LUND UNIVERSITY

Hepatitis C virus infection in patients receiving opiate substitution therapy in Sweden.

Jerkeman, Anna

2014

Link to publication

Citation for published version (APA):
Jerkeman, A. (2014). *Hepatitis C virus infection in patients receiving opiate substitution therapy in Sweden.* [Doctoral Thesis (compilation)]. Infectious Diseases Research Unit.

Total number of authors:
1

General rights
Unless other specific re-use rights are stated the following general rights apply:
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.
• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the public portal

Read more about Creative commons licenses: https://creativecommons.org/licenses/

Take down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

LUND UNIVERSITY

PO Box 117
221 00 Lund
+46 46-222 00 00

Download date: 24. Apr. 2024

Hepatitis C virus infection in patients receiving opiate substitution therapy in Sweden

Anna Jerkeman

LUND
UNIVERSITY

DOCTORAL DISSERTATION
by due permission of the Faculty of Medicine, Lund University, Sweden.

To be defended in Lilla Aulan, MFC, Jan Waldenströms gata 5, Skåne University Hospital, Malmö on December 12 2014 at 1.00 pm.

Faculty opponent

Associate professor Rune Wejstål, MD, PhD, Department of Infectious Diseases, Institute of Biomedicine, University of Gothenburg, Gothenburg, Sweden

Organization	Document name
LUND UNIVERSITY Faculty of Medicine	DOCTORAL DISSERTATION
Department of Clinical Sciences, Malmö, Sweden	Date of issue December 12, 2014
Author Anna Jerkeman	Sponsoring organization

Title and subtitle: Hepatitis C virus infection in patients receiving opiate substitution therapy in Sweden

Abstract The hepatitis C virus (HCV) is a blood borne virus effectively spread through injection practices. Consequently, people who inject drugs (PWID) are at the center of the current HCV epidemic in industrialized countries, with regards both to prevalence and incidence. Through progressive liver fibrosis, chronic HCV infection conveys a substantial risk of liver cirrhosis and end-stage liver disease. These complications can be prevented by successful HCV treatment resulting in HCV clearance. HCV treatment uptake has hitherto been low among PWID, due to barriers on patient- as well as health care provider levels. PWID also have a multitude of other risk factors affecting morbidity and mortality. The major causes of death are directly drug related. Opiate substitution therapy (OST) reduces drug related mortality in heroin using PWID, which might allow for chronic conditions, such as HCV infection, to impact morbidity and mortality. OST also improves social functioning and has been shown to improve HCV treatment outcomes for heroin users, hence OST clinics could serve as important points of contact for HCV management. The aim of this thesis was to investigate different aspects of HCV infection in Swedish OST recipients. In a cross-sectional multi center study of OST receiving patients in Stockholm, Gothenburg and Malmö we assessed the prevalence of HCV infection and the burden and severity of liver fibrosis in relation to potential risk factors. We evaluated feasibility of peginterferon/ribavirin based HCV treatment, in the same cohort, with special attention to psychiatric status and health related quality of life (HRQoL). In a register based study we evaluated liver related mortality in relation to OST exposure in heroin users recruited from a needle exchange program. In the OST cohort we found high rates of HCV exposure (88% anti-HCV positive) and 67% of viremic patients showed significant fibrosis with association to alcohol intake, elevated BMI and exposure to hepatitis B virus. In HCV treated subjects we observed rates of completion (83%) and SVR rates (46%) in line with previous reports on peginterferon/ribavirin based HCV treatment in PWID, in spite of low scores on HRQoL and high occurrence of depression already at baseline. In the heroin using population recruited from a needle exchange program we found a significantly elevated (HR 3.08, 95%CI (1.09, 8.68), p=0.03) risk of liver related death related to OST exposure. In conclusion, HCV related liver disease is a significant problem in Swedish OST patients and may be an increasingly common cause of death. Thus, targeted management of HCV and risk factors for liver fibrosis progression should be an integral part of comprehensive care provided in OST clinics. Our findings of satisfactory completion rates with treatment based on peginterferon/ribavirin holds promise of even higher rates of both completion and SVR once new interferon free treatment regimens with higher efficacy, less toxicity and shorter duration, are implemented. However, for more efficient therapies to be able to impact morbidity and mortality, increasing uptake of HCV assessment and treatment for OST recipients is essential

