overall were assessed and categorized into:

A. Low risk of bias: plausible bias unlikely to seriously alter the results; B. High risk of bias: plausible bias that seriously weakens confidence in the results; C. Unclear risk of bias: plausible bias that raises some doubt about the results.

Measures of treatment effect

The primary outcome measure was change in HRQL scores, using the mean difference (MD) with standard deviation (SD) or confidence interval (95%CI), as well as the minimal clinically important difference (MID) (Ringash et al., 2007; Le et al., 2013) for scores reported by both EQ-5D and SF-36 questionnaires. This was applied from baseline throughout treatment and follow-up.

Secondary outcome measures were changes from baseline in the predictive factors of HRQL, using OR and confidence interval of 95% or mean differences (MD) with SD, for sociodemographic factors (e.g. age and gender), clinical and biological parameters (i.e. comorbid HIV infection, history of psychiatric disorders or drug abuse, and the presence of cirrhosis), and sustained virologic response (SVR) (i.e. whether or not treatment had been successful).

Assessment of heterogeneity

We inspected all the studies to judge clinical and methodological heterogenity.

Heterogeneity between trials was assessed using both the chi-square and I-square tests I^2 statistic was used to estimate the percentage of inconsistency thought to be due to chance. Between-study heterogeneity was considered to be significant for a p-value < 0.1 on the chi-square test. If there was no heterogeneity, a fixed model was used. In the event of heterogeneity, a random effects model was used (Moher et al., 2009).

Assessment of reporting biases

Publication bias was examined in a funnel plot using mean differences against its standard error, using Begg's test, while the degree of asymmetry was

tested statistically using Egger's unweighted regression asymmetry test (Egger et al., 1997; Higgins et al., 2008).

Data synthesis

The fixed or the random-effects model by DerSimonian and Laird (1986) were used for all analyses. Random effects were used in case of high heterogeneity (p-value < 0.1 on the chi-square test).

References

DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88.

Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315(7109):629–34.

Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions, Version 5.0.1*. The Cochrane Collaboration; 2008. http:// www.handbook.cochrane.org/. Updated September 2008. Accessed November 20, 2016.

Messina JP, Humphreys I, Flaxman A, Brown A, Cooke GS, ...Pybus O, et al. Global distribution and prevalence of hepatitis c virus genotypes. *Hepatology* 2015;61:77-7.

Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6(7):e1000097.

Muhlberger N, Schwarzer R, Lettmeier B, Sroczynski G, Zeuzem S, Siebert U. HCV-related burden of disease in Europe: a systematic assessment of incidence, prevalence, morbidity, and mortality. *BMC Public Health* 2009;9:34.

Scalone L, Fagiuoli S, Ciampichini R, Gardini I, Bruno R, Pasulo L, Mantovani LG. The societal burden of chronic liver diseases: results from the COME study. *BMJ Open Gastroenterol* 2014;2:e000025.

Spiegel BM, Younossi ZM, Hays RD, Revicki D, Robbins S, Kanwal F. Impact of hepatitis C on health related quality of life: a systematic review and quantitative assessment. *Hepatology* 2005;41:790-800.

Walker DR, Pedrosa MC, Manthena SR, Patel N, Marx SE. Early View of the Effectiveness of New Direct-Acting Antiviral (DAA) Regimens in Patients with Hepatitis C Virus (HCV). *Adv Ther* 2015;32:1117.

Capuron L, Miller AH. Immune system to brain signaling: neuropsychopharmacological implications. *Pharmacol Ther* 2011;130:226–38.

Ringash J, O'Sullivan B, Bezjak A, Redelmeier DA. Interpreting clinically significant changes in patient-reported outcomes. *Cancer* 2007;110:196-202.

II PRISMA guidelines

Table 1. Checklist of items to include when reporting a systematic review (with or without meta-analysis).

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figure 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N. A.
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

III Excluded studies for EQ-5D

HRQL not or poorly reported

Litwin AH, Soloway IJ, Cockerham-Colas L, Reynoso S, Heo M, Tenore C, et al. Successful treatment of chronic hepatitis C with triple therapy in an opioid agonist treatment program. *Int J Drug Policy* 2015;26(10):1014-9.

Clinical Trial Investigators. Evaluation of the Health-Related Quality of Life During Combined Treatment of Chronic Hepatitis Due to Hepatitis C Virus Under Habitual Clinical Practise Conditions. 2015. Identifier: NCT00863109

Clinical Trial Investigators. An Observational Study of Pegasys (Peginterferon Alfa-2a) Plus Copegus (Ribavirin) in Participants With Chronic Hepatitis C (CHC), Genotype 2, 3, 1 or 4, Undergoing Opioid Maintenance Therapy (PEGHOPE). 2012. Identifier: NCT01416610

Everson T, Di Bisceglie AM, Lee WM, Ghany M, Dienstag JL, Shiffman M, et al. Long Term Interferon for Patients Who Did Not Clear Hepatitis C Virus With Standard Treatment (HALT-C). 2010. Identifier: NCT00006164

Clinical Trials Investigators. A Study of PEGASYS (Peginterferon Alfa-2a (40KD)) in Combination With Copegus (Ribavirin) in Patients With Chronic Hepatitis C (CHC) Enrolled in a Methadone Maintenance Treatment Program. 2016. Identifier: NCT00087594

Asher AK, Portillo CJ, Cooper BA, Dawson-Rose C, Vlahov D, Page KA. Clinicians' views of hepatitis C virus treatment candidacy with direct-acting antiviral regimens for people who inject drugs. *Substance Use & Misuse* 2016;51(9):1218-23.

Kuniholm MH, Leach T, Lunievicz J, Olivo N, Anastos K, Vazquez Y, et al. Hepatitis C direct acting antiviral therapies in a New York City HIV/AIDS special needs plan: Uptake and barriers. *AIDS Patient Care and STDs* 2015;29(12):643-5.

Woodrell C, Weiss J, Branch A, Gardenier D, Krauskopf K, Kil N, et al. Primary care-based hepatitis C treatment outcomes with first-generation direct-acting agents. *J Addict Med* 2015;9(5):405-10.

Cattie JE, Letendre SL, Woods SP, Barakat F, Perry W, Cherner M, et al. Persistent neurocognitive decline in a clinic sample of hepatitis C virus-infected persons receiving interferon and ribavirin treatment. *J Neurovirology* 2014;20(6):561-70.

Maier MM, He H, Schafer SD, Ward TT, Zaman A. Hepatitis C treatment eligibility among HIV-hepatitis C virus coinfected patients in Oregon: a population-based sample. AIDS *Care* 2014;26(9):1178-85.

Kauf TL, Mohamed AF, Hauber AB, Fetzer D, Ahmad A. Patients' willingness to accept the risks and benefits of new treatments for chronic hepatitis C virus infection. *Patient* 2012;5(4):265-78.

Stein MR, Soloway IJ, Jefferson KS, Roose RJ, Arnsten JH, Litwin AH. Concurrent group treatment for hepatitis C: implementation and outcomes in a

methadone maintenance treatment program. *J Subst Abuse Treat* 2012;43(4):424-32.

Brogan AJ, Talbird SE, Thompson JR, Miller JD, Rubin J, Deniz B. Cost-effectiveness of Telaprevir combination therapy for chronic hepatitis C. *PLoS One* 2014. 6;9(3):e90295.

Pearlman BL, Ehleben C, Perrys M. The combination of simeprevir and sofosbuvir is more effective than that of peginterferon, ribavirin, and sofosbuvir for patients with hepatitis C-related Child's class A cirrhosis. *Gastroenterology* 2015;148(4):762-70.e2; quiz e11-2.

Dan YY, Ferrante SA, Elbasha EH, Hsu TY. Cost-effectiveness of boceprevir co-administration versus peginterferon alpha-2b and ribavirin only for patients with hepatitis C genotype 1 in Singapore. *Antivir Ther* 2014.

Younossi ZM, Stepanova M, Henry L, Gane E, Jacobson IM, Lawitz E, et al. Minimal Impact of Sofosbuvir and Ribavirin on Health Related Quality of Life in Chronic Hepatitis C (CH-C). *J Hepatol* 2014;60(4):741-7.

