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Maastricht University

Doctoral dissertation submitted to obtain the degree of
Doctor of Biomedical Sciences, to be defended by

Amber Arain

DOCTORAL DISSERTATION

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Proefschrift voorgelegd tot het behalen van de graad van
Doctor in de Biomedische Wetenschappen

Met dank aan het 'Limburg Clinical Research Program (LCRP) UHasselt-ZOL-Jessa', met ondersteuning van de stichting Limburg Sterk Merk, de provincie Limburg, de Vlaamse overheid, de Universiteit Hasselt, het Ziekenhuis Oost-Limburg en het Jessa Ziekenhuis.

Contents

List of abbreviations

AIDS	Acquired immunodeficiency syndrome
Ab	Antibody
Anti-HCV	Anti-hepatitis C antibody
APRI	Aminotransferase/platelet ratio index
AUDIT-C	Alcohol Use Disorders Identification Test
BOC	Boceprevir
CM	Christelijke mutualiteit (Belgian Christian health insurance)
DAA(s)	Direct-acting antiviral(s)
DASS-21	21-item Depression, Anxiety and Stress Scale
DBS test	Dried blood spot test
DOT	Directly observed treatment
EASL	European association for the study of the liver
ELF test	Enhanced liver fibrosis test
EMCDDA	European Monitoring Center for Drugs and Drug Addiction
EU	European Union
FDA	The Food and Drug Administration
FIB-4	Fibrosis-4
GP	General practitioner
GT(s)	Genotype(s)
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IDU	Injection drug use
IFN	Interferon
INHSU	International Network on Hepatitis among Substance Users
IV	Intravenous
KCE	Belgian Health Care Knowledge Center
MSM	Men who have sex with men

NSP(s)	Needle and syringe program(s)
NS protein	Non-structural protein
OST	Opioid substitution therapy
PCR	Polymerase chain reaction
PegIFN	Pegylated interferon
PWID	Person who inject drugs
PWUD	Person who use drugs
RBV	Ribavirin
Riziv	Rijksinstituut voor ziekte- en invaliditeitsverzekering
RNA	Ribonucleic acid
SVR	Sustained viral response
TPV	Telaprevir
UNAIDS	The Joint United Nations Programme on HIV/AIDS
UNODC	The United Nations Office on Drugs and Crime
USA	United States of America
WHO	The World Health Organization
95% CI	95% confidence interval

Samenvatting

Hoofdstuk 1
Dit hoofdstuk geeft achtergrondinformatie over HCV epidemiologie, virologie, verloop van de infectie, diagnose, behandeling, HCV management van intraveneus drug gebruikers en bespreekt ten slotte de doelstellingen van de uitgevoerde studies.

Hoofdstuk 2
Dit hoofdstuk beschrijft een prospectieve multicenter cohort studie in België. Het doel van de studie was om kenmerken van de HCV geïnfecteerde cliënten van substitutie behandelingsklinieken te identificeren en om mening van de behandelende artsen omtrent HCV behandeling (pegylated interferon en ribavirine) te bepalen. De meerderheid (90%) van de deelnemers wilden HCV behandeling krijgen. Anderzijds was maar 43% geschikt voor behandeling volgens de behandelende artsen en in 6% HCV behandeling was aangewezen.

Hoofdstuk 3
Dit hoofdstuk geeft de resultaten weer van een retrospectieve studie waarbij uitkomst van HCV behandeling werden vergeleken tussen injecterende drug gebruikers en niet-injecterende drug gebruikers die behandeld werden met telaprevir of boceprevir in combinatie met pegylated interferon en ribavirine. Het klaren van de virus was gelijkaardig in de twee groepen.

Hoofdstuk 4
Dit hoofdstuk bespreekt een gerandomiseerde en gecontroleerde studie. In deze studie bestudeert men de invloed van een interventie, bestaande uit formele informatie en peer educatie gecombineerd met FibroScan meting, op HCV kennis en bereidheid voor HCV screening en behandeling in drug gebruikers.

De interventie verbeterde de HCV kennis in druggebruikers, maar resulteerde niet in stijging van bereidheid tot HCV screening en behandeling.

Hoofdstuk 5
Dit hoofdstuk bespreekt een internationale retrospectieve studie. In deze studie vergelijkt men het resultaat van HCV behandeling (pegylated interferon en ribavirine) tussen behandelingscentra waarbij addictie behandeling en HCV behandeling plaatsvindt op dezelfde locatie/onder één dak of niet onder één dak. Volgens de resultaten van deze studie is een setting die onder één dak werkt niet beter/superieur dan settingen die niet onder één dak werken.

Hoofdstuk 6
Dit overzichtsartikel bespreekt HCV voorkomen, transmissie, screening en behandeling in gevangenissen. Er werden aanbevelingen geformuleerd om hepatitis C preventie, screening en behandeling in gevangenissen te verbeteren.

Hoofdstuk 7
De algemene discussie bespreekt eerst recente richtlijnen/aanbeveling om de "HCV care cascade" te verbeteren. Dan wordt de HCV zorg in België besproken. Daarna, worden de bevindingen van de uitgevoerde studies, die in hoofdstukken 2 tot 5 worden besproken, in een bredere context bekeken. Tot slot, wordt de HCV zorg in België besproken en een aantal suggesties/aanbevelingen voorgesteld om de HCV zorg in België te verbeteren.

Summary

Chapter 1
This chapter provides background information related to the HCV epidemiology, virology, natural history, diagnosis, treatment and HCV management in persons who injected drugs. At the end of this chapter, the aims of the performed studies are summarised.

Chapter 2
In this chapter a prospective multicentre cohort study in Belgium is described. This study investigated the characteristics of the clients of an opioid substitution treatment clinics infected with HCV and patients' and physicians' opinion regarding HCV treatment (Pegylated interferon and ribavirin).
Among the participants, the majority (90%) was willing to receive the antiviral treatment for HCV. Whereas, 43% was suitable for treatment in physician's opinion and in only 6% HCV treatment was recommended.

Chapter 3
In this chapter the results of a retrospective study are presented. This study compared the outcome of HCV treatment among PWID and non-PWID patients who received treatment with telaprevir or boceprevir combined with Pegylated interferon and ribavirin.
The treatment outcome, sustained viral response rates, were similar in the two groups.

Chapter 4
This chapter discusses a randomized and controlled study. This study evaluated the influence of an intervention, combining formal and peer education with FibroScan measurement, on HCV-related knowledge and willingness for HCV screening and treatment among persons who use drugs.

The intervention improved HCV knowledge among persons who use drugs, but did not accomplish a higher uptake for screening and treatment.

Chapter 5

This chapter discusses an international retrospective study. In this study, the outcome of HCV treatment (Peg-interferon and ribavirin), provided in a setting working under one roof to treat addiction and HCV, was compared with settings not working under one roof. According to these results a setting under one roof is not superior to the other two settings.

Chapter 6

This review discusses the HCV prevalence, transmission, screening and treatment in prisons. In this review article, recommendations are formulated to improve hepatitis C prevention, screening and treatment in prisons.

Chapter 7

The general discussion first discusses recent guidelines/recommendations to improve HCV care cascade. Then, the HCV care in Belgium is discussed. Subsequently, the findings of the performed studies, discussed in chapters 2 to 5, are discussed in a broader context. Next, the situation and the ways to improve of HCV care in Belgium are discussed. Finally, the HCV care in Belgium is discussed and some suggestions/recommendations to improve HCV care in Belgium are presented.

Chapter 1

General introduction

1.1 The HCV epidemic

Worldwide, approximately 115 million (1.6% world population) persons are anti-hepatitis C antibody (anti-HCV) positive and 71 million (1% of world population) individuals have chronic hepatitis C virus (HCV) infection. (1, 2) HCV was first identified in 1989 by Choo et al. (3) as a non-A, non-B type hepatitis virus, mainly transmitted through blood transfusions. Soon after this discovery in 1991, the first generation assays for anti-HCV became available. This allowed for screening of blood donors, leading to a dramatic decrease of post-transfusion HCV infection in developed countries. (4) Prevalence of HCV infection among persons who inject drugs (PWID) is much higher than among the general population. The prevalence of anti-HCV is 67% among PWID globally and approximately 10 million PWID were anti-HCV positive in 2010. (5) A review published in 2017 estimated that in 2015 globally (in the population aged 15-64) an estimated 15.6 million people injected drugs and 52·3% of current PWID have been exposed to hepatitis C (anti-HCV positive), equating to 8·2 million people. (6)

The epidemic of HCV infection in Europe is continuously changing due to the change in epidemiological parameters such as prevalence, incidence, transmission patterns and genotype (GT) distribution. Increased blood transfusion safety, improvement of healthcare conditions and continuous expansion of intravenous (IV) drug use and immigration are the main reasons for this change. (7) A study published in 2014 estimated that the anti-HCV prevalence in the general population was 0.9% (3.7/425 million) in Western Europe, 1.3% (1.5/119 million) in Central Europe and 3.3% (6.8/207 million) in Eastern Europe. (1) In these European regions, 70-80% of the anti-HCV positive population is viremic. (1) A systemic review of literature published during 2005–2015 evaluating HCV prevalence among at risk groups in Europe found the highest prevalence of anti-HCV among people in prison (4.3% - 86.3%) and PWID (13.8% - 84.3%) followed by men who have sex with men (MSM) (0.0% - 4.7%). (8)

The seven HCV GTs and their subtypes show a diverse global distribution. Genotype 1 is most common and GT 1, 2 and 3 have a broad geographical distribution while GT 4, 5 and 6 are prevalent in specific regions. Genotype 4 is mainly present in Africa and the Middle East. Genotype 5 and 6 are predominantly found in South Africa and Southeast Asia. Genotype 7 is found in central African immigrants in Canada (9, 10)

Although HCV is curable in the majority of cases, it causes nearly half a million deaths each year. (11) HCV infection is a growing global health challenge as treatment uptake within the PWID, the main risk group, remains low even though it would prevent further morbidity and mortality. (12)

1.2 Virology

The hepatitis C virus belongs to the family of Flaviviridae, genus Hepacivirus and is an enveloped positive-stranded RNA virus. The viral genome is translated into a polypeptide which is then processed into ten mature proteins. The N-terminus holds the structural core protein (C) and envelope proteins E1 and E2 which are highly glycosylated and play a role in cell entry. The C-terminus holds the non-structural (NS) proteins NS3, NS4A, NS4B, NS5A and NS5B. The NS3 protein is an HCV protease, which disrupts the interferon and toll-like receptor 3 signaling pathways. The NS4A protein acts as a co-factor for the NS3 protease and the small NS4B is a protein required for the recruitment of other viral proteins. NS5A is needed for viral replication and NS5B is an RNA polymerase, which lacks proofreading and error correction mechanisms. In between the N- and C-terminus are two most likely non-structural proteins (p7 and NS2). The p7 protein serves as a signal sequence for the translocation of the NS2 protein to the endoplasmatic reticulum and is also essential for particle assembly and the release of infectious virions. The NS2 protein is then further cleaved and becomes a transmembrane protein responsible for viral replication. (13)

A chronic infection is the result of rapid virus production, a lack of a T-cell immune response and continuous cell-to-cell spread. This rapid production, in addition to a lack of error proofreading by the viral RNA polymerase NS5B, causes the viral genome to mutate frequently, resulting in seven different GTs (numbered 1 through 7) and multiple subtypes (e.g., 1a, 1b, 2a, …). (10, 14) The heterogeneity of the hepatitis C virus has made the search for a vaccine challenging and to date, none is available.

There are different reasons why the development of a prophylactic vaccine is very important. For example HCV treatment does not provide protection against reinfection and treatment in later stages does not reverse all disease/liver damage. (15) Barriers for vaccine development include virus diversity, lack of animal models for testing vaccines, and our incomplete understanding of protective immune responses. (16, 17) The vaccine development strategies mainly aimed at either producing broadly neutralizing antibodies that would neutralize the infectivity of the virus or generating potent virus-specific CD4 and CD8 T cells that can eliminate infected hepatocytes. (17) Different vaccine regimens have been tested over the years. Two vaccines were able to reach human trials. The first is a recombinant form of the virus envelope glycoproteins E1 and E2 aimed at inducing neutralizing antibodies and CD4 helper T cells. (18, 19) The second is a viral vector-based vaccine encoding non-structural proteins of the virus (NS3-NS5). (20) This vaccine regimen was shown to induce high frequencies of virus-specific polyfunctional CD4 and CD8 T cells in healthy volunteers and is currently in phase 2 clinical trials in PWIDs. (21) Results of this clinical trial are pending.

1.3 Natural history of HCV infection

1.3.1 Routes of transmission

The hepatitis C virus is primarily transmitted through blood-to-blood contact. In different areas of the world or countries, the importance of the risk factors is different.

Blood transfusions remain a dominant source of infection in developing countries where systematic HCV testing in blood products has not been introduced. (4) In developing countries iatrogenic exposure, mainly unsafe therapeutic injection practices, are responsible for most infections. In developed countries injection drug use is the major risk factor for HCV infection. (4) Among PWID HCV is not only transmitted through sharing of syringes and needles but also other injecting paraphernalia such as spoons, filters and rinse water. (22) Non-injecting drug use is associated with a higher risk of HCV infection. A possible way of HCV transmission in such cases is through intranasal transmission by using contaminated drug sniffing paraphernalia such as straws, used to snort cocaine, heroin, and other powdered drugs. (23, 24)
Recent reports also highlight the transmission of HCV infection among Human immunodeficiency virus (HIV) infected men who have sex with men. (25, 26) Other risk factors for HCV infection include occupational exposure, birth from an infected mother, solid organ transplantation from an infected donor, haemodialysis, household exposure and intranasal cocaine use as well as any other activities involving exposure to blood products through tattooing, body-piercing, acupuncture, cosmetic procedures or sharing cottons or other injecting paraphernalia. (27)

The estimated risk for infection after a needlestick or cut exposure to HCV-infected blood is approximately 1.8%. In the case of HIV and hepatitis B virus (HBV) this risk of infection is 0.3% and 6%-30%, respectively. (28)

1.3.2 Hepatitis C disease progression and mortality

Acute HCV infections are clinically silent in 70%-85% of infected individuals. (9) The symptomatic onset ranges from 2 to 12 weeks after exposure and symptoms may include malaise, weakness, anorexia and jaundice. (9, 12)

The HCV infection is considered to be chronic if an acute HCV infection persists and HCV RNA can be detected in the blood at least 6 months after onset. Clearance of acute HCV infection occurs in 15-45% and the remaining 55-85% will develop a chronic HCV infection (Figure 1.1).(29) According to a systematic review by Wiessing et al. (2014) among HCV ab+ PWID in Europe the level of chronic infection ranged between 53% and 97% with a median of 72%. (30)
The viral clearance is affected by many factors, including age at the time of infection, gender, ethnicity, duration of drug use, immunosuppression, etc. (9, 12)

HCV-related liver disease gradually advances from chronic HCV infection to several stages of fibrosis (METAVIR fibrosis score F1 to F3). Cirrhosis (F4) will develop in 20% to 30% of patients after 20-30 years (31) and eventually hepatocellular carcinoma (HCC) develops in 1% to 4% of the patients with HCV-related liver cirrhosis per year. (32) Cirrhosis is the end-stage of any chronic liver disease and only manifests after 10 to 15 years of HCV infection in the worst-case scenario. (33) Generally the course of liver disease progression is slow and can take decades before patients develop cirrhosis. (34) Cirrhosis causes impaired liver function, and can result in several complications. Although liver failure is initially compensated, it can evolve to liver decompensation: portal hypertension (35) with variceal hemorrhage, ascites, and hepatic encephalopathy. (36) Once decompensation occurs, the 5-year survival rate falls to 50%. (32)

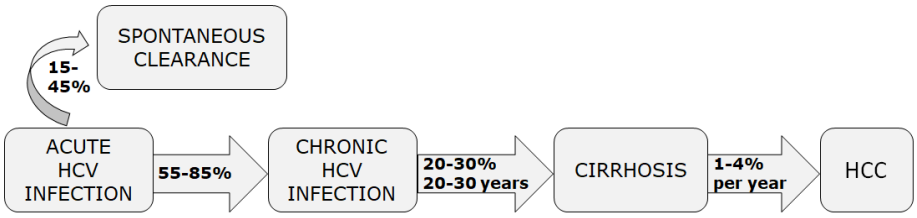

Figure 1.1. Schematic representation of the disease progression of an HCV infection.

Several factors can speed up damage to the liver, but alcohol consumption appears to be one of the most influential factors driving fibrosis progression. (37-40) Another factor significantly associated with the rate of fibrosis is the age at the time of infection. (41) The stage of fibrosis appears to be higher in patients that were infected at an older age (>40 years). (42) This suggests that the progression of liver fibrosis in HCV infection is non-linear and may progress faster as the patient ages. Co-infection of HCV with HIV speeds up the progression to acquired immunodeficiency syndrome (AIDS). Conversely, HIV-HCV co-infection seems to accelerate liver fibrosis. Similarly, co-infection with hepatitis B virus (HBV) leads to higher rates of cirrhosis. (43, 44) Other comorbid conditions also play an important role in the progression of liver fibrosis. Immunosuppression has been associated with more aggressive liver disease and shows higher rates of progression to cirrhosis than in immunocompetent patients. (45, 46) Insulin resistance appears to be associated with worsening liver fibrosis and even decreased response to HCV treatment. (47, 48)

The number of deaths due to hepatitis C is increasing. Globally, the total number of deaths due to HCV was 333000 in 1990, 499000 in 2010 and 704000 in 2013. (11, 49) A study by Grebely et al. (33) identified drug-related, liver disease-related and HIV-related deaths as the three major disease-specific groupings for mortality in patients with HCV infection based on data from Australia, Sweden,

Scotland and Denmark. Innes et al. reported in 2016 the total fraction of liver mortality attributed to chronic HCV by using national HCV diagnosis and mortality registers from Denmark and Scotland. Their findings indicated that in Scotland, 55% (95% CI: 44-66) of liver death among persons with chronic HCV could be attributed to chronic HCV exposure. In Denmark, this fraction was higher at 66% (95% CI: 55-78). (50) In countries such as Australia and the USA, with injection drug use as the main route of HCV transmission and ageing cohorts of people with chronic HCV, drug related deaths are stable or declining while liver related deaths are increasing. (51, 52) In countries such as Japan, Egypt and Taiwan with iatrogenic exposure as the main route of transmission, liver-related deaths caused by HCV disease progression are more evident. (9)

1.4 HCV epidemiology and disease progression in Belgium

The first study investigating HCV prevalence in a sample of the general population in Belgium was published by Beutels et al. (53) in 1997 (Table 1.1). They used residual blood samples from several hospitals in Flanders collected in 1994 and estimated the HCV prevalence to be 0.87%. In 2007, Quoilin et al. (54) published results from a mail-based study in Flanders in 2003. They measured anti-HCV in oral fluid and estimated the HCV prevalence at 0.12%. The 2012 report from the Belgian Health Care Knowledge Center (KCE) presented an HCV prevalence of 1.23% among patients (general population) who were reimbursed for a HCV ab test by one of the seven national health insurance funds between 1995 and 2009. (55) In 2019, Litzroth et al. (56) studied nationwide HCV prevalence in the Belgian general population by testing residual sera samples from 2013-2015. They estimated that in the Belgian general population HCV seropositivity is 0.22% (95% CI: 0.09–0.54%) and chronic HCV infection prevalence is 0.12% (95% CI: 0.03–0.41). In individuals aged 20 years and older, HCV seropositivity is 0.26% (95% CI: 0.10–0.64%) and chronic HCV prevalence of 0.13% (95% CI: 0.04–0.43). Of the total

estimated number of HCV seropositive individuals in Belgium, 66% were between 50 and 69 years old.

In 2005, Matheï et al. (57) compared the HCV prevalence in patients in methadone maintenance program in two geographic regions in Belgium. HCV prevalence rates among this population were 84.4% in Antwerp and 66.2% in the mixed urban-rural area of Limburg. Plasschaert et al. (2004-2005) reported an HCV prevalence of 50% among PWID and 3% among non-PWID in drug treatment centers. Among PWID sharing their injecting equipment HCV prevalence rate was 61%. (58) In 2011-2012 Bollearts et al. interviewed and collected saliva samples from 180 PWID recruited through various low threshold drug treatment centres. An HCV prevalence of 43.3% was found among the participants who injected during the last 12 months. (59)

In 2008, 147 anti-HCV positive serum samples from PWID recruited all over Belgium were tested for the presence of HCV RNA and genotyped. The HCV RNA prevalence was 67%. (60)

Table 1.1. Summary of anti-HCV and HCV RNA prevalence in general population and PWID population in Belgium based on blood samples or saliva samples.

Study	Study population	Methods	Results
Beutels et al. (1997) (53)	General population	3987 hospital-based blood samples	Anti-HCV+ 0,87% (95% CI 0,5-1,1)
Quoilin et al. (2007) (54)	General population	1834 oral fluid samples collected by postal service in Flanders	Anti-HCV+ 0,12% (95% CI 0,09-0,39)
Gerkens et al. (2012) (55):	General population	Patients who received reimbursement for anti-HCV blood test	Anti-HCV+ 1,23%
Litzroth et al. (2019) (56)	General population	3209 residual sera samples collected by 28 laboratories in 2013-2015	Anti-HCV+ 0,22% (95% CI 0,09-0,54) HCV-RNA+ 0.12% (95% CI: 0.03–0.41)
Mathei et al. (2005) (57)	Patients on methadone program	310 patients seen in a methadone program in 18-month period, not previously treated for hepatitis C	Antwerp: Anti-HCV+ 84% Limburg: Anti-HCV+ 66,2%
Plasschaert et al. (2005) (58)	PWID	1017 patients in drug treatment centres and 117 in prisons interviewed and blood samples collected	Overall anti-HCV+: 30%. PWID: Anti-HCV+ 50% non-PWID: Anti-HCV+ 3%. PWID sharing injecting equipment: Anti-HCV+ 61% PWID in prison: Anti-HCV+ 76%
Bollaerts et al. (2012) (59)	PWID	180 PWID in low threshold drug treatment centers interviewed and saliva samples collected	PWID: Anti-HCV+ 43.3%
Micalessi et al. (2008) (60)	PWID	147 anti-HCV+ serum samples from PWID recruited at treatment centers all over Belgium	HCV RNA+ 67%

A study investigating HCV GT distribution in Flanders and Brussels reported that in the general patient population HCV GT 1 (60.9%) is dominant, followed by GT 3 (20.3%), GT 4 (8.0%), GT 2 (6.3%) and GT 5 (4.5%). (61)
A study published in 2018, evaluated the prevalence of HCV genotypes in Belgium. This multicentre study collected data from all the 19 Belgian laboratories performing reimbursed HCV genotyping assays for the period from 2008 till 2015. Among the 11,033 unique records, HCV GT1 was the most prevalent (53.6%) genotype in Belgium. Genotype 3 was the next most prevalent (22.0%). The GT 4, 2, and 5 were responsible for respectively 16.1%, 6.2%, and 1.9% of HCV infections. Further, GT 6 and 7 comprise the remaining <1%.
This pattern of distribution corresponds to the findings of studies evaluating the HCV GT distribution among PWID. Mathei et al. studied HCV GT distribution among PWID engaged in a methadone maintenance program between 1999-2000. In this population GT 3 (45.9%) was the most prevalent GT, followed by GTs 1 (43.1%), 4 (9%) and 2 (1.6%). (62) Another group studied prevalence of HCV GTs among PWID recruited at treatment centres all over Belgium. They also reported that GT 1 (38%) and 3 (49%) were the most common genotypes followed by GT 4 (9%) and GT 2 (2%). (60)

The study that reported on HCV fibrosis stage among anti-HCV positive patients in the general population in 9 Belgian hospital centres between 2003-2004, reported that among the 190 who received a liver biopsy minimal fibrosis (METAVIR F0-F1) was present in 43%, moderate fibrosis (F2) in 35% and advanced stages (F3-F4) in 22%. (63)

In the general population, HCV accounted for 20% of the cases among 411 patients with cirrhosis according to data from three hospitals in southern Belgium. Up to 30% of patients waiting for a liver transplant were infected with HCV and 40% of end-stage cirrhosis was caused by HCV. (64) In this study 44% of 57 HCC cases were associated with HCV. In another study among 131 new diagno-

ses of HCC in 14 Belgian centres cirrhosis was present in 92% (n=120) in 2003. The aetiology of the underlying liver disease was HCV in 41% (n=54). (65) A publication by Bruggmann et al. (66) summarized that from 2008 to 2012, in Belgium 1159 liver transplants were performed, of which 146 (12.6%) were attributable to HCV infection. In 2011, 299 transplants were performed, 38 (12.7%) of which were attributable to HCV. According to a panel of experts (66) from centres in Ghent and Leuven 10-15% of the performed liver transplants resulted from HCV infection. While in Liège and Erasme in 25% of the liver transplantations, HCV infection was the underlying cause.

1.5 Diagnosis

Acute HCV infections often are asymptomatic. Therefore indications for screening for an HCV infection are often based on the patient's possible risk behaviour such as IDU or aberrant liver function results rather than patient's symptoms. (67)

There is no formal HCV screening strategy in Belgium. However the Belgian association of the study of the liver recommends targeted HCV screening for high-risk populations including individuals with a blood transfusion or major medical event prior to 1 July 1990, intranasal or IDU and dialysis patients in addition to non-targeted screening among pre-operative patients and pregnant women. (55)

An HCV antibody test is used to determine whether the patient has come in contact with the virus and consequently has anti-HCV present in the blood serum. (67) After the initial 3 months almost all patients will develop anti-HCV. However, antibody titers can be extremely low or even undetectable in immunodeficient patients. Also less invasive, without venipuncture, HCV antibody tests such as rapid point-of care oral saliva and fingerstick capillary blood testing and dried blood spot (DBS) testing are available. (68-72) The OraQuick HCV test is a rapid, point-of-care diagnostic test to detect anti-HCV. It

can be used with oral fluid, fingerstick blood and venous blood. This test provides a result within 20 to 40 minutes. Sensitivity of OraQuick test is slightly lower for oral fluid samples compared to blood based samples. The sensitivity and specificity of OraQuick test in oral fluid was 90.8-99.2 and 92.1-100.0, in fingerstick blood 95.9-100.0 and 99.9-100.0 and in whole blood 94.4-100.0 and 98.8-100.0, respectively. (73-77) For the Dried blood spot (DBS) test only a drop of blood is spotted onto a special filter paper. This paper can then be analysed for anti-HCV and also HCV RNA. For the detection of anti-HCV a sensitivity ranging from 95 to 99 % and specificity from 99 to 100% was reported for DBS. Studies found sensitivities for the detection of HCV RNA ranging from 93.8–100% and specificities ranging from 94.0–100%. (78-80)

Subsequent to an anti-HCV positive result, an HCV RNA test is performed by means of PCR to determine the presence of the virus. HCV RNA can already be detected in the blood serum one to two weeks after exposure and rises rapidly in the first few weeks. (81)

To evaluate the possible damage to the liver, different techniques can be used. (82) A liver biopsy is an invasive procedure, during which a cylinder of tissue is taken from the liver, to determine the stage of fibrosis. In contrast the FibroScan is a non-invasive and painless imaging method to assess liver fibrosis by means of transient elastography. (83) The most frequently used scoring system for grading the extent of fibrosis is the METAVIR system, which numbers the stages of fibrosis F0 to F4. Stage 0 is used when no fibrosis is present, stage 1 means periportal fibrosis expansion, stage 2 is used when fibrosis includes at least one septum (or more), stage 3 is defined as septal fibrosis with no cirrhosis and stage 4 is used in case of cirrhosis. (41)
There are also liver fibrosis tests based on blood indices such as the aminotransferase/platelet ratio index (APRI), the FIB-4 scores and the FibroTest available. The FIB-4 scores measures indirect markers of fibrosis such as alanine transam-

inase, aspartate aminotransferase and platelet count. The FibroTest measures other indirect markers of fibrosis such as haptoglobin, bilirubin etc. (82)
The enhanced liver fibrosis (ELF) blood test measures direct markers of fibrosis. This test combines three serum biomarkers (hyaluronic acid, procollagen III amino terminal peptide and tissue inhibitor of metalloproteinase 1), which have been shown to correlate to the level of liver fibrosis assessed by liver biopsy. The algorithm measures each of these markers by immunoassay, to create an ELF score, from which a designation for fibrosis severity can be determined. A higher concentration of individual biomarkers leads to a higher ELF score and indicates a greater likelihood of more severe fibrosis. (84)

1.6 The available HCV therapies and barriers to access HCV care

1.6.1 The current standard of care and developing therapies

The goal of HCV therapy is to eradicate the infection in order to prevent any complications of HCV-related liver diseases such as fibrosis, cirrhosis, liver decompensation, HCC and death. The endpoint of therapy is a sustained viral response (SVR), defined as having no detectable HCV RNA either 12 weeks or at 24 weeks after the end of treatment. (85) Long-term follow-up studies have shown that an SVR corresponds to a definitive cure of HCV infection in more than 99% of cases. (86)

Initially, a monotherapy of interferon (IFN) was used in the 1980s, which cured the HCV infection in less than 10% of patients. (87) From 2000, standard of care for the treatment of chronic HCV has been a combination of pegylated interferon (PegIFN) and ribavirin (RBV) for 24 to 48 weeks. However, this combination therapy was accompanied by significant side effects in 75% of patients and a low SVR rate in GT 1 HCV infected patients (40%-50% vs. more than 70% in GT 2 or 3). (88)

PegIFN and ribavirin have several mechanisms of action against HCV infection. PegIFN have immunostimulatory activity and also stimulates production of proteins that prevents synthesis of viral proteins. Ribavirin is a nucleoside analogue structurally similar to guanosine with broad spectrum of antiviral activity such as inhibition of viral replication and also shows immunomodulatory activity etc. (89, 90) Adverse effects of IFN include but are not limited to flu-like symptoms, dermatologic, gastro-intestinal and neuropsychiatric complications. Adverse effects of RBV include reproductive, metabolic and hematologic complications. (89, 90)

In 2011, two first-generation NS3/4A protease inhibitors telaprevir (TPV) and boceprevir (BOC) (Figure 1.2 and 1.3) were approved for use as a triple therapy in combination with PegIFN and RBV and SVR rates improved to 65% to 75%. (91) In spite of their success, TPV and BOC also had drawbacks such as serious systemic side effects and a high daily pill burden. (92)

In 2014 three new direct acting antivirals (DAAs), sofosbuvir, simeprevir and daclatasvir, were licensed in the European Union (EU). (93-95)
Sofosbuvir, simeprevir and daclatasvir can be used as a component of a triple combination regimen with PegIFN and RBV, showing SVR rates of 60–100%. The IFN-free combinations of these new DAAs also show high rates of SVR ranging between 80-98%. (94, 96-100)
In the last decade different drugs and drug combinations were approved in Europe, the combination of ledispavir plus sofosbuvir was approved in 2014, in 2016 the combinations sofosbuvir plus velpatasvir and grazoprevir plus elbasvir were approved. In 2017 the combination sofosbuvir plus velpatasvir plus voxilaprevir and glecaprevir plus pibrentasvir were approved. (101)

The type of treatment and treatment duration depend on several factors such as HCV GT, treatment experience, response to previous treatment, the stage of liver fibrosis, comorbidities etc. For this reason, guidelines are developed regu-

larly by the European association for the Study of the Liver in the light of the results of the latest research. (94, 102, 103)

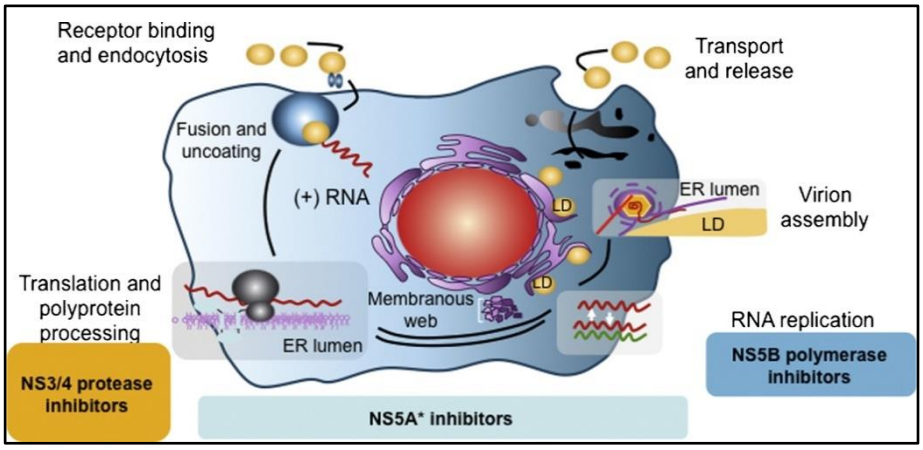

Figure 1.2. The HCV life cycle and targets of the direct-acting antivirals (figure from Bruno R et al. (104)

Explanation cell cycle: The virus enters the cell by receptor-mediated endocytosis. After membrane fusion and uncoating, the genomic HCV RNA is released from the nucleocapsid into the cytoplasm. The genomic HCV RNA is than translated and a single large polyprotein is generated. This polyprotein is processed into 10 mature HCV proteins. These proteins form a membrane bound replication complex. This complex replicates the RNA genome. New virions are assembled when the newly produced RNA is combined with viral glycoproteins in the Golgi apparatus. Virions mature on their way to the cell membrane where mature virions are released from the cell through budding. (104, 105)

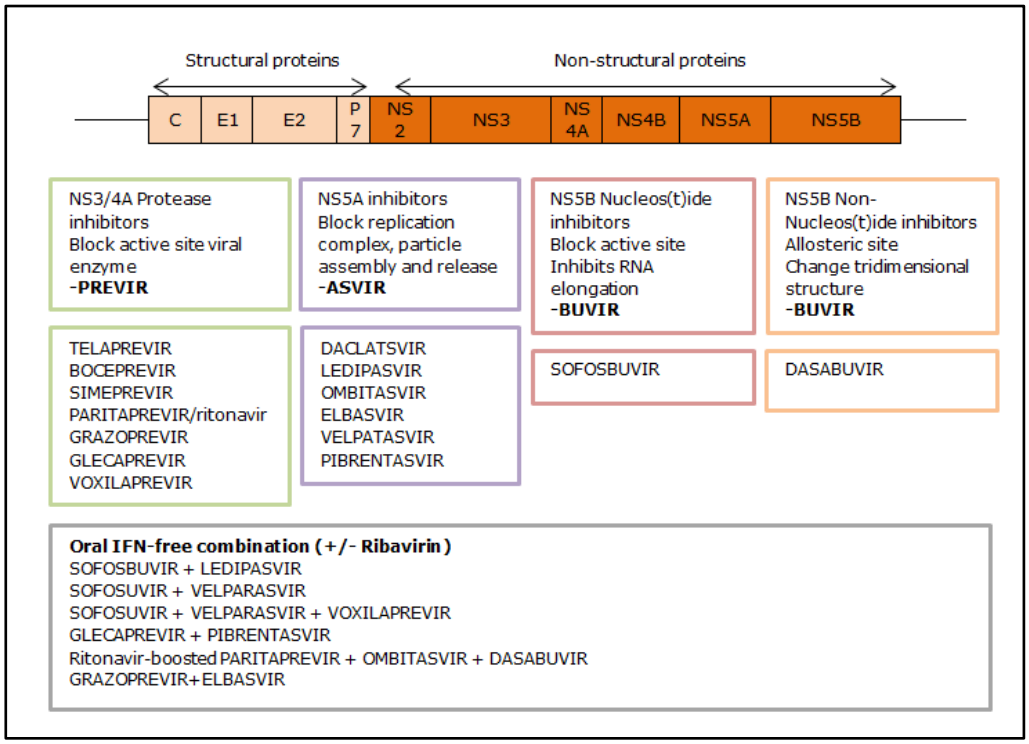

Figure 1.3. Directly acting antivirals approved for treatment of hepatitis C virus (figure based on figure 1 by Perales et al. (106) and information from FDA (106, 107) and EASL guidelines. (103)

Interferon-free DAAs did revolutionize and drastically improve HCV treatment outcomes.