Key words Hepatitis C, opiate substitution therapy, liver fibrosis, mortality, treatment completion

Classification system and/or index terms (if any)

Supplementary bibliographical information	Language English
ISSN and key title 1652-8220; Lund University, Faculty of Medicine Doctoral Dissertation Series 2014:136	ISBN 978-91-7619-065-4

Recipient's notes	Number of pages	Price
	Security classification	

I, the undersigned, being the copyright owner of the abstract of the above-mentioned dissertation, hereby grant to all reference sources permission to publish and disseminate the abstract of the above-mentioned dissertation.

Signature Date 2014-11-07

Hepatitis C virus infection in patients receiving opiate substitution therapy in Sweden

Anna Jerkeman

LUND
UNIVERSITY

Copyright Anna Jerkeman

Department of Clinical Sciences, Malmö
Faculty of Medicine, Lund University, Sweden
ISBN 978-91-7619-065-4
ISSN 1652-8220

Printed in Sweden by Media-Tryck, Lund University
Lund 2014

Till mina kära

Contents

List of papers 9
Paper I 9
Paper II 9
Paper III 9
Abbreviations 11
Introduction 13
Objectives 15
Background 17
Hepatitis C virology 17
Diagnosis 20
Epidemiology and natural history 21
Manifestations and effects of chronic HCV disease 22
Liver disease 23
Extrahepatic disease 24
Effects on quality of life 24
Effects on mortality 25
Assessment of liver fibrosis 25
Liver biopsy 26
Transient elastometry 27
Biochemical scoring systems 27
HCV treatment 28
The Swedish drug scene and opiate substitution treatment (OST) 31
HCV effects on morbidity and mortality in PWID 33
HCV prevention in PWID 34
HCV treatment in PWID 34

Methods and data collection 37
Study setting 37
Setting study I-II 37
Setting study III: 37
Study design 38
Study I 38
Study II 39
Study III 41
Statistical analysis 41
Study I 41
Study II 42
Study III 42
Results and Discussion 45
Prevalence of HCV infection 45
Burden and severity of HCV related liver disease in relation to risk factors 48
Feasibility of HCV treatment in the OST setting 49
Psychiatric status and health-related quality of life 52
Effect of OST on liver related mortality and all cause mortality in heroin users recruited from a needle-exchange program. 55
Conclusions 59
General discussion 61
Populärvetenskaplig sammanfattning 65
References 73

List of papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

Paper I

Jerkeman A, Westin J, Lagging M, Norkrans G, Lidman C, Frimand J, Simonsberg C, Kakko J, Widell A, Björkman P

Chronic hepatitis C in Swedish subjects receiving opiate substitution therapy-factors associated with advanced fibrosis.

Scandinavian journal of infectious diseases 2014;46:340-347.

Paper II

Jerkeman A, Norkrans G, Lidman C, Westin J, Lagging M, Frimand J, Simonsberg C, Kakko J, Widell A, Björkman P

Treatment for chronic hepatitis C in a cohort of opiate substitution therapy recipients in three Swedish cities - completion rates and efficacy.

European journal of gastroenterology & hepatology 2014;26:523-531.

Paper III

Jerkeman A, Håkansson A, Rylance R, Wagner P, Alanko-Blomé M, Björkman P

Death from liver disease in a cohort of injecting opioid users in a Swedish city in relation to registration for opioid substitution therapy

Manuscript

Abbreviations

Anti-HBc antibody	anti-hepatitis B core antibody
APRI	AST to platelet ratio index
ART	anti-retroviral therapy
AST	aspartate aminotransferase
AUROC	area under ROC (receiver operator characteristics)
BMI	body mass index
CMR	crude mortality rate
DAA	direct-acting antivirals
E1 and E2	envelope protein 1 and 2
EHM	extrahepatic manifestation
γGT	gamma-glutamyltransferase
GUCI	Göteborg University Cirrhosis Index
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HBV-DNA	hepatitis B virus deoxy-ribonucleic acid
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health related quality of life
HTA	host-targeting agent
HVR	hyper variable region
ICD	International Classification of Diseases and Related Health Problems
IL28B	interleukin 28B
INHSU	International Network on Hepatitis in Substance Users
INR	international normalized ratio
IQR	interquartile range
kPa	kilopascal