Anderson RT, Baran RW, Erickson P, Revicki DA, Dietz B, Gooch K. Psychometric evaluation of the hepatitis C virus patient-reported outcomes (HCV-PRO) instrument: validity, responsiveness, and identification of the minimally important difference in a phase 2 clinical trial. *Qual Life Res* 2014;23:877-86.

Ferrante SA, Chhatwal J, Brass CA, El Khoury AC, Poordad F, Bronowicki JP, et al. Boceprevir for previously untreated patients with chronic hepatitis C Genotype 1 infection: a US-based cost-effectiveness modeling study. *BMC Infect Dis* 2013;13:190.

Schaefer M, Sarkar R, Knop V, Effenberger S, Friebe A, Heinze L, et al. Escitalopram for the prevention of peginterferon-α2a-associated depression in hepatitis C virus-infected patients without previous psychiatric disease: a randomized trial. *Ann Intern Med* 2012;157(2):94-103.

Bezemer G, Van Gool AR, Verheij-Hart E, Hansen BE, Lurie Y, Esteban JI, et al. Long-term effects of treatment and response in patients with chronic hepatitis C on quality of life. An international, multicenter, randomized, controlled study. *BMC Gastroenterol* 2012;12:11.

Kamal SM, Ahmed A, Mahmud S, Nabegh L, El Gohary I, Obadan I, et al. Enhanced efficacy of pegylated interferon alpha-2a over pegylated interferon and ribavirin in chronic hepatitis C genotype 4A randomized trial and quality of life analysis. *Liver Int* 2011:401-461.

Snow KK, Bonkovsky HL, Fontana RJ, Kim HY, Sterling RK, Di Bisceglie AM, Morgan TR, et al. Changes in quality of life and sexual health are associated with low-dose peginterferon therapy and disease progression in patients with chronic hepatitis C. *Aliment Pharmacol Ther* 2010 Apr;31(7):719-34.

Siebert U, Sroczynski G. Clinical effectiveness and cost-effectiveness of initial combination therapy with interferon/peginterferon plus ribavirin in patients with chronic hepatitis C in Germany: a health technology assessment

commissioned by the German Federal Ministry of Health and Social Security. *J Technol Assess Health Care* 2005;21(1):55-65.

Zeuzem S, Yoshida EM, Benhamou Y, Pianko S, Bain VG, Shouval D, et al. Albinterferon alfa-2b dosed every two or four weeks in interferon-naïve patients with genotype 1 chronic hepatitis C. *Hepatology* 2008;48(2):407-417.

Bergmann JF, Vrolijk JM, van der Schaar P, Vroom B, van Hoek B, van der Sluys Veer A, et al. Gamma-glutamyltransferase and rapid virological response as predictors of successful treatment with experimental or standard peginterferon-alpha-2b in chronic hepatitis C non-responders. *Liver Int* 2007;27(9):1217-1225.

Sjogren MH, Sjogren R Jr, Lyons MF, Ryan M, Santoro J, Smith C, et al. Antiviral response of HCV genotype 1 to consensus interferon and ribavirin versus pegylated interferon and ribavirin. *Dig Dis Sci* 2007;52(6):1540-1547.

Bonkovsky HL, Snow KK, Malet PF, Back-Madruga C, Fontana RJ, Sterling RK, et al. Health-related quality of life in patients with chronic hepatitis C and advanced fibrosis. *J Hepatol* 2007;46(3):420-431.

Bronowicki JP, Ouzan D, Asselah T, Desmorat H, Zarski JP, Foucher J, et al. Effect of ribavirin in genotype 1 patients with hepatitis C responding to pegylated interferon alfa-2a plus ribavirin. *Gastroenterology* 2006;131(4):1040-8.

Mathew A, Peiffer LP, Rhoades K, McGarrity TJ. Improvement in quality of life measures in patients with refractory hepatitis C, responding to re-treatment with Pegylated interferon alpha -2b and ribavirin. *Health Qual Life Outc* 2006;4(30).

Arora S, O'Brien C, Zeuzem S, Shiffman ML, Diago M, Tran A, et al. Treatment of chronic hepatitis C patients with persistently normal alanine aminotransferase levels with the combination of peginterferon alpha-2a (40 kDa) plus ribavirin: impact on health-related quality of life. *J Gastroenterol Hepatol* 2006;21(2):406-12.

Grieve R, Roberts J, Wright M, Sweeting M, DeAngelis D, Rosenberg W, et al. Cost effectiveness of interferon alpha or peginterferon alpha with ribavirin for histologically mild chronic hepatitis C. *Gut* 2006;55(9):1332-8.

Wright M, Forton D, Main J, Goldin R, Torok E, Tedder R, et al. Treatment of histologically mild hepatitis C virus infection with interferon and ribavirin: a multicentre randomized controlled trial. *J Viral Hepat* 2005;12(1):58-66.

Younossi Z, Henry L. The impact of the new antiviral regimens on patient reported outcomes and health economics of patients with chronic hepatitis C. *Dig Liver Dis* 2014;46S5:S186-96.

Hauser G, Awad T, Brok J, Thorlund K, Štimac D, Mabrouk M, Gluud C, Gluud LL. Peginterferon plus ribavirin versus interferon plus ribavirin for chronic hepatitis C. *Cochrane Database Syst Rev* 2014;(2):CD005441.

Hauser G, Awad T, Thorlund K, Štimac D, Mabrouk M, Gluud C. Peginterferon alpha-2a versus peginterferon alpha-2b for chronic hepatitis C. *Cochrane Database Syst Rev* 2014;(2):CD005642.

Lamers MH, Broekman M, Drenth JP, Gluud C. Aminoadamantanes for chronic hepatitis C. *Cochrane Database Syst Rev* 2014;5:CD010125.

Hartwell D, Jones J, Baxter L, Shepherd J. Peginterferon alfa and ribavirin for chronic hepatitis C in patients eligible for shortened treatment, re-treatment or in HCV/HIV co-infection: a systematic review and economic evaluation. *Health Technol Assess* 2011;15(17):1-210.

Gluud LL, Krogsgaard K, Gluud C. Ribavirin with or without alpha interferon for chronic hepatitis C. *Cochrane Database Syst Rev* 2007;(2):CD002234.

Shepherd J, Brodin H, Cave C, Waugh N, Price A, Gabbay J.Pegylated interferon alpha-2a and -2b in combination with ribavirin in the treatment of chronic hepatitis C: a systematic review and economic evaluation. *Health Technol Assess* 2004;8(39):1-125.

Hornberger J, Farci P, Prati D, Zeuzem S, Green J, Patel KK. The economics of treating chronic hepatitis C patients with peginterferon alpha-2a (40 kDa) plus ribavirin presenting with persistently normal aminotransferase. *J Viral Hepat* 2006;13(6):377-386.

Pawłowska M. [Retreatment strategies for the patients with HCV infection]. *Przegl Epidemiol* 2005;59(2):591-4.

Siebert U, Sroczynski G. Clinical effectiveness and cost-effectiveness of initial combination therapy with interferon/peginterferon plus ribavirin in patients with chronic hepatitis C in Germany: a health technology assessment commissioned by the German Federal Ministry of Health and Social Security. *J Technol Assess Health Care* 2005;21(1):55-65.

Reviews, protocols…

Hauser G, Awad T, Thorlund K, Štimac D, Mabrouk M, Gluud C. Peginterferon alpha-2a versus peginterferon alpha-2b for chronic hepatitis C. *Cochrane Database Syst Rev* 2014 Feb 28;(2):CD005642.

Jakobsen JC, Nielsen EE, Feinberg J, Fobian K, Katakam KK, Hauser G, et al. Direct-acting antivirals for chronic hepatitis C (Protocol). *Cochrane Database Syst Rev* 2016;4:CD012143.

Gurusamy KS, Toon CD, Thorburn D, Tsochatzis E, Davidson BR. Pharmacological treatments for chronic hepatitis C liver disease: a network meta-analysis (Protocol). *Cochrane Database Syst Rev* 2015;4:CD011641.