1.6.2 The price and reimbursement of direct-acting antivirals

The price of HCV therapy is often high and not the same everywhere. The price depends on the communication between the pharmaceutical companies and the governments of the different countries. In the United States the price of sofosbuvir treatment exceeds 50,000 US dollars per patient even after negotiated

discounts. Some countries such as India were successful in accessing DAA therapy at much lower price. Sofosbuvir is available at a price below 900 US dollars per patient for 12 weeks of treatment in India. This is the result of direct negotiations with the manufacturers and by the introduction of generic medicines. (82, 108)

The reimbursement of the treatment depends on the health insurance system and the decisions of health care authorities related to the reimbursement. Since January 2017, the DAAs with or without RBV are reimbursed for patients with F2, F3 and F4 liver fibrosis stage in Belgium. Also patients with fibrosis stage F0-F1 were reimbursed in some conditions for example HIV or HBV co-infection etc. Before 2017, only patients with more advanced liver disease, with F3 and F4 fibrosis stage, were reimbursed. The summary of treatment options and the cut-offs for the fibrosis stages F2, F3 and F4 are provided in detail by the Belgian Association for the Study of the Liver. (109)

From January 2019, DAAs are also reimbursed for patients with liver fibrosis stage F0-F1 in Belgium. (110, 111)

1.6.3 HCV occurrence and recurrence after HCV treatment

Some studies suggested in the last few years that HCC may occur or recur in patients with chronic HCV infection who achieved SVR with DAA therapy. (112) In the era of interferon-based treatment, patients with HCV cirrhosis who achieved SVR were shown to be less likely to develop HCC. (113) Because this phenomenon was not seen in patients treated with interferon or ribavirin, some experts speculate that the immunostimulatory as well as direct antineoplastic effects of interferon may inherently lower the risk of HCC development in patients who achieved SVR with interferon treatment. (112)

Rob et al. (114) investigated the HCC occurrence and recurrence rates within six months after treatment with DAA with or without PEG-IFN in real life in 15 hospitals in Belgium. No difference in early occurrence of new HCC between patients treated with DAA with (1.7%) and without (1.1%) PegIFN ($p=0.540$),

was observed. The early recurrence rate was 0% in patients treated with PegIFN combined with DAA, and 15.0% in patients treated with DAA without PegIFN (p=0.857).

1.6.4 Barriers for HCV antiviral management among PWID

Patients have to face several impediments before they can receive antiviral treatment. (115) These barriers are present at multiple levels. Patients themselves can serve as an obstacle and they may not seek treatment due to insufficient awareness of HCV, other competing life priorities, fear of side effects, anxieties of being stigmatized, etc. At the level of the clinical management team, frequently there is a lack of experience. There is also a paucity of treatment settings adapted for the needs of PWID. Also the lack of HCV knowledge in addiction and primary care centers prevents them from treating PWID. At the level of government, insufficient funding and lack of treatment are important barriers. (115)

1.7 HCV management in persons who injected drugs

1.7.1 HCV infection among PWID

According to the joint UNODC/WHO/UNAIDS/World Bank estimate, worldwide 246 million (±5%) people aged 15 to 64 used an illicit drug in 2013. Approximately 27 million people were problem drug users, suffering from drug use disorders or drug dependence. Almost half of the problem drug users (12.19 million or 0.26% of the adult population aged 15-64) are PWID. (116) Injection drug use is most commonly associated with opioid use. (117) The estimated number of PWID in Europe was 3.68 million (0.67%) of the population aged 15-64. (116)

The prevalence of anti-HCV is 60-80% among PWID. Nelson et al. estimated in 2011 that worldwide about 10 million PWID might be anti-HCV positive. (5)

According to a systemic review published in December 2017, globally, 52.3% (42·4–62·1%) of PWID are HCV-antibody positive. (6)

HCV infected PWID represent a large proportion of patients at risk for liver disease and are the major reservoir for the continued spread of the virus. The risk factors for transmission are well known in this community: sharing of needles and syringes, sharing of cookers, cotton filters, water and even swabs. (4)

1.7.2 Injection drug use and substitution treatment in Belgium

According to the most recent estimates, the prevalence rate of injection drug use in Belgium was 3.5 per 1000 residents aged 15-64 in 2010. The estimated total number of ever-PWID was 24 664 (95% CI: 17565; 34403) with 41% currently injecting in 2010. (118) This prevalence rate remained stable in the period 2002-2013. (118-120) Mathei et al. provided an estimation of current PWID population and their involvement in opioid substitution therapy and needle and syringe programs in 2015 (Figure 1.4)

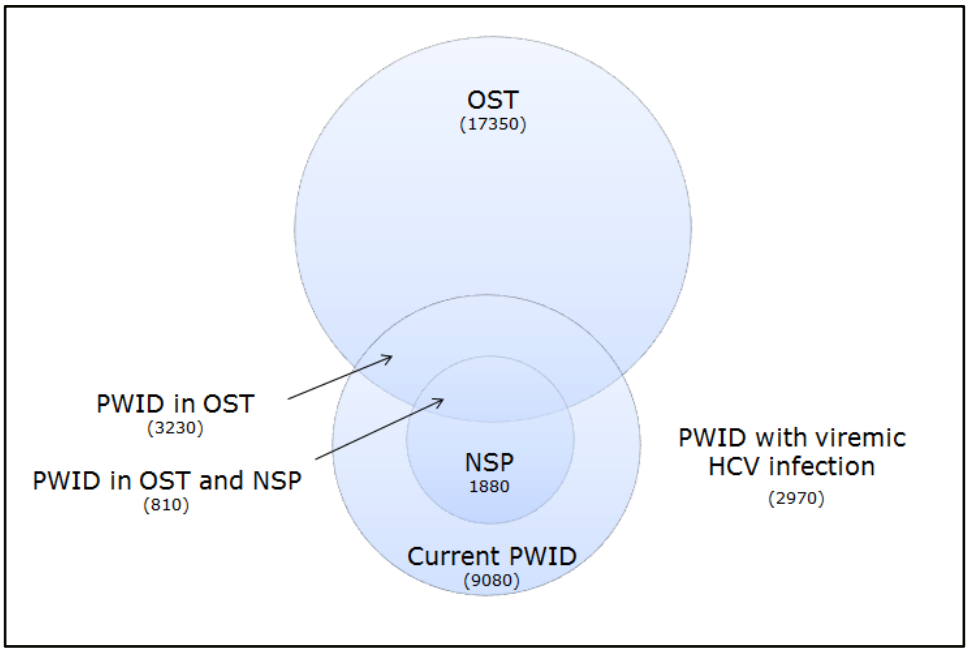

Figure 1.4. Estimated size of current PWID, OST and NSP population in 2015 (Figure based on figure 1 by Mathei et al. (121))

In 1997, the Belgian Ministry of Health established medico-social centers to provide medical and psychosocial care to illegal drug users. These centers follow the principles of harm reduction, which comprise a set of practical strategies to reduce the negative effects of drug use. (57) One of these strategies is opiate substitution therapy (OST), where heroin dependence is treated with methadone to help manage the addiction. Needle and syringe programs (NSP) have been implemented since 2001 in Flemish community and since 1994 in the French community. (119) PWID can exchange used needles for sterile ones, but also sterile spoons, alcohol swabs, aluminum foil and needle containers can be obtained anonymously and for free. (122)

Opioid substitution therapy can provide an ideal context for HCV screening and studies have shown that OST is associated with an increased chance of detecting

an HCV infection in drug users (123), and can even help protect against HCV acquisition. (124)

1.7.3 Efficacy, adherence and completion of HCV treatment and reinfection in PWID

Several studies delivered evidence that IFN based antiviral HCV treatment (125-130), first generation DAAs (TPV and BOC) (131) and the novel DAA-based IFN-free HCV treatment (96-100) are safe and effective for the PWID population.

Studies in the era of IFN- based therapies have shown that a history of injection drug use (IDU) does not compromise adherence to treatment, treatment completion or SVR. In contrast, recent drug use and frequent drug use during HCV treatment have an impact on treatment adherence, treatment completion and SVR (67, 102). IFN-based therapy did have several side effects and long (6-12 months) treatment duration while IFN-free therapies have almost no side effects and short (3 months) treatment duration. High adherence has been observed among PWIDs in recent studies with DAAs. (132-134) A study published in 2017 demonstrated that adherence was excellent among marginalized people with a history of drug use when treated with DAA (Sofosbuvir/Ledipasvir and Sofosbuvir/ribavirin) and that only moderate to heavy alcohol use was associated with weeks with missed doses. This study provides valuable insights into real-world adherence patterns and treatment outcomes among people who use drugs outside of OST- based clinical settings. (133) Further data in the IFN-free era are needed.

A review published in 2015 (135) reported that the incidence of HCV reinfection following successful treatment among PWID ranged from 0.0 to 5.3 cases per 100 person-years. Among persons reporting ongoing injection drug use after successful treatment, the incidence of reinfection ranged from 1.8 to 33.0 cases per 100 person years. Midgard et al. (2016) (136) reported based on their review a pooled incidence of reinfection (from 11 studies) following IFN-based

treatment among PWID of 2.1 per 100 person-years among those with ever IDU and 5.6 per 100 person-years among those with post-treatment IDU. According to the results of a multicentre trial (137), reinfection was common over time (7 years follow-up) among PWID who relapsed to injection drug use after successful HCV treatment. In this trial persistent reinfection was found in 11% of all patients (10/94) with a history of injection drug use before therapy (incidence rate: 1.7 per 100 person-years) and in 27% of patients who relapsed after treatment (10/37; incidence rate 4.9 per 100 person-years). These findings suggest that besides HCV screening and treatment scale –up efforts should be made to improve and enhance preventive actions.

1.8 HCV among prisoners

According to a meta-analysis (138) the estimate of anti-HCV in general detainees was 26% and 64% in detainees with a history of IDU. These prevalence rates are clearly higher compared to the anti-HCV prevalence of 1.6% in the general population. (1) Globally 2.2 million prisoners are anti-HCV positive. (138) Among prisoners, the estimated prevalence is 15.4% in Western Europe and 20.7% in Eastern Europe. (139) Also in prisons the main risk factor associated with HCV is IDU. Even though drug use is forbidden in prisons, nearly half of the drug users continue using drugs during imprisonment. (140) The lack of sterile injecting equipment in the prisons results in widespread sharing of equipment which leads to higher risk of HCV transmission. In prison other risk factors associated with HCV infection are older age, previous imprisonment, being infected with HIV and/or HBV and to a lesser extent tattooing, sharing toiletries and dental procedures. (140) In two studies, HCV infection was observed more frequently in female inmates than in males, reflecting the higher rates of females incarcerated for drug-related offences. (140)

The high rates of imprisonment among PWID and the lack of harm reduction interventions such as provision of sterile injecting equipment, places the prisoners at high risk of HCV infection. (141-144)

1.9 Aim of the performed studies reported in this thesis

The general aim of this thesis is to study the profile of the Belgian HCV infected PWID population and how it relates to HCV care, whether the outcome of the new therapies (at that time TPV and BOC) is comparable with non-PWID population and how we can improve HCV care.

To improve HCV care by enhancing HCV screening and treatment in the PWID population, it is important to know the population and the factors that have an influence on treatment uptake according to the patients themselves and their addiction care physicians. For this reason a study (chapter 2) was performed to study the characteristics, patients' willingness for HCV treatment, physicians' opinion regarding the suitability of the patients for HCV treatment, the referral rate and factors associated with referral to a hepatologist for HCV treatment, among a population of PWID with chronic HCV infection in an OST setting in Belgium.

At the time when the first generation DAA (TPV and BOC) became available for the treatment of HCV GT 1 infection, there were no published trials on the outcome of BOC and TPV in PWID. Therefore we performed a study (chapter 3) to compare the outcome of antiviral HCV therapy including BOC or TPV among PWID and non-PWID infected with GT 1 in Belgium

Insufficient knowledge on HCV and a low perceived need for treatment are important barriers for HCV treatment uptake. (145, 146) Therefore a study (chapter 4) was designed to assess the influence of a combination of formal education, peer education and assessment with the Fibroscan on knowledge of

HCV and willingness for HCV screening and treatment in persons who use drugs (PWUD).

HCV treatment has been delivered to PWID through different multidisciplinary approaches. (147-151) A study (chapter 5) was performed to evaluate whether a treatment setting under one roof is superior than other treatment settings providing addiction care and HCV care at different locations.
There is a close relationship between injection drug use, HCV infection and imprisonment. Although HCV prevalence is high among prisoners, provision of HCV therapy is uncommon in this population. (143) A review (chapter 6) was performed to discuss the prevalence and HCV care in prisons and to define recommendations to improve the HCV care in custodial settings.

Chapter 2

Patient characteristics, willingness and referral for hepatitis C treatment in people who injected drugs in a substitution program

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Submitted

2.1 Abstract

Background and aim: Despite the high prevalence of HCV infection among persons who inject drugs, the access to treatment remains low in this population. Baseline characteristics, patients' willingness for HCV treatment, physicians' opinion regarding the suitability of the patients for HCV treatment, referral rate and factors associated with referral for HCV treatment, among a population of PWID with chronic HCV infection in an OST setting are poorly known.

Methods: Therefore, a prospective multicentre cohort study in Belgium assessed the demographic characteristics, socio-financial situation, drug use behaviour, HCV related health, mental health, opinion about treatment in clients of OST clinics, who are infected with HCV, by means of questionnaires completed by the participants and their care providers.

Results: At baseline, most participants (n=170) were male, younger than 45 years and had received secondary education. More than 80% of the patients reported past heroin, cocaine and benzodiazepine use.

The majority (90%, 95% CI [85;94]) were willing to receive the antiviral treatment for HCV. However in the addiction care physician's opinion 43% (95% CI [35;51]) was suitable for treatment and in 17% (11/64, 95% CI [8;26]) of the participants who attended the appointment with the hepatologist, HCV treatment was actually recommended. The factors 'no recent heroin, cocaine and methamphetamine use or injection', 'receiving more than 4 take away doses of OST per week', 'ever having sought treatment', 'planning to receive treatment within one year', 'having received a liver biopsy' were associated with being referred to the hepatologist for HCV treatment.

Conclusion: At the baseline visit, the majority of the patients were willing to receive treatment while in the physician's opinion only less than half were

suitable for treatment. The patients' and care providers' reasons for delaying or withholding treatment need to be addressed.

2.2 Background

Hepatitis C virus infection is an important health issue worldwide. Injection drug use has become the main transmission route of HCV in developed countries (9, 152). Chronic HCV infection can lead to the progression of liver disease, liver cirrhosis and hepatocellular carcinoma, resulting in half million deaths every year. (11) Among PWID, the rates of liver disease complications, liver related morbidity and mortality and the associated health care costs continue to rise. (9, 33)

Previous studies have shown that HCV treatment is safe and effective in this population. (125, 126, 153) Treating PWID for HCV might reduce the number of new HCV infections, the incidence of liver transplantations and the number of deaths due to hepatic failure. The treatment of HCV among PWID is encouraged by international guidelines. (82, 94, 154, 155) However the current uptake of treatment among PWID is low. (145, 156-159)

The low uptake of treatment among PWID is probably attributed to both physician and patient-associated factors. Increasing the proportion assessed for HCV infection and understanding factors associated with HCV treatment uptake among those assessed is important.

The purpose of this study was to evaluate the baseline characteristics of the patient population, the patients' and physicians' opinion regarding treatment, the referral rate to a hepatologist for HCV treatment and factors associated with the referral rate.

2.3 Methods

2.3.1 Study design and population

The Link study is a prospective multicentre cohort study. The study was approved by the ethical committee of Ziekenhuis Oost-Limburg. This report includes the results of inclusion (baseline) questionnaires collected between June 2012 and December 2013 by a group of seven OST clinics located throughout Belgium (Liège, Limburg, Brussels and Antwerp).

Patients who were 18 years or older, with a history of IDU, chronic HCV infection (positive for anti-HCV and HCV RNA), were invited to participate in the study. More specifically, the addiction care provider (physician and/or nurse) identified the eligible patients (18 years or older, history of IDU and with Chronic HCV infection) by cross-checking the list of the patients attending the substitution program. Eligible patients were asked to participate in the study during their daily or weekly visit to the addiction care center.

Not all eligible patients participated in the study. The participating centres were not requested to report the reasons for non-participation.

In one of the participating OST centre, Free clinic Antwerp, the cascade from HCV screening to participation the study was described.

According to the exclusion criteria, patients with an acute HCV infection, negative or unknown anti-HCV/HCV RNA status, currently on HCV treatment or successfully treated previously for HCV, were not included in the study. The participants received a fee of 10 euro to complete the questionnaire.

2.3.2 Data collection

The study participants were asked to complete an enrolment questionnaire after inclusion in the study. Two follow-up visits were planned after one and two years to complete the follow-up questionnaires. If a participant started treatment within the two follow-up years, a treatment questionnaire had to be completed which for these participants was the last questionnaire.

The questionnaires consisted of two parts:

The first part, completed by the participants, was a questionnaire about demographics, drug use/injecting history, alcohol use, tobacco use, drug and alcohol treatment, history of HCV (diagnosis and treatment history), social situation, mental health, treatment willingness and willingness to start treatment within a year. Alcohol use was assessed by an adapted version -the same three questions as described by Bush et al. (160) were used without the part: "in the past year"- of the Alcohol Use Disorders Identification Test (AUDIT)–C with scores >3 and >4 indicating high-risk consumption among women and men, respectively) (160). The social situation was evaluated through an adapted 6-item social functioning scale (161) with a higher score indicating lower social functioning. The 6 questions described by Lawrinson et al. (161) were adapted by only replacing the part "last 3 months" by "previous month". This social functioning scale measured the participants' levels of financial hardship; conflict in relationships with spouses/partners, other relatives and employers/school staff and students; time spent living with a drug user and time spent with non-drug using friends. Mental health was assessed by the 21-item Depression, Anxiety and Stress Scale (DASS-21) (162).

The second part of the questionnaire was completed by the care provider (physician and/or nurse) and assessed psychological health, medical/psychiatric history, possible source of infection, suitability for treatment, referral to a hepatologist for HCV treatment, attendance of the hepatologist appointment by the patient and the HCV treatment related decision after this appointment.

2.3.3 Statistical analysis

To characterise the study population, descriptive statistics of patient characteristics are presented. For continuous variables, means and standard deviations are presented. For categorical variables, proportions and percentages are given.

To identify the factors associated with referral to a specialist, bivariate analyses were performed using a Chi-square test or Fisher exact test, as appropriate. A p-value <0.05 was considered as statistically significant.

2.4 Results

2.4.1 Cascade from HCV screening to study participation of one participating centre

In figure 2.1 the number of patients who were tested for anti-HCV, HCV RNA and who participated in this study in Free Clinic Antwerp are presented. Also the reasons for no test-uptake and non-participation in the study are described.

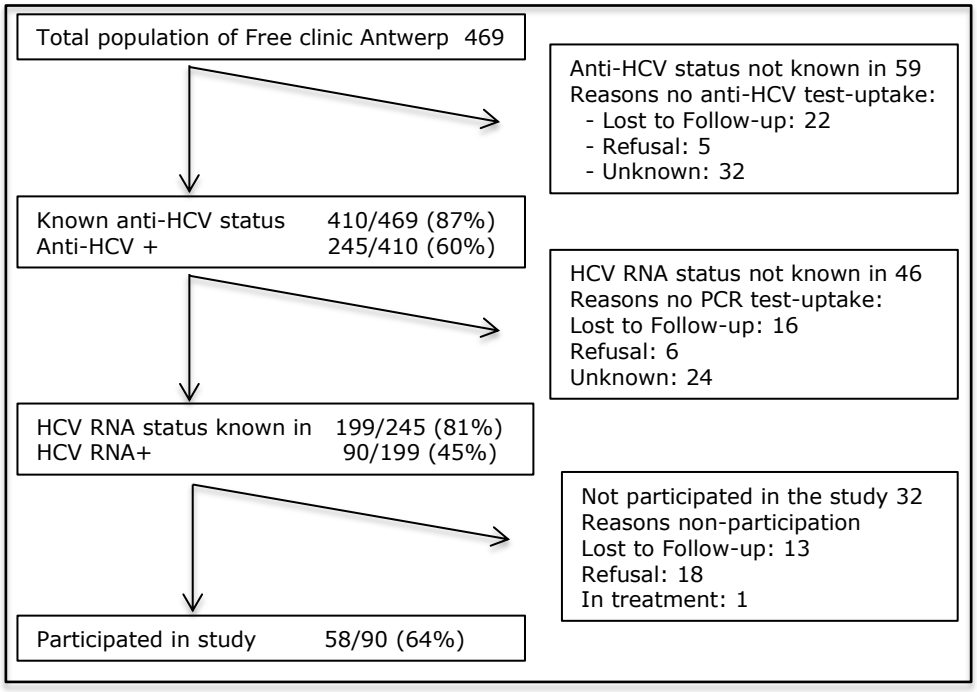

Figure 2.1. Hepatitis C screening and participation in the study in Free clinic Antwerp.

2.4.2 Demographics and baseline clinical data

Demographic characteristics of the patients (n=170), who were included and completed the baseline questionnaire, are described in Table 2.1. Most patients were men, younger than 45 years and had received secondary education. Only a limited number of patients (8%) were full or part-time employed. Most of the patients (78%) received a replacement income from the government or health insurance and 78% had a monthly income between 700 –1200 euro. Almost 70% were paying off their debts. Almost everyone (95%) had a health insurance. Fifty-two percent were living with a partner or relatives and 79% had stable housing (rented or owned).

Past imprisonment was reported in 78% of the clients and 8% was imprisoned during the last 6 months. A vast majority of the patients (95%) was on opioid substitution treatment. Fifty-seven percent of the clients were infected with genotype 1 HCV and the remaining 43% with genotype 2, 3 or 4. In 49% of the participants the viral load was higher than 800000 IU/ml.

According to the DASS 21 questionnaire more than 70% of the participants had a moderate to extremely severe level of depression, anxiety and stress. Forty-two percent of the clients reported high risk alcohol consumption. Overall, 53% of the participants reported a higher level of social functioning (lower than the median score <6.0).

Table 2.1. Enrolment demographic characteristics of participants (n =170).

Characteristics	Total participants: 170
Gender	
Male	142/170 (83.5%)
Female	27/170 (15.9%)
Transgender	1/170 (0.6%)
Age	
<35	36/170 (21%)
≥35 and ≤45	73/170 (43%)
>45	61/170 (36%)
Average age when started injecting (±sd)	22 (±7)
Country of birth (Belgium)	114/170 (67%)
Education	
Primary	25/168 (15%)
Secondary	135/168 (80%)
Higher	8/168 (5%)
Main source of income	
Full or part-time employment, n (%)	14/168 (8%)
Replacement income	131/168 (78%)
No income	12/168 (7%)
other	11/168 (7%)
Netto monthly income, n (%)	
Less than €700	18/165 (10.9%)
€700 – €1200	128/165 (77.6%)
€1200 – €2200	18/165 (10.9%)
More than €2200	1/165 (0.6%)
Paying off debts, n (%)	115/169 (68%)
Health insurance, n (%)	162/170 (95%)
Living with spouse/friends/family/relatives, n (%)	88/169 (52%)
Rented or owned housing in last 6 months, n (%)	134/169 (79%)
Past imprisonment, n (%)	133/170 (78%)
Imprisonment within the last 6 months, n (%)	14/170 (8%)
Receiving opioid substitution treatment n (%)	158/166 (95%)
HCV genotype, n (%)	
Genotype 1	58/102 (57%)
Genotype 2, 3, 4	44/102 (43%)
HCV-RNA level, IU/ml	
≥ 800000	40/82 (49%)
< 800000	42/82 (51%)
DASS 21 results	
Depression (normal to mild)	43/151 (28%)
Depression (moderate to extremely severe)	108/151 (72%)
Anxiety (normal to mild)	40/151 (26%)
Anxiety (moderate to extremely severe)	111/151 (74%)
Stress (normal to mild)	33/151 (22%)
Stress (moderate to extremely severe)	118/151 (78%)
Social functioning score, median (range)	6 (0-16)
Higher social functioning (<6)	90/169 (53%)
High-risk alcohol consumption	71/170 (42%)

2.4.3 Baseline drug use

More than 90% of the participants reported heroin and cocaine use (Table 2.2). Past non-prescribed benzodiazepine use was reported by 88% of the participants. Use of non-prescribed benzodiazepines, heroin and cocaine during the last four weeks was present in 49%, 35% and 29% of the participants, respectively. More than 70% ever injected heroin or cocaine while in the last 4 weeks heroin and cocaine was injected by 15% and 16% of the participants, respectively.

Table 2.2. Drug use reported at baseline.

Characteristics				
	Ever used	Use in last 4 weeks	Ever injected	Injected in last 4 weeks
Heroin	166/169 (98%)	59/169 (35%)	149/169 (88%)	25/163 (15%)
Cocaine	157/169 (93%)	49/167 (29%)	122/169 (72%)	27/168 (16%)
Morphine or other opiates	68/165 (41%)	5/165 (3%)	34/167 (20%)	1/166 (1%)
Benzodiazepines	147/167 (88%)	81/166 (49%)	5/167 (3%)	0
Methamphetamine	98/166 (59%)	14/166 (8%)	56/168 (33%)	8/164 (5%)

2.4.4 Participants' and physicians' point of view regarding health, HCV infection and treatment at baseline

More than 60% of the participants scored their health as 'poor to fair" (Table 2.3). The majority (85%) indicated IV drug use as the way they were infected. Ninety percent (95% CI [85;94]) of the participants were willing to receive the antiviral treatment and 68% (95% CI [61;75]) were willing to do so within one year. The most common reasons for not planning to receive treatment within one year were concerns for side effects (34%, 18/53), absence of symptoms (11%, 6/53) and the presence of other medical issues (9%, 5/53).

Table 2.3. Participants' opinion regarding their health, HCV infection and treatment.

Characteristics	
My health is in general	
Poor to fair	111/170 (65%)
Good	55/170 (32%)
Very good to excellent	4/170 (2%)
Most likely source of infection	
Intravenous drug use	132/156 (85%)
Non-intravenous drug use	5/156 (3%)
Blood transfusion	2/156 (1%)
Tattoo	1/156 (1%)
Occupational	12/156 (8%)
Sexual contact	4/156 (3%)
Willingness to receive treatment	
yes	151/168 (90%)
no	5/168 (3%)
I do not know	12/168 (7%)
Planning to receive treatment within 12 months	
Yes, within 12 months	111/164 (68%)
Yes but later than a year	49/164 (30%)
Never	4/164 (2%)

According to their addiction care physicians, 94% of the participants were infected by IV drug use and only 43% was suitable for treatment at the moment (Table 2.4). Unstable drug use, psychiatric comorbidity and unstable housing were the most common reasons for not being suitable for treatment. Of the participants 60% (n=90) were referred to a hepatologist. This percentage (60%) is higher than the percentage of patients who were suitable for HCV treatment (43%) according to the addiction care physician. The addiction care physician referred also some patients (Table 2.4) for a second opinion. Of the patients referred to the hepatologists 75% (n=64) attended the appointment. Treatment was recommended by the hepatologist for 17% (n=11), delayed in 73% (n=47) and not recommended in 9% (n=6) of the patients.

Table 2.4. Physicians' opinion regarding HCV infection and treatment.

Characteristics	
Most likely source of infection	
Intravenous drug use	144/154 (94%)
Non-intravenous drug use	4/154 (3%)
Sexual contact	2/154 (1%)
Other (by accident and sexual contact or IDU)	3/154 (2%)
Patient suitable for HCV treatment?	
yes	65/152 (43%)
Not at this stage	38/152 (25%)
Not sure	42/152 (28%)
No	7/152 (5%)
Most common reasons why patient is not suitable for treatment*	
Unstable drug use	17/67 (25%)
Psychiatric comorbidity	21/67 (31%)
Unstable housing	18/67 (27%)
Patient referred to a specialist	90/150 (60%)
Patients attended appointment	64/85 (75%)
Outcome of the specialist appointment?	
Treatment not recommended	6/64 (9%)
Treatment recommended but delayed	47/64 (73%)
Treatment recommended	11/64 (17%)

*Often more than one reason per patient was reported

2.4.5 Patients' characteristics associated with being referred to a hepatologist for HCV treatment by the addiction care physician

'No heroin use in the last 4 weeks' and 'no heroin injected in the last 4 weeks' were associated with being referred to a hepatologist for HCV treatment (Table 2.5). This was also the case for the factors, 'no cocaine use in the last 4 weeks' and 'no cocaine injected in the last 4 weeks', 'no methamphetamine use in the last 4 weeks', 'no methamphetamine injection in the last 4 weeks', 'receiving more than 4 take away doses of OST per week', 'ever sought treatment', 'willingness to receive treatment within one year' and 'having received a liver biopsy'.

Table 2.5. Factors associated with referral for HCV treatment.

Characteristics	Referred to specialist	95% CI	P value
No heroin use in last 4 weeks	73/103 (71%)	[62;80]	<0.05
No heroin injection in last 4 weeks	80/124 (65%)	[56;73]	<0.05
No cocaine use in last 4 weeks	71/104 (68%)	[59;72]	<0.05
No cocaine injection in last 4 weeks	82/126 (65%)	[57;73]	<0.05
No methamphetamines use in last 4 weeks	86/136 (63%)	[55;71]	<0.05
No methamphetamines injection in last 4 weeks	87/139 (63%)	[55;71]	<0.05
Receiving more than 4 take away doses of OST/week	48/72 (67%)	[56;78]	<0.05
Sought HCV treatment in the past	68/111 (61%)	[52;70]	<0.05
Plan to receive HCV treatment within one year	70/98 (71%)	[62;80]	<0.05
Received liver biopsy	35/43 (81%)	[70;93]	<0.05

2.5 Discussion

In only one participating centre (Free Clinic Antwerp) the cascade from HCV screening to participation in this study was available. The rate for anti-HCV screening and HCV RNA screening, which is studied in one of the participating centres (Free clinic Antwerp), is high 87% and 81%, respectively. An important reason for no test-uptake was lost to follow-up. This suggests that persons who are not screened were often difficult to contact.

The main findings of this study are that this population of chronic HCV patients with drug use history under OST consisted mainly of men, younger than 45 years and with secondary education as the highest level of education. Past heroin and cocaine use was present in more than 80%. Although 90% of the patients were willing to receive treatment, in 17% (11/64, 95% CI [8;24]) treatment was recommended by the hepatologist at the start. No recent drug heroin, cocaine and/or methamphetamine use, being more stabilized on OST

reflected by being allowed to have more than 4 take away doses of OST per week, being more interested in antiviral treatment indicated by 'ever having sought treatment' and 'willingness to receive treatment within one year' and being further in the diagnosis process -having received a liver biopsy- were associated with being referred to the hepatologist for HCV treatment. In the addiction care physicians' opinion unstable drug use, psychiatric comorbidity and unstable housing were the most common reasons for not being considered suitable for HCV treatment.

Similar populations with a history of IDU have also been studied by other researchers around the world. We did search on PubMed and in the references of other related articles for similar studies that investigated HCV treatment willingness and referral for HCV treatment. Common in these study populations is that the majority of patients are male and older than 40 years of age. (148, 163-165) They differ, however, in their education level depending on the country studied. In our study population most patients (80%) have finished high school and 5% have completed higher education while in the Australian cohort (165) only 19% of the patients have finished high school or higher education. In our Belgian cohort 8% were full or part time employed. Similarly in the Australian cohort (165) 9% were full or part time employed while the employment rate was 15% in a New York population (148) and only 4% in Toronto. (166) For the majority of the participants in our population (79%) and the Australian population (81%) (165), housing was stable (rented or owned). Imprisonment rate during the last six months was also almost the same in our population (8%) and in the Australian (165) PWID population (9%).
In the Australian cohort (165) 38% of the participants were infected with genotype 1 and 41% by genotype 2,3 or 6 while in this Belgian PWID population 57% were infected with genotype 1 and the remaining 43% by genotype 2, 3 or 4. In this Belgian population more than 70% suffered from moderate to severe depression, anxiety and stress according the DASS 21 questionnaire while in the Australian cohort this was lower (50-60%). Also in Zurich, Switzerland the psy-

chiatric comorbidity in this population was high, 72% of the 85 participants suffered from a psychiatric comorbidity. (167)
The similarities and differences in characteristics among the studied PWID populations suggest that to improve screening and uptake of treatment, probably different strategies/multidisciplinary approaches depending on the characteristics and needs of the population should be applied.

Ninety percent of the participants were willing to receive antiviral treatment in the future and 68% planned to initiate treatment within one year. Similar proportions (86% and 74% respectively) were observed by Alavi et al. (165) in a cohort in New South Wales, Australia. Concerns about side effects were the most common reason for not planning to receive treatment within one year. Also in other studies side effects have been identified as the main reason for treatment avoidance. (146) Informing patients about the new antiviral treatments with almost no side effects and very high success rates and making these antivirals available for this population will increase the proportion of patients ready to start treatment.

In this study 'no recent (in the last 4 weeks) heroin, cocaine, methamphetamine use or injection' and 'receiving more than 4 take away doses of OST per week' was associated with referral to a hepatologist for HCV treatment. This indicates that recent drug use remains a contraindication for HCV treatment in Belgium even when the international guidelines recommend to prioritize treatment among individuals at risk of transmitting HCV including active injection drug users (94) and recommend to take the decision of treatment based on case-by-case basis because history of injection drug use or recent drug use are not associated with reduced SVR. (154) According to expert opinion not the recent or active drug use but the chaotic lifestyle -closely associated with active drug use- is seen as the main contraindication by the addiction care physician in Belgium. (168) Also in other studies current drug use has been identified as a predictor of treatment deferral. (169, 170) The majority of clinicians only want

to treat PWIDs stable on OST. (171) This was also the case in this study because patients stable on OST/receiving more than 4 take way doses of OST were more likely to be referred to a hepatologist for HCV treatment by the addiction care physician.

As also expected, participants who had ever sought treatment, were willing to receive treatment within one year and who had received a liver biopsy to stage liver fibrosis (which was necessary in Belgium to apply for reimbursement by the health insurance at the time this study was performed), were more likely to be referred to a hepatologist for discussing the treatment options and starting HCV treatment.

In this study, the most common reasons why patients were not suitable for treatment in the addiction care physician's opinion were unstable drug use, psychiatric comorbidity and unstable housing. Similar results were shown by other studies as in the study by Jack et al. (172): the reasons for withholding HCV treatment were ongoing high drug consumption (69%), excess alcohol intake (18%), unstable housing (7%), significant mental illness (4%) and other medical conditions (2%).

These patient and care provider level barriers can be addressed by improving/updating the information provided to patients and care providers. Also the involvement of social workers and psychiatric/mental health care providers who help the patients to stabilise their housing and provide treatment/support for psychiatric comorbidity can play a role.

There are a number of limitations to this study. The study population may represent a group of drug users that is more engaged in health care services, resulting in an overestimation of proportions referred for treatment. The data relied on a self-reported socio-financial situation and drug use behaviour. They might not be the accurate estimation of the real situation.

We can conclude that despite the high willingness for treatment in this population, the referral rate for treatment is low. To improve access to antiviral HCV treatment, different strategies need to be implemented. The role of harm reduction centres providing substitution treatment and other support to substance users' needs to grow beyond only follow-up of the patient referred to hepatology clinics. These centres need to adapt their infrastructure and personnel in order to implement prevention strategies, increase HCV screening and treatment and post-treatment follow-up of the patients.

To improve the HCV care it is very important for every setting to identify for each case/patient the barriers to receive HCV treatment and to remove these barriers by a multidisciplinary team of social workers and medical care providers.

Chapter 3

Belgian experience with triple therapy with boceprevir and telaprevir in genotype 1 infected patients who inject drugs

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J Med Virol. 2016 Jan;88(1):94-9

3.1 Abstract

Background: No data have been reported yet on treatment outcome in persons who inject drugs infected with hepatitis C virus treated with BOC or TPV in combination with PegIFN and RBV. Additionally, there are concerns about the safety of BOC and TPV in some subgroups of patients with HCV.

Methods: In a cohort of HCV patients infected with GT 1 in Belgium, treatment outcome of patients infected due to IDU was analyzed and compared with patients who have no history of substance use.