MADRS	Montgomery Åsberg Depression Rating Scale
MC	mixed cryoglobulinemia
MNEP	Malmö needle exchange program
MSM	men who have sex with men
NEP	needle exchange program
NIN	national identity number
NMMT	National Register of Methadone Maintenance Treatment
NS2-5	non-structural proteins 2 to 5
OST	opiate substitution therapy
PWID	people who inject drugs
PCR	polymerase chain reaction
Py	person-years
RNA	ribonucleic acid
SF-36	Short Form 36 health survey
SNBHW	Swedish National Board of Health and Welfare
SNP	single nucleotide polymorphism
SOC	standard of care
SPDR	Swedish Prescribed Drug Register
SVR	sustained virological response
TE	transient elastometry
WHO	World Health Organization

Introduction

Since the relatively recent discovery of the hepatitis C virus (HCV) in 1989[1], the accumulated knowledge about this pathogen and the disease it causes has grown exponentially.

We now know that approximately 170 million people worldwide are infected with this blood-borne virus, with widely varying prevalences (<1-15%) between countries[2]. A majority of infected subjects (75-90%) are unaware of their infection[3, 4]. Sweden is a country with a low estimated prevalence (<0.5%) corresponding to approximately 41 000 individuals with chronic infection[5].

After the initial years, when HCV infection was considered a relatively innocuous condition, with longer observation time, there has been a growing awareness of the long time consequences of chronic HCV infection with cirrhosis and end-stage liver disease as dreaded complications[6]. Without effective therapeutic interventions, the burden of disease related to these complications is expected to follow a continually upward slope over the next decade[7, 8]. Luckily, due to intense research in the field of HCV, treatment options for hepatitis C have improved immensely during the last decade and there is also clear evidence that successful treatment reduces the incidence of HCV complications[9, 10]. Even more efficient HCV therapies, with shorter treatment durations and fewer side effects will be introduced in the coming years and global HCV eradication has been discussed as a goal within reach[11].

In the Western World, people who inject drugs (PWID) constitute the core of the HCV epidemic both with regard to prevalence (60%) and incidence (80%)[12]. Still, treatment uptake among PWID has been low, only 1-10% of current or former PWID in Australia, Europe, Canada and the United States have received anti-HCV therapy[13-17]. Along with the rapid development in the therapeutic field there has been a growing consciousness of barriers to treatment for this group, existing on the patient, provider and system level[18]. It has become obvious that HCV therapeutic effectiveness in PWID is not only a question of drug efficacy but also of HCV awareness, diagnosis, assessment of liver disease and treatment access.

When assessing the importance of hepatitis C in the context of injection drug use, it is important to acknowledge that PWID have a multitude of factors that might influence patterns of morbidity and mortality. Compared to the general population,

drug users have higher rates of mortality mainly due to drug related causes such as drug overdoses, trauma and suicide[19-22]. This is particularly pronounced in opiate users, who have up to 15 times excess mortality[23].

Patients under opiate substitution therapy (OST) constitute a subset of opiate dependent drug users whose drug related mortality has been shown to be significantly reduced in several studies[24, 25], enabling other chronic diseases, among them HCV, to emerge as important factors for morbidity and mortality. The significance of chronic HCV disease in this setting has however not been fully elucidated. Besides reduced mortality, OST also confers better social functioning[26] and has been shown to improve HCV treatment outcomes for PWID[27], suggesting that OST programs could be suitable points of contact for HCV management in this group.

Objectives

This thesis investigates different aspects of HCV infection in Swedish OST recipients as a platform for further discussions and policymaking regarding HCV assessment and treatment in this group. The specific objectives were:

I To estimate the prevalence of HCV infection in a cohort of Swedish OST recipients.

II To assess the burden and severity of HCV related liver disease in relation to risk factors in the same cohort.