Pelayo Alvarez M, Westeel V, Cortés-Jofré M, Bonfill Cosp X. Chemotherapy versus best supportive care for extensive small cell lung cancer. *Cochrane Database Syst Rev 2013*;11:CD001990.

Cella D, Li JZ, Cappelleri JC, Bushmakin A, Charbonneau C, Kim ST, et al. Quality of life in patients with metastatic renal cell carcinoma treated with sunitinib or interferon alfa: results from a phase III randomized trial. *J Clin Oncol* 2008 Aug 1;26(22):3763-9.

Younossi Z, Henry L. The impact of the new antiviral regimens on patient reported outcomes and health economics of patients with chronic hepatitis C. *Dig Liver Dis*.2014;46S5:S186-96.

Hauser G, Awad T, Brok J, Thorlund K, Štimac D, Mabrouk M, Gluud C, Gluud LL. Peginterferon plus ribavirin versus interferon plus ribavirin for chronic hepatitis C. *Cochrane Database Syst Rev* 2014;(2):CD005441.

Hauser G, Awad T, Thorlund K, Štimac D, Mabrouk M, Gluud C. Peginterferon alpha-2a versus peginterferon alpha-2b for chronic hepatitis C. *Cochrane Database Syst Rev* 2014 Feb 28;(2):CD005642.

Lamers MH, Broekman M, Drenth JP, Gluud C. Aminoadamantanes for chronic hepatitis C. *Cochrane Database Syst Rev* 2014;5:CD010125.

Hartwell D, Jones J, Baxter L, Shepherd J. Peginterferon alfa and ribavirin for chronic hepatitis C in patients eligible for shortened treatment, re-treatment or in HCV/HIV co-infection: a systematic review and economic evaluation. *Health Technol Assess* 2011;15(17):1-210.

Gluud LL, Krogsgaard K, Gluud C. Ribavirin with or without alpha interferon for chronic hepatitis C. *Cochrane Database Syst Rev* 2007;(2):CD002234.

Shepherd J, Brodin H, Cave C, Waugh N, Price A, Gabbay J.Pegylated interferon alpha-2a and -2b in combination with ribavirin in the treatment of chronic hepatitis C: a systematic review and economic evaluation. *Health Technol Assess* 2004;8(39):1-125.

Hornberger J, Farci P, Prati D, Zeuzem S, Green J, Patel KK. The economics of treating chronic hepatitis C patients with peginterferon alpha-2a (40 kDa) plus ribavirin presenting with persistently normal aminotransferase. *J Viral Hepat* 2006;13(6):377-386.

Siebert U, Sroczynski G. Clinical effectiveness and cost-effectiveness of initial combination therapy with interferon/peginterferon plus ribavirin in patients with chronic hepatitis C in Germany: a health technology assessment commissioned by the German Federal Ministry of Health and Social Security. *J Technol Assess Health Care* 2005;21(1):55-65.

No HCV

Lipp A, Sandroni P, Low PA.Systemic postganglionic adrenergic studies do not distinguish Parkinson's disease from multiple system atrophy. *J Neurol Sci* 2009;281(1-2):15-9.

Sheldon K, Howitt D. Sexual fantasy in paedophile offenders: Can any model explain satisfactorily new findings from a study of Internet and contact sexual offenders?. *Legal Criminol Psychol* 2008;13(1):137-58.

Scott J, Rosa K, Fu M, Cerri K, Peeters M, Beumont M, et al. Fatigue during treatment for hepatitis C virus: results of self-reported fatigue severity in two Phase IIb studies of simeprevir treatment in patients with hepatitis C virus genotype 1 infection. *BMC Infect Dis* 2014;14:465.

Heller T. Pegylated Interferon to Treat Chronic Hepatitis D. 2012. Identifier: NCT00023322

Marcellin P, Lau GK, Zeuzem S, Heathcote EJ, Pockros PJ, Reddy KR, et al. Comparing the safety, tolerability and quality of life in patients with chronic

hepatitis B vs chronic hepatitis C treated with peginterferon alpha-2a. *Liver Int* 2008;28(4):477-485.

Age <18 or >65 years

Hartwell D, Cooper K, Frampton GK, Baxter L, Loveman E. The clinical effectiveness and cost-effectiveness of peginterferon alfa and ribavirin for the treatment of chronic hepatitis C in children and young people: a systematic review and economic evaluation. *Health Technol Assess* 2014;18(65):i-xxii, 1-202.

Murray KF, Rodrigue JR, González-Peralta RP, Shepherd J, Barton BA, Robuck PR, et al. Design of the PEDS-C trial: pegylated interferon +/- ribavirin for children with chronic hepatitis C viral infection. *Clin Trials* 2007;4(6):661-673.

Sample size

Stambough M, Roman M, Blair DC, Sidman EF, Miller CD. Preemptive antiretroviral therapy modifications for the management of potential clinically significant drug interactions with direct acting hepatitis C therapies. *Int J STD & AIDS* 2016;27(3):235-7.

Tanwar S, Wright M, Foster GR, Ryder SD, Mills PR, Cramp ME, et al. Randomized clinical trial: a pilot study investigating the safety and effectiveness of an escalating dose of peginterferon α-2a monotherapy for 48 weeks compared with standard clinical care in patients with hepatitis C cirrhosis. *Eur J Gastroenterol Hepatol* 2012;24(5):543-550.

Study design

Clinical Trial Investigators. Impact of Physician Directed Education on Patient Compliance With Hepatitis C Therapy (OPTIMAL). 2011. Identifier: NCT01405027

Wright M, Grieve R, Roberts J, Main J, Thomas HC. Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. *Health Technol Assess* 2006 Jul;10(21):1-113, iii.

Clinical Trial Investigators. Escitalopram for the Prevention of PEGASYS-associated Depression in Hepatitis C Virus-infected Patients. 2014. Identifier: NCT00136318

No antiviral treatment

Nikolova K, Gluud C, Grevstad B, Jakobsen JC. Nitazoxanide for chronic hepatitis C. *Cochrane Database Syst Rev* 2014 Apr 6;(4):CD009182.

Lamers MH, Broekman M, Drenth JP, Gluud C. Aminoadamantanes for chronic hepatitis C. *Cochrane Database Syst Rev* 2014;5:CD010125.

Language restriction

Malaguarnera M, Vacante M, Bertino G, Neri S, Gargante MP, et al. The supplementation of acetyl-L-carnitine decreases fatigue and increases quality of life in patients with hepatitis C treated with pegylated interferon-α 2b plus ribavirin. [Article in Italian]. *J Interferon Cytokine Res* 2011;31(9):653-659.

Romantsov MG, Sologub TV, Goriacheva LG, Kovalenko SN, Sukhanov DS, Shul'diakov AA, et al. Pathogenetically substantiated therapy of patients with virus hepatitis C, quality of life, and the disease outcome risk (clinical survey). [Article in Russian]. *Antibiot Khimioter* 2010;55(3-4):45-55.

Pawłowska M. Retreatment strategies for the patients with HCV infection. [Article in Russian]. *Przegl Epidemiol* 2005;59(2):591-4.

IV Excluded studies for SF-36

Study design

Fraenkel L, Lim J, Garcia-Tsao G, Reyna V, Monto A, Bridges, John FP. Variation in treatment priorities for chronic hepatitis C: A latent class analysis. *The Patient* 2016;9(3):241-9.

Zhang S, Rust G, Cardarelli K, Felizzola J, Fransua M, Stringer HG. Adherence to highly active antiretroviral therapy impact on clinical and economic outcomes for Medicaid enrollees with human immunodeficiency virus and hepatitis C coinfection. *AIDS Care* 2015;27(7):829-35.

Pereira M, Fialho R, Canavarro MC. Prevalence and correlates of emotional distress in HIV/HCV coinfection. *AIDS Care* 2014;26(1):S56-S64.