Results: The study population consisted of 179 patients: 78 PWID and 101 controls treated with BOC (n=79) or TPV (n=100) additional to PegIFN and RBV; 53 (30%) had advanced disease (F3, F4) and 79 (44%) had an antiviral therapy previously. There were no significant differences in the baseline characteristics between both groups, except that PWID patients were more frequently infected with GT 1a (67% vs 21%), were younger and were predominantly male. Psychiatric complaints during follow-up occurred more frequently in the PWID patients: 24% vs 11% (p=0.02). Treatment failure for other reasons than absence of viral response was 70% and 64% in PWID and non-PWID, respectively. The sustained viral response rates were similar in both groups (71% in PWID vs 72% in non-PWID); with a non-inferiority test with -5% margin there is a difference of -1% (95% CI [-15%, 13%]) and p= 0.30.

Conclusions: There are no reasons to exclude PWID from treatment with BOC, TPV and novel antiviral therapies.

3.2 Introduction

Worldwide 130-150 million people are chronically infected with HCV and every year more than 350 000 people die because of HCV-related diseases. (173) During the past decade therapy with PegIFN and RBV for 48 weeks was the standard of care for treating HCV GT 1 infection. This dual treatment was successful in 40-50% of the patients. (174, 175) In 2011 the DAAs, BOC and TPV were approved to be used in combination with PegIFN and RBV for adult patients chronically infected with HCV GT 1. (67, 176, 177) This therapy results in increased viral clearance but is a serious burden for the patients (medication intake, side effects) and BOC and TPV can interfere with a lot of medications. (178) New generation DAAs are now becoming available, which are characterized by very high SVR rate, a short treatment period and almost no side effects. (179) However, the cost of treatment is extremely high and the medications are therefore only reimbursed in a limited number of countries.

Substance users are an important group of HCV infected patients in the developed world and have become the main source of new HCV infections all over the world. (5, 152) We previously reported excellent outcome of antiviral therapy without DAA in this group of patients. (130, 180) However, this population is thought to be less compliant and at high risk of drug toxicity because of the concomitant use of various chemical substances. Currently there is some reluctance to prescribe the DAAs to those PWID patients. Treatment is also deferred due to the misconception that there is a high risk for reinfection in this population. The rate of HCV reinfection among PWID is low, at approximately 1-5 per 100 person-years, even among persons who continue injection drug use during and after treatment. (181)

At this moment there are no published trials on the outcome of BOC and TPV in PWID. Therefore we performed a study during which we compared the outcome of antiviral therapy including BOC or TPV in PWID and non-PWID.

3.3 Materials and methods

3.3.1 Study design

This is a national retro/prospective, interventional cohort study conducted between 2008 and 2013 in 11 Belgian centres during which patients infected with GT 1 were treated with BOC or TPV in combination with PegIFN and RBV. All centres were experienced in treating HCV infected patients who were infected due to substance use. PWID were part of a substitution programme and if necessary, they received daily methadone or other substitution medications. When enrolling patients in this programme, they were questioned about their risk behaviours and tested for infectious diseases such as HCV, HBV and HIV. Patients who tested positive for HCV infection were referred to a gastro-enterologist/ hepatologist to consider antiviral treatment. The addiction care physician and specialized nurses were involved in further HCV related care of the patient. In case antiviral treatment was started data were collected in a central database.
In parallel the centres were asked to collect also the same data in the patients they treated with DAAs during the same period but without a history of drug use. Patients with decompensated cirrhosis were excluded.

Applied definitions or criteria:
In case of non-response during treatment the antiviral therapy was interrupted, as defined by the guidelines. (67) Diagnosis of depression was made by the clinicians according to the DSM criteria. Treatment completion was defined as return to the outpatient clinic at the end of treatment. The stage of fibrosis was scored before treatment initiation on the liver biopsies according to the METAVIR criteria. (182)

3.3.2 Study population

In total 179 patients were included in the study: 78 patients were PWID and 101 were non-substance users. Thirty-seven percent (n=29) of the PWID were treated with substitution therapy (28 with methadone and 1 with suboxone) during

the antiviral treatment. Twenty-one (27%) and twenty-nine (37%) patients were active substance and benzodiazepine users, respectively. Active users used heroin and/or cocaine and/or cannabis during the antiviral treatment period.

3.3.3 Endpoints of the study

The primary endpoints were treatment completion and viral clearance: early virological response at 3 months and SVR 24 weeks after the end of treatment. In addition to these also patient characteristics, addiction treatment and side effects of antiviral HCV treatment were studied.

3.3.4 Statistics

In order to characterize the patients in the study, descriptive statistics of patient characteristics are presented. For continuous variables means and standard deviation are presented. For categorical variables, proportions and percentage are given.
Regression methodology was used to compare patient groups (PWID and non-PWID) in terms of continuous responses or continuous patient characteristics (such as age and body mass index). Comparison of patient groups for a categorical variable (such as fibrosis stage, treatment completion, viral response) was performed by means of the Chi-square test. A p-value <0.05 was considered as statistically significant.

For the primary endpoints of this study (SVR and treatment completion) a non-inferiority hypothesis with a 5% margin was specified to compare the PWID and non-PWID group.

3.4 Results

3.4.1 Baseline characteristics

PWID were significantly younger, were predominantly male and had a signifi-

cantly lower BMI compared to controls (Table 3.1). Most patients in the two groups were Caucasian.

The prevalence of infection with HCV GTs 1a and 1b was different between the two groups. In the PWID group significantly more patients were infected with GT 1a HCV (67%) compared to controls (21%) (Table 3.1). Approximately 70% of the patients had a high viral load (HCV RNA level >800,000 IU per milliliter) at baseline. The viral load was similar in both groups. There was no significant difference in the stage of fibrosis between PWID and controls. Thirty percent (n=53) had an advanced stage of liver disease (F3, F4). Fifty six percent (n=100) were naïve for treatment. This percentage was higher in the PWID group (64%) but not significantly different from the control group (50%).

Table 3.1. Demographic and HCV related characteristics.

Characteristics	**PWID (n=78)**	**Non-PWID (n=101)**	**P value**
Age (mean ± SD)	44,7 ± 9,1	52,5 ± 11,4	<0,0001
Male gender	60 (77%)	54 (54%)	0,0012
Caucasian race	75 (96%)	96 (95%)	NS
BMI (mean ± SD)	24,6 ± 3,6	26,3 ± 4,8	0,0152
HCV genotype (1a)	52 (67%)	21 (21%)	<0,0001
Viral load (>800000IU/ml)	49/77 (64%)	75 (74%)	NS
Stage of fibrosis (biopsy)			NS
- F0	4/74 (5%)	15/89 (17%)	
- F1	27/74 (37%)	26/89 (29%)	
- F2	21/74 (28%)	17/89 (19%)	
- F3	9/74 (12%)	11/89 (12%)	
- F4	13/74 (18%)	20/89 (23%)	
Treatment history			
- Naïve	50 (64%)	50 (50%)	NS

3.4.2 Antiviral Treatment

There was no difference in the number of patients treated with BOC and TPV in both groups (Table 3.2). In both groups slightly more patients were treated with TPV.

In general, the occurrence of side effects was not different between the two groups, although the development of psychiatric complaints (depression, etc.) was significantly higher in the PWID group (24% in PWID vs 11% in control group (p= 0.02)) with a higher need to start antidepressants (p= 0.06). Dermalogic side effects such as rash, dry skin did occur in 31% of PWID vs 37% of non-PWID (p=0.41). Anemia did occur in 35% of PWID and 46% of non-PWID (p=0.11).

In PWID and controls the antiviral treatment was modified due to side effects in respectively 28% and 45% (p=0.03). This was mostly due to dose adjustment of RBV because of anemia (respectively 77 and 69%) (p=not significant (NS)).

Table 3.2. Antiviral HCV treatment related characteristics.

Antiviral treatment	**PWID (n=78)**	**Non-PWID (n=101)**	**P value**
Type of treatment:			NS
- Boceprevir	37 (47 %)	42 (42%)	
- Telaprevir	41 (53%)	59 (58%)	
Occurrence of side effects	68 (87%)	90 (89%)	NS
- Psychiatric complaints	19 (24%)	11 (11%)	0,02
- Skin rash	24 (31%)	37 (37%)	NS
- Anaemia	27 (35%)	47 (47%)	NS

Interruption of the treatment due to viral non-response (Table 3.3) during the treatment was 8/27 (30%) vs 8/22 (36%) in PWID and non-PWID respectively. The difference in treatment interruption equals -6% (95% CI [-33%, 20%]). The p-value when using a non-inferiority test with a +5% margin is 0.19. Interruption of the treatment in case of naïve patients was 11/50 (22%) in PWID vs

7/50 (14%) in non-PWID. There is a difference of 8% (95% CI [-7%, 23%]), and the p-value when tested in a non-inferiority setting (with a margin of +5%) is 0.65. Failure of treatment completion for other reasons than viral non-response was: 19/27 (70%) and 14/22 (64%) respectively in the PWID and non-PWID group (p= NS). In the PWID group this was particularly due to side effects (n=8), financial reasons (n=1), substance abuse (n=1), non-compliance (n=1) and mortality of unknown cause during treatment (n=2). One non-substance user died during antiviral treatment due to myasthenia gravis. SVR (table 3.3) was 49/69 (71%) in the PWID patients and 68/94 (72%) in the control group. A non-inferiority statistical test with -5% margin resulted in a p-value of 0.30. The difference in SVR between PWID and non-PWID group is -1% (95% CI [-15%, 13%]).

Table 3.3. Results of non-inferiority statistical analysis comparing endpoints between PWID and non-PWID.

	PWID (n=78)	**Non-PWID (n=101)**	**Difference**	**95% CI**	**P value**
Failure of treatment completion	27 (35%)	22 (22%)	13	[0;26]	0.87
Reasons for non-completion					
- Absence of viral response	8/27 (30%)	8/22 (36%)	-6	[-33;20]	0.19
- Other reasons*	19/27 (70%)	14/22 (64%)	6	[20;33]	0.55
SVR	49/69** (71%)	68/94** (72%)	-1	[-15;13]	0.30
- Naïve patients	39/49 (80%)	40/48 (83%)	3.7	[-19.2;11.7]	0.44

* Other reasons were substance or alcohol use, side effects, comorbidities, socio-financial situation, non-compliance, death, lost to follow-up or decision of the patient.

** 69 and 94: These are the total number of PWID and non-PWID with known result for SVR (yes or no) and in other patients SVR result was missing due to death, lost to follow-up etc.

3.4.3 Factors affecting outcome in the PWID patients

Substitution treatment did not affect treatment completion: 20/29 (69%) vs 31/49 (63%), (p= NS); neither modification of medication: 8/29 (28%) vs 14/49 (29%), (p= NS); nor viral clearance at week 12: 24/26 (92%) vs 40/49 (82%), (p= NS); nor SVR: 18/24 (75%) vs 31/45 (69%), (p= NS). However, significantly more patients in a substitution program started antidepressants: 8/9 (89%) vs. 6/13 (46%) (p=0.04) during the treatment compared to patients not on substitution treatment. Active use of substances such as heroin, cocaine, cannabis in 21/78 (27%) of the cases and the use of benzodiazepines in 29/78 (37%) of the patients neither affected treatment completion nor viral clearance at week 12 or SVR, reasons for non-completion, start of antidepressants or modification of medication.

3.5 Discussion

This study demonstrates that, as for previous combination therapy with PegIFN and RBV, combination therapy with BOC or TPV yielded similar SVR rates in PWID and in non-PWID patients.

Three patients died before an SVR test was performed, 10 patients were lost to follow-up, for 3 patients SVR test was not performed because of early treatment stop (2 patients) and nonresponse (1 patient) during the treatment. The SVR results were comparable to the registration trials reporting SVR rates between 60-80 percent. (183-190) There were significantly more treatment naïve patients in the PWID group. There were more GT 1a infected patients in the PWID group. This was also shown in other studies. (191, 192)

The triple treatment with DAA is challenging for HCV infected drug users. The treatment consists of oral intake of antiviral medication during food intake twice or thrice a day, and always at the same time besides the intake of RBV twice a day and subcutaneous administration of PegIFN once a week. This might be very difficult in substance users and could cause a lack in treatment adherence.

Adherence to treatment is important for a successful treatment. A recent study demonstrated adherence over 80% with PegIFN/RBV in substance users. (193) A pooled PegIFN/RBV treatment completion rate of 83% among drug users was reported in a meta-analysis. (126) There are currently no published studies reporting treatment completion among substance users on TPV/BOC. In our study, treatment completion rate in PWID was 65%, which is not significantly different from non-PWID. It corresponds to the non-difference in adherence found in IFN and RBV based studies in PWID. (130) In registration trials with first generation DAA in combination with PegIFN and RBV 63-75% of treatment- naıve and 59-66% of treatment-experienced patients achieved an SVR. (187-189, 194)

Pharmacokinetic studies performed on TPV and BOC with OST (methadone and buprenorphine) found no clinically important interactions. (195-197) In this real life study, active substance users did use heroin, cocaine, cannabis, and benzodiazepine. There were no arguments for clinical interaction of substitution therapy in the DAA metabolism since the patients treated with substitution therapy had similar viral clearance and side effects as non-PWID.

It was suggested that the ongoing use of substances might influence the metabolisation of TPV and BOC on Cytochrome p450 3A family and have an influence on the availability of these medications in the body and consequently the viral clearance. (198) In this study, we noticed that in patients actively using those substances (21/78) there was no influence on viral clearance. Major side effects were not reported. However, two substance users died because of an unknown reason not related to substance overdose.

Recently, a lower SVR rate (42%) has been found in post-marketing studies (199). One of the possible predictive factors in the latter study was the high baseline HCV RNA being more than 800 000 IU/ml. (200) We could not confirm this in our study.

The use of substances did not influence the adherence ratio in this TPV/BOC based treatment study. This is comparable to the previous IFN and RBV based studies in PWID. (130) The most common reason for treatment non-completion

other than viral nonresponse was side effects in both PWID and non-PWID. The reasons for non-completion were not significantly different between PWID and non-PWID (p=0.48) suggesting that PWID do not end treatment early due to their drug addiction and other life style related issues.

In the present study a large number of GT 1 infected patients was studied. This is quite unique since in substance users in some regions GT 3 infected HCV patients are predominantly diagnosed.

There were some limitations of these data including the small number of patients. Due to the small number of patients there was not enough statistical power. In treatment experienced patients it was often not reported whether they were previous non-responders or relapsers. This is why we could not compare treatment outcome and completion in naïve, non-responders and relapsers.

As these treatments with BOC and TPV are more challenging both in terms of medical follow-up, compliance and costs, our feasibility, efficacy and compliance results show that there are no reasons to exclude PWID from treatment with BOC and TPV and novel antiviral strategies. There is no need to withhold HCV treatment due to concerns about reinfection alone because the rate of HCV reinfection is low after HCV antiviral treatment.

In some countries the new generation DAAs will not be available/ reimbursed and TPV and BOC base triple therapy will therefore be the alternative for the newer all-oral treatments. However, more studies are required to study more the side effects related to substances use in detail.

Chapter 4

Pilot study: Combining formal and peer education with FibroScan to increase HCV screening and treatment in persons who use drugs

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J Subst Abuse Treat. 2016 Aug;67:44-9

4.1 Abstract

Background: Treatment uptake for HCV infection remains low in persons who inject drugs because of lack of knowledge and low perceived need for treatment. Therefore we conducted a pilot study to assess the influence of information on knowledge and willingness for HCV screening and treatment among PWUD combining formal and peer education with FibroScan measurement.

Methods: Clients of the Center for Alcohol and other Drug problems (CAD) in Limburg (Belgium) were randomized into a control group which received the standard of care and an intervention group which received formal and peer education followed by FibroScan. Knowledge on HCV and willingness for screening and treatment were evaluated at baseline, after intervention and 1 and 3 months after intervention by means of questionnaires.

Results: Baseline knowledge was similar for the control (N=27) and intervention group (N=25) (58% vs. 59%; p=0,67) but increased to 86% (p<0,001) in the intervention group immediately after the information session. After 3 months knowledge decreased significantly (69%; p=0,01). No significant changes in knowledge were found in the control group. Baseline willingness for treatment was 81% in both control and intervention group and decreased after one month in the control group (44%) and remained stable in the intervention group (75%). Differences in actual screening uptake between the control and intervention group were not significant (7% vs. 20%). Four percent from the intervention group and nobody from the control group started treatment.

Conclusion: The small number of subjects should be considered when interpreting the results of this study. In brief, the single information session significantly improved HCV knowledge among PWUD, but did not result in a higher uptake for screening and treatment. This could signify that there are other important reasons, besides lack of knowledge, not to undergo screening or

start treatment. The fact that knowledge decreased after 3 months indicates that it would be beneficial to repeat the information session regularly.

4.2 Background

Hepatitis C is a viral infection caused by the hepatitis C virus and affects 130-170 million people worldwide (201, 202). HCV is primarily transmitted through blood-to-blood contact associated with IDU. The WHO therefore categorized PWID as the main risk group for infection in western countries and emphasizes the importance of screening and treatment within this population.

However, despite safe and very effective, new treatment options, screening and treatment uptake for HCV infection among PWID remains low. (203) This could be explained by the many barriers PWID have to overcome, which are related to mistrust of the healthcare system, fear, financial and social status and physical or psychiatric health problems. (204, 205) Other important factors are an insufficient knowledge on HCV and a low perceived need for treatment. (145, 146)

In Belgium, medico-social centers were established in 1997 to provide drug users with accessible medical and psychosocial care to lower the threshold towards making health improving decisions. Previous studies have shown that formal education significantly improves knowledge on HCV (206-212), screening for HCV (211, 213), treatment uptake and adherence (207, 208, 214, 215) and reduces infection-related risk behavior (216). Peer education can be used to reach PWUD and guide them towards screening and treatment. This method already appeared to be effective for a number of other chronic diseases such as diabetes, HIV and heart disease. (217) FibroScan is a fast, non-invasive, painless and therefore patient-friendly method to assess the stiffness of the liver, which is an accurate indication of the stage of liver fibrosis and damage to the liver in persons with hepatitis C viral infection. (83)

In short these studies demonstrate that formal education, peer education and FibroScan assessment can improve HCV-related knowledge, uptake for HCV screening and treatment.

Therefore we did design an innovative approach by combining formal education, peer education and FibroScan assessment. In this pilot study, one session of formal and peer education was combined with FibroScan to assess the influence on knowledge, and willingness for HCV screening and treatment among PWUD attending OST program.

4.3 Patients and methods

4.3.1 Study population and study center

Clients of the Center for Alcohol and other Drug problems (CAD) located in Limburg comprise of former and current substance users. CAD is a multidisciplinary center with physicians, social workers, psychologists, psychiatrists, nurses. The center provides OST but also treats/refers patients for the treatment of other comorbidities. Each year care is provided to approximately 1300 clients with illegal substance use problems. The population of CAD clients on OST remains stable. There is some in and out movement in the population. Every year approximately 13% of the clients, who did leave the program for short time period, reenter the program. A limited number of new clients join the substitution program every year.

The multidisciplinary network to treat substance users with HCV operates as follows: in CAD the addiction care physician (often assisted by a nurse) sends patients' blood to the lab for anti-HCV and HCV RNA quantitative testing. If the patient is positive for antibodies and HCV RNA they refer the patient to the hepatologist at the nearest hospital, located only three kilometers away from the CAD center. The hepatologist handles further testing/diagnosis such as HCV RNA quantitative test, HCV genotyping, other blood tests, liver biopsy etc., in line

with the Belgian reimbursement criteria related to HCV diagnosis and treatment. After each appointment with the hepatologist, the reports are posted to the addiction care physician who referred the patient, because the addiction care physicians also act as general practitioners for these patients and treat them for other comorbidities. Even during the HCV treatment, there is a close collaboration between the hepatologist and the addiction care physician.

Eligible clients were asked to participate in the study during their daily or weekly visit to CAD. The study was conducted between February 2014 and December 2014. At that time IFN based therapy was the standard of care for HCV antiviral therapy in Belgium. The first generation of DAAs, TPV and BOC, were available. Reimbursement for the newer DAAs for HCV infection was approved in Belgium starting on January 1, 2015.

Inclusion criteria for this study included: 1) age ≥ 18 years, 2) signed informed consent, 3) history of substance use and substitution treatment at CAD Limburg. Exclusion criteria were defined as suffering from cognitive disorders and/or an inadequate knowledge of the Dutch language. Eligible patients were identified by cross-checking the list of the patients attending the substitution program with the care provider. While checking the patient file for eligibility, it was checked whether the patient suffered from a cognitive disorder. In CAD the diagnosis of a cognitive disorder was made by a psychologist- psychiatrist according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria.

This study was approved by the ethical review board of Hasselt University and Ziekenhuis Oost-Limburg (ZOL).

4.3.2 Study design

For this pilot study, the participants were randomized into two groups: the control group, who received the current standard of care, and the intervention group, who received an information session followed by a FibroScan. The study

was single blind, as it was impossible to blind the research team due to the researcher's involvement in the information session and its coordination.

In the control group, it was announced that information brochures on hepatitis C virus infection were available in the waiting room of the CAD center, which is considered the 'standard of care'. The brochure available at the CAD provided information about HCV transmission routes, diagnosis, treatment and how to prevent HCV infection.

For the intervention group, information sessions were organized at CAD Limburg in a meeting room with coffee and sandwiches. The information session was organized for small groups with 5 to 10 clients and lasted approximately one hour. Essential information was given by a video and a didactic PowerPoint presentation in Dutch. The presentation given by the care provider covered the following topics: hepatitis C virus, effects on the liver, disease course, viral transmission, symptoms of hepatitis C infection, diagnosis, prevention of liver damage, treatment for hepatitis C infection and re-infection. After the power point presentation additional information was given by peers who shared personal experiences about the medication, side effects, duration of treatment, costs, family support and the effect of the treatment on their life. Afterwards, there was time for questions and discussion. Requirements for being a peer were having successfully completed treatment for HCV infection, having a history of drug use and still being connected to or following the substitution program. These peers previously received a short training on hepatitis C viral infection.

Shortly after the information session, a FibroScan was performed at Ziekenhuis Oost-Limburg, Genk, located on three kilometers from the CAD center. The participation in this study was not affected by the fact that FibroScan could not be performed on site at CAD because the transport to the hospital and the total cost was covered by the study coordinators. The patients were transported by taxi, seating 5-7 passengers, from the CAD to the hospital. Depending on the

number of participants, who were scheduled to undergo FibroScan, the study coordinators booked a taxi a couple of days before the visit. The participants were picked up at CAD and brought back afterwards and they were accompanied by a member of the study team. Before the participants underwent the FibroScan, it was explained that this technique is used to measure liver fibrosis. After the FibroScan, the outcome was communicated with the participants and further explanation was given to each participant individually by a hepatologist. Ten valid measurements were performed with a medium (M-) probe.

4.3.3 Data collection and statistical analysis

At baseline, a questionnaire about demographic characteristics was completed. Participants completed a questionnaire assessing HCV knowledge as well as willingness to undergo screening and, if indicated, treatment. This questionnaire was completed at baseline and was repeated immediately after the information session and 1 and 3 months afterwards to assess whether the participants had retained the knowledge over time. This questionnaire consisted of 19 true/false questions regarding HCV-related knowledge (Table 4.2). The addiction care physician and care workers were contacted to determine whether blood samples were taken from the participants for HCV screening and, if positive, whether they consulted a hepatologist for diagnosis and treatment.

A sample size calculation was not possible because the common standard deviation is not known. Therefore, the rule of thumb for sample size determination in pilot studies was used. This led to 12 participants per group (or 24 in total) that would have to fill in the questionnaires across all three time points. To account for any participants lost to follow-up, as many as possible CAD clients were asked to participate, resulting in a total of 52 participants.

Patient characteristics were analyzed with descriptive data analysis and summarized using mean ± SD and frequencies. Patient characteristics were also tested for possible differences between control and intervention groups with Chi

square/Fisher's Exact Test. Continuous data that had no normal distribution were shown with median values and interquartile range (IQR). Mann-Whitney U tests were used to assess the differences between the control and intervention groups. To assess the change in knowledge scores over time, a Wilcoxon signed rank test was used. To determine the changes in willingness for a screening test and treatment, a McNemar test was used. A Fisher's Exact Test was performed to test whether being in the intervention group was significantly associated with HCV screening and treatment uptake. A P-value ≤0,05 was considered significant. IBM SPSS Statistics 22 was used to analyze the data.

In order to control for missing data regarding willingness for screening and willingness for treatment, a sensitivity analysis examined the effect in two possible situations. In the first situation all participants with missing data were considered to be willing to receive screening and treatment. In the second situation all participants with missing data were considered not willing to receive screening and treatment.

4.4 Results

Fifty-two clients participated in this study but only 17 completed all questionnaires. Twenty-seven patients were randomized to the control group, 25 to the intervention group. During this study, 7 participants were incarcerated, 2 were hospitalized, 24 left the substitution program and 2 persons died.

4.4.1 Patient characteristics

Most participants were Belgian males with a mean age of 39±8 years. Non-Belgian participants were most frequently from Moroccan (10%), Turkish (6%) or Italian (6%) origin. Fifty-two percent of the total study population graduated from secondary school. Participants most often lived alone in a rented house or flat and received a replacement income with a mean of 959 EUR. Sixty-nine percent of all the participants reported that they used drugs intravenously, and

49% admitted that they had injected drugs in the past 3 months. Water and tourniquets were the items that were most often shared when using IV drugs, respectively 29% and 23%. Sixty-seven percent were tattooed and 85% was ever incarcerated. One out of five had received a blood transfusion, but nobody ever received a liver transplant. Almost all participants were heterosexual (Table 4.1). No significant differences in patient characteristics were found between the control and intervention group.

4.4.2 HCV knowledge

At baseline, the knowledge scores were an average of 58% for the control group (n=27) and 59% for the intervention group (n=25) (Table 4.2). No significant differences were found in baseline knowledge scores between the control and intervention groups (p=0,67) (Figure 4.1).

Immediately after the information session, average knowledge scores increased by 27% (p<0,001) to 86% in the intervention group (n=25) (Figure 4.1).

One month after the information session knowledge scores (86%) did not decrease significantly in the intervention group (n=11, p=0,60). After 3 months, knowledge scores (69%) decreased significantly in the intervention group (n=12) by 17% (p=0,008). However, the knowledge scores were still significantly higher than baseline scores (p=0,02). No significant differences in knowledge scores were observed in the control group after one month (n=11, p=0,14) or three months (n=6; p=1) (Figure 4.1).

Table 4.1. Characteristics of the study population.

Characteristics	Control group	Intervention group	Total
Age mean ± SD (years)	40 ± 9	38 ± 9	39 ± 8
Males (%)	20/27 (74%)	20/25 (80%)	40/52 (77%)
Belgian origin (%)	15/27 (56%)	19/25 (76%)	34/52 (65%)
Education (%)			
None	5/27 (19%)	6/25 (24%)	11/52 (21%)
Primary school	7/27 (26%)	4/25 (16%)	11/52 (21%)
Secondary school	15/27 (56%)	12/25 (48%)	27/52 (52%)
Higher education	0	3/25 (12%)	3/52 (6%)
Source of income (%)			
No income	2/27 (7%)	2/25 (8%)	4/52 (8%)
Full/part time job	3/27 (11%)	3/25 (12%)	6/52 (12%)
Health insurance	17/27 (63%)	16/25 (64%)	33/52 (63%)
Other	5/27 (19%)	4/25 (16%)	9/52 (17%)
Monthly income (EUR)	977 ± 369	938 ± 390	959 ± 375
Living alone (%)	16/27 (59%)	14/25 (56%)	30/52 (58%)
Housing (%)			
Homeless	3/25 (12%)	2/25 (8%)	5/50 (10%)
Own property house/flat	3/25 (12%)	1/25 (4%)	4/50 (8%)
Rented house/flat	15/25 (60%)	19/25 (76%)	34/50 (68%)
Social housing	1/25 (4%)	3/25 (12%)	4/50 (8%)
Other	3/25 (12%)	0	3/50 (6%)
Liver transplant (%)	0	0	0
HCV risk factors (%)			
Ever used IV drugs	15/26 (58%)	20/25 (80%)	35/51 (69%)
Injection drug use in last 3 months	6/17 (35%)	12/20 (60%)	18/37 (49%)
Sharing equipment			
Needles or syringes	3/16 (19%)	4/20 (20%)	7/36 (19%)
spoons/ cookers	3/15 (20%)	3/20 (15%)	6/35 (17%)
Filters	4/15 (27%)	3/20 (15%)	7/35 (20%)
Tourniquets	4/15 (27%)	4/20 (20%)	8/35 (23%)
Water	4/15 (27%)	6/20 (30%)	10/35 (29%)
Tattooed (%)	20/27 (74%)	15/25 (60%)	35/52 (67%)
Blood transfusion (%)	8/27 (30%)	2/25 (8%)	10/52 (19%)
Incarceration (%)	24/27 (89%)	20/25 (80%)	44/52 (85%)
Sexual orientation (%)			
Heterosexual	25/26 (96%)	23/25 (92%)	48/51 (94%)
Homosexual	0	0	0
Bisexual	1/26 (4%)	1/25 (4%)	2/51 (4%)
I don't know	0	1/25 (4%)	1/52 (2%)

Table 4.2. HCV knowledge at baseline in control and intervention group.

TRUE/FALSE QUESTIONS	CORRECT AT BASELINE (%)		
	Control	Intervention	Total
1. Hepatitis C is caused by a virus	46	65	56
2. Hepatitis C is spread by sharing needles for drugs	85	89	87
3. Hepatitis C is mainly spread by unprotected sex	35	35	35
4. A person can get hepatitis C by getting a tattoo or piercing	62	62	62
5. A person can get hepatitis C by sharing personal material like razors or tooth brushes	77	73	75
6. To be certain of a hepatitis C infection, a blood test is necessary	81	77	79
7. Hepatitis C damages the liver and can cause liver failure	92	77	85
8. Hepatitis C can lead to liver cancer	81	50	65
9. Some people can live many years without symptoms	73	62	67
10. Part of the people infected with the hepatitis C virus can cure spontaneously	27	23	25
11. Drinking a lot of alcohol is a good idea for someone with hepatitis C	65	73	69
12. There is a vaccine to prevent hepatitis C	39	31	35
13. The treatment for hepatitis C cures everyone who is treated	54	54	54
14. The treatment for hepatitis C currently consists of injections and taking pills	42	65	56
15. The treatment for hepatitis C has to be taken lifelong	35	42	39
16. The treatment for hepatitis C can cause side effects like depression	62	62	62
17. Substitution treatment can be followed during hepatitis C treatment	65	73	64
18. Once you completed a treatment for hepatitis C, a re-infection is impossible because you’re immune	65	58	62
19. If you have hepatitis C it is not necessary to get a vaccination for hepatitis A or B	35	31	33
TOTAL MEAN SCORE (%)	58	59	59

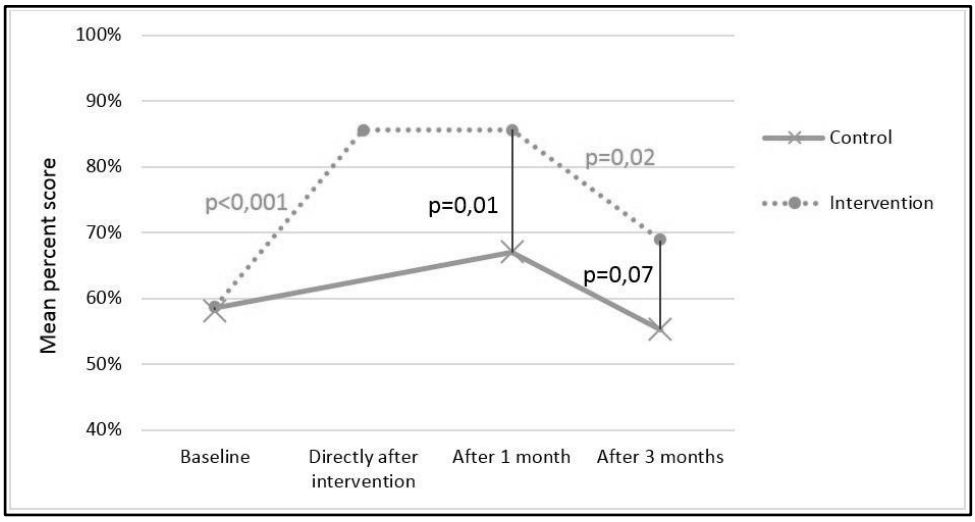

Figure 4.1. Change in mean percent knowledge scores across all time points.

4.4.3 Willingness to undergo screening and treatment

At baseline, the majority of the participants were willing to give a blood sample for HCV testing, 89% (24/27) in the control group and 86% (19/22) in the intervention group. Willingness decreased after one month in the control group from 89% (24/27) to 60% (5/9). In the intervention group, willingness for HCV testing increased from 86% (19/22) to 96% (22/23) after the information session. After one month and after the FibroScan, willingness was 100% (Table 4.3). After 3 months, willingness to undergo screening increased in the control group to 67% (4/6), but decreased in the intervention group to 77% (10/13) (Table 4.3).

In the intervention group the percentage of patients willing to start treatment increased slightly after the intervention (87%) compared to baseline (81%) but there were no significant differences between the different time points. In the control group the number of participants willing to immediately start treatment decreased after one month from 81% to 44%. At baseline 4% did not want to

start treatment and after one month all participants wanted to consider treatment. After 3 months willingness remained the same in the control group (50%) but increased in the intervention group (85%). A McNemar test showed no significant changes in willingness for HCV testing or treatment across the different time points (Table 4.3).

Table 4.3. Willingness to undergo screening and treatment.

Willingness for	CONTROL			INTERVENTION				
	Baseline	After 1 month	After 3 months	Baseline	After info	After 1 month	After 3 months	After FibroScan
	(n=27)	(n=9)	(n=6)	(n=21)	(n=23)	(n=8)	(n=13)	(n=12)
Screening (%)	89	56	67	86	96	100	77	100
Treatment (%)								
Yes	81	44	50	81	87	75	85	75
Yes, but not now	15	56	50	10	9	25	8	8
No, never	4	0	0	9	4	0	7	17

At baseline, 1 month after and 3 months after the intervention there were no significant differences in willingness for screening (baseline p=1, 1 month after p=0,08, 3 months after p=1) and willingness for treatment (baseline p=0,64, 1 month after p=0,34, 3 months after p=0,10) between the 2 groups.

At baseline, reasons to postpone or decline treatment in the intervention group included having no symptoms (n=4; 24%), concerns about side effects (n=3; 18%), financial problems (n=3; 17%), insufficient knowledge about HCV (n=3; 17%), doctor told treatment was not necessary (n=2; 12%), and still injecting or using drugs (n=2; 12%). In the control group reasons to refuse treatment at baseline were insufficient knowledge about HCV (n=5; 42%), having no symptoms (n=2; 17%), still injecting or using drugs (n=2; 17%), financial problems (n=1; 8%), other more important medical problems (n=1; 8%) and other reasons (n=1; 8%).

In the control group, 7% (n=2) of the participants gave a blood sample for screening in comparison to 20% (n=5) in the intervention group (p=0,41). Four percent (n=1) of the intervention group went to the hepatologist after the HCV screening and FibroScan and started treatment while no one of the control group saw a hepatologist (p=1).

According to the sensitivity analysis to control for missing data regarding willingness for screening and treatment, there were no significant differences (all the p values were > 0,05) at the three time points (at baseline, 1 month after and 3 months after) between the control and the intervention groups for both situations.

4.5 Discussion

This manuscript describes the first controlled study to combine formal and peer education with FibroScan measurement to increase HCV specific knowledge, screening and treatment uptake.

Knowledge of modifiable factors affecting HCV-related liver disease progression was low and HCV knowledge scores at baseline were mid-range as already described by Treloar et al. (218) It is alarming that most participants thought that there is a vaccine available to prevent HCV infection (65%) and that the treatment for hepatitis C viral infection has to be followed lifelong (41%). Knowledge scores were comparable to the studies of Surjadi et al. (212) and Gupta et al. (207). Any differences can be explained by the different questioning methods, namely multiple choice or true/false (212) or attendance at the hepatology clinic (207).

Some of the questions that were answered incorrectly by the majority of our participants were misunderstood. The question 'Hepatitis C is mainly spread by unprotected sex' was sometimes misunderstood as if unprotected sex was a possibility to contract hepatitis C rather than being the main source of hepatitis

C. Additionally, the question 'If you have hepatitis C, it is not necessary to get a vaccination for hepatitis A or B' was difficult because of the negation in the sentence.