III To assess the feasibility of HCV treatment in OST recipients, in a multidisciplinary setting, with special attention to psychiatric status and health-related quality of life.

IV To evaluate the effect of OST on liver related mortality and all cause mortality in heroin users recruited from a needle-exchange program through linkage of data from national registers.

Background

Hepatitis C virology

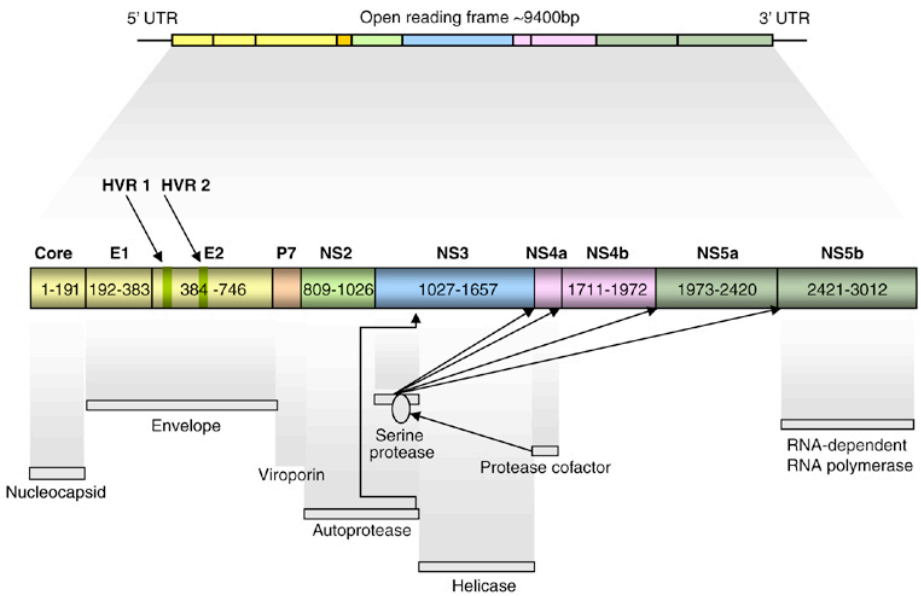

Figure 1. The hepatitis C virus genome.
The open reading frame of approximately 9400 nucleotides is translated into a single polypeptide. The polypeptide is cleaved into 10 proteins. Functions of protein products are indicated. From Lloyd AR, Jagger E, Post JJ, Crooks LA, Rawlinson WD, Hahn YS, et al. Host and viral factors in the immunopathogenesis of primary hepatitis C virus infection. Immunology and cell biology 2007;85:24-32. Reprinted with permission from Nature Publishing Group.

The hepatitis C virus is a positive-strand RNA virus. As a member of the genus hepacivirus, within the family of the Flaviviridae, it is unrelated to other hepatitis viruses affecting humans. The virus was first isolated in 1989[1] and the genome, consisting of approximately 9400 nucleotides, was sequenced in 1991[28]. The HCV life cycle has since been well described [29-32]. Through interaction with co-receptors on the surface of hepatocytes, the HCV particle enters the host cell via endocytosis. After cell entry, the viral RNA is uncoated and translated by host

ribosomes. The gene product is a polyprotein that is cleaved into three structural and seven non-structural (NS) proteins (Figure 1). The group of structural proteins consists of a nucleocapsid core (C) and two envelope proteins (E1, E2). The NS proteins, named NS2-NS5, have different functions, sometimes more than one. NS3 operates as both helicase and protease and NS5 has RNA polymerase activity. Together the non-structural proteins form a replication complex that replicates HCV RNA via a negative RNA strand, using the untranslated regions (UTR) in the 3´- and 5´-ends for initiation. The 5´UTR further contains an internal ribosomal entry site to initiate translation of the viral protein that is cleaved by host and viral proteases. Assembly of HCV RNA and structural proteins to form new viral particles is followed by viral exocytosis from the cell.