Farrell G, Comiskey C. Dualities of living with HIV/HCV co-infection: Patients' perspectives from those who are ineligible for or nonresponsive to treatment. *JANAC: Journal of the Association of Nurses in AIDS Care* 2014;25(1):9-22.

Hopwood M. Perspectives of a self-selected sample of former patients on the long-term health outcomes of interferon-based hepatitis C treatments: An exploratory study. *Psychol Health Med* 2013;18(6):742-50.

Préau M, Protopopescu C, Raffi F, Rey D, Chêne G, Marcellin F; The ANRS CO8 APROCO-COPILOTE Study Group. Satisfaction with care in HIV-infected patients treated with long-term follow-up antiretroviral therapy: The role of social vulnerability. *AIDS Care* 2012;24(4):434-43.

Groessl EJ, Weingart KR, Gifford AL, Asch SM, Ho SB. Development of the hepatitis C self-management program. *Patient Educat Counseling* 2011;83(2):252-5.

Wurst FM, Thon N, Yegles M, Halter C, Weinmann W, Laskowska B, et al. Optimizing heroin-assisted treatment (HAT): Assessment of the contribution of direct ethanol metabolites in identifying hazardous and harmful alcohol use. *Drug Alc Dep* 2011;115(1-2):57-61.

Silberbogen AK, Ulloa E, Mori DL, Brown K. A telehealth intervention for veterans on antiviral treatment for the hepatitis C virus. *Psychological Services* 2012;9(2):163-73.

Clinicaltrials.gov. A service of the U.S. National Institutes of Health. http://clinicaltrials.gov/ct2/show/NCT01854528 (accessed Nov 14, 2016)

Clinicaltrials.gov. A service of the U.S. National Institutes of Health. http://clinicaltrials.gov/ct2/show/NCT01074008 (accessed Nov 14, 2016)

Clinicaltrials.gov. A service of the U.S. National Institutes of Health. http://clinicaltrials.gov/ct2/show/NCT01854697 (accessed Nov 14, 2016)

No HRQL

Sheridan DA, Bridge SH, Crossey MME, Felmlee DJ, Thomas HC, Neely RDG, et al. Depressive symptoms in chronic hepatitis C are associated with plasma apolipoprotein E deficiency. *Metabol Brain Dis* 2014;29(3):625-34.

Mathias S, Crosby RD, Bayliss MS, L'Italien G, Sapra S. Measurement properties of the Flu-Like Symptom Index from the Hepatitis Physical Symptom Severity Diary. *Qual Life Res* 2014;23(5):1489-96.

No CHC

Marcellin F, Protopopescu C, Abé C, Boyer S, Blanche J, Ongolo-Zogo P; EVAL Study Group. Desire for a child among HIV-infected women receiving antiretroviral therapy in Cameroon: Results from the national survey EVAL (ANRS 12-116). *AIDS Care* 2010;22(4):441-51.

Ito J, Suda G, Yamamoto Y, Nagasaka A, Furuya K, Kumagai K; NORTE Study Group. Prevalence and characteristics of naturally occurring sofosbuvir resistance-associated variants in patients with hepatitis C virus genotype 1b infection. *Hepatol Res* 2016.

Younossi ZM, Stepanova M, Sulkowski M, Naggie S, Puoti M, Orkin C, Hunt SL. Sofosbuvir and Ribavirin for Treatment of Chronic Hepatitis C in Patients Coinfected With Hepatitis C Virus and HIV: The Impact on Patient-Reported Outcomes. *J Infect Dis* 2015;212(3):367-77.

Younossi ZM, Stepanova M, Sulkowski M, Naggie S, Henry L, Hunt S. Sofosbuvir and ledipasvir improve patient-reported outcomes in patients co-infected with hepatitis C and human immunodeficiency virus. *J Viral Hepat* 2016;23(11):857-65.

Language restriction

Godzik P, Komorowski M, Cielecka-Kuszyk J, Madaliński K. [Inhibitors of hepatitis C virus--therapeutic possibilities]. [Article in Polish] *Przegl Epidemiol* 2010;64(4):479-84.

Age <18 or >65 years old

Younossi ZM, Stepanova M, Nader F, Henry L. Patient-Reported Outcomes of Elderly Adults with Chronic Hepatitis C Treated with Interferon- and Ribavirin-Free Regimens. *J Am Geriatr Soc* 2016;64(2):386-93.

Reviews

Hussaini T. Paritaprevir/ritonavir-ombitasvir and dasabuvir, the 3D regimen for the treatment of chronic hepatitis C virus infection: a concise review. *Hepat Med* 2016;8:61-8.

Younossi ZM, Stepanova M, Henry L, Nader F, Younossi Y, Hunt S. Adherence to treatment of chronic hepatitis C: from interferon containing regimens to interferon and ribavirin free regimens. *Medicine (Baltimore)* 2016;95(28):e4151.

Younossi ZM, Stepanova M, Feld J, Zeuzem S, Sulkowski M, Foster GR, et al. Sofosbuvir and Velpatasvir Combination Improves Outcomes Reported by Patients With HCV Infection, Without or with Compensated or Decompensated Cirrhosis. *Clin Gastroenterol Hepatol* 2016.

No DAA used

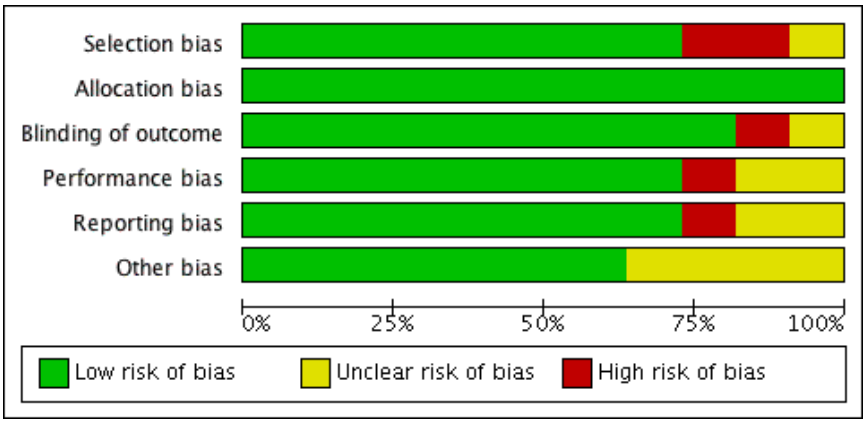
Nogueira JBC, Sena LCS, de Souza Siqueira Quintans J, da Silva Almeida JRG, França AVC, Júnior LJQ. Side effects of the therapy with peginterferon and ribavirin in chronic hepatitis C: A small audit. *J Pharm Pract* 2012;25(1):85-8.

Di Sciascio G, Calò S, Nardini M. Haematological abnormalities and quality of life in patients with chronic hepatitis C who meet major depression disorder during antiviral therapy. *Italian J Psychopathol* 2010;16(1):4-10.

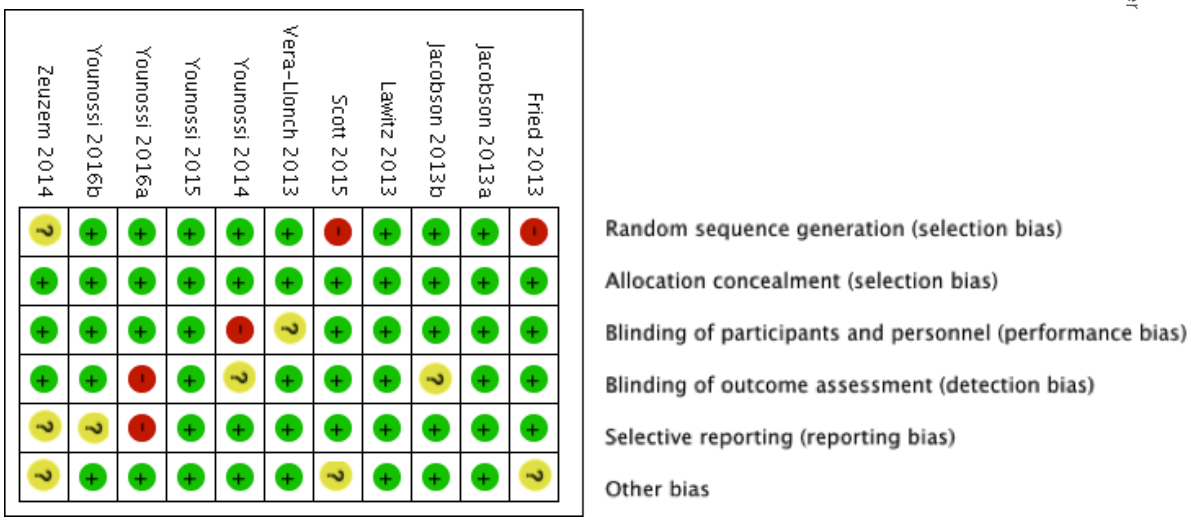
Clinicaltrials.gov. A service of the U.S. National Institutes of Health. http://clinicaltrials.gov/ct2/show/NCT02716779 (accessed Nov 14, 2016)