Knowledge scores were comparable at baseline between the control and intervention group (58% vs. 59%). The information session increased the knowledge scores with 27% in the intervention group and this information was retained up to one month after the information session. However, knowledge scores decreased significantly after 3 months, which could indicate that the information session should be repeated regularly. Knowledge scores also improved non-significantly in the control group when baseline scores were compared with the scores one month after the information session. This can be explained by the fact that the participants discussed the questionnaire after completion and asked for information when they didn't agree.

When comparing the improvement in knowledge scores in our study (27%) to the study by Surjadi et al. (212) (14%) and Gupta et al. (207) (15,8%), it is clear that our method reached a higher improvement. This could be explained by the more individual approach in comparison to Surjadi et al. (212), or by the longer information session in comparison to Gupta et al. (207) which only lasted for 20 minutes.

While willingness for HCV screening improved slightly in the intervention group one month after the information session, willingness for HCV screening decreased in the control group. Fewer participants than expected filled in this questionnaire due to incarceration, deaths and hospital or psychiatric admissions.

The study of Ti et al. (219) found that peer education was a factor that was statistically significantly associated with HCV screening. Also, in the study of Grebely et al. (147) in which a weekly support group with peers was organized, 53% of the patients underwent HCV assessment. This is much higher than in our

study where after one session only 20% of the intervention group asked for HCV screening.

Reasons for refusing treatment varied but were consistent with the study of Grebely et al. (33). Different reasons to decline or postpone treatment were reported by the participants such as no symptoms, concerns about side effects, financial problems, insufficient knowledge about HCV, a previous consulted doctor told treatment was not necessary, current injecting or using drugs and the presence of other more important medical problems. Concerning financial problems, almost all CAD clients are insured and if not than health insurance is arranged for the clients. In the case that a patient is eligible for treatment, after assessment by the hepatologist, a large part of the cost of HCV treatment is reimbursed and a small amount is paid by the patients. But if these patients have financial problems for example they are paying debts than for these patients paying even a little amount themselves is not possible and they might delay or not start treatment at all.

One person of the intervention group started treatment before the end of this study, which is consistent with 2% of the total of participants and 4% of the intervention group.

These results indicate that there might be other important reasons, besides lack of knowledge, not to undergo screening or start treatment for HCV infection. A study by Swan et al. investigated the barriers for HCV care in injecting drug users and found that the absence of noticeable symptoms can result in a low perceived need for treatment. Also unstable housing, lack of transportation, poverty and social stigma complicate HCV care. Motivators for HCV treatment were becoming symptomatic, responsibility for children and wanting to move on from drug use. (220)

Based on the available literature, Robaeys et al. published recommendations for the management of HCV in PWID. (128) They recommended the use of non-

invasive liver fibrosis assessment because it can enhance liver disease screening. (221, 222) These guidelines (128) also recommended that pre-therapeutic education should include discussions of HCV transmission, risk factors for fibrosis progression, treatment, reinfection risk, and harm reduction strategies because poor HCV knowledge and inaccurate perceptions are barriers for accessing care. (223-226) In 2014 a study by Treloar et al. suggested that particularly among PWID who feel well/ without symptoms non-invasive ways of liver damage assessment may facilitate entry into HCV care. (227) Despite these guidelines and evidence encouraging to increase awareness of HCV and the use of non-invasive liver disease assessment, there are no governmental efforts, even in several developed western countries.

There were some limitations to this study: a small number of participants reached the end of follow-up (resulting in an underpowered study) and the follow-up period (3 months) was short. This study was a pilot to check the feasibility of the approach and to get preliminary results in this diverse population in order to start a larger project. Due to the small sample size and practical considerations only two groups, a control and intervention group, were studied. Therefore, no individual effects of education by provider, peer education and FibroScan could be compared with the standard of care. During the study period 24 participants left the OST program. Some of these participants might have received HCV screening and treatment in another health care setting. In the future with a larger study population the willingness for screening and treatment could be studied with multiple intervention groups (e.g. information session with or without FibroScan, a group who receives only a FibroScan, etc.).

During this study we noticed that participants, who received the intervention, were very positive about the information sessions with peer education in combination with a FibroScan. In the future regular repetition of short and simple information sessions with essential information are recommended. An incentive like cake or pastries for the participants together with a fun and interactive presentation helps to motivate them to listen to the information and is highly

appreciated. With a few adjustments, this intervention might be a good method to educate this population about HCV infection.
In the PWUD population good guidance towards HCV testing and treatment is essential. In our opinion it would be very helpful if a nurse or care worker, who they trust and has regular contact with these patients, would motivate them towards screening and treatment, take blood samples, advocate for consultations with the hepatologist and support them during treatment. This population needs a lot of attention and personalized care for their mental and physical health.

In the future there is a need to perform a larger study with a longer follow-up period to investigate the effect of interventions such as education on HCV, peer education, FibroScan, involvement of nurses or other care takers in guiding patients through the whole process of screening and treatment. The results of these future studies can be used to improve HCV care.

4.6 Conclusion

When interpreting the results and conclusions of this study, it is important to consider the small sample size and short follow-up period of this pilot project. The results of this pilot study suggest that one single information session significantly improves HCV knowledge. However, this does not lead to a higher uptake of screening and treatment as seen in previous studies. This could be a result of the limited impact of a single session or the short follow-up period in this study but it could also signify that there are other important reasons, besides lack of knowledge, not to undergo screening or start treatment. The fact that knowledge decreases after 3 months indicates that one session might not be sufficient and that it might be beneficial to repeat the information session more regularly.

Chapter 5

The impact of the organization of anti-HCV treatment in persons who inject drugs on the outcome of hepatitis C treatment. Results of an international cohort study

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Submitted

5.1 Abstract

Background and aim: Different multidisciplinary settings to treat chronic hepatitis C viral infection in persons who inject drugs are available. The aim of this international retrospective study was to investigate whether a treatment setting working under one roof is superior to other treatment settings.

Methods: In this international retrospective study, the outcome of HCV treatment in a setting providing addiction care and HCV treatment under one roof (setting 2) was compared to settings providing addiction care and HCV treatment on different locations but in close collaboration (settings 1 and 3).

Results: Data of 363 patients (100, 92 and 171 from resp. setting 1, 2 and 3) were analysed. Age at treatment, gender and race did not differ (p=not significant=NS). The duration of drug use and the drug use behaviour were different between the treatment settings. Side effects did occur in 100, 95 and 62% of the patients in resp. setting 2, 1 and 3 ($p<0.05$). Bivariate analysis showed no significant difference between the three settings in treatment completion rate and SVR rate. Multivariate analysis showed no higher completion rate or SVR rate in the setting under one roof. On the contrary in the multivariate analysis being treated in setting 1 was independently related with SVR. Other factors independently associated with SVR were age <35 years, a viral load <800000 IU/ml and treatment completion.

Conclusion: In contrast to what was expected, being treated in a multidisciplinary setting not working under one roof was not inferior to a setting working under one roof.

5.2 Introduction

Injection drug use is nowadays the main transmission route for HCV infections. It is estimated that in the European Union (EU) around one million injection drug users may be infected with HCV. (228)

Even though different clinical trials showed that in former drug users, active drug users and patients taking substitution therapy for opioid dependence the sustained viral response and adherence was not different from control populations (153, 229, 230), this population is less frequently evaluated and treated by medical personnel compared to other patients. (224) In the United States, Canada, and Australia, only 1–6% of current and former PWID have received HCV treatment. (145, 156, 231) In the countries of the EU of those diagnosed with a chronic hepatitis C infection, a median of 9.5% (IQR 3.5–15) entered treatment. (30)

Increasing the proportion of HCV infected illicit drug users assessed and treated for HCV infection might be a crucial and necessary component towards reducing the future disease and cost burden of HCV in the developed world. (232)

HCV treatment has been delivered through several HCV care settings in PWID. A multidisciplinary approach is common in the different treatment settings. Collaboration between physicians, nursing staff, addiction care providers, psychiatric services and other support services is present. (147-151)

The purpose of this study was to evaluate whether a treatment setting under one roof is superior to the other management systems. In Switzerland the patients are treated for their drug addiction and chronic HCV infection under one roof. In Belgium the specialised addiction care centres and centres treating patients for HCV (Gastro-enterology department of regional hospitals) are located separately (± 5 km from each other). Patients with a history of drug use and who have risk behaviours are screened for HCV infection and are referred to the gastro-enterologist for further care. In Greece, the addiction care physician accompanies the patient to the consultation with the specialist. They also work in collaboration.

The primary objective was to compare treatment outcome of chronic HCV infection between these three settings. The secondary objective was to describe the characteristics of the patients that may affect treatment outcome.

5.3 Methods

This is an international retrospective study to compare the outcome of antiviral HCV treatment in a treatment setting providing addiction care and HCV treatment under one roof (setting 2) to other treatment settings providing addiction care and HCV treatment on different locations but in close collaboration (1 and 3).

The hypothesis for this study is that an HCV antiviral treatment setting under one roof (setting 2) is superior to multidisciplinary treatment settings (setting 1 and setting 3) regarding treatment completion and treatment outcome.

5.3.1 Centre description

Setting 1

In the two participating addiction care centres Free clinic Antwerp and CAD Limburg in Belgium approximately 600 patients are enrolled, respectively. Care is provided in each centre by ±5 physicians, 1-2 psychiatrists, 2 psychologists, 4-6 nurses, 8 social workers, 1-5 persons engaged in sterile needle exchange programme and administrative staff.

The addiction care centres provide besides psycho-medical care also assistance to patients in socio-financial matters such as housing, in receiving welfare allowances, and in juridical matters.

The addiction treatment, primary health care and specialized care for HCV are partially reimbursed by the health insurance. The hepatology clinic (often a part of a city hospital) is located at approximately 5 km distance from the addiction care centre. The procedures such as screening for HCV RNA, ultrasonography,

transient elastography (fibroscan) and liver biopsy are performed at the liver clinic.

Patients with risk behaviour are screened for anti-HCV in the addiction care centre. If positive, patients are referred to a hepatologist/gastroenterologist in the nearest liver clinic and the addiction care nurses and physician follow the patient through letters/telephone contact with the specialist and during the administration of substitution therapy.

Setting 2

In Arud Centres for Addiction Medicine (Zurich, Switzerland) 1500 patients are registered. There are 14 physicians, 37 nurses, 6 psychologists, 3 social workers, 4 hepatitis C nurses, 11 internal medicine specialists and primary care specialists and 40 other employees. The patients are treated for HCV in one of the four multidisciplinary outpatient clinics. The treatment including addiction treatment, primary health care and HCV treatment is fully covered by health insurance.
Internal medicine specialists and primary care specialists are responsible for the HCV treatment. They consult with off-site hepatologists to discuss patient care issues if necessary. If needed the patient is referred to a hepatologist for a liver biopsy. A liver biopsy is, however, not a prerequisite to start HCV treatment. There is an opportunity to perform abdominal ultrasound and fibroscan testing at the centre. In this treatment setting the social workers also provide support in solving social and financial issues.

Setting 3

The Greek Organisation Against Drugs (OKANA) operates as different treatment units in Athens and Thessaloniki. The participating units contain approximately 1500 patients under close supervision of the doctors working in this multidisciplinary network. In each unit, care is provided by 1-2 psychiatrists, 3-4 nurses, 1-2 psychologists, 1-2 social workers and a part-time physician

specialised in internal medicine. The units are fully run and paid by the state and the majority of the patients are covered by the social security system. When needed also social and psychological support (together with psychiatric treatment when needed) is provided. Every patient registered at the centre is screened for HCV. Depending on the HCV status, the health insurance coverage and the will of the patient a further evaluation is performed. After the evaluation and if the patient remains stable and motivated an appointment with the hepatologist is arranged. The addiction care physician is present once a week in the hepatology department of the collaborating hospital and participates in the hepatology consultation of the patient. After patients are referred to the hepatologist, the specialised addiction care centre closely follows the HCV treatment of their patients both through regular appointments at the OKANA unit and through the scheduled visits at the hepatology department.

5.3.2 Patient population and definitions

In each participating centre data were collected of all PWID who received treatment for HCV infection between 2000 and 2013. Data were collected utilizing a standardized data collection form and entered into a Microsoft excel datasheet. Data were extracted on demographics, psychiatric history, past and present substance use, opioid substitution therapy, HCV viral load and genotype, liver biopsy, antiviral HCV treatment side effects, treatment completion and SVR.

Depression was defined as being diagnosed by the psychiatrist according to the classification used in each country (DSM-IV).

Treatment completion was defined as medication intake until the end of treatment period as advised by the treating physician. Each setting treated their patients with the medication available in their country at that time. The duration of treatment depended on the HCV genotype and the medication used.

SVR was defined as HCV RNA undetectable at 6 months post-treatment.

5.3.3 Statistics

Descriptive statistics of patient characteristics are presented for the three settings. Means and standard deviations are presented for continuous variables. For categorical variables, proportions and percentage are given.

To study the factors associated with treatment completion and SVR, bivariate analyses were performed using Chi-square test or Fisher exact test, as appropriate. A p-value <0.05 was considered as statistically significant.

A multivariable regression model was used to investigate differences in terms of the primary outcome, SVR after HCV treatment and treatment completion, between the 3 settings. The variables 'age', 'gender', 'drug use during HCV treatment', 'substitution treatment during HCV treatment', 'viral load', 'HCV genotype', 'treatment completion', 'depression during the current HCV treatment' and 'antidepressant use during the current HCV treatment' were included to fit the model for the outcome variable 'SVR'. The variables 'age', 'gender', 'type of illegal drugs used (heroin, cocaine, benzodiazepines, cannabis, amphetamines and XTC use)', 'drug use during HCV treatment', 'substitution treatment during HCV treatment', 'HCV genotype', 'number of HCV treatments received' (treatment experience), 'occurrence of side effects', 'past depression', 'depression during the current HCV treatment' and 'antidepressant use during the current HCV treatment' were included to fit the model for the outcome variable 'treatment completion'. The treatment setting was considered as a fixed effect in the regression model in order to make a fair comparison between the three treatment settings. Regression model selection was performed according to stepwise elimination. For all analyses, statistically significant differences were assessed at $P < 0.05$; P values were 2-sided. The fit of the model was tested using Hosmer-Lemeshow test. All analyses were performed using the statistical package SAS 9.4.

5.4 Results

Treatment data between 2000 -2013 were available for 100 patients in setting 1, 92 in setting 2 and 171 in setting 3.

5.4.1 Patient characteristics in the three settings

The majority of patients were male Caucasians, between 35 and 45 years old in all three settings (Table 5.1). Most patients finished secondary education in setting 1 (80%) and setting 2 (70%) while in setting 3, 46 % finished secondary education and 38% received only primary education ($P<0.05$).

Viral load was high (HCV RNA level ≥800,000 IU per milliliter) in 62% of the patients in setting 1, 56% of setting 2 and 45% in setting 3 ($p<0.05$). The HCV genotype 1 infection was most common in setting 1, while in setting 2 and setting 3 genotype 3 was most prevalent ($p<0.01$) (Table 5.1). Liver biopsy was performed in more than 90% of the patients in setting 1 while in the other settings around 20% of the patients received a liver biopsy ($p<0.05$). In all three settings most patients who were examined had fibrosis stage 1 and 2.

Table 5.1. Demographic characteristics of the patients in the three models.

Characteristics	setting								
	1		2		3		total		P value
	N	%	N	%	N	%	N	%	
Age									0.93
<35	28	28	23	25	51	30	102	28	
≥35 and ≤45	51	51	50	54	85	50	186	52	
>45	21	21	19	21	33	20	73	20	
Gender									0.18
Male	73	73	71	77	141	82	285	79	
Race									0.23
African			1	1			1	0	
Caucasian	99	100	91	99	170	100	360	100	
Education									<0.01
Primary	16	16	22	28	14	38	52	24	
Secondary	80	80	56	70	17	46	153	71	
Higher	4	4	2	3	6	16	12	6	
Viral load									0.04
≥ 800000 IU/ml	59	62	50	56	57	45	166	54	
< 800000 IU/ml	36	38	39	44	69	55	144	46	
Genotype									<0.01
1	52	53	26	28	35	21	113	31	
2			4	4	9	5	13	4	
3	38	38	50	54	108	64	196	54	
4	9	9	12	13	18	11	39	11	
Liver biopsy									<0.01
Yes	90	94	22	25	39	23	151	43	
No	6	6	67	75	131	77	204	57	
Fibrosis stage									0.29
0	8	9	1	7			9	6	
1	33	37	5	36	12	31	50	35	
2	32	36	5	36	12	31	49	34	
3	5	6	2	14	6	15	13	9	
4	12	13	1	7	9	23	22	15	
Past depression									<0.01
Yes	35	36	53	58	6	4	94	26	
No	62	64	38	42	165	96	265	74	
Past antidepressant use *									<0.01
Yes	31	97	43	81	5	83	79	87	
No	1	3	10	19	1	17	12	13	

*The percentage of patients who did use antidepressants is calculated by the total number of patients who reported use/non-use of antidepressants because there might also be anti-

depressant use in patients without suffering from depression in that case used for another psychiatric disorder.

The past drug use behaviour of the patients was also significantly different between the three settings (percentages and P values are presented in Table 5.2). More than 95% of the patients in each setting used heroin and cocaine use was very high (92%) in setting 2 while in setting 1 and 3 it was around 60%. In setting 3, 56% used benzodiazepines compared to 43% in setting 2 and only 18% in setting 1. Also the use of other substances such as cannabis, amphetamines and XTC was significantly different between the three settings (Table 5.2). Reported intravenous drug use was lower in setting 2 (81%) compared to setting 1 and setting 3, respectively 97 and 99%. Drug use during the HCV treatment was significantly higher in setting 2 compared to the other two settings (Table 5.2). Benzodiazepine use (prescribed or illegal) during the HCV treatment was the lowest (20%) in setting 3 compared to 38% and 37% of the patients in setting 1 and setting 2.
Average duration of being involved in drug use was 25 years (± 8) in setting 1, 19 years (± 6) in setting 2 and 12 years (± 6) in setting 3 ($p< 0.05$).
The number of patients on OST during HCV treatment was 71%, 87% and 91%, in setting 1, 2 and 3, respectively ($p<0.05$).

The treatment consisted of PegIFN plus RBV in the majority of patients in the three settings at that time. Only a limited number of patients in the three settings were treatment experienced (Table 5.3).
In setting 2 all patients suffered from side effects, in setting 1 95% and in setting 3 only 62% ($p<0.05$) (Table 5.3). Flu like symptoms were reported in all settings but most frequently (62%) in patients from setting 2. Also other side effects such as weight loss, psychiatric side effects, skin related side effects and anemia were reported more often in setting 1 and 2 compared to setting 3 (Table 5.3). During the current HCV treatment, depression was reported in 44%,

52% and 6% of the patients in setting 1, setting 2, and setting 3 respectively ($p<0.05$).

The rate of treatment modification and the reasons for treatment modification were not significantly different between the three settings (Table 5.3).

In all 3 treatment settings approximately 70% of the patients completed the treatment. However the reasons for non-completion were significantly different between the settings ($p<0.05$). In setting 1 the most common reason for non-completion was lost-to follow-up, followed by side effects and non-response. In setting 2 and 3 the most common reason for non-completion was side effects followed by the decision of the patient to stop the treatment early (for percentages see Table 5.3).

Table 5.2. Drug use and opioid substitution treatment in the three settings.

Characteristics	Setting								
	1		2		3		total		P value
	N	%	N	%	N	%	N	%	
Heroin use									0.04
Yes	96	96	86	97	170	100	352	98	
No	4	4	3	3	0	0	7	2	
Cocaine use									<0.01
Yes	57	57	82	92	104	61	243	68	
No	43	43	7	8	66	39	116	32	
Benzodiazepine use									<0.01
Yes	18	18	38	43	96	56	152	42	
No	82	82	51	57	74	44	207	58	
Cannabis use									0.01
Yes	44	44	58	65	103	61	205	57	
No	56	56	31	35	67	39	154	43	
Amphetamines use									<0.01
Yes	14	14	0	0	0	0	14	4	
No	86	86	89	100	170	100	345	96	
XTC use									<0.01
Yes	2	2	13	15			15	4	
No	98	98	76	85	170	100	344	96	
Intravenous drug use									<0.01
Yes	97	97	73	81	167	99	337	94	
No	3	3	17	19	2	1	22	6	
Drug use during HCV treatment									<0.01
Yes	56	57	61	67	45	26	162	45	
No	43	43	30	33	125	74	198	55	
Benzodiazepine use/ misuse during HCV treatment									0.01
Yes	37	38	34	37	25	20	96	31	
No	61	62	57	63	98	80	216	69	
Past substitution treatment									0.19
Yes	86	90	85	97	158	92	329	93	
No	10	10	3	3	13	8	26	7	
OST during HCV treatment									<0.01
Yes	70	71	80	87	156	91	306	85	
No	29	29	12	13	15	9	56	15	

Table 5.3. Antiviral HCV treatment related characteristics.

Characteristics	Setting								
	1		2		3		total		P value
	N	%	N	%	N	%	N	%	
Number of treatment									0.19
1	87	87	83	90	161	94	331	91	
2	13	13	9	10	9	5	31	9	
3					1	1	1	0	
Type of treatment									<0.01
PegIFN + RBV	83	84	91	99	158	92	332	92	
IFN + RBV	6	6			11	6	17	5	
PegIFN + RBV +BOC	3	3					3	1	
PegIFN + RBV +TPV	7	7	1	1			8	2	
IFN					2	1	2	1	
Occurrence of side effects									<0.01
Yes	94	95	89	100	102	62	285	81	
No	5	5			62	38	67	19	
Side effect: flu-like									<0.01
Yes	35	35	55	62	32	20	122	35	
No	64	65	34	38	129	80	227	65	
Side effect: weight loss									0.12
Yes	20	20	9	10	21	13	50	14	
No	79	80	80	90	140	87	299	86	
Side effect: psychiatric									<0.01
Yes	33	33	39	44	31	19	103	30	
No	66	67	50	56	130	81	246	70	
Side effect: skin related									<0.01
Yes	32	32	33	37	3	2	68	19	
No	67	68	56	63	158	98	281	81	
Side effect: anaemia									<0.01
Yes	11	11	69	78	33	21	113	32	
No	88	89	20	22	128	80	236	68	
Depression during treatment									<0.01
Yes	43	44	47	52	11	6	101	28	
No	54	56	44	48	160	94	258	72	
Antidepressants during current treatment									<0.01
Yes	29	64	16	34	7	70	52	51	
No	16	36	31	66	3	30	50	49	
Modification of medicine									0.05
Yes	20	22	18	20	18	11	56	16	
No	73	78	72	80	144	89	289	84	
Modification type									0.33
PegIFN	4	20	9	50	4	50	17	37	
RBV	10	50	6	33	2	25	18	39	
PegIFN + RBV	6	30	3	17	2	25	11	24	
Reason modification									0.20
Anaemia	5	31	4	22	5	71	14	34	

Anaemia+other side effects	3	19	3	17			6	15	
Other side effects	8	50	11	61	2	29	21	51	
Treatment completion									0.77
Yes	70	70	65	71	126	74	261	72	
No	30	30	27	29	45	26	102	28	
Reason non-completion***									<0.01
Substance use					3	7	3	3	
Side effects	7	23	10	37	17	38	34	33	
Nonresponse	7	23	7	26	7	16	21	21	
Financial situation	2	7					2	2	
Social situation	2	7					2	2	
Non-compliance	2	7			2	4	4	4	
Died	1	3	1	4	1	2	3	3	
Lost-to-follow-up	8	27			1	2	9	9	
Decision patient	1	3	9	33	11	24	21	21	
Other					3	7	3	3	
SVR****									0.10
Yes	66	80	60	66	111	72	237	72	
No	16	20	31	34	44	28	91	28	

**The percentage of patients who did use antidepressants is calculated by the total number of patients who reported use/non-use of antidepressants because there might also be anti-depressant use in patients without suffering from depression in that case used for another psychiatric disorder or as prevention of depression during HCV treatment.

*** For the different reasons of non-completion, percentage of patients was calculated using the number of patients who did not complete treatment as dominator (for model 1; 30, for model 2; 27 and for model 3; 45)

****The percentage of patients who achieved SVR is calculated according to per protocol analysis: the dominator is total number of patients who completed treatment and were tested for SVR.

5.4.2 Factors affecting SVR

The SVR rate was 80% in setting 1, 66% in setting 2 and 72% in setting 3 (p=NS). A logistic regression model was fitted with variable "treatment setting" forced to stay in the model. The result was a model containing treatment setting, age, viral load, HCV genotype and treatment completion (Table 5.4). Being treated in setting 1, age under 35 years, a viral load <800000 IU/ml and completion of the treatment were independently associated with SVR. This model had an area under the curve value of 0.80 meaning that this model predicted SVR very well. The Hosmer-Lemeshow test used to test the goodness of fit of the model had a p value of 0.98.

Table 5.4. The description of variables associated with achievement of SVR after multivariable logistic regression model fitting.

Characteristics	Achieved SVR (n=273)	OR (95% CI)	P values
Treatment setting			0.01
1	62/76 (82%)	3.35 (1.39-8.06)	0.01
2	55/84 (65%)	ref	.
3	78/113 (69%)	0.84 (0.42-1.70)	0.64
Age			<0.01
<35	65/75 (87%)	3.68 (1.38-9.82)	0.01
≥35 and ≤45	92/139 (66%)	0.87 (0.41-1.85)	0.71
>45	38/59 (64%)	ref	.
Viral load			0.02
≥ 800000 IU/ml	99/148 (67%)	0.47 (0.25-0.90)	0.02
< 800000 IU/ml	96/125 (77%)	ref	.
Genotype			0.01
1	52/85 (61%)	0.73 (0.27-1.97)	0.54
2	8/12 (67%)	2.31 (0.46-11.73)	0.31
3	114/143 (80%)	2.31 (0.90-5.94	0.08
4	21/33 (64%)	ref	.
Treatment completion			<0.01
yes	170/211 (81%)	6.56 (3.32-12.95)	<0.01
No	25/62 (40%)	ref	.

5.4.3 Factors affecting treatment completion

Treatment completion rate was 70% in setting 1, 71% in setting 2 and 74% in setting 3 (p=NS). A logistic regression model was also fitted to predict treatment completion. No other characteristics besides "treatment setting" (which was forced to stay in the model) remained in the model (Table 5.5). This model had an "area under the curve" value of 0.52 which means that it is not a good predictor of treatment completion. The p value for the Hosmer-Lemeshow was 1.00.

Table 5.5. The description of variables associated with treatment completion after multivariable logistic regression model fitting.

Characteristics	Treatment completed	OR (95% CI)	P values
Treatment setting			0.90
1	60/80 (75%)	1.17 (0.59-2.33)	0.66
2	59/82 (72%)	ref	.
3	83/110 (74%)	1.12 (0.59-2.13)	0.72

5.5 Discussion

We examined whether an HCV antiviral treatment setting under one roof (setting 2) is superior to other multidisciplinary treatment settings (setting 1 and setting 3). In bivariate analysis the treatment outcome was not superior in the setting under one roof in comparison with other decentralised treatment settings. On the contrary in multivariate analysis being treated in setting 1, a setting working not under one roof, is associated with achieving SVR.

Given the heterogeneity of the PWID population and healthcare infrastructure in different settings, it is necessary to develop various tailored models of HCV care to fulfil the specific needs of local PWID in each setting. (233, 234) In a multivariable meta-regression analysis the involvement of multidisciplinary teams was positively correlated with SVR rates. (126) However a single treatment setting cannot meet all the needs of different local PWID populations. For example in high income countries where there is well functioning health insurance system and monthly income is assured through unemployment and sickness allowance, less financial support for the patients is required compared to low income countries. Until now several studies have been published showing the results of different interventions or approaches. Successful treatment outcomes were achieved by involving peer workers (235, 236) and nurse educators/practitioners (215), managing psychiatric problems by psychoeducation (237), providing direct observed treatment (238, 239), increasing general practitioners' capacity to manage and treat HCV (240),

providing HCV treatment through primary care-based clinics (241) and linking medical care with substance abuse treatment services to address the medical needs of PWID. (242, 243) With respect to the latter one would expect an "under one roof setting" providing HCV treatment in the specialised addiction care setting to perform the best. However, multivariate analysis showed a setting not working under one roof to be independently related with SVR.

The SVR rates of 80% in setting 1, 66% in setting 2 and 72% in setting 3 were consistent with previously reported SVR rates in opiate-dependent patients. (127, 148, 244) Other factors independently associated with SVR were young age, low viral load, HCV genotype 3 and treatment completion. Also in other studies younger age, low baseline viral load, genotypes other than 1 (mostly genotype 3) were predicting factors for achieving SVR. (245-248) The reason for no significant difference in SVR rate between the settings in bivariate analysis might be the HCV genotype as a confounder. HCV genotype 1 infection is associated with lower SVR rates after treatment with PegIFN and RBV. (67) In this study in setting 1 there were significantly more patients with genotype 1 infection (Table 5.1). However, a subset of these patients was treated with direct acting antivirals (TPV/BOC) which results according to the treatment trials in a higher SVR rate. (67) Thus in the bivariate analysis the high rate of HCV genotype 1 infected patients might influence the SVR rate.

The results clearly show that the occurrence of side effects was significantly different between the settings. For most of the side effects such as flu-like symptoms, skin related side effects, depression the occurrence rates in setting 3 were significantly lower compared to the other 2 settings. This could be explained by the retrospective nature of the study allowing to collect data only present in the patient files. Some centres for example in setting 3 reported only side effects that needed treatment in patient files and thus reported the side effects such as flu-like symptoms and skin related side effects less frequently.

Compliance or adherence to prescribed treatment is important for a successful treatment. A meta-analysis reported a pooled PegIFN/RBV treatment completion

rate of 83% ranging between 36.4% and 100%. (126) In our study treatment was completed in approximately 70% of the patients in the three settings. Although treatment completion rate was not significantly different between the three settings, the reasons for non-completion were significantly different. Side effects were in all three settings an important reason for non-completion. This will change in the future because the new antivirals have almost no side effects. When we take a closer look at the reported reasons for non-completion more people were 'lost-to-follow-up' in setting 1 while for more people in setting 2 and 3 'decision of the patient' was recorded. The sum of these two reasons was similar in the three settings. Depending on the interpretation of each setting of the information available in the patient file one site may have reported the reason as lost-to-follow-up while another site as decision of the patient. An underlying reason for differences in reasons for non-completion might also be difference in the care settings. For example in some settings more attention might be paid on improving the social situation of the patients while in other settings the priority might be lying in improving the financial situation by helping to find a job.

Widespread HCV infection in PWID is an essential point for the healthcare authorities that requires the attention of policy makers and the allocation of substantial resources to prevent the spread of the infection.

The main limitation of this study is its retrospective design. Some of the observed differences for example differences in rate of depression and anaemia might be the result of less accurate reporting or the use of different definitions of diseases and different care provision to them depending on the practice in a health care systems. Another limitation is that patients who started HCV treatment might be more engaged and compliant to health care services and due to this might show better treatment completion and outcome compared to substance users who are not engaged to health care and substitution treatment services. It is also a limitation that only one centre of each type of treatment setting was studied.

For future research it is important to perform large controlled studies to evaluate the added value of the new implemented practices and to compare the different settings for earlier steps in the HCV care (HCV screening, treatment uptake) because patients starting treatment have already crossed different barriers. Furthermore, in the era of new interferon free HCV antiviral drugs where SVR rate exceeds 90%, the role of screening and treatment uptake has become even more important. These might be different between these settings. For example, in the treatment setting working under one roof patients might have fewer barriers for screening and treatment uptake because screening and treatment are available at the same site. Further research is necessary to evaluate this.

In conclusion, our results demonstrate that PWID dealing with complex medical and psychiatric comorbidities and socio-financial issues can be effectively treated for HCV in any of the three different multidisciplinary approaches. A setting under one roof is not superior to other management settings.

Chapter 6

Hepatitis C in European prisons: a call for an evidence -informed response

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BMC Infect Dis. 2014;14 Suppl 6:S17

6.1 Abstract

Globally, over 10 million people are held in prisons and other places of detention at any given time. People who inject drugs comprise 10-48% of male and 30-60% of female prisoners. The spread of hepatitis C in prisons is clearly driven by injection drug use, with many infected prisoners unaware of their infection status. Risk behaviour for acquisition of hepatitis C via common use of injecting equipment is widespread in many prison settings.

In custodial settings, effective and efficient prevention models applied in the community are very rarely implemented. Only approximately 60 out of more than 10,000 prisons worldwide provide needle exchange. Thus, HCV prevention is almost exclusively limited to verbal advice, leaflets and other measures directed to cognitive behavioural change. Although the outcome of HCV antiviral treatment is comparable to non-substance users and substance users out of prison, the uptake for antiviral treatment is extremely low.

Based on a literature review to assess the spread of hepatitis C among prisoners and to learn more about the impact for the prison system, recommendations regarding hepatitis C prevention, screening and treatment in prisons have been formulated in this article.

6.2 Introduction

Globally, more than 10 million people are held in prisons and other places of detention at any given time. (249) Due to the high turnover rate in the prison population, it is estimated that more than 30 million people spend time in prisons each year. Drug users in particular often spend relatively short periods in prisons before returning to their communities.

Many people held in prisons have severe problems associated with drug use, together with related health and social disadvantages. Those categorised as problematic drug users constitute a substantial proportion of prison populations in Europe. Counting only sentenced prisoners with drug offences as the main offence, 15 of 26 European countries for which information is available report proportions over 15%. (250) The number of drug users in prisons is even higher. A systematic review of international studies – with a preponderance of studies conducted in the United States – found that 10% to 48% of men and 30% to 60% of women were dependent on or used illicit drugs in the month before entering prison. (251) In the European Union, it has been estimated that about half of all members of the prison population have used illicit drugs at some time in their lives. (252)

Hepatitis C virus infection, which is both preventable and treatable, is a major concern in correctional settings. People who inject drugs (PWID) have high rates of imprisonment, largely due to the criminalization of their drug use and to the tendency to fund drug use through crime. The dynamics of illicit drug use, HCV infection and imprisonment are closely intertwined. (253) One study found that in Australian prisons, one-third of entering inmates tested positive for anti-HCV. The proportion of positive results among entering inmates who injected drugs was 56%. Furthermore, one-third of inmates who were anti-HCV positive were unaware of their infection status.

In general, 80% of HCV-infected individuals develop chronic HCV. Of these, 10% to 15% will develop liver cirrhosis. (254) Three to four percent of patients with

cirrhosis develop HCC every year. (141, 255) Worldwide, 25% of liver cancer cases are attributable to HCV infection. (256)

Given the interplay between HCV, drug use and incarceration, HCV has the potential to impose a major disease burden on European prison populations. The purpose of this article is to review evidence and formulate recommendations regarding how to address this situation.