According to variations in the viral genome, seven different genotypes of HCV have been phylogenetically identified (Figure 2). Within these seven genotypes, a further division into 67 subtypes has been made[33]. Between genotypes, sequence similarity is approximately 70 % and within each subtype there is a variation of 20-25%[33]. The distribution of genotypes varies geographically [34, 35]. Some of them (genotype 1, 2 and 3) are distributed worldwide whereas others seem to be confined to certain regions. Genotype 4 is for example more common in the Middle East and Central Africa, genotype 5 is seen commonly only in South Africa and genotype 6 more often in South East Asia. The newest genotype 7 was found in patients in Belgium and Canada with a link to Central Africa. In Sweden, as in the rest of the Western world, genotypes 1, 2 and 3 seem to dominate. There is also a variation in genotype distribution related to route of transmission. Among European PWID, the most frequently occurring genotypes are genotype 1a and 3a, with a reported increase in genotype 4 in some countries [17].

Despite being an RNA virus, the hepatitis C virus has the unusual ability to establish chronic infection in humans. The basis for this phenomenon lies in the ability to modify and escape both innate and adaptive immune responses from the host. Some viral proteins (core, E2, NS3/4A, NS5A) have been shown to actively interfere with innate immunity, most notably the host interferon response. Importantly and as an effect of both rapid viral replication (10^{10} to 10^{12} virions per day) and lack of proof reading in the RNA polymerase, HCV soon after onset of infection starts to appear as a swarm of related viruses called quasispecies. Quasispecies are viral variants that are rapidly selected under the influence of the host´s humoral and cellular immune response, facilitating for viral escape and chronicity of infection. Another means of avoiding the immune defense is the heavy glycosylation of the HCV envelope proteins on the viral surface, thereby hiding potential antigenic epitopes. Likewise, since HCV particle formation, maturation and excretion is closely linked with fat metabolism, HCV circulates in the blood partly hidden in Very Low Density Lipid particles, for HCV called lipoviral particles, which also may hide HCV from immune recognition. Taken together - unless the host can provide early and efficient both innate and adaptive

immune responses and with, neutralizing antibodies and a Th1 response rather than Th2, this transient phase for clearance may be passed and the patient goes into a chronic infection, gradually exhausting the adaptive immune response[36, 37].

Figure 2. Hepatitis C virus phylogenetic tree.
Phylogenetic tree of 129 representative complete coding region sequences. Up to two representatives of each confirmed genotype/subtype were aligned and a neighbor joining tree constructed using maximum composite likelihood nucleotide distances between coding regions using MEGA5. Sequences were chosen to illustrate the maximum diversity within a subtype. Tips are labeled by accession number and subtype (*unassigned subtype). For genotypes 1, 2, 3, 4, and 6, the lowest common branch shared by all subtypes and supported by 100% of bootstrap replicates (n=1000) is indicated by •.

From Smith DB, Bukh J, Kuiken C, Muerhoff AS, Rice CM, Stapleton JT, et al. Expanded classification of hepatitis C virus into 7 genotypes and 67 subtypes: updated criteria and genotype assignment. Web resource. Hepatology 2014;59:318-327.

Diagnosis of HCV infection

Diagnosis of HCV infection is based on serological methods, on antigen detection and on molecular methods (polymerase chain reaction, PCR), the latter for HCV RNA detection.

Screening for anti HCV antibodies is performed by immunosorbent assays using recombinant antigens based on HCV core, NS3, NS4 and in some assays NS5 proteins. Although sensitivity and specificity of these tests are high, almost 100%, [38] false negative test results occur, especially in early HCV infection and in immunocompromised individuals. A reactive result of a screening antibody test can be confirmed with an immunoblot assay. These confirmatory tests use similar antigens, but each HCV antigen is instead placed as a separate band on a plastic strip. This allows for discrimination between antibodies to different HCV antigens. Reactivity to two or more antigens is regarded as confirmed HCV antibody and one band only as indeterminate, calling for a follow up sample in a month to see if further bands appear. More recently, a new approach has been applied on patient sera that are found positive in a screening antibody test. These sera are directly tested for viremia without previous immunoblot testing. If viremia is detected, no further confirmation of HCV antibody is necessary. However, if no viremia can be established, immunoblot is performed and follow-up testing by PCR is suggested.