Clinicaltrials.gov. A service of the U.S. National Institutes of Health. http://clinicaltrials.gov/ct2/show/NCT01258101 (accessed Nov 14, 2016)

V Risk of bias graph



VI Risk of bias summary

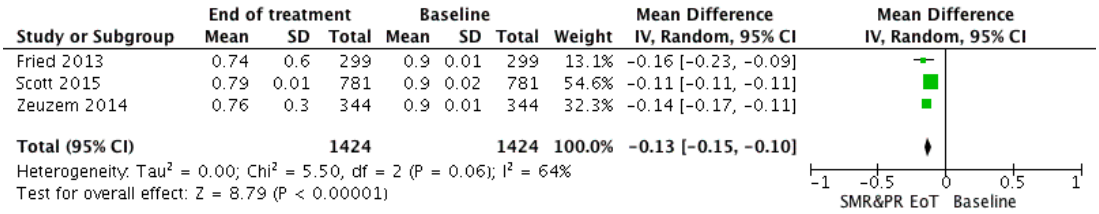


VII Forest plot figures

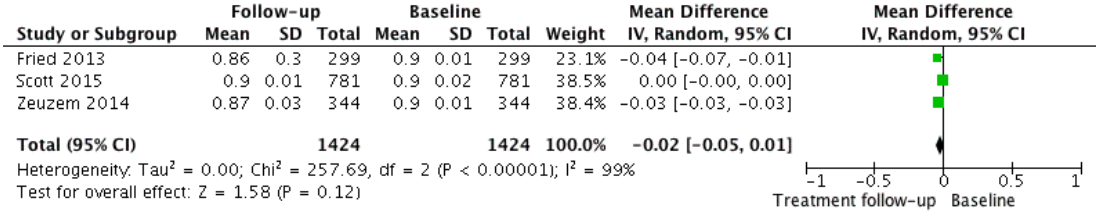
1. Meta-analysis: SMV & PR (treatment group) versus PR (control group)

A. SMV & PR group:

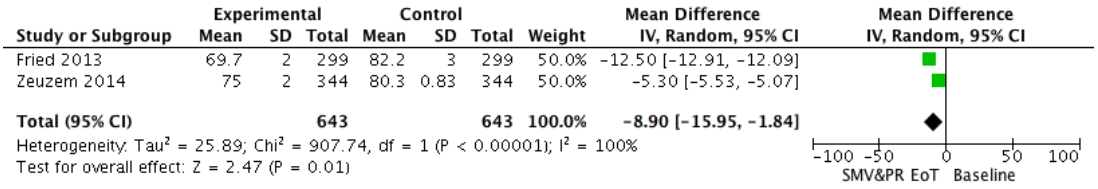
Index scores at end of treatment compared to baseline:



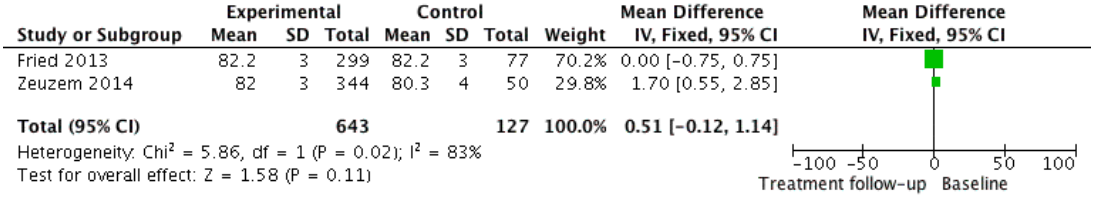
Index scores at follow-up compared to baseline:



EQ-VAS scores at end of treatment compared to baseline:



EQ-VAS scores at follow-up compared to baseline:

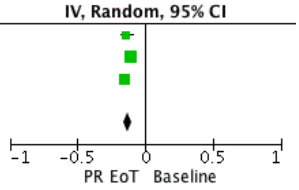


B. PR group:

Index scores at end of treatment compared to baseline:

Study or Subgroup	End of treatment Mean	SD	Total	Baseline Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Fried 2013	0.76	0.2	77	0.9	0.03	77	22.9%	-0.14 [-0.19, -0.09]
Scott 2015	0.79	0.03	781	0.9	0.03	781	40.6%	-0.11 [-0.11, -0.11]
Zeuzem 2014	0.75	0.06	50	0.9	0.02	50	36.5%	-0.15 [-0.17, -0.13]
Total (95% CI)			**908**			**908**	**100.0%**	**-0.13 [-0.16, -0.10]**

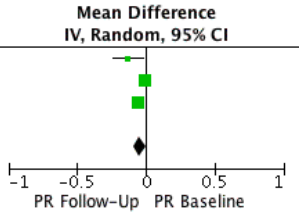
Heterogeneity: Tau² = 0.00; Chi² = 21.00, df = 2 (P < 0.0001); I² = 90%
Test for overall effect: Z = 7.90 (P < 0.00001)



Index scores at follow-up compared to baseline:

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Fried 2013	0.77	0.5	77	0.9	0.03	77	12.7%	-0.13 [-0.24, -0.02]
Scott 2015	0.89	0.02	781	0.9	0.03	781	44.6%	-0.01 [-0.01, -0.01]
Zeuzem 2014	0.84	0.05	50	0.9	0.02	50	42.7%	-0.06 [-0.07, -0.05]
Total (95% CI)			**908**			**908**	**100.0%**	**-0.05 [-0.09, 0.00]**

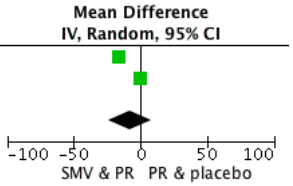
Heterogeneity: Tau² = 0.00; Chi² = 46.22, df = 2 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.94 (P = 0.05)



EQ-VAS scores at end of treatment compared to baseline:

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Fried 2013	67.6	5	299	83.6	5	77	50.0%	-16.00 [-17.25, -14.75]
Zeuzem 2014	80.5	5	344	80.5	2.22	50	50.0%	0.00 [-0.81, 0.81]
Total (95% CI)			**643**			**127**	**100.0%**	**-7.99 [-23.67, 7.69]**

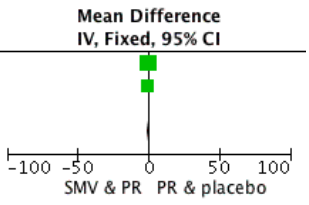
Heterogeneity: Tau² = 127.71; Chi² = 441.74, df = 1 (P < 0.00001); I² = 100%
Test for overall effect: Z = 1.00 (P = 0.32)



EQ-VAS scores at follow-up compared to baseline:

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Fried 2013	82.2	3	299	82.5	4	77	59.3%	-0.30 [-1.26, 0.66]
Zeuzem 2014	82	3	344	83	4	50	40.7%	-1.00 [-2.15, 0.15]
Total (95% CI)			**643**			**127**	**100.0%**	**-0.59 [-1.32, 0.15]**

Heterogeneity: Chi² = 0.84, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 1.56 (P = 0.12)