6.3 HCV transmission, risk factors and prevention in prisons

Imprisonment is an independent risk factor for HCV infection for PWID in the community. (257-262) All modes of HCV transmission that occur in the community also occur in prisons. In particular, HBV, HCV and HIV are transmitted in prisons through the sharing of contaminated injecting equipment, and also through unsafe sexual contact, unsafe skin penetration (such as piercing and tattooing, sharing of razors, and blood-sharing rituals) and the improper sterilisation or reuse of medical or dental instruments. (263) Some PWID continue to use drugs such as opioids, including by injection, while incarcerated, and some people initiate injecting in prison. (264) In Australian prisons about half of all imprisoned people who inject drugs continue to inject drugs in prison. (265)

One of the most important risk factors for HCV infection is IDU while in prison. (259, 262) A meta-analysis of 30 studies from different countries showed a clear association between the prevalence of HCV infection in prisoners and their history of injecting drug use. There were weaker associations with female gender and with tattooing. The results showed that HCV seroprevalence was approximately 11% higher among already-detained inmates, as opposed to inmates entering prison. A strong association between HCV infection and the length of time spent in prison was also seen. These findings suggest that intra-prison transmission may contribute considerably to high HCV levels in prison populations. (141)

The prevalence of HCV infection among prison inmates is many times higher in most custodial settings than in the general population (266, 267), primarily because of the high proportion of PWID (254) who are known to be at high risk of

infection. Esteban et al. concluded that HCV prevalence in the general population in Western Europe is 0.5%, and that it is 2.5% and 6% in Southern Europe and Eastern Europe respectively. (7) A meta-analysis performed by Vescio et al., showed that there is a high HCV prevalence in inmates in several countries around the world. HCV prevalence in inmates was approximately 30% to 40% (range: 2%–58%). (141)
Different studies from Europe, Australia and the United States suggest that hepatitis C prevalence rates in prisons range from 8% to 57%. (128, 143, 256, 268)

In prisoners with a history of injecting drug use, the global summary prevalence was 64% (138). Data on anti-HCV prevalence among injecting drug users in European prisons between 2005 and 2010 were reported by five countries, with prevalence ranging from 12% in Hungary to 91% in Luxembourg. (269) Among female prisoners the prevalence is two in three. Among female PWID, the prevalence can be even higher, ranging from 49% to 88%. (270)
Patterns of hepatitis C prevalence in custodial settings include increasing prevalence with age; higher prevalence among female prisoners; and increasing prevalence with multiple admissions to prisons (AIHW 2010). Infection with more than one strain of HCV may also be common in prison populations; one study found 24% prevalence of multiple infections within a cohort of prisoners who inject drugs. (271)
The mortality rate for HCV-induced liver disease in prisons is high. Chronic liver disease-related deaths accounted for 16% of deaths among male Texan prisoners from 1989 to 2003. Either hepatitis B virus (HBV) or HCV has been identified as a causal factor in more than one third of chronic liver disease-related deaths. (272)

6.4 Health care for prison inmates

Prisoners are entitled, without discrimination, to a standard of health care equivalent to that available in the outside community, including preventive

measures. This principle of equivalence is fundamental to the promotion of human rights and best health practice within prisons, and is supported by international guidelines on prison health and prisoners' rights, as well as national prison policy and legislation in many countries. (273)

People should not leave custody in a worse condition or with poorer health than when they entered. (265) The period of incarceration should be viewed as a public health window of opportunity, including HCV testing, treatment, care and support. (274) There is consensus among international organisations that all blood-borne virus prevention, treatment and care interventions that are available in the community, including harm reduction interventions, must also be available to prisoners. (275-277)

Effective and efficient prevention models that are applied in the community are very rarely implemented in custodial settings. Only about 60 out of more than 10,000 prisons worldwide provide needle exchange. (278) Thus, HCV prevention is almost exclusively limited to verbal advice, leaflets and other measures directed toward cognitive behavioural change. As HCV spreads primarily via injecting drug use in prisons, dependence-driven behaviour can be expected to predominate. (279)

6.5 HCV screening in prisons

Many people enter prison with social, medical, and mental health conditions and re-enter the community with few of these conditions having been addressed while incarcerated. Hepatitis C is one such condition, and its management challenges both the correctional and public health systems. Identifying all cases of HCV among inmates is an essential first step, but testing strategies for blood-borne viruses and test coverage vary globally between jurisdictions. In some countries there is no testing procedure at all (280), while some use voluntary screening and others use a targeted approach. This situation suggests a need for ongoing surveillance using a standardized approach to reliably report preva-

lence. Ideally, surveillance should include collection of data on incident cases. (253)

Screening for HCV infection and uptake of antiviral therapy are low in prisons. Uptake for screening ranges between 9% and 24%. (213, 281) In a nationwide survey in the United States, only one of 36 states reported routine screening, and only one reported conducting a seroprevalence study in custodial care. (254) Of 3,034 new prisoners at Dartmoor Prison (England), 12% were screened, with 16% of these found to be seropositive. Seventy-nine percent of seropositive prisoners with a positive polymerase chain reaction result were confirmed as cases of positive viremia, and 27% of these prisoners had a biopsy. Two prisoners were eligible for treatment. (282)

The results of a recent cost-effectiveness study (72) indicated that the introduction of dried blood spot testing compared to venipuncture for HCV case-finding was likely to be cost-effective in prisoners in the United Kingdom and the United States if a minimum level of continuity of care in treatment or referral between prison and the community could be ensured.

Qualitative research has described barriers to testing such as a lack of proactive approaches to offering testing, prisoners' fears and lack of knowledge about HCV, low motivation for testing, and concerns about confidentiality and stigma, which may mean fewer people are tested. (283, 284) More work is needed to increase the level of testing in prisons.

6.6 HCV treatment for prisoners

With good adherence, HCV treatment outcomes for incarcerated patients who take combination therapy (PegIFN and RBV) are comparable to those observed in non-incarcerated patients at similar stages of disease. (285, 286) Studies performed in custodial settings show acceptable results and SVR rates ranging between 36% and 66%. (285-290)

Rates of HCV treatment completion and SVR observed in correctional populations have been similar to those reported in community samples. (285-290) The

re-infection rate after successful antiviral treatment in prisons is low (7%) (291), and is comparable to re-infection rates outside of prisons. Antiviral treatment in prison also appears to be cost-effective according to a modelling study that looked at a US prison population. (292)

Several groups have argued that correctional institutions are an important setting for health interventions such as screening, diagnosis, prevention, and treatment of HCV infection. (293-295) One of the reasons is that in prison it is possible to monitor patients more closely, and to address side-effects and provide psychiatric care as necessary. (296) A second reason is that prisons provide an opportunity to engage with a difficult-to-reach population – incarceration may be the first or only time that many inmates intersect with the healthcare system. A third reason is that medical management and adherence to antiviral therapy require lifestyle stability, which can be provided by incarceration, particularly for offenders with a history of mental illness or substance abuse. (294)

6.7 Programmes developed to improve HCV treatment in prison

In a few studies, intervention programs were developed or tested to improve the management of hepatitis C in prisons. Arora et al. developed Project ECHO, a programme that utilized teleconferencing, videoconferencing, and e-mail communication to connect specialists with primary care providers in prisons and rural areas in order to improve access to quality health care for New Mexicans with hepatitis C. (297) Through Project ECHO, 226 patients received IFN and RBV treatment for hepatitis C.

In the US state of New York, a programme was created to provide continuity of HCV treatment to prisoners upon their release. (298) A referral process was developed, staff were mobilized, and health-care facilities in the community were recruited to accept referrals. This programme included 70 prisons and 21 health care facilities. Until March 2006, 24 inmates were enrolled.

Another treatment programme was developed in the North Dakota Department of Corrections and Rehabilitation. (299) The treatment protocol followed National Institutes of Health guidelines for primary therapy for hepatitis C, with the exception of replacing weekly PegIFN administration with three times- weekly consensus IFN administration. The programme resulted in sustained viral responses of 54% for GT 1, 75% for GTs 2 and 3, and 64% overall.

Research indicates that nurses play a crucial role in providing education, support and management of patients infected with hepatitis C. (215, 300-302) The involvement of nurses enhances access to treatment, treatment adherence and response to treatment. (215, 302, 303) A study by Lloyd et al. (304) evaluated the safety and effectiveness of a nurse model of care for inmates. In this study, treatment was initiated in 108 patients (28% of the 291 patients enrolled in the study) and the SVR rate among patients with complete follow-up data was 69%. This first prospective treatment programme in a prison setting demonstrated that the nurse-led model of hepatitis C care enhanced treatment uptake and reduced the burden of disease.

6.8 Staff training and support

Staff training and support are important because all people working in prisons should be aware of blood-borne viruses and of the universal and special precautions that are recommended for preventing transmission. Training and support should be tailored to the needs of different types of staff working within and outside of health services. Prison administrators are advised to: (128, 305)

- Provide target-group specific peer education and training on hepatitis and other communicable diseases, routes of transmission in the workplace (e.g., the risk of needlestick injuries occurring during searches of cells), confidentiality, drug use, hepatitis prevention measures, hepatitis testing and treatment opportunities, drug dependence treatment, universal precautions and use of protective equipment, and the rationale for and content of prison rules and policies related to hepatitis to all prison

staff as part of their initial training, and update this training on a regular basis during the course of employment.

- Ensure that the training of prison staff addresses hepatitis-related discrimination and homophobia, reduces staff opposition to the provision of hepatitis prevention measures to prisoners, emphasises the importance of confidentiality and non-disclosure of hepatitis status and medical information, and promotes the compassionate treatment of prisoners living with hepatitis. Ensure access to appropriate post-exposure prophylaxis and counselling.

6.9 General recommendations

The following recommendations can be made regarding hepatitis C prevention, screening and treatment in prisons:

- Close collaboration between prison and public (or community) health services is needed (e.g. in order to facilitate community follow-up of treatment). (254, 306) Ensure continued hepatitis C treatment and care when there is movement between custodial settings, and when inmates receiving treatment re-enter the community. (141, 265, 298)
- Incarcerated persons with risk factors for HCV infection should be screened for viral hepatitis infections. (307)
- There is a need to develop approaches to increase the uptake of testing by raising awareness amongst prisoners about HCV infection, optimising testing pathways that support appropriate testing at appropriate times during a prisoner's stay in prison, ensuring adequate pre- and post-test discussion, and developing care pathways for HCV that enable seamless continuity of care. (283) Proven nurse led intervention models could be transferred into the prison setting in order to guarantee guidance.
- Prisoners should be provided with substance abuse treatment. Opiate agonist therapy (methadone, buprenorphine or diacetylmorhpine) should

be administered to opiate-dependent subjects with hepatitis B and C infections in order to reduce the risks of transmission and reinfection.

- There is a need to provide sterile injecting equipment and other harm reduction measures to those who inject while in prison. (308, 309) HCV-infected persons should be counselled on how to avoid transmitting HCV to others. (310)
- Health education activities (including peer education) should be carried out, in particular for inmates with no or minimal prior health education. (204, 311)
- Depression and psychosis, which are common in prison settings, occur with IFN treatment. It is essential to provide psychiatric evaluation of patients prior to and during treatment, in order to avoid or control the possible appearance of mental side effects. (294, 312)
- A multidisciplinary approach through the collaboration of addiction specialists, hepatologists, infectious disease experts, clinical psychologists, nurses and prison physicians should be adopted. (244)
- If possible, a directly observed treatment (DOT) strategy, which ensures supervision of oral therapy administration and the injection of subcutaneous therapy by health care professionals, should be used, as occurs in anti-HIV and tuberculosis treatment in prison inmates. (266)

6.10 Conclusion

HCV prevalence is very high in prisons. Intravenous drug use while in prison is one of the most important risk factors. The utilization of harm reduction strategies in order to prevent transmission of HCV in prisons lags far behind similar efforts taking place outside of prisons. The scarcity of prison-based needle exchange programmes is a prominent example of this problem. Although testing for HCV in prisons should be a cornerstone in the health care of prison inmates, levels of screening for HCV infection and uptake of antiviral therapy in prisons are low. Since HCV treatment outcomes for incarcerated patients are compara-

ble to those observed in non-incarcerated patient, programmes to improve HCV treatment in prison, staff support and recommendations regarding HCV have been developed and must be implemented. Treatment for HCV in prison should be routinely available and offered under standard guidelines and protocols equivalent to those applied in the community.

Chapter 7

General discussion

The aim of this PhD thesis was to identify how HCV care for persons who use or inject drugs can be improved. To achieve this, studies were performed mainly between 2011-2015 to shed a light on some under-investigated topics at that time.

The first project (chapter 2) aimed to study the characteristics of the substance user population (clients of opioid substitution treatment clinics in Belgium) and patients' and physicians' opinion regarding HCV treatment (PegIFN and RBV). In the Belgian drug user population registered in an addiction care program, most patients (90%) were willing to receive HCV treatment, however only 43% were eligible for treatment in physicians' opinion.
The second project (chapter 3), a retrospective study, evaluating HCV treatment (TPV or BOC combined with PegIFN and RBV) outcome among PWID and non-PWID in Belgium, showed that treatment outcome and compliance were similar in the two groups.
The third project (chapter 4) demonstrated that an intervention, combining formal and peer education with FibroScan measurement, improved HCV knowledge among persons who use drugs, but did not accomplish a higher uptake for screening and treatment after one intervention session.
The fourth project (chapter 5), an international retrospective study, investigated whether HCV treatment outcome and compliance in a treatment setting working under one roof is superior to other treatment settings. The results suggested that being treated in a multidisciplinary setting not working under one roof was not inferior to a setting working under one roof.
The fifth project (chapter 6) is a literature review concluding that HCV prevalence and transmission are high in prisons. Intravenous drug use while in prison is one of the most important risk factors for HCV infection. Levels of screening for HCV infection and uptake for antiviral therapy in prisons are low. Harm reduction strategies in prison are scarce. In this international review, recommen-

dations are formulated to improve hepatitis C prevention, screening and treatment in prisons.

7.1 HCV care cascade

In April 2016, the WHO released an update of its "Guidelines for the screening, care and treatment of patients with chronic hepatitis C infection" published in 2014. (82, 313) The recommendations published in 2014 (313) covered the topics: who should be tested, how to assess for liver fibrosis and what treatment regimens should be used. These guidelines strongly recommended to:

- Offer HCV screening to individuals who are part of a (sub-)population with high HCV prevalence or with a history of HCV risk exposure/behaviour.
- Screen for alcohol use and offer counselling to reduce moderate and high levels of alcohol intake
- Assess all adults and children with chronic HCV infection, including people who inject drugs, for eligibility for antiviral treatment.
- Treat with PegIFN and RBV for the treatment of chronic HCV infection rather than standard non-pegylated IFN with RBV.

Since the release of these guidelines, several new direct acting antivirals have been approved and they changed the HCV treatment landscape. For the updated guidelines (82) the evidence on the safety and efficacy of the new DAA was reviewed and the WHO came up with three broad new recommendations. The first recommendation is that countries should move to all-oral HCV regimens, because they are safer, highly effective and becoming cheaper because of the production of generic products. The second main recommendation is to no longer use TPV and BOC, which were the first generation protease inhibitors. Third, these new guidelines also provide guidance on which specific regimens should be used (called "preferred regimens") based on a patient's clinical history as well as the HCV genotype.

The updated guidelines in April 2016 also promote the scale-up of HCV treatment, particularly in low- and middle-income countries where most people with HCV live and only few people currently have access to hepatitis treatment. The WHO recognizes that implementation of the recommendations may not be immediate, because the treatments can be expensive and the drugs are not yet approved in many countries. (82)

For the PWID population the WHO guidelines recommend to:

- Offer HCV screening to all PWID as an integral component of a comprehensive package of harm reduction interventions and to repeat screening in individuals at risk of reinfection.
- To provide HCV care without discrimination or stigmatisation and to integrate addiction treatment with other required services such as harm reduction strategies
- To assess all PWID with chronic HCV infection for eligibility for treatment

In May 2016, the World Health Assembly endorsed the Global Health Sector Strategy on viral hepatitis 2016–2021. The Global Health Sector Strategy calls for the elimination of viral hepatitis as a public health threat by 2030 (reducing new infections by 90% and mortality by 65%). (314)

In July 2018, the WHO released an update of the guidelines based on new evidence; the fast evolution in DAA regimens improvement and substantial price reduction of DAAs. The WHO recommends firstly to treat all persons (12 years or older, irrespective of disease stage) with chronic HCV infection, rather than reserving treatment for persons with more advanced disease. (315) Secondly, the need for genotyping to guide treatment decisions is reduced due to the availability of several new pangenotypic DAAs. Therefore the WHO recommends the use of pangenotypic DAA regimens for the treatment of persons with chronic HCV infection aged 18 years and above. For adolescents between 12-17 years of

age (weighing at least 35 kg) the WHO recommends to use 3 regimens: sofosbuvir/ledipasvir for 12 weeks in genotypes 1, 4, 5 and 6, sofosbuvir/ribavirin for 12 weeks in genotype 2 and sofosbuvir/ribavirin for 24 weeks in genotype 3. For children aged less than 12 years the WHO recommends to defer treatment until 12 years of age and to no longer treat with interferon-based regimens. Thirdly, the continued substantial reduction in the price of DAAs has enabled treatment to be rolled out rapidly in a number of low- and middle-income countries. To help countries improve access to effective hepatitis services, the WHO describes eight key good practice approaches across the continuum of care: national planning to eliminate HCV, simple and standardized algorithms, strategies to improve linkage from testing to care, integration of HCV care in other services, decentralisation of testing and treatment, community engagement and peer support, strategies for more efficient procurement and supply management and data systems to monitor the quality of individual care and coverage. (315)

In many countries, PWID are the main reservoir of HCV infection. (9) The burden of HCV-related liver disease continues to rise and it is a major cause of morbidity and mortality among PWID. (33) Substance users were excluded from antiviral HCV therapy at the end of the nineties (1997). (316) By 2009, they were no longer excluded from antiviral therapy and international guidelines started recommending treatment for PWID. (128, 174, 317)

Although PWID are the major source for HCV infection and evidence shows favourable outcomes of HCV antiviral therapy in PWID, still very few have received HCV treatment. Even in high-income countries, the HCV treatment uptake of PWID remains low. (318) Therefore the guidelines developed by the International Network for Hepatitis in Substance Users (INHSU) emphasise the need for the implementation of strategies to enhance HCV testing, linkage to care, assessment, treatment and prevention of HCV reinfection in the PWID population. (128, 154) Recently, a paper by INHSU presents recommended

actions for PWID in order to meet the WHO hepatitis C elimination goals by 2030. (319)

People with HCV infection need to fulfil several steps along the HCV care cascade/continuum, to achieve optimal health outcomes. (320, 321) Passing through this care cascade/continuum individuals must 1) be tested for, diagnosed with and made aware of their HCV infection, 2) engage with the specific health care provider (linkage to care) 3) be assessed for specific treatment, 4) initiate specific treatment 5) adhere to and complete the treatment and 6) prevent re-infection. (321)

To improve HCV care, addressing several steps in the cascade of HCV care is required. (320-322). A systematic review (321) summarized evidence-based interventions targeting one or more steps along the chronic HCV care continuum. This review clearly shows that several interventions facilitating one or multiple steps of the HCV care cascade have already been designed and studied. More in detail the authors reviewed interventions to improve the diagnosis or case-finding, linkage to HCV care, pre-therapeutic evaluation or treatment initiation and treatment adherence. Interventions such as free counselling and testing, dried blood spot testing, point of care testing (oral fluid testing), provider education about HCV treatment guidelines with nursing support were effective at identifying new cases of chronic HCV. Linkage to care was improved by for example peer interventions and the involvement of trained nurses who were responsible for HCV assessment, treatment and post treatment follow-up in a prison setting. Treatment initiation was improved by interventions such as peer programs and behavioral interventions that included motivational interviewing, care coordination through case management and education services. Interventions such as DOT and multidisciplinary support programs involving collaboration between physicians and nurses to improve treatment were effective to improve adherence to treatment. Most interventions described in this review were studied for IFN-based HCV treatments. Thus future research

need to address how these interventions apply to the context of new DAAs. (321) In 2017, Bajis et al. (323) also performed systemic review to evaluate the effectiveness of interventions to enhance HCV testing, linkage to care, and treatment uptake among PWID. But all the identified studies were conducted in the interferon treatment era and there were no studies conducted in low- and middle-income countries. Thus, further data is needed to identify strategies to enhance HCV testing, linkage to care, and treatment in the DAA era to strive towards HCV elimination among PWID. (323)

In 2015, Ford et al. (324) outlined ten key priorities for scaling up HCV treatment for PWID in low and middle income countries including: 1) Affordable access to IFN-free HCV treatment; 2) increased awareness and testing; 3) standardization of treatment; 4) simplification of service delivery; 5) integration of services; 6) peer support; 7) treatment within a framework of comprehensive prevention (including NSP and OST); 8) tracking progress; 9) funding; and 10) enabling policies. (324) In my opinion these are also applicable for most developed/high income countries such as Belgium because in most high income countries not all of these priorities are fulfilled and there are still gaps in HCV care.
Before and during this PhD project, our research group did focus on some aspects of the HCV care cascade.

7.2 HCV prevalence, screening, treatment and liver disease progression in Belgium

Before starting to test and implement strategies to improve the HCV care cascade, it is important to review the current situation of HCV prevalence, rate of screening, treatment and liver disease progression.
There are only a few dated studies that evaluated the prevalence/incidence of HCV in the general population and in substance users in Belgium. In brief, these studies suggested that the prevalence rate in the general population was around 1% and according to a recent estimate by Litzroth et al. (56) 0.22%, while in

the PWID population it was much higher (in detail described in section 1.4). (53, 57)

7.3 The interest of PWID and care providers in HCV treatment

Studies did show that 53-86% of PWID reported willingness to receive treatment for HCV with PegIFN/RBV. (165, 223, 325) The study by Doab et al. (223) demonstrated that the willingness to receive HCV treatment increased from 63% to 93% under treatment success scenarios of 40% to 70%, respectively. One can expect willingness for treatment to be even higher in the era of the new IFN-free antivirals with less side effects and very high response rates. Among patients not willing or delaying treatment, several barriers have been observed such as poor knowledge about HCV, absence of symptoms, unemployment, unstable housing, etc. (326) In 2017, Mah et al. (327) demonstrated that HCV knowledge was associated with more HCV treatment willingness.

On the other hand physicians/care providers are reluctant to refer or to treat substance users based on concerns related to ongoing/active substance use, psychiatric comorbidity and perceptions about poor adherence. Some addiction medicine physicians do not see HCV treatment as their "core" business. Moreover, not only among patients, also among physicians lack of HCV knowledge results in low HCV screening and treatment rates. (326)

To improve an important step of the HCV care cascade: "treatment initiation" it is important to know the HCV infected population on OST and the factors affecting referral for HCV treatment. Therefore we studied (chapter 2) the characteristics, patients' willingness for HCV treatment, physicians' opinion regarding the suitability of the patients for HCV treatment, the referral rate and factors associated with referral to a hepatologist for HCV treatment, among a population of PWID with chronic HCV infection in an OST setting. This prospective multicentre study showed that also in our Belgian PWID population the majority (90%) was willing to receive HCV treatment. However, only 43% of the participants was

suitable for treatment in addiction care physician's opinions and in only 17% of the participants referred to and seen by a hepatologist, HCV treatment was recommended.

7.4 PWID patients can achieve similar treatment outcomes as non-PWID

As already described in the introduction, there is a lot of evidence showing that PegIFN/RBV treatment was safe and effective among PWID and treatment outcomes were similar to the non-PWID population. (125-129) Our research group was the first to compare the outcome of antiviral HCV therapy including BOC or TPV among PWID and non-PWID infected with GT 1 in Belgium (Chapter 3). Treatment outcomes were similar in PWID and non-PWID. Also other studies found comparable response rates among PWID under OST and a non-PWID population. (131, 328) The trials that aimed to study the response rates of IFN-free DAA treatments showed similar results. (96-98, 329-332). In Belgium, Bielen et al. (134) compared outcome of DAA treatment for HCV in PWID and non-PWID. This study showed similar rates of treatment completion (95.7% vs 98.1%; p=0.244) and SVR (93.0% vs 94.8%; p=0.430) between PWID and non-PWID, respectively.

In short, there is sufficient evidence to support that the PWID population delivered similar treatment outcomes and adherence to antiviral treatment when compared to the general population, even for IFN-based treatments, when the treatment period was much longer and treatment was accompanied with several side effects.

There is a lack of data on treatment outcomes with the new IFN-free HCV therapies in the PWID population. Trials to investigate the outcome of and uptake for the new antivirals in this population are required. It is also important to study the reinfection rate after HCV treatment with the new antivirals. There is a possibility that the PWID population might have higher rates of relapse to risk be-

havior (sharing injection material) because of these simple, easy and short treatments with almost no side effects. If this might be the case then patient education and harm reduction to minimize the risk of reinfection should be implemented.

7.5 HCV screening and treatment rate can be enhanced through providing HCV-related information and non-invasive diagnosis

Among PWID, a low perceived need and fear for treatment has been associated with limited knowledge about hepatitis C and concerns about treatment-related side effects. (145, 165, 224, 333-335) Thus, these studies suggest that lack of knowledge is also a barrier to seeking HCV care. A number of studies investigating HCV-related knowledge among PWID found that HCV knowledge, depending on the study, was poor to moderate. (218, 223, 333, 334, 336-339) It is difficult, however, to compare these studies because different instruments were used and the studies were performed in different settings/countries.

Also in OST settings, where there is repeated contact with health care providers, poor HCV knowledge and low rates of assessment and treatment were observed. (165, 218, 225, 340) This suggests that some of the OST settings, in their current form, are not successful in providing a sufficient level of patient-provider contact to facilitate HCV assessment and treatment. (227)

Even simple educational interventions, such as informational presentations, can significantly improve HCV knowledge. (211) It is important to address the barrier "lack of knowledge" because higher HCV knowledge is associated with higher willingness for treatment, a greater likelihood of receiving HCV assessment and treatment. (146, 225, 340)

Liver biopsy, which is an invasive procedure, is a barrier to HCV assessment and treatment among PWID. (220, 223) Liver disease can also be assessed by non-invasive techniques such as transient elastography/FibroScan. This is an ultra-

sound technique that evaluates the extent of liver fibrosis or damage. (341, 342) Transient elastography can enhance liver disease screening among PWID. (221, 222, 343) Performing a FibroScan may also facilitate the entry into care, especially in patients with a lack of HCV-related symptoms such as PWID who report this as a reason not to seek HCV care. (227)

To improve HCV screening which is the first step of the HCV care cascade we performed a pilot study (chapter 4) to evaluate the effect of HCV related education and Fibroscan measurement on knowledge and willingness for HCV screening and treatment among PWUD in a local addiction care setting in Limburg, Belgium. There was a significant improvement in HCV-related knowledge. Uptake for screening and treatment did also show a trend towards improvement but not statistical significant.

During this study, in our personal experience we did notice that besides giving information, there is also need for close follow-up of the patients by a care provider/nurse/ other member of the care provider team who is regularly in contact with the patients. The primary role of this person should be to repeat the information regularly, to discuss barriers to HCV screening and treatment, try to resolve these barriers and engage the patients in HCV care.

For the future, additional studies are required to evaluate educational interventions designed to improve HCV and liver disease knowledge among substance users.

7.6 The ideal settings and approaches to provide HCV care

HCV care can be improved by providing all the necessary support in each stage of the HCV care cascade, which is the process from screening to post-treatment follow-up. An integrated multidisciplinary approach to HCV treatment can be provided by utilizing community-based and hospital-based clinics, as well as OST and drug detoxification centres. (147-150, 172, 244) For example, the integration of an addiction medicine specialist from an OST program in a hepatitis clinic proved to be an effective and efficient way to deliver HCV evaluation and treat-

ment to patients in OST. (164) A meta-analysis by Dimova et al. (126) identified "treatment of addiction during HCV therapy" as a parameter leading to higher treatment completion. (126) Integrating HCV care into primary care, addiction care and general practices has also proved to be effective. (148, 166, 167, 241, 344, 345) Tait et al. demonstrated that introduction of a multidisciplinary care network did not only increase engagement and access to HCV treatment but also reduced all-cause mortality. (346, 347)
Related to this topic, we did compare (chapter 5) the treatment (Peg-IFN and RBV) outcome in an integrated/multidisciplinary care setting providing addiction and HCV treatment under one roof and two multidisciplinary settings working not under one roof. The results suggested that the setting under one roof was not superior for HCV treatment outcome compared to the other settings.

The integration of psychologist-led interventions into a hepatology unit increased HCV treatment eligibility in an underserved population with mental health and substance abuse comorbidities. (348) This trial by Evon et al. (348) enrolled HCV patients deferred from antiviral therapy, owing to mental health or substance abuse. The integrated care intervention group received counselling and case management. Patients in the intervention group received monthly phone and in-person intervention sessions with the hepatology psychologist for up to nine months. In an intention-to-treat analysis, 42% of intervention group participants became eligible for therapy compared to 18% of standard care participants ($p=0.009$).

The involvement of nurse educators/practitioners or specialised nurses for assessment, HCV treatment, psychotherapy and systematic follow-up of the patients can also greatly improve HCV management. (215, 304, 349) Several studies evaluating task shifting (between specialists and primary care providers) demonstrated its success in improving access to HCV care in interferon based regimens and also in the DAA era. (297, 350-356)

In the era of PegIFN and/or RBV treatment models of HCV treatment incorporating direct observed treatment (DOT) (238, 239, 357), peer support (122, 147, 358, 359) and group treatment (358) were effective. For example the involvement of peers stimulated the development of positive and healthy behaviours, and has been shown to increase assessment, treatment and prevention of HCV. (122, 147, 358-362)

There is emerging evidence supporting the role of "case management" in order to improve HCV care. A modelling study evaluated the effect of four hypothetical intervention strategies: linkage to care, treatment initiation, integrated case management and peer navigator, to improve HCV care among a hypothetical cohort of individuals with chronic HCV infection, recently screened positive for anti-HCV. Peer navigators were peers who worked with patients from the time they were diagnosed as HCV-infected until completion of HCV treatment. This study demonstrated that interventions addressing multiple points along the HCV cascade, such as peer navigators or integrated case management, may provide the best value for money and should be prioritized for future development and prospective evaluation. (363) A prospective randomized trial in the United States compared the results of usual care to an integrated care intervention including case management. They demonstrated that integrated care with a mental health provider as case manager increased the proportion of patients with HCV infection and psychiatric illness and/or substance abuse who initiated antiviral therapy and achieved SVR, without serious adverse events. (364) A study published in 2015, was the first to examine the experience of people with chronic disease and family members, who participated in a case management intervention in primary care. The overall experience of patients and family members was very positive. Participants reported that their case management nurse improved access, communication, coordination, and involvement in decision-making as well as better health care transitions. (365)

Settings such as OST programs, community health centres and prisons, where large numbers of PWID can be reached, are present in many countries. By building on the existing infrastructure and adapting according to the needs of the PWID, these settings might become very successful in treating HCV in this population. (147, 151, 159, 165, 304, 344, 366) Recent studies indicated that besides these existing settings PWID, who are not engaged in health care services, can be reached by ''bring a friend'' approach. (367, 368) In this way HCV care can be provided in close social and injecting networks, usually "invisible" for the care providers.

Current knowledge suggests that none of the models meets all the needs of a heterogeneous patient population. In short "one size does not fit all", thus offering a setting adapted to the needs of local PWID is the best way to reach the most important needs of PWID. Close collaboration of all involved health professionals is crucial for every model to be successful. To improve the communication between all care providers and to enhance the linkage to care for patients, a case manager can play an important role. Furthermore, acceptance of the individual circumstances of PWID will determine the level of success of any model of HCV management, rather than rigid exclusion criteria. (151)

Since new strategies need to be built upon the existing infrastructure, some settings/countries might need fewer efforts compared to others. Future research is needed to study the effect of existing strategies when applied to a certain existing setting. There is also need to design and study interventions/strategies that are affordable and facilitate several steps of the HCV care cascade.

7.7 Harm reduction and enhanced HCV screening and treatment in a custodial setting is essential to control further spread of HCV

HCV prevalence among the prison population is much higher (30-40%) than in the general population. (369) A literature review by Dolan et al. demonstrated that globally 15.1% (1 546 500) of the 10.2 million incarcerated people were HCV ab+ on any given day in 2014. (139) This high prevalence can be explained by high incarceration rate among PWID and high rates of risk behaviour such as sharing of injecting materials in prison. (141-143)

During the period 2006-2010 more than 60% of the Belgian prisoners indicated to have used illegal drugs in the past and 30 to 36% during the current detention. At the first place cannabis followed by heroin and illegal medication use are the most common in prisons. One out of three prisoners is imprisoned due to drug related offenses. These findings suggest that prisons are a window of opportunity to reach this difficult-to-reach population. (370)

As elsewhere in the world, data and interventions related to HCV care in prisons are scarce in Belgium. Plasschaert et al. (2004-2005) interviewed and tested 117 DUs in prisons. In the prison population an HCV prevalence rate of 53% was recorded among DUs and 73% among PWID. (58)

Without access to services such as harm reduction programs (needle and syringe programs), HCV screening and treatment, equivalent to community standards, HCV infections will continue to occur among this most vulnerable population. This will result in significant societal and health care costs related to the management of these infections. (371)

Efforts to reduce new HCV infections by providing harm reduction interventions such as NSPs, systematic HCV screening, counselling and treatment are therefore essential among the prison population.

7.8 HCV care for PWID, the shortcomings and the ways to improve HCV care in Belgium

7.8.1 The most common way of receiving HCV care among PWID

In Belgium, in most addiction care centres, care is provided by a team of physicians, psychiatrists, psychologists, nurses and social workers.
Patients with risk behaviour are screened for anti-HCV and HCV RNA in some addiction care centres. If positive, patients are referred to a hepatologist/gastroenterologist in the nearest liver clinic. The procedures such as ultrasonography, transient elastography (Fibroscan) and liver biopsy are performed at the liver clinic. If eligible for treatment the hepatologist starts the treatment and follows the patient during and after the treatment. The addiction care physicians and nurses communicate with the hepatologist through letters/telephone contact.
The addiction treatment, primary health care and specialized care for HCV are partially reimbursed by the health insurance.

7.8.2 Shortcomings of HCV care in Belgium

Although the Belgian Association for the Study of the Liver recommends targeted HCV screening for high risk populations, including individuals with a blood transfusion or a major medical event prior to July 1, 1990, intranasal or injection drug users, and dialysis patients, there is still no formal screening strategy present in Belgium. (55) Efforts to increase screening/diagnosis and treatment rates are urgently required.

In 2014, an action plan, the "Hepatitis C Plan", was developed in Belgium to improve prevention, diagnosis and treatment of HCV. The main aims of this plan

were to increase the rate of screening, to improve the treatment quality of life of the patients and to develop a national network to improve HCV care. Yet, the problem is that this action plan did not define specific actions to achieve these goals. There is no information available how this plan will be realized, nor whether some budget is made available for people (interested hepatologists/ addiction care personnel/researchers) who want to take initiatives. (372) Until the end of 2018, the HCV plan has not been implemented. Very recently screening programs are starting to be supported by the Flemish health ministry at the Centre for alcohol and other drugs problems in selected provinces in Belgium. (373)

Newly discovered HCV treatments such as sofosbuvir show high efficacy, have simplified dosing (one pill all oral), short duration and almost no side effects. Due to the high cost these new antivirals are not available for all the diagnosed patients. Up to 2017, the new generation DAAs were only reimbursed for patients with advanced (F3-F4) liver disease in Belgium. (109) From January 2017, also patients with F2 fibrosis stage and higher are reimbursed for HCV antiviral treatment. (374, 375) The criteria for reimbursement are revised recently. From January 2019 on reimbursement for HCV treatment is approved for all genotypes also for patients with fibrosis stage F0-F1. (110, 111)

The PWID population is a heterogeneous population; some of them have multiple problems such as comorbidities and socio-financial problems. Even if treatment is available and reimbursed for all infected PWID, this will not make HCV treatment being a priority for all those PWID. Through communication with addiction care physicians during this PhD project, it was noticed that screening was not performed or delayed and treatment was not started several years after screening in a certain number of patients because during that period of their life they were facing many other problems. Thus even if treatment is available and effective, a broad expansion of harm reduction strategies remains important. There is also need for case managers who ensure that we do not loose patients

on their way to treatment and who identify and try to remove the barriers for each patient/case by activating members of the multidisciplinary team when needed.

7.8.3 Results of modelling studies and suggestions based on these results to scale up HCV treatment in Belgium

A modelling study by Nevens et al. published in 2012 (376) evaluated the cost of care of chronic HCV according to the different severity stages of the disease in Belgium. They concluded that treatment of patients with chronic HCV in an early stage had the potential to be cost-effective. Once complications of chronic HCV occur, hospitalization costs far exceed the cost of antiviral therapy. (376) A modelling study published in 2014 showed that by increasing the SVR rate and the number of cases treated, in 2030 the cases with cirrhosis, decompensated cirrhosis and HCC would be significantly lower compared to 2013. (377)

A modelling study was conducted in 2016 by Bourgeois et al. (378) to identify the steps necessary to achieve WHO recommendations (82) for a 65% reduction in liver-related deaths and a 90% reduction in new infections by 2030. They started with baseline estimates of 66 200 viremic infections in Belgium in 2015, approximately 43% of which were diagnosed, 1350 patients treated and 2280 viremic newly diagnosed cases. The results showed that WHO recommendations can be achieved in Belgium by extending treatment to ≥ F0 patients by 2018, including people who inject drugs and other individuals at risk of transmitting HCV, diagnosing 2030 persons and treating up to 4060 patients annually by 2018. Additionally, to achieve a 90% reduction in new infections, annual treatment of people who are currently injecting required alongside efforts to prevent new infections in the general and HIV+ MSM populations. To achieve these goals improved case finding, linkage to care and treatment for the population at greatest risk of transmitting HCV (PWID and HIV+MSM) is required. Also in-

creased awareness among the general population and the general practitioners is recommended.

A modelling study by Mathei et al. (121) assessed the impact of treatment on the total number of HCV infections as well as the number of secondary infections following a HCV cure in the Belgian PWID population. The estimated number of PWID in Belgium in 2015 was 9080. Of this PWID population, 47% were engaged in harm reduction interventions including NSP and/or OST. In 2015, 33% (n=2970) of the PWID were HCV infected, with an estimated 160 new HCV infections. The results demonstrated that treating 370 PWID annually (12.5% of 2015 population) with oral DAAs will result in a >90% reduction in HCV infected PWID by 2030. Based on this finding implementation of a screening and treatment strategy among PWID combined with an expansion of harm reduction programs was recommended.

In Belgium there is a clear need to improve HCV care in every step of the HCV care cascade. This can be achieved by adapting and implementing existing evidence based interventions. (321)

7.8.4 Strategies to improve HCV care in Belgium

To achieve elimination of HCV, in some countries such as Scotland, Germany, France, Portugal, The Netherlands and Australia successful practices were developed through political engagement, use of evidence based interventions and by focusing on the high risk populations including drug users and prison population. (379-382) For example Scotland was successful in linking HCV patients to care by translating research into public health policy. (383-385) The aims of the Action Plan on Hepatitis C launched in 2006 by the Scottish government were (384) to prevent the spread of the infection, particularly among PWID, to diagnose HCV-infected people and to ensure that those infected receive optimal treatment, care and support. During the first phase of this plan evidence about the epidemiology of HCV in Scotland was gathered through the development of

databases to collect data on diagnosis, data on the numbers of patients attending specialist care and being treated and record-linkage of these HCV databases with other national hospital and deaths registries, providing data on the numbers advancing to end-stage disease and death. The results of a modelling study using these data showed that over 2000 HCV-infected people in Scotland, involving 1900 people who had ever injected drugs, were living with cirrhosis in 2005, and the annual number developing decompensated cirrhosis was projected to double between 2000 and 2020, unless treatment rates were scaled-up considerably. (383)
During the second phase services were developed to improve HCV testing and referral and to enhance treatment uptake in line with the targets of the government. (383) The efforts have led to an increase in the proportion of people diagnosed, greater numbers initiating treatment and a reduction in overall prevalence. (383)
Dillon et al. discussed in 2016 the barriers to improving HCV care for PWID and best practices in HCV prevention, diagnosis and treatment in PWID in Europe and provided policy recommendations to address unmet needs in PWID in the European Union. They concluded that strategic action at the policy level is urgently needed to increase access to HCV prevention, testing and treatment among PWID. (386)

In Belgium in some local settings there is a well-functioning infrastructure to deliver OST treatment and to guide substance users to handle socio-financial issues in addiction care centres. There is also a good communication between addiction care centres and the specialised departments located in hospitals to diagnose and treat HCV in these settings.

There are a couple of addiction care settings where the whole team tries to implement evidence-based strategies to engage patients with HCV care. Moreover, Free clinic Antwerp implements internationally recognized peer interventions such as peer intervention; "C-buddy-project" where buddies are

patients who have successfully completed HCV treatment. In the first step these buddies inform ex-drug users about HCV, how it is transferred, the screening opportunities and motivate them to do so, and they guide ex-drug users towards screening and treatment. In the second step, during the treatment the buddies keep track of the calendar, remind people of their appointments. After the treatment they guide patients through psycho-education and harm reduction to prevent reinfection. (387) Another internationally recognized and innovative program is the implementation and evaluation of case management to improve HCV screening and treatment uptake in the centre for alcohol and drug problems in Limburg (Belgium). In a prospective interventional cohort study the effect of case management was studied on four groups of PWIDs: 163 persons who received methadone at their local pharmacy, 144 persons who received methadone at the OST setting, 18 persons who were active users in a needle exchange program and 9 persons who were recruited after referral to the hospital (former PWID). This showed that case management was a very effective intervention. In all the groups more than 80% of the cases were screened, except in the pharmacy group. The lower screening rate in the pharmacy group could be explained by their low visiting rate (few times a year) at the OST setting. In the PWID cohort 29% was HCV RNA positive. Sixty-two percent of these chronically infected PWID could be assessed for treatment and 95% of them were eligible for HCV treatment. Mainly due to the Belgian reimbursement criteria at that time in 2015-2016 (≥F3 Metavir fibrosis score), treatment was only started in 43% of the patients. (388)

The main problem we faced in Belgium up to now is that at a national level there was no engagement of the government to provide guidance and budget to implement programmes to enhance screening and treatment, to improve harm reduction to reach drug users who are invisible for the health care system.

Almost all initiatives aiming to improve the HCV care in Belgium are taken by interested hepatologists, addiction care physicians and researchers often working in local settings and receiving funding from pharmaceutical companies.

In my opinion the first step at governmental level should be to organise a meeting platform for all care providers such as addiction care providers, nurses, hepatologists and persons in charge of harm reduction/NSP programmes to discuss how to improve the HCV care for PWID.

Based on the previous evidence, a number of recommendations to improve HCV care in Belgium are formulated:

- To know the exact numbers of HCV prevalence, HCV related liver disease progression, HCV screening and treatment, on national level health authorities need to implement a database/registry system. Therefore providing funding and guidelines to addiction care settings to collect data on HCV screening, disease progression status and treatment in their data management systems is required. Also a national prevalence study is urgently needed.

- Persons/patients linked to addiction care centers benefit from harm reduction services such as NSP. Awareness campaigns about the risk of HCV transmission and about available harm reduction services for younger recently injecting people, will reduce the number of new infections

- HCV screening can be increased by providing free anti-HCV testing, by using point of care testing and less invasive tests such as dried blood spot and saliva testing and by providing HCV related education of care providers (addiction care physicians, nurses) and patients. By organizing regular outreach testing events, HCV screening can be provided to PWID not linked to addiction care centers. Also increasing awareness among

general practitioners and general population will enhance screening and linkage to care.

- Case managers/trained nurses, who follow and guide patients from screening to post-treatment follow-up and who facilitate communication between the different care providers such as addiction care physicians, specialists (hepatologists) who work at different locations in Belgium, are required. They will improve care at the different levels of the HCV care continuum.

- The very recent revision of HCV treatment reïmbursement criteria will positively affect the treatment rate. It is also important to treat young patients who often have F0/F1 liver fibrosis stage, but who are still injecting and who can infect others. In these patients besides offering HCV treatment also education about HCV, risk behaviour and engagement in harm redution are essential.

- In prisons a systematic screening for HCV and referral for HCV antiviral treatment has to be offered. Also harm reduction strategies such as NSP and OST has to be available.

In short, based on evidence delivered by global research and our own work, we conclude that in order to control HCV infection targeted strategies to improve every step of the "HCV care cascade", which includes HCV diagnosis, linkage to HCV care, treatment uptake, response to HCV treatment and screening for reinfection, are required in Belgium.

7.9 Strengths and shortcomings of the performed studies

The studies performed in this PhD project date from the years 2011-2015 and during this time period patients were treated with combination of PegIFN and Ribavirin and later first generation DAAs boceprevir and telaprevir combined

with PegIFN and Ribavirin. At that time, the treatment duration was longer and HCV treatments were associated with several side effects. The situation has changed drastically with the availability of the new DAAs with shorter treatment period, almost no side effects and high SVR rates.

When evaluating the patients' and physicians' opinion regarding HCV treatment in an HCV population that was considered to be difficult to manage (chapter 2), the results demonstrated that most patients (90%) were willing to receive HCV treatment, however only 43% were eligible for treatment in physicians' opinion. Patients delayed treatment due to concerns about side effects. The patients were not suitable for treatment in the addiction care physicians' opinion mainly due to unstable drug use, psychiatric comorbidity and unstable housing. With the current available DAA treatments, with almost no side effects, short treatment period and high success rates, some of the barriers we identified are partially solved. The strong point of this project is that it allowed to identify the characteristics of this patient population. This project was a pioneer project at the time when in Belgium not much attention was paid to HCV management in substance users. Based on this project, new projects were started to improve HCV screening and linkage to care. Examples are two projects performed by our research group to improve the uptake for HCV screening and treatment in an OST setting (in Limburg, Belgium) and in subgroups who are isolated from care such as young opiate injectors (in Limburg and Antwerp, Belgium) by means of case management (388) and outreach (389), respectively.

Secondly, regarding HCV treatment completion and outcome in patients treated with telaprevir or boceprevir combined with PegIFN and RBV (chapter 3), treatment completion was similar in PWID and non-PWID. With the availability of the new DAAs, treatment compliance will improve because of the shorter treatment period and less discomfort due to side effects. But there might be more relapse to high risk behaviour if patients do not take the HCV disease seriously due to

the easy, short and comfortable treatment. Thus, harm reduction programs focusing on patient education on the risk of reinfection and awareness about the cost of these expensive medications are important.

Thirdly, in chapter 5, treatment compliance and outcome (SVR rate) was not superior in a treatment setting providing addiction care and HCV treatment under one roof in comparison to the treatment settings providing addiction care and HCV care not under one roof. However, we realised in this international study that comparing treatment centres in different European countries is not easy due to the differences in the drug use profiles and cultural background. Also other studies confirmed that the drug use/injecting profile varies by demographic group and geographic area. (6)
In this era of the new DAAs, policy makers, pharma companies and all other contributors should realize that only the availability of these new treatments is not enough to eradicate HCV. Developing tailored strategies according to the needs of regional PWID populations to link the patients to HCV care, have become very important.

In chapter 4, an intervention, combining formal and peer education with FibroScan measurement improved HCV-related knowledge but not the willingness for HCV screening and treatment among persons who use drugs after one intervention session. An important limitation of this project was a small number of participants who reached the end of the follow-up period (3 months), resulting in an underpowered study. It was also seen in other studies on linkage to care that there is loss of large numbers of patients at each step of the care cascade. (347) The introduction of existing services, such as dried blood spot testing to enhance the access to care, can improve the linkage to care and reduce the number of patients lost at every step of the HCV care cascade.

In the era of the new DAAs, information about HCV and the treatment options need be scaled up in addiction care centres. But also patients not linked to addiction care have to be informed through outreach programs. On the other hand, patients education about risk of reinfection and prevention of reinfection has to be improved. There is increasing concern that HCV reinfection might be more likely in the interferon-free era. The new DAAs treatment periods are shorter. The DAAs are better tolerated and much more effective than interferon-based therapy, which might lead to being less careful about avoiding reinfection.

In the performed studies (chapter 2, 3, 4 and 5), the study population may represent a group of drug users that is more engaged in health care services, and the results might be different in the drug user population not properly engaged with health services as clients of substitution centres who are not active users (invisible for addiction care) or active users not covered by substitution therapy. It is important to implement programs to identify the drug user population "invisible" for the health care system and to improve linkage to care for these patients.

Chapter 6 is one of the first review manuscripts covering different aspects from HCV prevalence to HCV treatment in prisons. I focused on this topic because HCV, drug use and incarceration are related to each other and the spread of hepatitis C in prisons is clearly driven by injection drug use. This internationally referred manuscript was the base for propositions for further interventions and guidelines. (140, 144, 390)

References

1. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol. 2014;61(1 Suppl):S45-57.
2. Polaris Observatory, HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol. 2017;2(3):161-76.
3. Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, et al. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science. 1989;244(4902):359-62.
4. Alter MJ. HCV routes of transmission: what goes around comes around. Semin Liver Dis. 2011;31(4):340-6.
5. Nelson PK, Mathers BM, Cowie B, Hagan H, Des Jarlais D, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. Lancet. 2011;378(9791):571-83.
6. Degenhardt L, Peacock A, Colledge S, Leung J, Grebely J, et al. Global prevalence of injecting drug use and sociodemographic characteristics and prevalence of HIV, HBV, and HCV in people who inject drugs: a multistage systematic review. Lancet Glob Health. 2017;5(12):e1192-e207.
7. Esteban JI, Sauleda S, Quer J. The changing epidemiology of hepatitis C virus infection in Europe. J Hepatol. 2008;48(1):148-62.
8. Falla AM, Hofstraat SHI, Duffell E, Hahne SJM, Tavoschi L, et al. Hepatitis B/C in the countries of the EU/EEA: a systematic review of the prevalence among at-risk groups. BMC Infect Dis. 2018;18(1):79.
9. Hajarizadeh B, Grebely J, Dore GJ. Epidemiology and natural history of HCV infection. Nat Rev Gastroenterol Hepatol. 2013;10(9):553-62.
10. Smith DB, Bukh J, Kuiken C, Muerhoff AS, Rice CM, et al. Expanded classification of hepatitis C virus into 7 genotypes and 67 subtypes: updated criteria and genotype assignment web resource. Hepatology. 2014;59(1):318-27.
11. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, et al. 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. 2012;380(9859):2095-128.
12. Chen SL, Morgan TR. The natural history of hepatitis C virus (HCV) infection. Int J Med Sci. 2006;3(2):47-52.
13. Popescu CI, Riva L, Vlaicu O, Farhat R, Rouille Y, et al. Hepatitis C virus life cycle and lipid metabolism. Biology (Basel). 2014;3(4):892-921.
14. Naderi M, Gholipour N, Zolfaghari MR, Moradi Binabaj M, Yegane Moghadam A, et al. Hepatitis C virus and vaccine development. Int J Mol Cell Med. 2014;3(4):207-15.
15. Cox AL. HCV Vaccine Development: Where Do We Stand. 5th International Symposium on Hepatitis Care in Substance Users; 2016; Oslo, Norway.

16. Bailey JR, Barnes E, Cox AL. Approaches, Progress, and Challenges to Hepatitis C Vaccine Development. Gastroenterology. 2019;156(2):418-30.
17. Shoukry NH. Hepatitis C Vaccines, Antibodies, and T Cells. Front Immunol. 2018;9:1480.
18. Frey SE, Houghton M, Coates S, Abrignani S, Chien D, et al. Safety and immunogenicity of HCV E1E2 vaccine adjuvanted with MF59 administered to healthy adults. Vaccine. 2010;28(38):6367-73.
19. Law JL, Chen C, Wong J, Hockman D, Santer DM, et al. A hepatitis C virus (HCV) vaccine comprising envelope glycoproteins gpE1/gpE2 derived from a single isolate elicits broad cross-genotype neutralizing antibodies in humans. PLoS One. 2013;8(3):e59776.
20. Swadling L, Capone S, Antrobus RD, Brown A, Richardson R, et al. A human vaccine strategy based on chimpanzee adenoviral and MVA vectors that primes, boosts, and sustains functional HCV-specific T cell memory. Sci Transl Med. 2014;6(261):261ra153.
21. ClinicalTrials.gov. A Staged Phase I/II Study, to Assess Safety, Efficacy and Immunogenicity of a New Hepatitis C Prophylactic Vaccine Based on Sequential Use of AdCh3NSmut1 and MVA-NSmut 2018 [updated 17 August 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT01436357].
22. Pouget ER, Hagan H, Des Jarlais DC. Meta-analysis of hepatitis C seroconversion in relation to shared syringes and drug preparation equipment. Addiction. 2012;107(6):1057-65.
23. Scheinmann R, Hagan H, Lelutiu-Weinberger C, Stern R, Des Jarlais DC, et al. Non-injection drug use and Hepatitis C Virus: a systematic review. Drug Alcohol Depend. 2007;89(1):1-12.
24. Caiaffa WT, Zocratto KF, Osimani ML, Martinez PL, Radulich G, et al. Hepatitis C virus among non-injecting cocaine users (NICUs) in South America: can injectors be a bridge? Addiction. 2011;106(1):143-51.
25. Chan DP, Sun HY, Wong HT, Lee SS, Hung CC. Sexually acquired hepatitis C virus infection: a review. Int J Infect Dis. 2016;49:47-58.
26. Jordan AE, Perlman DC, Neurer J, Smith DJ, Des Jarlais DC, et al. Prevalence of hepatitis C virus infection among HIV+ men who have sex with men: a systematic review and meta-analysis. Int J STD AIDS. 2017;28(2):145-59.
27. Lee MH, Yang HI, Yuan Y, L'Italien G, Chen CJ. Epidemiology and natural history of hepatitis C virus infection. World J Gastroenterol. 2014;20(28):9270-80.
28. Centers for Disease Control and Prevention. What is the risk of infection after an occupational exposure? [updated July 2003. Available from: https://www.cdc.gov/hai/pdfs/bbp/exp_to_blood.pdf].
29. Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. J Viral Hepat. 2006;13(1):34-41.
30. Wiessing L, Ferri M, Grady B, Kantzanou M, Sperle I, et al. Hepatitis C virus infection epidemiology among people who inject drugs in Europe: a

systematic review of data for scaling up treatment and prevention. PLoS One. 2014;9(7):e103345.
31. Rodger AJ, Roberts S, Lanigan A, Bowden S, Brown T, et al. Assessment of long-term outcomes of community-acquired hepatitis C infection in a cohort with sera stored from 1971 to 1975. Hepatology. 2000;32(3):582-7.
32. Seeff LB. The history of the "natural history" of hepatitis C (1968-2009). Liver Int. 2009;29 Suppl 1:89-99.
33. Grebely J, Dore GJ. What is killing people with hepatitis C virus infection? Semin Liver Dis. 2011;31(4):331-9.
34. Freeman AJ, Dore GJ, Law MG, Thorpe M, Von Overbeck J, et al. Estimating progression to cirrhosis in chronic hepatitis C virus infection. Hepatology. 2001;34(4 Pt 1):809-16.
35. Garcia-Tsao G, Lim JK. Management and treatment of patients with cirrhosis and portal hypertension: recommendations from the Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program. Am J Gastroenterol. 2009;104(7):1802-29.
36. Garcia-Tsao G, Bosch J. Management of varices and variceal hemorrhage in cirrhosis. N Engl J Med. 2010;362(9):823-32.
37. Peters MG, Terrault NA. Alcohol use and hepatitis C. Hepatology. 2002;36(5 Suppl 1):S220-5.
38. Wiley TE, McCarthy M, Breidi L, Layden TJ. Impact of alcohol on the histological and clinical progression of hepatitis C infection. Hepatology. 1998;28(3):805-9.
39. Noda K, Yoshihara H, Suzuki K, Yamada Y, Kasahara A, et al. Progression of type C chronic hepatitis to liver cirrhosis and hepatocellular carcinoma--its relationship to alcohol drinking and the age of transfusion. Alcohol Clin Exp Res. 1996;20(1 Suppl):95A-100A.
40. Corrao G, Arico S. Independent and combined action of hepatitis C virus infection and alcohol consumption on the risk of symptomatic liver cirrhosis. Hepatology. 1998;27(4):914-9.
41. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet. 1997;349(9055):825-32.
42. Ryder SD, Irving WL, Jones DA, Neal KR, Underwood JC. Progression of hepatic fibrosis in patients with hepatitis C: a prospective repeat liver biopsy study. Gut. 2004;53(3):451-5.
43. Lesens O, Deschenes M, Steben M, Belanger G, Tsoukas CM. Hepatitis C virus is related to progressive liver disease in human immunodeficiency virus-positive hemophiliacs and should be treated as an opportunistic infection. J Infect Dis. 1999;179(5):1254-8.
44. Di Martino V, Rufat P, Boyer N, Renard P, Degos F, et al. The influence of human immunodeficiency virus coinfection on chronic hepatitis C in injection drug users: a long-term retrospective cohort study. Hepatology. 2001;34(6):1193-9.

45. Berenguer M, Ferrell L, Watson J, Prieto M, Kim M, et al. HCV-related fibrosis progression following liver transplantation: increase in recent years. J Hepatol. 2000;32(4):673-84.
46. Bjoro K, Froland SS, Yun Z, Samdal HH, Haaland T. Hepatitis C infection in patients with primary hypogammaglobulinemia after treatment with contaminated immune globulin. N Engl J Med. 1994;331(24):1607-11.
47. Fartoux L, Poujol-Robert A, Guechot J, Wendum D, Poupon R, et al. Insulin resistance is a cause of steatosis and fibrosis progression in chronic hepatitis C. Gut. 2005;54(7):1003-8.
48. D'Souza R, Sabin CA, Foster GR. Insulin resistance plays a significant role in liver fibrosis in chronic hepatitis C and in the response to antiviral therapy. Am J Gastroenterol. 2005;100(7):1509-15.
49. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;385(9963):117-71.
50. Innes H, Hutchinson SJ, Obel N, Christensen PB, Aspinall EJ, et al. Liver mortality attributable to chronic hepatitis C virus infection in Denmark and Scotland--using spontaneous resolvers as the benchmark comparator. Hepatology. 2016;63(5):1506-16.
51. Grebely J, Raffa JD, Lai C, Kerr T, Fischer B, et al. Impact of hepatitis C virus infection on all-cause and liver-related mortality in a large community-based cohort of inner city residents. J Viral Hepat. 2011;18(1):32-41.
52. Degenhardt L, Randall D, Hall W, Law M, Butler T, et al. Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: risk factors and lives saved. Drug Alcohol Depend. 2009;105(1-2):9-15.
53. Beutels M, Van Damme P, Aelvoet W, Desmyter J, Dondeyne F, et al. Prevalence of hepatitis A, B and C in the Flemish population. Eur J Epidemiol. 1997;13(3):275-80.
54. Quoilin S, Hutse V, Vandenberghe H, Claeys F, Verhaegen E, et al. A population-based prevalence study of hepatitis A, B and C virus using oral fluid in Flanders, Belgium. Eur J Epidemiol. 2007;22(3):195-202.
55. Gerkens S, Martin NK, Thiry N, Hulstaert F. [Hepatitis C: screening and prevention] HEPATITIS C: SCREENING EN PREVENTIE. Belgian Health Care Knowledge Center (KCE), 2012.
56. Litzroth A, Suin V, Wyndham-Thomas C, Quoilin S, Muyldermans G, et al. Low hepatitis C prevalence in Belgium: implications for treatment reimbursement and scale up. BMC Public Health. 2019;19(1):39.
57. Mathei C, Robaeys G, van Damme P, Buntinx F, Verrando R. Prevalence of hepatitis C in drug users in Flanders: determinants and geographic differences. Epidemiol Infect. 2005;133(1):127-36.
58. Plasschaert S, Ameye L, De Clercq T, Walckiers D, Sartor F, et al. Study on HCV, HBV and HIV seroprevalence in a sample of drug users in contact with treatment centres or in prisons in Belgium, 2004-2005. Brussels: Scientific Institute of Public Health. 2005.

59. Bollaerts K, Van Bussel JCH. Ontwikkeling en Validatie van een Serologisch en Gedragsgerelateerd Studieprotocol naar HCV-, HBV- en HIV-infecties bij Recent Injecterende Drugsgebruikers tot Realisatie van de Registratie van de Drugs Related Infectious Diseases (DRID). Brussels: WIV-ISP. 2012.
60. Micalessi MI, Gerard C, Ameye L, Plasschaert S, Brochier B, et al. Distribution of hepatitis C virus genotypes among injecting drug users in contact with treatment centers in Belgium, 2004-2005. J Med Virol. 2008;80(4):640-5.
61. Verbeeck J, Kwanten L, D'Heygere F, Beguin A, Michiels S, et al. HCV genotype distribution in Flanders and Brussels (Belgium): unravelling the spread of an uncommon HCV genotype 5a cluster. Eur J Clin Microbiol Infect Dis. 2010;29(11):1427-34.
62. Mathei C, Wollants E, Verbeeck J, Van Ranst M, Robaeys G, et al. Molecular epidemiology of hepatitis C among drug users in Flanders, Belgium: association of genotype with clinical parameters and with sex- and drug-related risk behaviours. Eur J Clin Microbiol Infect Dis. 2005;24(8):514-22.
63. De Maeght S, Henrion J, Bourgeois N, de Galocsy C, Langlet P, et al. A pilot observational survey of hepatitis C in Belgium. Acta Gastroenterol Belg. 2008;71(1):4-8.
64. Henrion J, De Maeght S, Deltenre P, Ghilain JM, Maisin JM, et al. Impact of hepatitis C virus infection on the aetiology of cirrhosis and hepatocarcinoma in three affiliated hospitals in southern Belgium. Acta Gastroenterol Belg. 2002;65(2):80-2.
65. Van Vlierberghe H, Colle I, Henrion J, Michielsen P, Delwaide J, et al. The HepCar registry: report on a one-year registration program of hepatocellular carcinoma (HCC) in Belgium. What is daily practice in HCC? Acta Gastroenterol Belg. 2005;68(4):403-11.
66. Bruggmann P, Berg T, Ovrehus AL, Moreno C, Brandao Mello CE, et al. Historical epidemiology of hepatitis C virus (HCV) in selected countries. J Viral Hepat. 2014;21 (Suppl 1):5-33.
67. EASL. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. J Hepatol. 2014;60(2):392-420.
68. Wong VW, Wong GL, Chim AM, Cheng TF, Cheung SW, et al. Targeted hepatitis C screening among ex-injection drug users in the community. J Gastroenterol Hepatol. 2014;29(1):116-20.
69. Jewett A, Smith BD, Garfein RS, Cuevas-Mota J, Teshale EH, et al. Field-based performance of three pre-market rapid hepatitis C virus antibody assays in STAHR (Study to Assess Hepatitis C Risk) among young adults who inject drugs in San Diego, CA. J Clin Virol. 2012;54(3):213-7.
70. Smith BD, Drobeniuc J, Jewett A, Branson BM, Garfein RS, et al. Evaluation of three rapid screening assays for detection of antibodies to hepatitis C virus. J Infect Dis. 2011;204(6):825-31.
71. Tuaillon E, Mondain AM, Meroueh F, Ottomani L, Picot MC, et al. Dried blood spot for hepatitis C virus serology and molecular testing. Hepatology. 2010;51(3):752-8.

72. Martin NK, Hickman M, Miners A, Hutchinson SJ, Taylor A, et al. Cost-effectiveness of HCV case-finding for people who inject drugs via dried blood spot testing in specialist addiction services and prisons. BMJ Open. 2013;3(8).
73. National Institute for Health and care Excellence. The OraQuick HCV point-of-care test for rapid detection of hepatitis C virus antibodies 2015 [Available from: https://www.nice.org.uk/guidance/mib24/resources/the-oraquick-hcv-pointofcare-test-for-rapid-detection-of-hepatitisc-virus-antibodies-63499045128901].
74. Drobnik A, Judd C, Banach D, Egger J, Konty K, et al. Public health implications of rapid hepatitis C screening with an oral swab for community-based organizations serving high-risk populations. Am J Public Health. 2011;101(11):2151-5.
75. OraSure Technologies, Inc. The OraQuick® HCV test is for detecting HCV antibodies in fingerstick and venipuncture whole blood 2013 [Available from: http://www.orasure.com/products-infectious/products-infectious-oraquick-hcv.asp].
76. Gao F, Talbot EA, Loring CH, Power JJ, Dionne-Odom J, et al. Performance of the OraQuick HCV rapid antibody test for screening exposed patients in a hepatitis C outbreak investigation. J Clin Microbiol. 2014;52(7):2650-2.
77. Pallares C, Carvalho-Gomes A, Hontangas V, Conde I, Di Maira T, et al. Performance of the OraQuick Hepatitis C virus antibody test in oral fluid and fingerstick blood before and after treatment-induced viral clearance. J Clin Virol. 2018;102:77-83.
78. Dokubo EK, Evans J, Winkelman V, Cyrus S, Tobler LH, et al. Comparison of Hepatitis C Virus RNA and antibody detection in dried blood spots and plasma specimens. J Clin Virol. 2014;59(4):223-7.
79. Bennett S, Gunson RN, McAllister GE, Hutchinson SJ, Goldberg DJ, et al. Detection of hepatitis C virus RNA in dried blood spots. J Clin Virol. 2012;54(2):106-9.
80. Greenman J, Roberts T, Cohn J, Messac L. Dried blood spot in the genotyping, quantification and storage of HCV RNA: a systematic literature review. J Viral Hepat. 2015;22(4):353-61.
81. Thimme R, Oldach D, Chang KM, Steiger C, Ray SC, et al. Determinants of viral clearance and persistence during acute hepatitis C virus infection. J Exp Med. 2001;194(10):1395-406.
82. WHO. Guidelines for the screening, care and treatment of persons with chronic hepatitis C infection. Updated version, April 2016 2016 [Available from: http://www.who.int/hepatitis/publications/hepatitis-c-guidelines-2016/en/].
83. Afdhal NH, Bacon BR, Patel K, Lawitz EJ, Gordon SC, et al. Accuracy of Fibroscan, Compared with Histology, in Analysis of Liver Fibrosis in Patients with Hepatitis B or C: A US Multi-center Study. Clin Gastroenterol Hepatol. 2014;13(4):772-9.e1-3.

84. Xie Q, Zhou X, Huang P, Wei J, Wang W, et al. The performance of enhanced liver fibrosis (ELF) test for the staging of liver fibrosis: a meta-analysis. PLoS One. 2014;9(4):e92772.
85. Martinot-Peignoux M, Stern C, Maylin S, Ripault MP, Boyer N, et al. Twelve weeks posttreatment follow-up is as relevant as 24 weeks to determine the sustained virologic response in patients with hepatitis C virus receiving pegylated interferon and ribavirin. Hepatology. 2010;51(4):1122-6.
86. Swain MG, Lai MY, Shiffman ML, Cooksley WG, Zeuzem S, et al. A sustained virologic response is durable in patients with chronic hepatitis C treated with peginterferon alfa-2a and ribavirin. Gastroenterology. 2010;139(5):1593-601.
87. Hoofnagle JH, Mullen KD, Jones DB, Rustgi V, Di Bisceglie A, 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):1575-8.
88. Antaki N, Craxi A, Kamal S, Moucari R, Van der Merwe S, et al. The neglected hepatitis C virus genotypes 4, 5 and 6: an international consensus report. Liver Int. 2010;30(3):342-55.
89. Te HS, Randall G, Jensen DM. Mechanism of action of ribavirin in the treatment of chronic hepatitis C. Gastroenterol Hepatol (N Y). 2007;3(3):218-25.
90. Chung RT, Gale M, Jr., Polyak SJ, Lemon SM, Liang TJ, et al. Mechanisms of action of interferon and ribavirin in chronic hepatitis C: Summary of a workshop. Hepatology. 2008;47(1):306-20.
91. Bonnet D, Guivarch M, Berard E, Combis JM, Remy AJ, et al. Telaprevir- and boceprevir-based tritherapies in real practice for F3-F4 pretreated hepatitis C virus patients. World J Hepatol. 2014;6(9):660-9.
92. Kayali Z, Schmidt WN. Finally sofosbuvir: an oral anti-HCV drug with wide performance capability. Pharmgenomics Pers Med. 2014;7:387-98.
93. Yau AH, Yoshida EM. Hepatitis C drugs: the end of the pegylated interferon era and the emergence of all-oral interferon-free antiviral regimens: a concise review. Can J Gastroenterol Hepatol. 2014;28(8):445-51.
94. EASL. EASL Recommendations on Treatment of Hepatitis C 2015. J Hepatol. 2015;63(1):199-236.
95. Kim DY, Ahn SH, Han KH. Emerging Therapies for Hepatitis C. Gut Liver. 2014;8(5):471-9.
96. Lalezari J, Sullivan JG, Varunok P, Galen E, Kowdley KV, et al. Ombitasvir/paritaprevir/r and dasabuvir plus ribavirin in HCV genotype 1-infected patients on methadone or buprenorphine. J Hepatol. 2015;63(2):364-9.
97. Litwin A. High rates of sustained virological response in people who inject drugs treated with sofosbuvir-based regimens. 4th International Symposium on Health Care in Substance Users; 2015; Sydney, Australia.
98. Puoti M, Cooper C, Sulkowski M, Foster GR, Berg T, et al. ABT-450/r/Ombitasvir + Dasabuvir with or without ribavirin in HCV Genotype 1-infected patients receiving stable opioid substitution treatment: Pooled analysis

of efficacy and safety in Phase 2 and Phase 3 trials. AASLD: The liver meeting. 2014, Boston, Massachusetts, USA.
99. Litwin AH, Agyemang L, Akiyama M, Feinstein A, Heo M, et al. High rates of sustained virological response in people who inject drugs treated with all-oral direct acting antiviral regimens. 5th International Symposium on Hepatitis Care in Substance Users; 2016; Oslo, Norway.
100. Hull L, Gallagher L, Pare D, Kason D, Persaud S, et al. Real-world outcomes of direct-acting antiviral therapy (DAA's) amongst persons who inject drugs treated in an inner city hepatitis C program in Vancouver, Canada. 5th International Symposium on Hepatitis Care in Substance Users; 2016; Oslo, Norway.
101. The European Medicines Agency (EMA) 2018 [Available from: https://www.ema.europa.eu/en/search/search/ema_editorial_content/ema_news?search_api_views_fulltext=hepatitis%20C].
102. EASL. EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol. 2017;66(1):153-94.
103. EASL. EASL Recommendations on Treatment of Hepatitis C 2018. J Hepatol. 2018;69(2):461-511.
104. Bruno R, Cima S, Maiocchi L, Sacchi P. Forthcoming challenges in the management of direct-acting antiviral agents (DAAs) for hepatitis C. Dig Liver Dis. 2011;43(5):337-44.
105. Holmes JA, Thompson AJ. Interferon-free combination therapies for the treatment of hepatitis C: current insights. Hepat Med. 2015;7:51-70.
106. Perales C, Quer J, Gregori J, Esteban JI, Domingo E. Resistance of Hepatitis C Virus to Inhibitors: Complexity and Clinical Implications. Viruses. 2015;7(11):5746-66.
107. FDA. Approved Treatments for Hepatitis C 2016 [Available from: http://hepatitiscnewdrugresearch.com/approved-treatments-for-hepatitis-c.html].
108. Gilead Sciences Inc. Chronic hepatitis C treatment expansion: generic manufacturing for developing countries 2015 [Available from: http://www.gilead.com/~/media/files/pdfs/other/hcv%20generic%20agreement%20fast%20facts%20101615.pdf?la=en].
109. The Belgian Association for the Study of the Liver. Treatment options and diagnostic cut-offs for HCV in Belgium 2015 [Available from: http://basl.be/sites/default/files/Belgian%20HCV%20therapy%20guidance%20update%20v24082016.pdf].
110. RIZIV. Rijksinstituut voor ziekte- en invaliditeitsverzekering. Antivirale geneesmiddelen tegen hepatitis C: vergoedingsvoorwaarden vanaf 1 januari 2019 [updated 13 December 2018. Available from: https://www.riziv.fgov.be/nl/themas/kost-terugbetaling/door ziekenfonds /geneesmiddel-gezondheidsproduct/ terugbetalen/specialiteiten /wijzigingen /Paginas/antivirale-hepatitisc-terugbetalingsvoorwaarden_20190101.aspx].
111. Federale overheidsdienst sociale zekerheid. 189e jaargang, 21 Januari 2019. Belgisch Staatsblad. p. 7345-66.