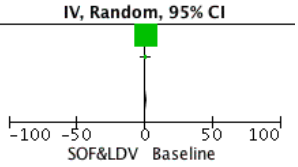
2. Meta-analysis: SOF & LDV (treatment) versus SOF & LDV & ribavirin (control group)

A. SOF & LDV group:

MCS scores at end of treatment compared to baseline:

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Younossi 2015 ION	51.3	8.8	1080	49.8	7	872	95.9%	1.50 [0.80, 2.20]
Younossi 2016b SIRIUS	42.8	10.7	78	42.1	10.8	76	4.1%	0.70 [-2.70, 4.10]
Total (95% CI)			**1158**			**948**	**100.0%**	**1.47 [0.78, 2.15]**

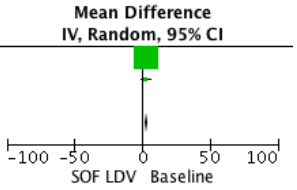
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.20$, df = 1 (P = 0.65); $I^2 = 0\%$
Test for overall effect: Z = 4.19 (P < 0.0001)



MCS scores at follow-up compared to baseline:

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Younossi 2015 ION	52.7	8.6	1080	49.8	7	1080	96.0%	2.90 [2.24, 3.56]
Younossi 2016b SIRIUS	44.6	9.9	78	42.1	10.8	78	4.0%	2.50 [-0.75, 5.75]
Total (95% CI)			**1158**			**1158**	**100.0%**	**2.88 [2.24, 3.53]**

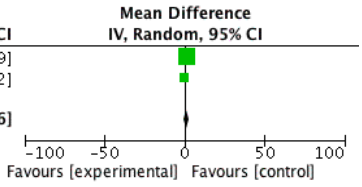
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.06$, df = 1 (P = 0.81); $I^2 = 0\%$
Test for overall effect: Z = 8.72 (P < 0.00001)



PCS scores at end of treatment compared to baseline:

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Younossi 2015 ION	53.1	6.1	1080	51.5	5	872	71.5%	1.60 [1.11, 2.09]
Younossi 2016b SIRIUS	47.5	6.7	78	47.5	6.7	76	28.5%	0.00 [-2.12, 2.12]
Total (95% CI)			**1158**			**948**	**100.0%**	**1.14 [-0.27, 2.56]**

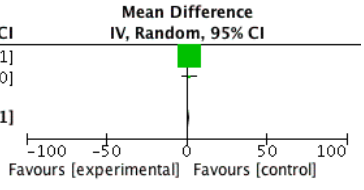
Heterogeneity: $Tau^2 = 0.67$; $Chi^2 = 2.08$, df = 1 (P = 0.15); $I^2 = 52\%$
Test for overall effect: Z = 1.59 (P = 0.11)



PCS scores at follow-up compared to baseline:

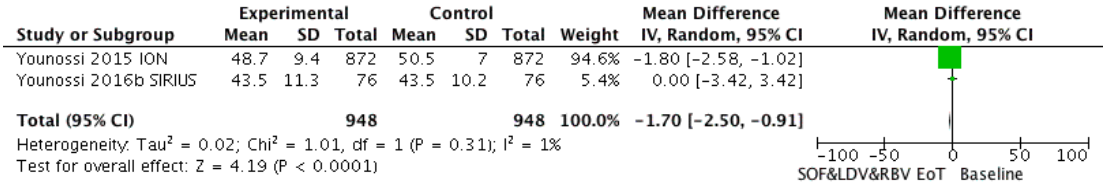
Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Younossi 2015 ION	53.2	6.4	1080	51.5	5	872	98.8%	1.70 [1.19, 2.21]
Younossi 2016b SIRIUS	49.4	19.1	78	47.5	6.7	76	1.2%	1.90 [-2.60, 6.40]
Total (95% CI)			**1158**			**948**	**100.0%**	**1.70 [1.20, 2.21]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.01$, df = 1 (P = 0.93); $I^2 = 0\%$
Test for overall effect: Z = 6.64 (P < 0.00001)

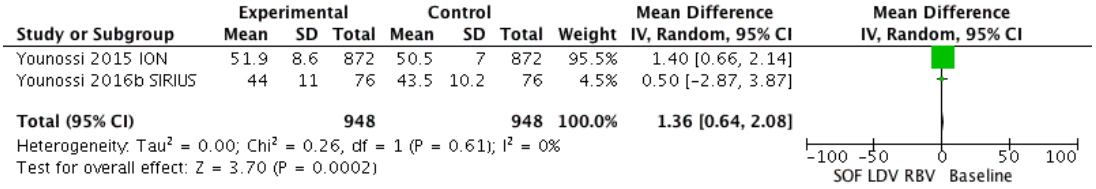


A. SOF & LDV & ribavirin group:

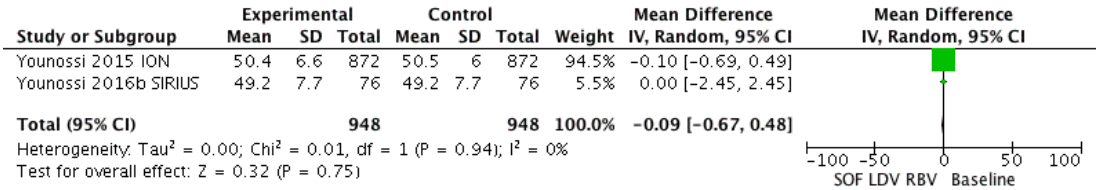
MCS scores at end of treatment compared to baseline:



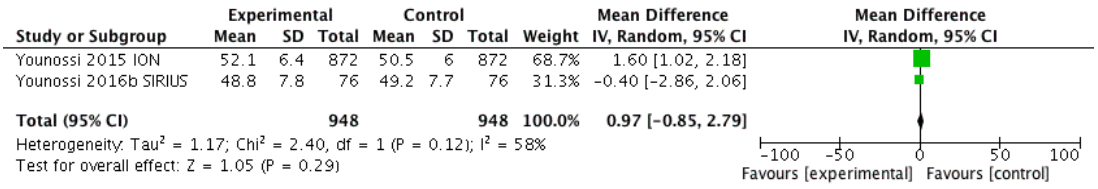
MCS scores at follow-up compared to baseline:



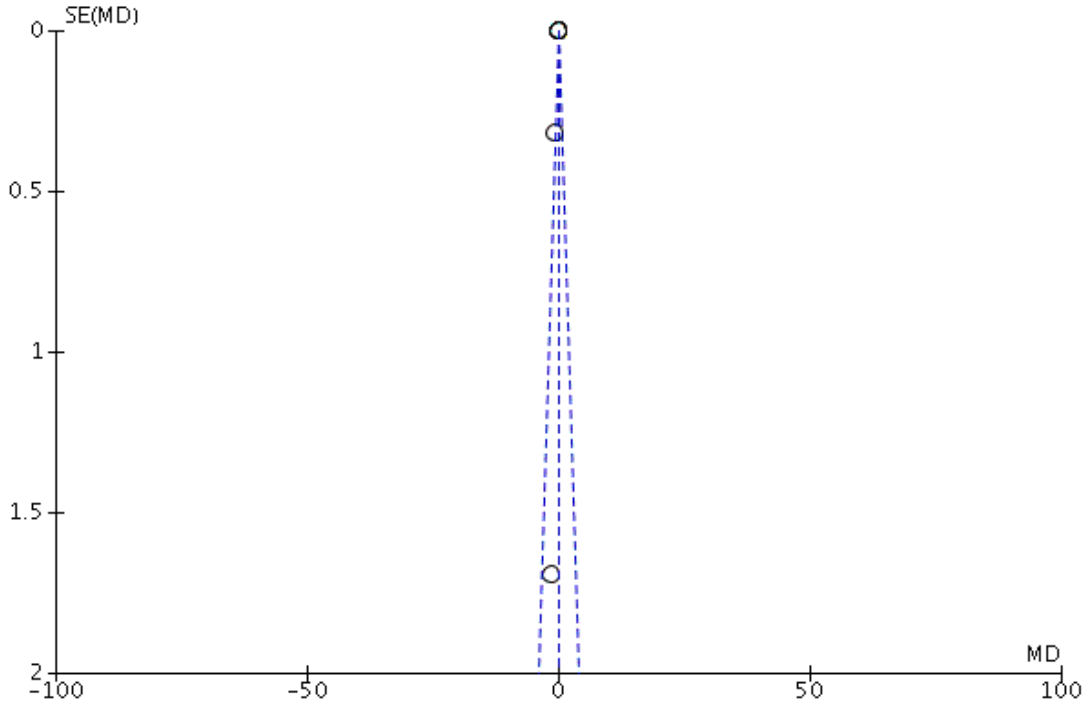
PCS scores at end of treatment compared to baseline:



PCS scores at follow-up compared to baseline:



VIII Funnel plot figure



Annex 2. Supplementary material Study II.