112. Grandhe S, Frenette CT. Occurrence and Recurrence of Hepatocellular Carcinoma After Successful Direct-Acting Antiviral Therapy for Patients With Chronic Hepatitis C Virus Infection. Gastroenterol Hepatol (N Y). 2017;13(7):421-5.
113. Conti F, Buonfiglioli F, Scuteri A, Crespi C, Bolondi L, et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. J Hepatol. 2016;65(4):727-33.
114. Bielen R, Moreno C, Van Vlierberghe H, Bourgeois S, Mulkay JP, et al. The risk of early occurrence and recurrence of hepatocellular carcinoma in hepatitis C-infected patients treated with direct-acting antivirals with and without pegylated interferon: A Belgian experience. J Viral Hepat. 2017;24(11):976-81.
115. Arain A, Robaeys G. Eligibility of persons who inject drugs for treatment of hepatitis C virus infection. World J Gastroenterol. 2014;20(36):12722-33.
116. UNODC. United Nations Office on Drugs and Crime, World Drug Report 2015 [updated May 2015. Available from: https://www.unodc.org/documents/wdr2015/World_Drug_Report_2015.pdf].
117. EMCDDA. European Monitoring Centre for Drugs and Drug Addiction. European Drug Report 2015: Trends and Developments 2015 [Available from: http://www.emcdda.europa.eu/publications/edr/trends-developments/2015].
118. Bollaerts K, Aerts M, Sasse A. Improved benchmark-multiplier method to estimate the prevalence of ever-injecting drug use in Belgium, 2000-10. Arch Public Health. 2013;71(1):10.
119. EMCDDA. European Monitoring Centre for Drugs and Drug Addiction. Country overview: Belgium. Key statistics on the drug situation in Belgium; 2014 [Available from: http://www.emcdda.europa.eu/countries/belgium].
120. Plettinckx E, Antoine J, Blanckaert P, De Ridder K, Vander Laenen F, et al. Belgian National Report on drugs 2014, New Developments and Trends. WIVISP, Brussels. 2014.
121. Mathei C, Bourgeois S, Blach S, Brixko C, Mulkay JP, et al. Mitigating the burden of hepatitis C virus among people who inject drugs in Belgium. Acta Gastroenterol Belg. 2016;79(2):227-32.
122. Martin NK, Hickman M, Hutchinson SJ, Goldberg DJ, Vickerman P. Combination interventions to prevent HCV transmission among people who inject drugs: modeling the impact of antiviral treatment, needle and syringe programs, and opiate substitution therapy. Clin Infect Dis. 2013;57 (Suppl 2):S39-45.
123. Larney S, Grebely J, Falster M, Swart A, Amin J, et al. Opioid substitution therapy is associated with increased detection of hepatitis C virus infection: A 15-year observational cohort study. Drug Alcohol Depend. 2015;148:213-6.
124. White B, Dore GJ, Lloyd AR, Rawlinson WD, Maher L. Opioid substitution therapy protects against hepatitis C virus acquisition in people who inject drugs: the HITS-c study. Med J Aust. 2014;201(6):326-9.
125. Aspinall EJ, Corson S, Doyle JS, Grebely J, Hutchinson SJ, et al. Treatment of hepatitis C virus infection among people who are actively injecting

drugs: a systematic review and meta-analysis. Clin Infect Dis. 2013;57 (Suppl 2):S80-9.
126. Dimova RB, Zeremski M, Jacobson IM, Hagan H, Des Jarlais DC, et al. Determinants of hepatitis C virus treatment completion and efficacy in drug users assessed by meta-analysis. Clin Infect Dis. 2013;56(6):806-16.
127. Hellard M, Sacks-Davis R, Gold J. Hepatitis C treatment for injection drug users: a review of the available evidence. Clin Infect Dis. 2009;49(4):561-73.
128. Robaeys G, Grebely J, Mauss S, Bruggmann P, Moussalli J, et al. Recommendations for the management of hepatitis C virus infection among people who inject drugs. Clin Infect Dis. 2013;57 (Suppl 2):S129-37.
129. Manns MP, Wedemeyer H, Cornberg M. Treating viral hepatitis C: efficacy, side effects, and complications. Gut. 2006;55(9):1350-9.
130. Robaeys G, Van Vlierberghe H, Mathei C, Van Ranst M, Bruckers L, et al. Similar compliance and effect of treatment in chronic hepatitis C resulting from intravenous drug use in comparison with other infection causes. Eur J Gastroenterol Hepatol. 2006;18(2):159-66.
131. Litwin AH, Soloway IJ, Cockerham-Colas L, Reynoso S, Heo M, 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.
132. Cunningham EB, Amin J, Feld JJ, Bruneau J, Dalgard O, et al. Adherence to sofosbuvir and velpatasvir among people with chronic HCV infection and recent injection drug use: The SIMPLIFY study. Int J Drug Policy. 2018;62:14-23.
133. Mason K, Dodd Z, Guyton M, Tookey P, Lettner B, et al. Understanding real-world adherence in the directly acting antiviral era: A prospective evaluation of adherence among people with a history of drug use at a community-based program in Toronto, Canada. Int J Drug Policy. 2017;47:202-8.
134. Bielen R, Moreno C, Van Vlierberghe H, Bourgeois S, Mulkay JP, et al. Belgian experience with direct acting antivirals in people who inject drugs. Drug Alcohol Depend. 2017;177:214-20.
135. Cunningham EB, Applegate TL, Lloyd AR, Dore GJ, Grebely J. Mixed HCV infection and reinfection in people who inject drugs--impact on therapy. Nat Rev Gastroenterol Hepatol. 2015;12(4):218-30.
136. Midgard H. Hepatitis C virus reinfection after successful treatment among PWID: clinical and public health implications. 5th International Symposium on Hepatitis Care in Substance Users; 2016; Oslo, Norway.
137. Midgard H, Bjoro B, Maeland A, Konopski Z, Kileng H, et al. Hepatitis C reinfection after sustained virological response. J Hepatol. 2016;64(5):1020-6.
138. Larney S, Kopinski H, Beckwith CG, Zaller ND, Jarlais DD, et al. Incidence and prevalence of hepatitis C in prisons and other closed settings: results of a systematic review and meta-analysis. Hepatology. 2013;58(4):1215-24.
139. Dolan K, Wirtz AL, Moazen B, Ndeffo-Mbah M, Galvani A, et al. Global burden of HIV, viral hepatitis, and tuberculosis in prisoners and detainees. Lancet. 2016;388(10049):1089-102.

140. Zampino R, Coppola N, Sagnelli C, Di Caprio G, Sagnelli E. Hepatitis C virus infection and prisoners: Epidemiology, outcome and treatment. World J Hepatol. 2015;7(21):2323-30.
141. Vescio MF, Longo B, Babudieri S, Starnini G, Carbonara S, et al. Correlates of hepatitis C virus seropositivity in prison inmates: a meta-analysis. J Epidemiol Community Health. 2008;62(4):305-13.
142. Awofeso N. Prisons as social determinants of hepatitis C virus and tuberculosis infections. Public Health Rep. 2010;125 (Suppl 4):25-33.
143. Post JJ, Arain A, Lloyd AR. Enhancing assessment and treatment of hepatitis C in the custodial setting. Clin Infect Dis. 2013;57 (Suppl 2):S70-4.
144. Bielen R, Stumo SR, Halford R, Werling K, Reic T, et al. Harm reduction and viral hepatitis C in European prisons: a cross-sectional survey of 25 countries. Harm Reduct J. 2018;15(1):25.
145. Mehta SH, Genberg BL, Astemborski J, Kavasery R, Kirk GD, et al. Limited uptake of hepatitis C treatment among injection drug users. J Community Health. 2008;33(3):126-33.
146. Zeremski M, Dimova RB, Zavala R, Kritz S, Lin M, et al. Hepatitis C virus-related knowledge and willingness to receive treatment among patients on methadone maintenance. J Addict Med. 2014;8(4):249-57.
147. Grebely J, Knight E, Genoway KA, Viljoen M, Khara M, et al. Optimizing assessment and treatment for hepatitis C virus infection in illicit drug users: a novel model incorporating multidisciplinary care and peer support. Eur J Gastroenterol Hepatol. 2010;22(3):270-7.
148. Litwin AH, Harris KA, Jr., Nahvi S, Zamor PJ, Soloway IJ, et al. Successful treatment of chronic hepatitis C with pegylated interferon in combination with ribavirin in a methadone maintenance treatment program. J Subst Abuse Treat. 2009;37(1):32-40.
149. Curcio F, Di Martino F, Capraro C, Angelucci F, Bulla F, et al. Together ... to take care: multidisciplinary management of hepatitis C virus treatment in randomly selected drug users with chronic hepatitis. J Addict Med. 2010;4(4):223-32.
150. Hill WD, Butt G, Alvarez M, Krajden M. Capacity enhancement of hepatitis C virus treatment through integrated, community-based care. Can J Gastroenterol. 2008;22(1):27-32.
151. Bruggmann P, Litwin AH. Models of care for the management of hepatitis C virus among people who inject drugs: one size does not fit all. Clin Infect Dis. 2013;57 (Suppl 2):S56-61.
152. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis. 2005;5(9):558-67.
153. Robaeys G, Buntinx F. Treatment of hepatitis C viral infections in substance abusers. Acta Gastroenterol Belg. 2005;68(1):55-67.
154. Grebely J, Robaeys G, Bruggmann P, Aghemo A, Backmund M, et al. Recommendations for the management of hepatitis C virus infection among people who inject drugs. Int J Drug Policy. 2015;26(10):1028-38.

155. AASLD/IDSA. Recommendations for testing, managing, and treating hepatitis C 2015 [Available from: www.hcvguidelines.org].
156. Grebely J, Raffa JD, Lai C, Krajden M, Kerr T, et al. Low uptake of treatment for hepatitis C virus infection in a large community-based study of inner city residents. J Viral Hepat. 2009;16(5):352-8.
157. Grebely J, Petoumenos K, Matthews GV, Haber P, Marks P, et al. Factors associated with uptake of treatment for recent hepatitis C virus infection in a predominantly injecting drug user cohort: The ATAHC Study. Drug Alcohol Depend. 2010;107(2-3):244-9.
158. Strathdee SA, Latka M, Campbell J, O'Driscoll PT, Golub ET, et al. Factors associated with interest in initiating treatment for hepatitis C Virus (HCV) infection among young HCV-infected injection drug users. Clin Infect Dis. 2005;40 (Suppl 5):S304-12.
159. Lindenburg CE, Lambers FA, Urbanus AT, Schinkel J, Jansen PL, et al. Hepatitis C testing and treatment among active drug users in Amsterdam: results from the DUTCH-C project. Eur J Gastroenterol Hepatol. 2011;23(1):23-31.
160. Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. Arch Intern Med. 1998;158(16):1789-95.
161. Lawrinson P, Copeland J, Indig D. Development and validation of a brief instrument for routine outcome monitoring in opioid maintenance pharmacotherapy services: the brief treatment outcome measure (BTOM). Drug Alcohol Depend. 2005;80(1):125-33.
162. Henry JD, Crawford JR. The short-form version of the Depression Anxiety Stress Scales (DASS-21): construct validity and normative data in a large non-clinical sample. Br J Clin Psychol. 2005;44(Pt 2):227-39.
163. Alavi M, Raffa JD, Deans GD, Lai C, Krajden M, et al. Continued low uptake of treatment for hepatitis C virus infection in a large community-based cohort of inner city residents. Liver Int. 2014;34(8):1198-206.
164. Martinez AD, Dimova R, Marks KM, Beeder AB, Zeremski M, et al. Integrated internist - addiction medicine - hepatology model for hepatitis C management for individuals on methadone maintenance. J Viral Hepat. 2012;19(1):47-54.
165. Alavi M, Grebely J, Micallef M, Dunlop AJ, Balcomb AC, et al. Assessment and treatment of hepatitis C virus infection among people who inject drugs in the opioid substitution setting: ETHOS study. Clin Infect Dis. 2013;57 (Suppl 2):S62-9.
166. Charlebois A, Lee L, Cooper E, Mason K, Powis J. Factors associated with HCV antiviral treatment uptake among participants of a community-based HCV programme for marginalized patients. J Viral Hepat. 2012;19(12):836-42.

167. Seidenberg A, Rosemann T, Senn O. Patients receiving opioid maintenance treatment in primary care: successful chronic hepatitis C care in a real world setting. BMC Infect Dis. 2013;13:9.
168. Mathei. C. Personal communication with author (Arain A.). Contraindication for antiviral treatment according to the addiction care physicians. 2016.
169. Gidding HF, Law MG, Amin J, Macdonald GA, Sasadeusz JJ, et al. Predictors of deferral of treatment for hepatitis C infection in Australian clinics. Med J Aust. 2011;194(8):398-402.
170. Stoove MA, Gifford SM, Dore GJ. The impact of injecting drug use status on hepatitis C-related referral and treatment. Drug Alcohol Depend. 2005;77(1):81-6.
171. Myles A, Mugford GJ, Zhao J, Krahn M, Wang PP. Physicians' attitudes and practice toward treating injection drug users with hepatitis C: results from a national specialist survey in Canada. Can J Gastroenterol. 2011;25(3):135-9.
172. Jack K, Willott S, Manners J, Varnam MA, Thomson BJ. Clinical trial: a primary-care-based model for the delivery of anti-viral treatment to injecting drug users infected with hepatitis C. Aliment Pharmacol Ther. 2009;29(1):38-45.
173. WHO. Hepatitis C. Fact Sheet No. 164 2014 [updated April 2014. Available from: http://www.who.int/mediacentre/factsheets/fs164/].
174. EASL. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. J Hepatol 2011; 55(2):245-64.
175. Ghany MG, Nelson DR, Strader DB, Thomas DL, Seeff LB, et al. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology. 2011;54(4):1433-44.
176. FDA. FDA news release. FDA approves Victrelis for Hepatitis C 2011 [Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2011/ucm255390.htm].
177. FDA. FDA approved drug products 2014 [Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails].
178. The University of Liverpool and eMedFusion. HEP drug interactions 2014 [Available from: http://www.hep-druginteractions.org/].
179. Feeney ER, Chung RT. Antiviral treatment of hepatitis C. BMJ. 2014;348:g3308.
180. Robaeys G, Nevens F, Starkel P, Colle I, Van Eyken P, et al. Previous intravenous substance use and outcome of liver transplantation in patients with chronic hepatitis C infection. Transplant Proc. 2009;41(2):589-94.
181. Grady BP, Schinkel J, Thomas XV, Dalgard O. Hepatitis C virus reinfection following treatment among people who use drugs. Clin Infect Dis. 2013;57 (Suppl 2):S105-10.

182. Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatology. 1996;24(2):289-93.
183. Hezode C, Forestier N, Dusheiko G, Ferenci P, Pol S, et al. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. N Engl J Med. 2009;360(18):1839-50.
184. McHutchison JG, Everson GT, Gordon SC, Jacobson IM, Sulkowski M, et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. N Engl J Med. 2009;360(18):1827-38.
185. Kwo PY, Lawitz EJ, McCone J, Schiff ER, Vierling JM, et al. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naive patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial. Lancet. 2010;376(9742):705-16.
186. McHutchison JG, Manns MP, Muir AJ, Terrault NA, Jacobson IM, et al. Telaprevir for previously treated chronic HCV infection. N Engl J Med. 2010;362(14):1292-303.
187. Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med. 2011;364(13):1207-17.
188. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med. 2011;364(25):2405-16.
189. Poordad F, McCone J, Jr., Bacon BR, Bruno S, Manns MP, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. 2011;364(13):1195-206.
190. Kumada H, Toyota J, Okanoue T, Chayama K, Tsubouchi H, et al. Telaprevir with peginterferon and ribavirin for treatment-naive patients chronically infected with HCV of genotype 1 in Japan. J Hepatol. 2012;56(1):78-84.
191. Silini E, Bono F, Cividini A, Cerino A, Maccabruni A, et al. Molecular epidemiology of hepatitis C virus infection among intravenous drug users. J Hepatol. 1995;22(6):691-5.
192. Love A, Sigurdsson JR, Stanzeit B, Briem H, Rikardsdottir H, et al. Characteristics of hepatitis C virus among intravenous drug users in Iceland. Am J Epidemiol. 1996;143(6):631-6.
193. Lewis H, Igbe R, Wilkinson M. Active injection drug use can be successfully treated for HCV and significantly reduce illicit drug use post treatment: real life cohort of 152 patients. J Hepatol 2012;56 (Suppl 2):S446.
194. Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, et al. Telaprevir for retreatment of HCV infection. N Engl J Med. 2011;364(25):2417-28.
195. Hulskotte E, Feng H, Bruce D, Webster L, Xuan F, et al. Pharmacokinetic interaction between HCV protease inhibitor boceprevir and methadone or buprenorphine in subjects on stable maintenance therapy. Abstract PK 09. In:

Seventh International Workshop on Clinical Pharmacology of Hepatitis Therapy, 27-28 June 2012 Cambridge, USA.
196. Luo X, Trevejo J, van Heeswijk R, Smith F, Garg V. Effect of telaprevir on the pharmacokinetics of buprenorphine in volunteers on stable buprenorphine/naloxone maintenance therapy. Antimicrob Agents Chemother. 2012;56(7):3641-7.
197. van Heeswijk R, Verboven P, Vandevoorde A, Vinck P, Snoeys J, et al. Pharmacokinetic interaction between telaprevir and methadone. Antimicrob Agents Chemother. 2013;57(5):2304-9.
198. Mauss S, Klinker H. Drug-drug interactions in the treatment of HCV among people who inject drugs. Clin Infect Dis. 2013;57 (Suppl 2):S125-8.
199. Maasoumy B, Port K, Deterding K, Honer Zu Siederdissen C, Markova AA, et al. Limited effectiveness and safety profile of protease inhibitor-based triple therapy against chronic hepatitis C in a real-world cohort with a high proportion of advanced liver disease. Eur J Gastroenterol Hepatol. 2014;26(8):836-45.
200. Vierling JM, Davis M, Flamm S, Gordon SC, Lawitz E, et al. Boceprevir for chronic HCV genotype 1 infection in patients with prior treatment failure to peginterferon/ribavirin, including prior null response. J Hepatol. 2014;60(4):748-56.
201. Denniston MM, Klevens RM, McQuillan GM, Jiles RB. Awareness of infection, knowledge of hepatitis C, and medical follow-up among individuals testing positive for hepatitis C: National Health and Nutrition Examination Survey 2001-2008. Hepatology. 2012;55(6):1652-61.
202. Fusfeld L, Aggarwal J, Dougher C, Vera-Llonch M, Bubb S, et al. Assessment of motivating factors associated with the initiation and completion of treatment for chronic hepatitis C virus (HCV) infection. BMC Infect Dis. 2013;13:234.
203. Solomon SS, Mehta SH, Srikrishnan AK, Solomon S, McFall AM, et al. Burden of hepatitis C virus disease and access to hepatitis C virus services in people who inject drugs in India: a cross-sectional study. Lancet Infect Dis. 2015;15(1):36-45.
204. Edlin BR, Kresina TF, Raymond DB, Carden MR, Gourevitch MN, et al. Overcoming barriers to prevention, care, and treatment of hepatitis C in illicit drug users. Clin Infect Dis. 2005;40 (Suppl 5):S276-85.
205. Roose RJ, Cockerham-Colas L, Soloway I, Batchelder A, Litwin AH. Reducing barriers to hepatitis C treatment among drug users: an integrated hepatitis C peer education and support program. J Health Care Poor Underserved. 2014;25(2):652-62.
206. Beste LA, Straits-Troster K, Zickmund S, Larson M, Chapko M, et al. Specialty care and education associated with greater disease-specific knowledge but not satisfaction with care for chronic hepatitis C. Aliment Pharmacol Ther. 2009;30(3):275-82.

207. Gupta K, Romney D, Briggs M, Benker K. Effects of a brief educational program on knowledge and willingness to accept treatment among patients with hepatitis C at inner-city hospitals. J Community Health. 2007;32(4):221-30.
208. Lubega S, Agbim U, Surjadi M, Mahoney M, Khalili M. Formal hepatitis C education enhances HCV care coordination, expedites HCV treatment and improves antiviral response. Liver Int. 2013;33(7):999-1007.
209. Nyamathi A, Tyler D, Sinha K, Marfisee M, Cohen A, et al. Predictors of hepatitis knowledge improvement among methadone maintained clients enrolled in a hepatitis intervention program. J Community Health. 2010;35(4):423-32.
210. Proeschold-Bell RJ, Hoeppner B, Taylor B, Cohen S, Blouin R, et al. An interrupted time series evaluation of a hepatitis C intervention for persons with HIV. AIDS Behav. 2011;15(8):1721-31.
211. Shah HA, Abu-Amara M. Education provides significant benefits to patients with hepatitis B virus or hepatitis C virus infection: a systematic review. Clin Gastroenterol Hepatol. 2013;11(8):922-33.
212. Surjadi M, Torruellas C, Ayala C, Yee HF, Jr., Khalili M. Formal patient education improves patient knowledge of hepatitis C in vulnerable populations. Dig Dis Sci. 2011;56(1):213-9.
213. Skipper C, Guy JM, Parkes J, Roderick P, Rosenberg WM. Evaluation of a prison outreach clinic for the diagnosis and prevention of hepatitis C: implications for the national strategy. Gut. 2003;52(10):1500-4.
214. Cacoub P, Ouzan D, Melin P, Lang JP, Rotily M, et al. Patient education improves adherence to peg-interferon and ribavirin in chronic genotype 2 or 3 hepatitis C virus infection: a prospective, real-life, observational study. World J Gastroenterol. 2008;14(40):6195-203.
215. Larrey D, Salse A, Ribard D, Boutet O, Hyrailles-Blanc V, et al. Education by a nurse increases response of patients with chronic hepatitis C to therapy with peginterferon-alpha2a and ribavirin. Clin Gastroenterol Hepatol. 2011;9(9):781-5.
216. Mateu-Gelabert P, Gwadz MV, Guarino H, Sandoval M, Cleland CM, et al. The staying safe intervention: training people who inject drugs in strategies to avoid injection-related HCV and HIV infection. AIDS Educ Prev. 2014;26(2):144-57.
217. Geibel S, King'ola N, Temmerman M, Luchters S. The impact of peer outreach on HIV knowledge and prevention behaviours of male sex workers in Mombasa, Kenya. Sex Transm Infect. 2012;88(5):357-62.
218. Treloar C, Hull P, Dore GJ, Grebely J. Knowledge and barriers associated with assessment and treatment for hepatitis C virus infection among people who inject drugs. Drug Alcohol Rev. 2012;31(7):918-24.
219. Ti L, Kaplan K, Hayashi K, Suwannawong P, Wood E, et al. Low rates of hepatitis C testing among people who inject drugs in Thailand: implications for peer-based interventions. J Public Health (Oxf). 2013;35(4):578-84.
220. Swan D, Long J, Carr O, Flanagan J, Irish H, et al. Barriers to and facilitators of hepatitis C testing, management, and treatment among current

and former injecting drug users: a qualitative exploration. AIDS Patient Care STDS. 2010;24(12):753-62.
221. Foucher J, Reiller B, Jullien V, Leal F, di Cesare ES, et al. FibroScan used in street-based outreach for drug users is useful for hepatitis C virus screening and management: a prospective study. J Viral Hepat. 2009;16(2):121-31.
222. Moessner BK, Jorgensen TR, Skamling M, Vyberg M, Junker P, et al. Outreach screening of drug users for cirrhosis with transient elastography. Addiction. 2011;106(5):970-6.
223. Doab A, Treloar C, Dore GJ. Knowledge and attitudes about treatment for hepatitis C virus infection and barriers to treatment among current injection drug users in Australia. Clin Infect Dis. 2005;40 (Suppl 5):S313-20.
224. Grebely J, Genoway KA, Raffa JD, Dhadwal G, Rajan T, et al. Barriers associated with the treatment of hepatitis C virus infection among illicit drug users. Drug Alcohol Depend. 2008;93(1-2):141-7.
225. Treloar C, Hull P, Bryant J, Hopwood M, Grebely J, et al. Factors associated with hepatitis C knowledge among a sample of treatment naive people who inject drugs. Drug Alcohol Depend. 2011;116(1-3):52-6.
226. Treloar C, Newland J, Rance J, Hopwood M. Uptake and delivery of hepatitis C treatment in opiate substitution treatment: perceptions of clients and health professionals. J Viral Hepat. 2010;17(12):839-44.
227. Treloar C, Rance J, Dore GJ, Grebely J, Group ES. Barriers and facilitators for assessment and treatment of hepatitis C virus infection in the opioid substitution treatment setting: insights from the ETHOS study. J Viral Hepat. 2014;21(8):560-7.
228. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Viral hepatitis and drug use [updated Page last updated: Friday, 27 July 2012. Available from: http://www.emcdda.europa.eu/topics/hepatitis].
229. Bruggmann P, Falcato L, Dober S, Helbling B, Keiser O, et al. Active intravenous drug use during chronic hepatitis C therapy does not reduce sustained virological response rates in adherent patients. J Viral Hepat. 2008;15(10):747-52.
230. Manolakopoulos S, Deutsch MJ, Anagnostou O, Karatapanis S, Tiniakou E, et al. Substitution treatment or active intravenous drug use should not be contraindications for antiviral treatment in drug users with chronic hepatitis C. Liver Int. 2010;30(10):1454-60.
231. Gidding HF, Topp L, Middleton M, Robinson K, Hellard M, et al. The epidemiology of hepatitis C in Australia: notifications, treatment uptake and liver transplantations, 1997-2006. J Gastroenterol Hepatol. 2009;24(10):1648-54.
232. Martin NK, Foster GR, Vilar J, Ryder S, Cramp ME, et al. HCV treatment rates and sustained viral response among people who inject drugs in seven UK sites: real world results and modelling of treatment impact. J Viral Hepat. 2015;22(4):399-408.
233. Bruggmann P. Accessing Hepatitis C patients who are difficult to reach: it is time to overcome barriers. J Viral Hepat. 2012;19(12):829-35.

234. Reimer J, Haasen C. Need-adapted HCV-treatment setting for injection drug users. Lancet. 2009;373(9681):2090-1.
235. Norman J, Walsh NM, Mugavin J, Stoove MA, Kelsall J, et al. The acceptability and feasibility of peer worker support role in community based HCV treatment for injecting drug users. Harm Reduct J. 2008;5:8.
236. Sylvestre DL, Zweben JE. Integrating HCV services for drug users: a model to improve engagement and outcomes. Int J Drug Policy. 2007;18(5):406-10.
237. Mravcik V, Strada L, Stolfa J, Bencko V, Groshkova T, et al. Factors associated with uptake, adherence, and efficacy of hepatitis C treatment in people who inject drugs: a literature review. Patient Prefer Adherence. 2013;7:1067-75.
238. Waizmann M, Ackermann G. High rates of sustained virological response in hepatitis C virus-infected injection drug users receiving directly observed therapy with peginterferon alpha-2a (40KD) (PEGASYS) and once-daily ribavirin. J Subst Abuse Treat. 2010;38(4):338-45.
239. Grebely J, Raffa JD, Meagher C, Duncan F, Genoway KA, et al. Directly observed therapy for the treatment of hepatitis C virus infection in current and former injection drug users. J Gastroenterol Hepatol. 2007;22(9):1519-25.
240. Hellard ME, Wang YH. The role of general practitioners in managing and treating hepatitis C. Med J Aust. 2009;191(10):523-4.
241. Baker D, Alavi M, Erratt A, Hill S, Balcomb A, et al. Delivery of treatment for hepatitis C virus infection in the primary care setting. Eur J Gastroenterol Hepatol. 2014;26(9):1003-9.
242. Laine C, Hauck WW, Gourevitch MN, Rothman J, Cohen A, et al. Regular outpatient medical and drug abuse care and subsequent hospitalization of persons who use illicit drugs. JAMA. 2001;285(18):2355-62.
243. Weisner C, Mertens J, Parthasarathy S, Moore C, Lu Y. Integrating primary medical care with addiction treatment: a randomized controlled trial. JAMA. 2001;286(14):1715-23.
244. Belfiori B, Ciliegi P, Chiodera A, Bacosi D, Tosti A, et al. Peginterferon plus Ribavirin for chronic hepatitis C in opiate addicts on methadone/buprenorphine maintenance therapy. Dig Liver Dis. 2009;41(4):303-7.
245. Mauss S, Hueppe D, John C, Goelz J, Heyne R, et al. Estimating the likelihood of sustained virological response in chronic hepatitis C therapy. J Viral Hepat. 2011;18(4):e81-90.
246. Sasadeusz JJ, Dore G, Kronborg I, Barton D, Yoshihara M, et al. Clinical experience with the treatment of hepatitis C infection in patients on opioid pharmacotherapy. Addiction. 2011;106(5):977-84.
247. Dalgard O, Bjoro K, Hellum KB, Myrvang B, Ritland S, et al. Treatment with pegylated interferon and ribavarin in HCV infection with genotype 2 or 3 for 14 weeks: a pilot study. Hepatology. 2004;40(6):1260-5.
248. Gazdik F, Gazdikova K, Laktis K, Okruhlica L, Fejdiova K, et al. High virologic sustained response for former young intravenous drug users with

chronic hepatitis C treated by pegylated interferon-alpha plus ribavirin. Bratisl Lek Listy. 2009;110(2):77-84.
249. Open Society Foundations. Improving Health in Pretrial Detention: Pilot Interventions and the Need for Evaluation 2011 [Available from: https://www.opensocietyfoundations.org/fact-sheets/improving-health-pretrial-detention].
250. Carpentier C, Royuela L, Noor A, Hedrich D. Ten Years of Monitoring Illicit Drug Use in Prison Populations in Europe: Issues and Challenges. The Howard Journal of Criminal Justice 2012;51(1):37-66.
251. Fazel S, Bains P, Doll H. Substance abuse and dependence in prisoners: a systematic review. Addiction. 2006;101(2):181-91.
252. Zurhold H, Haasen C, Stöver H. Female drug users in European prisons: a European study of prison policies, prison drug services and the women's perspectives. Oldenburg, D: Bibliotheks- und Informationssystem der Carl von Ossietzky Universität. 2005.
253. Reekie JM, Levy MH, Richards AH, Wake CJ, Siddall DA, et al. Trends in HIV, hepatitis B and hepatitis C prevalence among Australian prisoners - 2004, 2007, 2010. Med J Aust. 2014;200(5):277-80.
254. Spaulding A, Greene C, Davidson K, Schneidermann M, Rich J. Hepatitis C in state correctional facilities. Prev Med. 1999;28(1):92-100.
255. Macalino GE, Vlahov D, Sanford-Colby S, Patel S, Sabin K, et al. Prevalence and incidence of HIV, hepatitis B virus, and hepatitis C virus infections among males in Rhode Island prisons. Am J Public Health. 2004;94(7):1218-23.
256. Baillargeon J, Wu H, Kelley MJ, Grady J, Linthicum L, et al. Hepatitis C seroprevalence among newly incarcerated inmates in the Texas correctional system. Public Health. 2003;117(1):43-8.
257. van Beek I, Dwyer R, Dore GJ, Luo K, Kaldor JM. Infection with HIV and hepatitis C virus among injecting drug users in a prevention setting: retrospective cohort study. BMJ. 1998;317(7156):433-7.
258. Butler T, Boonwaat L, Hailstone S, Falconer T, Lems P, et al. The 2004 Australian prison entrants' blood-borne virus and risk behaviour survey. Aust N Z J Public Health. 2007;31(1):44-50.
259. Hellard ME, Hocking JS, Crofts N. The prevalence and the risk behaviours associated with the transmission of hepatitis C virus in Australian correctional facilities. Epidemiol Infect. 2004;132(3):409-15.
260. Hennessey KA, Kim AA, Griffin V, Collins NT, Weinbaum CM, et al. Prevalence of infection with hepatitis B and C viruses and co-infection with HIV in three jails: a case for viral hepatitis prevention in jails in the United States. J Urban Health. 2009;86(1):93-105.
261. Miller ER, Bi P, Ryan P. Hepatitis C virus infection in South Australian prisoners: seroprevalence, seroconversion, and risk factors. Int J Infect Dis. 2009;13(2):201-8.

262. Poulin C, Alary M, Lambert G, Godin G, Landry S, et al. Prevalence of HIV and hepatitis C virus infections among inmates of Quebec provincial prisons. CMAJ. 2007;177(3):252-6.
263. WHO; UNODC; UNAIDS. Technical Guide for countries to set targets for universal access to HIV prevention, treatment and care for injecting drug users. Geneva, Switzerland 2009 [Available from: http://www.unaids.org/en/media/unaids/contentassets/dataimport/pub/manual/2010/idu_target_setting_guide_en.pdf].
264. Hedrich D, Alves P, Farrell M, Stover H, Moller L, et al. The effectiveness of opioid maintenance treatment in prison settings: a systematic review. Addiction. 2012;107(3):501-17.
265. Hepatitis Australia. Consensus statement: Addressing hepatitis C in Australian custodial settings 2011 [Available from: https://www.phaa.net.au/documents/item/368].
266. Haber PS, Parsons SJ, Harper SE, White PA, Rawlinson WD, et al. Transmission of hepatitis C within Australian prisons. Med J Aust. 1999;171(1):31-3.
267. Vlahov D, Nelson KE, Quinn TC, Kendig N. Prevalence and incidence of hepatitis C virus infection among male prison inmates in Maryland. Eur J Epidemiol. 1993;9(5):566-9.
268. Crofts N, Hopper JL, Milner R, Breschkin AM, Bowden DS, et al. Blood-borne virus infections among Australian injecting drug users: implications for spread of HIV. Eur J Epidemiol. 1994;10(6):687-94.
269. EMCDDA. Prisons and Drugs in Europe: The problem and responses. Lisbon/Portugal 2012 [Available from: http://www.emcdda.europa.eu/publications/selected-issues/prison].
270. Viitanen P, Vartiainen H, Aarnio J, von Gruenewaldt V, Hakamaki S, et al. Hepatitis A, B, C and HIV infections among Finnish female prisoners--young females a risk group. J Infect. 2011;62(1):59-66.
271. Pham ST, Bull RA, Bennett JM, Rawlinson WD, Dore GJ, et al. Frequent multiple hepatitis C virus infections among injection drug users in a prison setting. Hepatology. 2010;52(5):1564-72.
272. Harzke AJ, Baillargeon J, Paar DP, Pulvino J, Murray OJ. Chronic liver disease mortality among male prison inmates in Texas, 1989-2003. Am J Gastroenterol. 2009;104(6):1412-9.
273. WHO. Prison Health as Part of Public Health. Declaration, Moscow 24 October 2003 [Available from: http://www.euro.who.int/__data/assets/pdf_file/0007/98971/E94242.pdf].
274. The Ministerial Advisory Committee on AIDS, Sexual Health and Hepatitis (MACASHH) for the prevention, treatment and care of hepatitis C in custodial settings. Hepatitis C Prevention, Treatment and Care: Guidelines for Australian Custodial settings evidence base for the Guidelines 2008 [Available from: https://www.health.gov.au/internet/main/publishing.nsf/Content/DA9F4D3AA93288EFCA257BF00021DF13/$File/prison-guidelines-evidence.pdf].

275. UNAIDS. Prisons and AIDS: UNAIDS point of view. Geneva, Switzerland 1997 [Available from: https://www.unodc.org/documents/hiv-aids/UNAIDS%20prison%20and%20AIDS.pdf].
276. UNODC; WHO; UNAIDS. HIV/AIDS Prevention, Care, Treatment and Support in Prison Settings. A Framework for an Effective National Response. New York, Vienna & Geneva: United Nations Office on Drugs and Crime, World Health Organization and Joint United Nations Programme on HIV/AIDS 2006 [Available from: http://www.unodc.org/pdf/criminal_justice/HIV-AIDS_Prevention_Care_Treatment_and_Support_in_Prison_Settings.pdf].
277. WHO. WHO guidelines on HIV infection and AIDS in prisons. Geneva 1993 [Available from: https://www.unodc.org/documents/hiv-aids/WHO%20guidelines%20prisons.pdf].
278. Hariga F, Stöver H. Guide to starting and managing prison-based needle and syringe programmes (PNSP). Revista Española de Sanidad Penitenciaria. Comunicaciones del IX Congreso de Sanidad Penitenciaria y XVI Jornadas de la SESP, Suplemento. 2012;14:S. 35.
279. Stöver H, Kastelic A. Health in Prison. A Practical Guide. Drug treatment and harm reduction in prisons. Pages 113-33 [Available from: http://www.euro.who.int/en/health-topics/health-determinants/prisons-and-health/who-health-in-prisons-programme-hipp].
280. Stöver H, Thane K. Towards a Continuum of Care in the EU Criminal Justice System A survey of prisoners' needs in four countries (Estonia, Hungary, Lithuania, Poland) Oldenburg/Germany: Bis-Verlag; 2011.
281. Sosman JM, MacGowan RJ, Margolis AD, Eldridge E, Flanigan T, et al. Screening for sexually transmitted diseases and hepatitis in 18-29-year-old men recently released from prison: feasibility and acceptability. Int J STD AIDS. 2005;16(2):117-22.
282. Horne JA, Clements AJ, Drennan P, Stein K, Cramp ME. Screening for hepatitis C virus in the Dartmoor prison population: an observational study. J Public Health (Oxf). 2004;26(4):372-5.
283. Khaw FM, Stobbart L, Murtagh MJ. 'I just keep thinking I haven't got it because I'm not yellow': a qualitative study of the factors that influence the uptake of Hepatitis C testing by prisoners. BMC Public Health. 2007;7:98.
284. Chew KW, Allen SA, Taylor LE, Rich JD, Feller E. Treatment outcomes with pegylated interferon and ribavirin for male prisoners with chronic hepatitis C. J Clin Gastroenterol. 2009;43(7):686-91.
285. Farley J, Vasdev S, Fischer B, Haydon E, Rehm J, et al. Feasibility and outcome of HCV treatment in a Canadian federal prison population. Am J Public Health. 2005;95(10):1737-9.
286. Sterling RK, Hofmann CM, Luketic VA, Sanyal AJ, Contos MJ, et al. Treatment of chronic hepatitis C virus in the virginia department of corrections:

can compliance overcome racial differences to response? Am J Gastroenterol. 2004;99(5):866-72.
287. Allen SA, Spaulding AC, Osei AM, Taylor LE, Cabral AM, et al. Treatment of chronic hepatitis C in a state correctional facility. Ann Intern Med. 2003;138(3):187-90.
288. Maru DS, Bruce RD, Basu S, Altice FL. Clinical outcomes of hepatitis C treatment in a prison setting: feasibility and effectiveness for challenging treatment populations. Clin Infect Dis. 2008;47(7):952-61.
289. Strock P, Mossong J, Hawotte K, Arendt V. Access to treatment of hepatitis C in prison inmates. Dig Dis Sci. 2009;54(6):1325-30.
290. Boonwaat L, Haber PS, Levy MH, Lloyd AR. Establishment of a successful assessment and treatment service for Australian prison inmates with chronic hepatitis C. Med J Aust. 2010;192(9):496-500.
291. Bate JP, Colman AJ, Frost PJ, Shaw DR, Harley HA. High prevalence of late relapse and reinfection in prisoners treated for chronic hepatitis C. J Gastroenterol Hepatol. 2010;25(7):1276-80.
292. Tan JA, Joseph TA, Saab S. Treating hepatitis C in the prison population is cost-saving. Hepatology. 2008;48(5):1387-95.
293. Hammett TM. Making the case for health interventions in correctional facilities. J Urban Health. 2001;78(2):236-40.
294. Spaulding AC, Weinbaum CM, Lau DT, Sterling R, Seeff LB, et al. A framework for management of hepatitis C in prisons. Ann Intern Med. 2006;144(10):762-9.
295. Ferguson L, Batey R. Prisons, prisoners, and hepatitis C. J Gastroenterol Hepatol. 2010;25(7):1184-6.
296. De Groot A, Stubblefield E, Bick J. Hepatitis C: A correctional-public health opportunity. Medscape Infectious Diseases. 2001;3:1–14.
297. Arora S, Thornton K, Jenkusky SM, Parish B, Scaletti JV. Project ECHO: linking university specialists with rural and prison-based clinicians to improve care for people with chronic hepatitis C in New Mexico. Public Health Rep. 2007;122 (Suppl 2):74-7.
298. Klein SJ, Wright LN, Birkhead GS, Mojica BA, Klopf LC, et al. Promoting HCV treatment completion for prison inmates: New York State's hepatitis C continuity program. Public Health Rep. 2007;122 (Suppl 2):83-8.
299. Martin CK, Hostetter JE, Hagan JJ. New opportunities for the management and therapy of hepatitis C in correctional settings. Am J Public Health. 2010;100(1):13-7.
300. Grogan A, Timmins F. Patients' perceptions of information and support received from the nurse specialist during HCV treatment. J Clin Nurs. 2010;19(19-20):2869-78.
301. Ehsani JP, Vu T, Karvelas M. Exploring the need for hepatology nurses and allied health professionals in Victorian liver clinics. Aust Health Rev. 2006;30(2):211-8.
302. Leone NE. The role of nursing in managing treatment-associated adverse effects in patients with hepatitis C. Gastroenterol Nurs. 2002;25(5):201-3.

303. Nazareth S, Piercey C, Tibbet P, Cheng W. Innovative practice in the management of chronic Hepatitis C: introducing the nurse practitioner model. Australian journal of advance nursing. Aust J Adv Nurs. 2008;25(4):107-13.
304. Lloyd AR, Clegg J, Lange J, Stevenson A, Post JJ, et al. Safety and effectiveness of a nurse-led outreach program for assessment and treatment of chronic hepatitis C in the custodial setting. Clin Infect Dis. 2013;56(8):1078-84.
305. Stöver H. Workshop results during 2nd International Symposium on Hepatitis care in substance users September 15-16, 2011. Brussels/Belgium; 2012.
306. ECDC; EMCDDA. Prevention and control of infectious diseases among people who inject drugs. Guidance in brief 2011 [Available from: http://www.emcdda.europa.eu/publications/ecdc-emcdda-guidance].
307. Weinbaum C, Lyerla R, Margolis HS. Centers for Disease Control and Prevention. Prevention and control of infections with hepatitis viruses in correctional settings. Centers for Disease Control and Prevention. MMWR Recomm Rep. 2003;52(RR-1):1-36; quiz CE1-4.
308. Lines R, Jürgens R, Betteridge G, Stöver H. Taking action to reduce injecting drug-related harms in prisons: The evidence of effectiveness of prison needle exchange in six countries. Int J Prison Health. 2005;1:1,49-64.
309. Stöver H, Nelles J. Ten years of experience with needle and syringe exchange programmes in European Prisons. . Int J Drug Policy. 2003;14(5/6):437–444.
310. MMWR. Recommendations and reports. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. Centers for Disease Control and Prevention 1998 [Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/00055154.htm].
311. Broadhead RS, Heckathorn DD, Altice FL, van Hulst Y, Carbone M, et al. Increasing drug users' adherence to HIV treatment: results of a peer-driven intervention feasibility study. Soc Sci Med. 2002;55(2):235-46.
312. Hauser P, Khosla J, Aurora H, Laurin J, Kling MA, et al. A prospective study of the incidence and open-label treatment of interferon-induced major depressive disorder in patients with hepatitis C. Mol Psychiatry. 2002;7(9):942-7.
313. WHO. Guidelines for the screening, care and treatment of persons with hepatitis C infection 2014 [Available from: http://www.who.int/hepatitis/publications/hepatitis-c-guidelines/en/].
314. WHO. Global health sector strategy on viral hepatitis 2016-2021 2016 [Available from: https://www.who.int/hepatitis/strategy2016-2021/ghss-hep/en/].
315. WHO. Guidelines for the Care and Treatment of Persons Diagnosed with Chronic Hepatitis C Virus Infection Geneva 2018 [Available from: http://www.ncbi.nlm.nih.gov/pubmed/30307724].
316. National Institutes of Health Consensus Development Conference Panel statement: management of hepatitis C. Hepatology. 1997;26(3 Suppl 1):2S-10S.

317. Ghany MG, Strader DB, Thomas DL, Seeff LB, American Association for the Study of Liver D. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology. 2009;49(4):1335-74.
318. Grebely J, Dore GJ. Can hepatitis C virus infection be eradicated in people who inject drugs? Antiviral Res. 2014;104:62-72.
319. Day E, Hellard M, Treloar C, Bruneau J, Martin NK, et al. Hepatitis C elimination among people who inject drugs: Challenges and recommendations for action within a health systems framework. Liver Int. 2019;39(1):20-30.
320. Yehia BR, Schranz AJ, Umscheid CA, Lo Re V, 3rd. The treatment cascade for chronic hepatitis C virus infection in the United States: a systematic review and meta-analysis. PLoS One. 2014;9(7):e101554.
321. Meyer JP, Moghimi Y, Marcus R, Lim JK, Litwin AH, et al. Evidence-based interventions to enhance assessment, treatment, and adherence in the chronic Hepatitis C care continuum. Int J Drug Policy. 2015;26(10):922-35.
322. Brown JL, Gause NK, Lewis D, Winhusen T. Examination of the Hepatitis C Virus care continuum among individuals with an opioid use disorder in substance use treatment. J Subst Abuse Treat. 2017;76:77-80.
323. Bajis S, Dore GJ, Hajarizadeh B, Cunningham EB, Maher L, et al. Interventions to enhance testing, linkage to care and treatment uptake for hepatitis C virus infection among people who inject drugs: A systematic review. Int J Drug Policy. 2017;47:34-46.
324. Ford N, Wiktor S, Kaplan K, Andrieux-Meyer I, Hill A, et al. Ten priorities for expanding access to HCV treatment for people who inject drugs in low- and middle-income countries. Int J Drug Policy. 2015;26(11):1088-93.
325. Grebely J, Tyndall MW. Management of HCV and HIV infections among people who inject drugs. Curr Opin HIV AIDS. 2011;6(6):501-7.
326. Grebely J, Oser M, Taylor LE, Dore GJ. Breaking down the barriers to hepatitis C virus (HCV) treatment among individuals with HCV/HIV coinfection: action required at the system, provider, and patient levels. J Infect Dis. 2013;207 (Suppl 1):S19-25.
327. Mah A, Hull MW, DeBeck K, Milloy MJ, Dobrer S, et al. Knowledge of hepatitis C and treatment willingness amongst people who inject drugs in an era of direct acting antivirals. Int J Drug Policy. 2017;47:137-43.
328. Robaeys G, Christensen S, Lucidarme D, Arain A, Bruggmann P, et al. Chronic Hepatitis C Treatment in Patients with Drug Injection History: Findings of the INTEGRATE Prospective, Observational Study. Infect Dis Ther. 2017;6(2):265-75.
329. Dore GJ, Altice F, Litwin AH, Dalgard O, Gane EJ, et al. Elbasvir-Grazoprevir to Treat Hepatitis C Virus Infection in Persons Receiving Opioid Agonist Therapy: A Randomized Trial. Ann Intern Med. 2016;165(9):625-34.
330. Grebely J, Dore GJ, Zeuzem S, Aspinall RJ, Fox R, et al. Efficacy and Safety of Sofosbuvir/Velpatasvir in Patients With Chronic Hepatitis C Virus Infection Receiving Opioid Substitution Therapy: Analysis of Phase 3 ASTRAL Trials. Clin Infect Dis. 2016;63(11):1479-81.

331. Grebely J, Mauss S, Brown A, Bronowicki JP, Puoti M, et al. Efficacy and Safety of Ledipasvir/Sofosbuvir With and Without Ribavirin in Patients With Chronic HCV Genotype 1 Infection Receiving Opioid Substitution Therapy: Analysis of Phase 3 ION Trials. Clin Infect Dis. 2016;63(11):1405-11.
332. Scherz N, Bruggmann P, Brunner N. Direct-acting antiviral therapy for hepatitis C infection among people receiving opioid agonist treatment or heroin assisted treatment. Int J Drug Policy. 2018;62:74-7.
333. Strauss SM, Astone-Twerell J, Munoz-Plaza CE, Des Jarlais DC, Gwadz M, et al. Drug treatment program patients' hepatitis C virus (HCV) education needs and their use of available HCV education services. BMC Health Serv Res. 2007;7:39.
334. Cohen-Moreno R, Schiff M, Levitt S, Bar-Hamburger R, Strauss S, et al. Knowledge about Hepatitis-C among methadone maintenance treatment patients in Israel. Subst Use Misuse. 2010;45(1-2):58-76.
335. Chen EY, North CS, Fatunde O, Bernstein I, Salari S, et al. Knowledge and attitudes about hepatitis C virus (HCV) infection and its treatment in HCV mono-infected and HCV/HIV co-infected adults. J Viral Hepat. 2013;20(10):708-14.
336. Stein MD, Maksad J, Clarke J. Hepatitis C disease among injection drug users: knowledge, perceived risk and willingness to receive treatment. Drug Alcohol Depend. 2001;61(3):211-5.
337. Carey J, Perlman DC, Friedmann P, Kaplan WM, Nugent A, et al. Knowledge of hepatitis among active drug injectors at a syringe exchange program. J Subst Abuse Treat. 2005;29(1):47-53.
338. Walley AY, White MC, Kushel MB, Song YS, Tulsky JP. Knowledge of and interest in hepatitis C treatment at a methadone clinic. J Subst Abuse Treat. 2005;28(2):181-7.
339. Norton BL, Voils CI, Timberlake SH, Hecker EJ, Goswami ND, et al. Community-based HCV screening: knowledge and attitudes in a high risk urban population. BMC Infect Dis. 2014;14:74.
340. Grebely J, Bryant J, Hull P, Hopwood M, Lavis Y, et al. Factors associated with specialist assessment and treatment for hepatitis C virus infection in New South Wales, Australia. J Viral Hepat. 2011;18(4):e104-16.
341. Castera L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. Gastroenterology. 2005;128(2):343-50.
342. Shaheen AA, Wan AF, Myers RP. FibroTest and FibroScan for the prediction of hepatitis C-related fibrosis: a systematic review of diagnostic test accuracy. Am J Gastroenterol. 2007;102(11):2589-600.
343. Marshall AD, Micallef M, Erratt A, Telenta J, Treloar C, et al. Liver disease knowledge and acceptability of non-invasive liver fibrosis assessment among people who inject drugs in the drug and alcohol setting: The LiveRLife Study. Int J Drug Policy. 2015;26(10):984-91.

344. Harris KA, Jr., Arnsten JH, Litwin AH. Successful integration of hepatitis C evaluation and treatment services with methadone maintenance. J Addict Med. 2010;4(1):20-6.
345. Butner JL, Gupta N, Fabian C, Henry S, Shi JM, et al. Onsite treatment of HCV infection with direct acting antivirals within an opioid treatment program. J Subst Abuse Treat. 2017;75:49-53.
346. Tait JM, Wang H, Stephens BP, Miller MH, G. MP, et al. Multi-disciplinary managed care networks- lifesaving interventions for hepatitis c patients. 5th International Symposium on Hepatitis Care in Substance Users; 2016; Oslo, Norway.
347. Tait JM, Wang H, Stephens BP, Miller M, McIntyre PG, et al. Multidisciplinary managed care networks—Life-saving interventions for hepatitis C patients. J Viral Hepat. 2017;24(3):207-15.
348. Evon DM, Simpson K, Kixmiller S, Galanko J, Dougherty K, et al. A randomized controlled trial of an integrated care intervention to increase eligibility for chronic hepatitis C treatment. Am J Gastroenterol. 2011;106(10):1777-86.
349. Knott A, Dieperink E, Willenbring ML, Heit S, Durfee JM, et al. Integrated psychiatric/medical care in a chronic hepatitis C clinic: effect on antiviral treatment evaluation and outcomes. Am J Gastroenterol. 2006;101(10):2254-62.
350. Cheng W, Nazareth S, Flexman JP. Statewide hepatitis C model of care for rural and remote regions. J Gastroenterol Hepatol. 2015;30 (Suppl 2):1-5.
351. Rossaro L, Torruellas C, Dhaliwal S, Botros J, Clark G, et al. Clinical outcomes of hepatitis C treated with pegylated interferon and ribavirin via telemedicine consultation in Northern California. Dig Dis Sci. 2013;58(12):3620-5.
352. Tazawa J, Sakai Y, Kusano F, Nagayama K, Fujiwara H. Collaboration between Hepatologists and Primary Care Physicians in Treating Patients with Chronic Hepatitis C. J Rural Med. 2011;6(2):54-9.
353. Backus LI, Belperio PS, Shahoumian TA, Mole LA. Impact of provider type on hepatitis C outcomes with boceprevir-based and telaprevir-based regimens. J Clin Gastroenterol. 2015;49(4):329-35.
354. Woodrell C, Weiss J, Branch A, Gardenier D, Krauskopf K, et al. Primary Care-Based Hepatitis C Treatment Outcomes With First-Generation Direct-Acting Agents. J Addict Med. 2015;9(5):405-10.
355. Arora S, Thornton K, Murata G, Deming P, Kalishman S, et al. Outcomes of treatment for hepatitis C virus infection by primary care providers. N Engl J Med. 2011;364(23):2199-207.
356. Kattakuzhy S, Gross C, Emmanuel B, Teferi G, Jenkins V, et al. Expansion of Treatment for Hepatitis C Virus Infection by Task Shifting to Community-Based Nonspecialist Providers: A Nonrandomized Clinical Trial. Ann Intern Med. 2017;167(5):311-8.
357. Grebely J, Genoway K, Khara M, Duncan F, Viljoen M, et al. Treatment uptake and outcomes among current and former injection drug users receiving

directly observed therapy within a multidisciplinary group model for the treatment of hepatitis C virus infection. Int J Drug Policy. 2007;18(5):437-43.
358. Stein MR, Soloway IJ, Jefferson KS, Roose RJ, Arnsten JH, et al. Concurrent group treatment for hepatitis C: implementation and outcomes in a methadone maintenance treatment program. J Subst Abuse Treat. 2012;43(4):424-32.
359. Crawford S, Bath N. Peer support models for people with a history of injecting drug use undertaking assessment and treatment for hepatitis C virus infection. Clin Infect Dis. 2013;57 (Suppl 2):S75-9.
360. Latka MH, Hagan H, Kapadia F, Golub ET, Bonner S, et al. A randomized intervention trial to reduce the lending of used injection equipment among injection drug users infected with hepatitis C. Am J Public Health. 2008;98(5):853-61.
361. Garfein RS, Golub ET, Greenberg AE, Hagan H, Hanson DL, et al. A peer-education intervention to reduce injection risk behaviors for HIV and hepatitis C virus infection in young injection drug users. AIDS. 2007;21(14):1923-32.
362. Mackesy-Amiti ME, Finnegan L, Ouellet LJ, Golub ET, Hagan H, et al. Peer-education intervention to reduce injection risk behaviors benefits high-risk young injection drug users: a latent transition analysis of the CIDUS 3/DUIT study. AIDS Behav. 2013;17(6):2075-83.
363. Linas BP, Barter DM, Leff JA, Assoumou SA, Salomon JA, et al. The hepatitis C cascade of care: identifying priorities to improve clinical outcomes. PLoS One. 2014;9(5):e97317.
364. Ho SB, Brau N, Cheung R, Liu L, Sanchez C, et al. Integrated Care Increases Treatment and Improves Outcomes of Patients With Chronic Hepatitis C Virus Infection and Psychiatric Illness or Substance Abuse. Clin Gastroenterol Hepatol. 2015;13(11):2005-14 e1-3.
365. Hudon C, Chouinard MC, Diadiou F, Lambert M, Bouliane D. Case Management in Primary Care for Frequent Users of Health Care Services With Chronic Diseases: A Qualitative Study of Patient and Family Experience. Ann Fam Med. 2015;13(6):523-8.
366. Hallinan R, Byrne A, Agho K, Dore GJ. Referral for chronic hepatitis C treatment from a drug dependency treatment setting. Drug Alcohol Depend. 2007;88(1):49-53.
367. Rolls DA, Sacks-Davis R, Jenkinson R, McBryde E, Pattison P, et al. Hepatitis C transmission and treatment in contact networks of people who inject drugs. PLoS One. 2013;8(11):e78286.
368. Latkin C, Yang C, Srikrishnan AK, Solomon S, Mehta SH, et al. The relationship between social network factors, HIV, and Hepatitis C among injection drug users in Chennai, India. Drug Alcohol Depend. 2011;117(1):50-4.
369. Fazel S, Baillargeon J. The health of prisoners. Lancet. 2011;377(9769):956-65.
370. Van Malderen S, Pauwels L, Walthoff-Born C, Glibert P, Todts S. Druggebruik in de Belgische gevangenissen. Monitoring van druggerelateerde gezondheidsrisico's 2010, Brussel: Federale Overheidsdienst Justitie. 2011.

371. Treloar C, McCredie L, Lloyd AR, HITS-p investigators. Acquiring hepatitis C in prison: the social organisation of injecting risk. Harm Reduct J. 2015;12:10.
372. Federale Overheidsdienst Volksgezondheid Veiligheid van de voedselketen en Leefmilieu. Protocolakkoord 'HCV-plan'. Belgisch staatsblad 08.08.2014 Moniteur Belge, 57926, [C-2014/24267]. 2014.
373. Vlaamse regering. Ministerieel besluit tot toekenning van een subsidie aan CAD Limburg voor "Screening en preventie door behandeling van hepatitis C infectie bij risicogroepen".
374. The Belgian Association for the Study of the Liver. Treatment options and diagnostic cut-offs for HCV in Belgium 2017 [Available from: http://www.basl.be/sites/default/files/Belgian%20HCV%20therapy%20guidance%20update%20january%202017_final_25012017.pdf].
375. The Belgian Association for the Study of the Liver. Treatment options and diagnostic cut-offs for HCV in Belgium 2018 [Available from: http://www.basl.be/sites/default/files/Belgian%20HCV%20therapy%20guidance%20update%20june%202018.pdf].
376. Nevens F, Colle I, Michielsen P, Robaeys G, Moreno C, et al. Resource use and cost of hepatitis C-related care. Eur J Gastroenterol Hepatol. 2012;24(10):1191-8.
377. Starkel P, Vandijck D, Laleman W, Van Damme P, Moreno C, et al. The disease burden of hepatitis C in Belgium: development of a realistic disease control strategy. Acta Gastroenterol Belg. 2014;77(2):280-4.
378. Bourgeois S, Blach S, Blach C, Laleman W, Mathei C, et al. Achieving WHO recommendations for Hepatitis C Virus Elimination in Belgium. Acta Gastroenterol Belg. 2016;79(2):222-6.
379. Hepatitis B and C public policy association. Hepatitis C: the beginning of the end-key elements for successful European and national startegies to eliminate HCV in europe. the first EU policy summit dedicated to the elimination of hepatitis C in Europe. Newsletter April 2016 [Available from: http://www.hepbcppa.org/newsletter-april-2016/].
380. Papatheodoridis GV, Hatzakis A, Cholongitas E, Baptista-Leite R, Baskozos I, et al. Hepatitis C: The beginning of the end-key elements for successful European and national strategies to eliminate HCV in Europe. J Viral Hepat. 2018;25 (Suppl 1):6-17.
381. Kracht PAM, Arends JE, van Erpecum KJ, Urbanus A, Willemse JA, et al. Strategies for achieving viral hepatitis C micro-elimination in the Netherlands. Hepatol Med Policy. 2018;3:12.
382. Wade AJ, McCormack A, Roder C, McDonald K, Davies M, et al. Aiming for elimination: Outcomes of a consultation pathway supporting regional general practitioners to prescribe direct-acting antiviral therapy for hepatitis C. J Viral Hepat. 2018;25(9):1089-98.
383. Hutchinson SJ, Dillon JF, Fox R, McDonald SA, Innes HA, et al. Expansion of HCV treatment access to people who have injected drugs through effective

translation of research into public health policy: Scotland's experience. Int J Drug Policy. 2015;26(11):1041-9.
384. Scottish Executive Health Department (SEHD). Hepatitis C Action Plan for Scotland. Phase I: September 2006-August 2008. Edinburgh: Scottish Executive 2006 [Available from: http://www.gov.scot/Publications/2005/06/14134528/45302].
385. Scottish Government. Hepatitis C Action Plan for Scotland: Phase II (May 2008-March 2011). Edinburgh: Scottish Government 2008 [Available from: http://www.gov.scot/Publications/2008/05/13103055/0].
386. Dillon JF, Lazarus JV, Razavi HA. Urgent action to fight hepatitis C in people who inject drugs in Europe. Hepatol Med Policy. 2016;1(1):2.
387. Free Clinic vzw. Jaarverslag 2015 [Available from: http://free-clinic.be/wp-content/uploads/2012/10/Jaarverslag-2015-Free-Clinic.pdf].
388. Bielen R. Case Management to Improve Uptake for Screening and Therapy of Hepatitis C viral infection in People Who Inject Drugs. AASLD The Liver Meeting®; 2016; Boston, United States.
389. Busschots D, Bielen R, Koc O, Dercon E, Windelinckx T, et al. FRI-224-Reaching out to the undiagnosed people with hepatitis C infection in Belgium: A pilot study. The International Liver Congress™; 2019.
390. Morey S, Hamoodi A, Jones D, Young T, Thompson C, et al. Increased diagnosis and treatment of hepatitis C in prison by universal offer of testing and use of telemedicine. J Viral Hepat. 2019;26(1):101-8.

Appendix

Curriculum Vitae

Personal information

Amber Arain

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Gender Female | **Date of birth** 07/01/1986 | **Nationality** Belgian

Work experience

2016-2018 **Clinical Research Associate**
Servier Benelux contracted by XPE Pharma & science

2018-ongoing **Clinical Research Associate**
Parexel Belgium BVBA

Education

2008-2010 **Master in Clinical Molecular Sciences**
Hasselt University (Diepenbeek)

2005-2008 **Bachelor in Biomedical Sciences**
Hasselt University (Diepenbeek)

2001-2005 **Sciences-Maths**
Ursula-Instituut (Herk-De-Stad)

Courses

Biosafety
The course was organized by Hasselt University, prof. dr. Sven Hendrix and dr. Kim Pannemans in cooperation with Patrick Rudelsheim, working at Perseus on May 25th 2011

Parametric and non-parametric statistical methods for life sciences
Part 1 and part 2. The courses were organized by Hasselt University, prof. dr. Geert Molenberghs and Prof. dr. Liesbeth Bruckers on June 7th 2011

Good scientific conduct and lab book taking
The courses were organized by the doctoral school for medicine and life sciences at Hasselt University on November 22nd 2011

Academic English
The course was given by Prof. Eric Caers at Hasselt University in May-June 2012

Medical statistics and clinical trial design statistics, how to best use them in clinical trials
The course was given by Dr. Gordon Taylor and Dr. Michael Harris on September 7th -8th, 2012

Theory and practice of questionnaire construction and analysis
Organized by Flanders Training Network for Methodology and Statistics (FLAMES). The course was given by dr. An Creemers on March 26th -28th, 2014

Good clinical practice for investigator site teams & Ethics committees
Organized by Formalis. The course was given by Mr. Jean -Paul Eycken (CEO Formalis SA) on January 21, 2016.

Publications

Arain A, Vandevenne J, Depeuter B, Smits J, Weyns F, Palmers Y. Paraganglioma of the cavernous sinus. JBR-BTR. 2012 May-Jun;95(3):124-5. PMID: 22880502

Robaeys G, Grebely J, Mauss S, Bruggmann P, Moussalli J, De Gottardi A, Swan T, **Arain A**, Kautz A, Stöver H, Wedemeyer H, Schaefer M, Taylor L, Backmund M, Dalgard O, Prins M, Dore GJ; International Network on Hepatitis in Substance Users. Recommendations for the management of

hepatitis C virus infection among people who inject drugs. Clin Infect Dis. 2013 Aug;57 Suppl 2:S129-37. PMID:23884061

Post JJ, **Arain A**, Lloyd AR. Enhancing assessment and treatment of hepatitis C in the custodial setting. Clin Infect Dis. 2013 Aug;57 Suppl 2:S70-4. Review. PMID: 23884069

Arain A, Robaeys G. Eligibility of persons who inject drugs for treatment of hepatitis C virus infection. World journal of gastroenterology. 2014 Sep 28;20(36):12722-33. PMID: 25278674.

Arain A, Robaeys G, Stöver H. Hepatitis C in European prisons: a call for an evidence-informed response. BMC Infect Dis. 2014;14 Suppl 6:S17. PMID: 25252822

Stoever H, **Arain A**, Robaeys G. Hepatitis C in Gefängnissen: Dringender handlungsbedarf. Suchtmedizin in Forschung und Praxis 01/2015; 16(6):275-282.

Arain A, Bourgeois S, de Galocsy C, Henrion J, Deltenre P, d'Heygere F, George C, Bastens B, Van Overbeke L, Verrando R, Bruckers L, Mathei C, Buntinx F, Van Vlierberghe H, Francque S, Laleman W, Moreno C, Janssens F, Nevens F, Robaeys G. The Belgian experience with triple therapy with boceprevir and telaprevir in genotype 1 infected patients who inject drugs. J Med Virol. 2015 Jun 29. PMID: 26121975.

Arain A, De Sousa J, Corten K, Verrando R, Thijs H, Mathei C, Buntinx F, Robaeys G. Pilot Study: Combining Formal and Peer Education with FibroScan to Increase HCV Screening and Treatment in Persons who use Drugs. J Subst Abuse Treat. 2016 Aug;67:44-9. PMID: 27296661.

Poster/Oral presentations

2nd International symposium on Hepatitis care in substance users, Brussels, Belgium, 15-16 September 2011

Poster presentation:
Interim analysis of international collection of antiviral management data in chronic hepatitis C patients infected after substance use. Authors: Arain A, Anagnostou O, Bruggmann P, Christensen P, Dalgard O, Dore G, Foster G, Grebely J, Moussali J, Richter C, Saiz de la Hoya Zamácola P, Swan T, Tefanova V, Robaeys G.

3rd International symposium on Hepatitis care in substance users, Munchen, Germany, 5-6 September 2013

Oral presentation:
The Belgian experience in treatment of persons who injected drugs with the new standard of care in genotype 1 HCV infected patients: an interim analysis of a real life study. Authors: Arain A, Bourgeois S, de Galocsy C, Deltenre P, Henrion J, D'Heygere F.G, Georges C, Bastens B, Van Overbeke L, Verrando R, Bruckers L, Mathei C, Buntinx F, Van Vlierberghe H, Francque S, Laleman W, Nevens F, Moreno C, Robaeys G.

Poster presentations:
High patient willingness but low referral ratio for HCV antiviral treatment by addiction physicians in addiction care centres: Interim analysis of the LINK study. Authors: Arain A, Mathei C, Verrando R, Dever L, Trabert C, Bourgeois S, Buntinx F, Robaeys G.

The impact of the organization of anti-HCV treatment in people who used drugs on the outcome of hepatitis C treatment. Results of an international cohort study. Authors: Arain A, Bruggmann P, Brunner N, Tsirogianni E, Goulis I, Anagnostou O, Kranidioti H, Manolakopoulos S, Bruckers L, Buntinx F, Verrando R, Mathei C, Bourgeois S, Robaeys G.

The Liver Meeting® organized by American association for the study of the liver diseases (AASLD), Washington, USA, 1-5 November 2013

Poster presentation:
The Belgian experience in treatment of persons who used drugs with the new standard of care in genotype 1 HCV infected patients. Authors: Arain A, Bourgeois S, de Galocsy C, Deltenre P, Henrion J, d'Heygere F, Georges C, Bastens B, Van Overbeke L, Verrando R, Bruckers L, Mathei C, Buntinx F, Van Vlierberghe H, Francque S, Laleman W, Moreno C, Nevens F , Robaeys G.

The XXVIth edition of the Belgian Week of Gastroenterology, Brussels, Belgium, 12-15 February 2014

Poster presentation:
Belgian experience in treatment of PWUDs with the new standard of care in GT1 HCV infected patients. Authors: Arain A, Bourgeois S, de Galocsy C, Deltenre P, Henrion J, D'Heygere F, Georges C, Bastens B, Van Overbeke L, Verrando R, Bruckers L, Mathei C, Buntinx F, Van Vlierberghe H, Francque S, Laleman W, Moreno C, Nevens F, Robaeys G.

European conference on Hepatitis C and drug use organized by The Hepatitis C Initiative, Berlin, Germany, on 23-24 October 2014

Oral presentation:
HCV treatment and care – the way forward
Treatment efficacy and safety results of first generation DAA-based regimes
Arain A, Robaeys G, Christensen S, Lucidarme D, Bruggmann P, Kunkel J, Keim S, Iraqi W, Jäkel M, DeMasi R, Lonjon-Domanec I, Foster GR.

4th International symposium on Hepatitis care in substance users, Sydney, Australia, 7-9 October 2015

Poster presentation:
Uptake for HCV screening and treatment in persons who inject drugs in opiate substitution therapy in Belgium
Arain A, Corten K, Lebbe C, Cornelis K, Buntinx F, Robaeys G

Oral presentation:
Pilot study: Combining formal and peer education with FibroScan to increase HCV screening and treatment in persons who inject drugs
Arain A, De Sousa J, Corten K, Verrando R, Thijs H, Mathei C, Buntinx F, Robaeys G.

Dankwoord

Als ik terugkijk naar de afgelopen jaren, waren het intensieve jaren maar ik heb ook veel leuke momenten mogen meemaken. Ik zou iedereen willen bedanken die heeft meegewerkt aan mijn thesis of onrechtstreeks mij heeft bijgestaan.

Ik wil graag Universiteit Hasselt, en in het bijzonder prof. Stinissen, decaan van de faculteit Geneeskunde en Levenswetenschappen, bedanken om mijn doctoraatsonderzoek aan de Universteit Hasselt te ondersteunen.

Ik zou graag de juryleden willen bedanken voor hun tijd en interesse in mijn thesis: Prof. dr. Sven Hendrix, Prof. Dr. Geert Robaeys, Prof. Dr. Catharina Mathei, Prof. Dr. Frank Buntinx, Prof. Dr. John Dillon, Prof. Dr. Ger Koek, Prof. Dr. Hans Van Vlierberghe, Prof. Dr. Sven Francque, Prof. Dr. Veerle Somers. Het was een eer voor mij om jullie als juryleden te mogen ontvangen.

Mijn promotor: Dr. Robaeys, bedankt om mij de kans te geven om aan dit project mee te werken. U was er altijd als ik u nodig had. Ondanks uw drukke agenda hoefde ik alleen maar eventjes naar de raadpleging te komen of u te bellen en u maakte tijd voor mij vrij. Bedankt om mij te blijven motiveren en voor al uw interessante ideeën. Ik heb heel veel bewondering voor u, hoe u uw werk combineert met zoveel onderzoeksprojecten.

Mijn co-promotors: Prof. Dr. Frank Buntinx en Prof. Dr. Catharina Mathei, bedankt om mij bij te staan tijdens het schrijven van mijn artikels. Jullie stonden steeds klaar om mijn artikels na te lezen en grondig te verbeteren.

Ik zou ook alle leden, de secretaressen, de verpleegkundigen, de artsen en assistenten, van de dienst Gastro-enterologie in het Ziekenhuis Oost-Limburg willen bedanken. Jullie waren altijd vriendelijk en ik voelde mij zeer welkom.

Ik zou ook alle addictie centra en ziekenhuizen die bijgedragen hebben aan dit project willen bedanken, in het bijzonder de hulpverleners in CAD Limburg en Free Clinic in Antwerpen.
Dr. Verrando, bedankt voor uw bijdrage en uw interesse. U hebt mij in verschillende projecten ondersteund. Ik werd door u geïntroduceerd in CAD Limburg. U bent heel erg gedreven en enthousiast. Elke keer dat ik u ontmoette, kwam ik vol energie terug. En bedankt om ervoor te zorgen dat ons vergaderingen niet te lang uitloopten ☺, U was altijd degene die tegen Dr. Robaeys zei: " Geert, ik ben moe, we gaan nu allemaal naar huis".

Ik zou ook Dr. Bourgeois willen bedanken voor de fijne samenwerking. We konden altijd op u rekenen als we met een project startten.

Mijn collega-doktoraatsstudenten: Kathleen, Ingrid, Laura, Cornelia, Frederik, Anneleen, Sharona, Philippe, Petra, Christophe, Joren, Ward, Kristof, Rob, Dorien, Lieselotte, Thijs en Pieter bedankt voor jullie steun en heel veel leuke momenten. Ons team bleef groeien en elk jaar kwamen er meer masterstudenten bij maar de sfeer bleef goed. Ik wens jullie het allerbeste!
Kathleen, Ingrid en Laura bedankt voor jullie steun en leuke motiverende gesprekken.
Cornelia, bedankt voor de grappige muziekmomenten: "de foute minuut", we kozen de raarste liedjes en voor een minuut werden ze dan afgespeeld. Sorry voor de collega's die maar moesten meeluisteren ;)

Lars bedankt voor je motiverende gesprekken en voor je hulp als ik computer problemen had.
Dank aan Helen Piccard om ondersteuning te bieden voor administratieve en financiële aspecten van mijn doctoraat.
Veronique Pousset, bedankt voor uw steun tijdens de eindfase van mijn thesis. Je maakte het een stukje lichter voor mij.

En tenslotte wil ik mijn familie en vrienden bedanken want zonder hun was het nooit gelukt. Mama en papa voor de kansen die jullie mij gegeven hebben. Jullie waren er altijd voor mij in leuke en moeilijke momenten. Mijn zussen en broer: Fozia, Asia, Mansoor en Aliya, bedankt voor jullie steun en de nodige afleiding. Ali, bedankt om mij altijd te blijven motiveren en een luisterend oor te zijn.
Zeeshan, mijn partner, bedankt om er altijd te zijn voor mij. Je hebt naast je werk vaak huishoudelijke taken van mij overgenomen omdat ik het druk had omdat ik een deadline moest halen. Jij hebt vaak alleen voor Ramis moeten zorgen als ik te druk had. Jij en Ramis zorgden ook voor de nodige afleiding. Zonder je steun zou het mij niet gelukt zijn. Dank je!!!