Analysis of the EQ-5D subscales during DAA treatment:

Table 1. Generalized linear mixed model adjusting for baseline values.

EQ-5D mobility	Estimate	S Error	z-value	p-values
(Intercept)	-5.755	2.380	-2.418	0.016
baseline	7.794	3.774	2.065	0.039
time	1.127	0.733	1.538	0.124
Liver cirrhosis	-0.616	1.243	-0.495	0.620
EQ-5D self-care				
(Intercept)	-3.767	1.431	-2.631	0.009
baseline	3.515	1442	2.439	0.015
time	0.665	0.686	0.970	0.332
Liver cirrhosis	-0.754	0.810	-0.931	0.352
EQ-5D daily activities				
(Intercept)	-1.850	0.719	-2.572	0.010
baseline	3.029	0.969	3.127	0.002
time	-0.214	0.447	-0.479	0.632
Liver cirrhosis	-0.557	0.667	-0.835	0.404
EQ-5D pain and discomfort				
(Intercept)	0.030	0.494	0.060	0.952
baseline	2.024	0.572	3.537	0.000
time	0.039	0.384	0.100	0.920
Liver cirrhosis	-1.072	0.535	-2.001	0.045
EQ-5D anxiety and depression				
(Intercept)	-2.664	1.022	-2.607	0.009
baseline	4.405	1.463	3.011	0.003
time	0.423	0.481	0.879	0.379
Liver cirrhosis	-0.223	0.700	-0.318	0.750

Table 2. Model-based estimation of OR 95%CI associated to cirrhosis.

EQ-5D subscale	Odds Ratio	95%CI low	95%CI up	p-values
Mobility	0.540	0.047	6.180	0.620
Self-care	0.471	0.096	2.300	0.352
Daily activities	0.573	0.155	2.119	0.404
Pain and discomfort	0.342	0.120	0.978	**0.045**
Anxiety and depression	0.800	0.203	3.154	0.750

Table 3. Depression, quality of life, fatigue, and irritability, before and after treatment including 48AT follow-up (**N=79 HCV patients**).

	Before DAA	**Post-treatment**	
	Baseline N (%)/M (SD)	**12AT** N (%)/M (SD)	**48AT** N (%)/M (SD)
PHQ-9 ≥ 5 to 9	17 (21.8)	18(23.1)	15 (19)
PHQ-9 ≥ 10	16 (20.3)	9 (11.5)	10 (12.7)
Any depression	33 (42.1)	27(34.6)	25 (31.7)
Fatigue VAS	46(24.6)	37.2(24.4)	39.3 (25.5)
Irritability VAS	38.15(24.6)	30.3(23.3)	32.1(22.2)
EQ-5D “any problem”			
Mobility	18 (34.6)	18 (35.3)	26 (50)*
Self-care	6 (11.5)	6 (11.8)	13 (25.0)*
Usual activities	19 (39.2)	20 (39.2)	19 (36.5)
Pain/discomfort	24 (46.1)	24 (47.1)	33 (63.5)*
Anxiety/depression	30 (38)	27 (34.6)	15 (18.9)
EQ-VAS	64.4 (20)	76.7 (18.9)	76.7 (22.2)
EQ-5D index	0.69	0.68	0.69

*p<0.05.

Annex 3. Spanish versions of questionnaires used in study II

Questionnaires included:

a. PHQ-9

b. EQ-5D-5L

c. EQ-VAS

d. VAS fatigue / irritability

a. CUESTIONARIO DE SALUD DEL PACIENTE (PHQ-9)

Este cuestionario es importante para poder ofrecerle la mejor asistencia sanitaria posible. Sus respuestas nos ayudarán a entender los problemas que pueda tener. Por favor, conteste a cada pregunta lo mejor que pueda, a menos que le pidan que se salte alguna pregunta.

2. Durante las últimas 2 semanas ¿con qué frecuencia le ha molestado alguno de los siguientes problemas?	**Nunca**	**Varios días**	**Más de la mitad de los días**	**Casi cada día**
a. Poco interés o alegría por hacer cosas	☐	☐	☐	☐
b. Sensación de estar decaído/a, deprimido/a o desesperanzado/a	☐	☐	☐	☐
c. Problemas para quedarse dormido/a, para seguir durmiendo o dormir demasiado	☐	☐	☐	☐
d. Sensación de cansancio o de tener poca energía	☐	☐	☐	☐
e. Poco apetito o comer demasiado	☐	☐	☐	☐
f. Sentirse mal consigo mismo/a; sentir que es un/a fracasado/a o que ha decepcionado a su familia o a sí mismo/a	☐	☐	☐	☐
g. Problemas para concentrarse en algo, como leer el periódico o ver la televisión	☐	☐	☐	☐
h. Moverse o hablar tan despacio que los demás pueden haberlo notado. O lo contrario: estar tan inquieto/a o agitado/a que se ha estado moviendo de un lado a otro	☐	☐	☐	☐
i. Pensamientos de que estaría mejor muerto/a o de querer hacerse daño de algún modo	☐	☐	☐	☐

b. EQ-5D-5L

Debajo de cada enunciado, marque UNA casilla, la que mejor describe su salud HOY.

MOVILIDAD

No tengo problemas para caminar	❑
Tengo problemas leves para caminar	❑
Tengo problemas moderados para caminar	❑
Tengo problemas graves para caminar	❑
No puedo caminar	❑

AUTO-CUIDADO

No tengo problemas para lavarme o vestirme	❑
Tengo problemas leves para lavarme o vestirme	❑
Tengo problemas moderados para lavarme o vestirme	❑
Tengo problemas graves para lavarme o vestirme	❑
No puedo lavarme o vestirme	❑

ACTIVIDADES COTIDIANAS *(Ej.: trabajar, estudiar, hacer las tareas domésticas, actividades familiares o actividades durante el tiempo libre)*

No tengo problemas para realizar mis actividades cotidianas	❑
Tengo problemas leves para realizar mis actividades cotidianas	❑
Tengo problemas moderados para realizar mis actividades cotidianas	❑
Tengo problemas graves para realizar mis actividades cotidianas	❑
No puedo realizar mis actividades cotidianas	❑

DOLOR / MALESTAR

No tengo dolor ni malestar	❑
Tengo dolor o malestar leve	❑
Tengo dolor o malestar moderado	❑
Tengo dolor o malestar fuerte	❑
Tengo dolor o malestar extremo	❑

ANSIEDAD / DEPRESIÓN

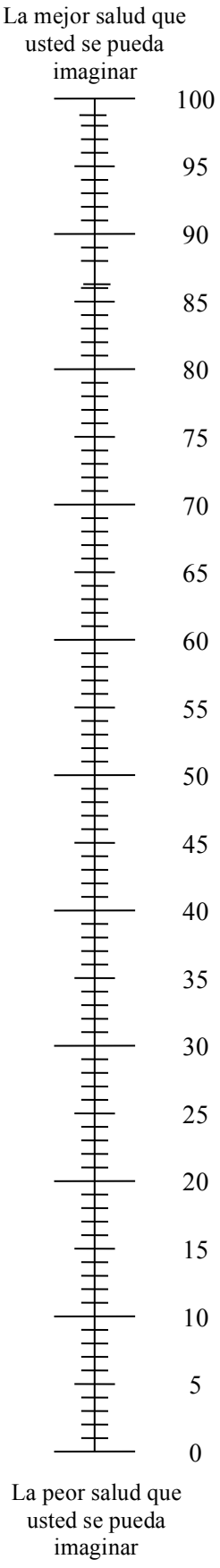
No estoy ansioso ni deprimido	❑
Estoy levemente ansioso o deprimido	❑
Estoy moderadamente ansioso o deprimido	❑
Estoy muy ansioso o deprimido	❑
Estoy extremadamente ansioso o deprimido	❑

c. EQ-VAS

- Nos gustaría conocer lo buena o mala que es su salud HOY.
- La escala está numerada del 0 al 100.
- 100 representa la mejor salud que usted se pueda imaginar.
  0 representa la peor salud que usted se pueda imaginar.
- Marque con una X en la escala para indicar cuál es su estado de salud HOY.

SU SALUD HOY = ☐

- Ahora, en la casilla que encontrará a continuación escriba el número que ha marcado en la escala.



d. Evaluación del grado de irritabilidad y cansancio o fatiga

a) Escala analógico-visual de irritabilidad

A continuación verá una línea. Representa **el grado de irritabilidad o impaciencia** que usted ha tenido durante **las últimas semanas** desde el 0, que representa el *mayor estado de tranquilidad* que pueda imaginarse hasta el 100, que representa el *mayor estado de irritabilidad e impaciencia* que pueda imaginarse.
Nos gustaría que nos indicara en esta escala, en su opinión, el nivel de irritabilidad que ha tenido en las dos últimas semanas.

_____|_____

0 **100**

Tranquilidad Irritabilidad

b) Escala analógico-visual de fatiga

A continuación verá una línea. Representa **el grado de cansancio o fatiga** que usted ha tenido durante **las últimas semanas** desde el 0, que representa el *mayor estado de energía* que pueda imaginarse hasta el 100, que representa el *mayor estado de cansancio y fatiga* que pueda imaginarse.
Nos gustaría que nos indicara esta escala, en su opinión, el nivel de cansancio o fatiga que ha tenido en las dos últimas semanas.

_____|_____

0 **100**

Energía Cansancio

Annex 4. Informed consent for the participant in study II

"Calidad de vida percibida de los pacientes con Hepatitis C crónica:
relación con su evolución y tratamiento antiviral"
(Versión 25 de Mayo de 2015)
Unidad Funcional de Hepatitis Víricas/Servei de Psiquiatria i Psicologia. Hospital Clínic. Barcelona

INFORMACIÓN AL PACIENTE

A. OBJETIVO DEL ESTUDIO

La hepatitis C crónica es un problema de salud pública prevalente, que puede tener graves consecuencias en un 20-40% de los casos (cirrosis, hepatocarcinoma, trasplante hepático). Desde los años 80, la hepatitis C crónica ha sido tratada con interferon-alfa subcuteaneo/semanal durante 24-48 semanas según genotipo vírico, y más adelante se ha añadido la ribavirina, tratamiento dual con el que se obtiene una buena respuesta al tratamiento denominada respuesta virológica sostenida (RVS), llegando al 50%.

Este tratamiento comporta numerosos efectos secundarios: anemia, fatiga, "síndrome gripal", y episodios depresivos en una tercera parte de los pacientes. La reciente introducción de farmacos orales antivirales directos de menor duración, menos efectos secundarios y mayor RVS ha abierto nuevas expectativas para la mayoría de los pacientes.

La calidad de vida percibida para las personas hace referencia a aspectos de salud física y de la salud mental, y se utiliza en Medicina y Psicología como indicador de evolución de enfermedades crónicas. En la hepatitis C crónica se ha descrito un deterioro de la calidad de vida asociada con los tratamientos antivirales.

En la unidad funcional de Hepatitis Víricas del Hospital Clínic de Barcelona proponemos estudiar la calidad de vida percibida de los pacientes con la hepatitis C crónica según su evolución y al tratamiento viral, teniendo en cuenta factores de riesgos psicosociales, clínicos, biológicos y relacionados con el tratamiento.

Le preguntamos su participación en este estudio para conocer mejor la calidad de vida percibida de las personas con hepatitis C crónica a lo largo de su enfermedad y durante el tratamiento antiviral. Su participación consiste en contestar unos cuestionarios del estudio y en algunos casos si valoramos una disminuicion de su calidad de vida percibida le hacemos una visita. En el caso de que Used empezará en tratamiento antiviral durante el tiempo del estudio, haurá de contestar los cuestionarios antes de empezar, a las 4 y 12 semanas del tratamiento, y en la visita del seguimiento a las 12 semanas de acabar el mismo. Además recogeramos datos de su enfermedad (nivel de fibrosis, datos de la función hepática, immunológica, anémia, tratamientos recibidos, efectos secundarios, …) de la historia clínica.

B: ASPECTOS ÉTICOS

Garantía de participación voluntaria

Su participación es totalmente voluntaria. Si accepta participar, en cualquier momento del estudio es Usted libre de abandonarlo sin tener que dar explicaciones.

Confidencialidad

El investigador se responsibilizará de mantener la confidencialidad con respecto a su identificación como participante del estudio. Su nombre y datos se archivarán de forma separada con un código, que será el mismo durante todo el estudio. Estos procedimientos están sujetos a la Lei Orgánica 15/1999 del 13 de diciembre sobre la protección de datos de carácter personal.

¿Qué hacen los investigadores con los datos que recogen?

Los datos se archivarán de forma confidential. Con los datos recogidos de la história clínica se realizarán análisis estadísticos para relacionar los resultados de la calidad de vida percibida

con diferentes momentos de su enfermedad, el tratamiento recibido y otros factores estudiados. Los resultados ayudarán a identificar factores de riesgo de mala calidad de vida, para el futuro prevención y para ahora el tratamiento, con el final de aconseguir personalizar el tratamiento a cada paciente. Finalmente los resultados se publicarán en revistas científicas.

"Calidad de vida percibida de los pacientes con Hepatitis C crónica: relación con su evolución y tratamiento antiviral"

Unidad funcional de Hepatitis Víricas/Servicio de Psiquiatría y Psicología. Hospital Clínic. Barcelona

CONSENTIMIENTO INFORMADO POR ESCRITO

Yo (nombre y apellidos)

_____

He leido la hoja de información que se me ha entregado
He podido hacer preguntas sobre el estudio
He recibido suficiente información sobre el estudio

He hablado con (nombre del investigador)

_____

Entiendo que mi participación es voluntaria
Entiendo que puede retirarme del estudio cuando quiero sin dar explicaciones

De conformidad con el establecimiento de la LO. 15/1999, de 13 Diciembre, de Protección de Datos de carácter personal, declaro haber estado informado:

De la existencia de un fichero o tratamiento de datos de carácter personal, de finalidad de la recogida de estos y de los destinatarios de la información.
Del carácter obligatorio o facultativo de mi respuesta a las preguntas que me sigen planteadas.
De las consecuencias de la obtención de los datos o de la negativa a suministrarlos.
De la posibilidad de solicitar la eliminación de las muestras en cualquier momento.
De la disponibilidad de ejercer los derechos de acceso, rectificación, cancelación y oposición dirigirme por escrito a: Dr. Xavier Forns, o Unitat d'Hepatitis Víriques, Hospital Clínic, Seu Maternitat, (Sabino Arana s/n), y a la Dra. Rocío Martín-Santos, al Centre de Salut Mental, Hospital Clínic (Rosselló 140, Barcelona 08036)

Y doy mi consentimiento que los datos clínicos referentes a mi enfermedad serán almacenados en un fichero automatizado, la información del cual podrá ser manejada exclusivamente para fins científicos. Entonces libremente mi conformidad para participar en el estudio.

(firma del participante y fecha) Barcelona, a ……. de …… 20……..

(firma del investigador y fecha) Barcelona, a ……. de …… 20……..

Este protocolo ha sido aprobado por el CEIC del Hospital Clínic, Barcelona

Annex 5. Permission obtained for figure in Chapter 1

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