Genotyping, in the clinical routine setting, is based on PCR targeting subgenomic regions such as core/E1 or NS5B, followed by sequencing and alignment with reference sequences. For more detailed characterization of the HCV genome, sequencing and phylogenetic analysis is performed on regions showing more diversity, such as the hypervariable region-1 of the E2 envelope protein.

In acute HCV infection, HCV-RNA is detectable in blood within 7-21 days after HCV transmission [39, 40] whereas anti-HCV antibodies appear on average 7 (range 3-12) weeks after HCV exposure. Thus, anti-HCV antibody test results may be negative in early acute hepatitis C infection. In this early phase, often referred to as the serological window phase, diagnosis relies on detection of HCV-RNA or HCV core antigen, but the finding must be confirmed by follow up sampling to verify that antibodies appear.

The presence of anti-HCV antibodies cannot differentiate between acute and chronic infection unless further bands appear by immunoblot during follow up in two subsequent samples, or if anti-HCV seroconversion is verified over a limited time period. It has not been possible to establish a valid specific IgM test similar to the useful IgM tests in hepatitis A and B. Following spontaneous or treatment induced viral clearance, anti-HCV antibodies most often persist but may decline and even disappear in some subjects.

The diagnosis of chronic HCV infection is based on the detection of both anti-HCV antibodies and HCV RNA in the presence of signs of chronic hepatitis either by elevated aminotransferases or by histology. In cases of newly acquired HCV infection, persistence of HCV RNA beyond six months defines chronic infection.

Epidemiology and natural history

The hepatitis C virus is effectively transmitted through blood exposure. Blood transfusions and invasive medical and surgical procedures are well known routes of transmission and most infections in resource-poor countries are still related to health-care related exposures, mostly unsafe injections, unscreened blood and tissue donations[41, 42]. Since the introduction of routine testing of blood donors in 1992, the iatrogenic spread of HCV in the Western world has been brought to a minimum and most HCV infections are now transmitted through injection of illicit drugs. People who inject drugs (PWID) dominate the HCV epidemic with respect to both incidence and prevalence[12, 43] in these regions. Although information on HCV incidence in PWID is scarce[17], estimates range between 10 and 40 cases per 100 person-years[44]. There are indications that the HCV incidence, in some PWID settings in the Western world, has decreased during recent decades[45-48]. However, in the group of young injectors (below 30 years of age) the incidence rate is still increasing and outbreaks of HCV have been described in this age group from different countries[49]. The global midpoint prevalence of anti HCV positivity in PWID has been estimated at 67%[12].

The risk of sexual transmission of HCV has been a matter of debate[50, 51], particularly if such transmission exists between heterosexual, monogamous partners. While some studies have reported on sexual transmission confirmed by molecular typing and with increasing risk with relationship duration, others have found little or no such risk. These conflicting results may be explained by the presence of confounding, alternate parenteral routes of household transmission, such as sharing of toothbrushes, razors, diabetic lancets needles and syringes. The risk of sexual HCV transmission in heterosexual, monogamous relationships seems to be low but increases in subjects with multiple sexual partners and sexually transmitted diseases, especially HIV. In recent years, there has been a rising number of reports of HCV infections among HIV positive men who have sex with men (MSM) [52, 53].

Vertical transmission from mother to child during pregnancy and delivery is possible, although a rare event. An estimated 4-8% of children born to HCV infected mothers acquire HCV infection[54, 55].

Since few subjects (approximately 10%) experience clinical symptoms of acute hepatitis after virus transmission, this phase of the infection often remains

unrecognized. In a minority of cases spontaneous viral clearance will occur, but the majority of patients (50-80%) develop a chronic HCV infection (Figure 3). The chance of spontaneous clearance is greater for younger individuals, for women, for those with a symptomatic course of their acute infection and for those infected with genotype 1. HIV co-infection and black ethnicity have been shown to diminish the chance of viral clearance[6, 56]. Specific single nucleotide polymorphisms (SNPs) in the interleukin 28B (IL28B) gene region on chromosome 19 have also been shown to impact the chance of HCV clearance [57]. This gene encodes IFN-λ3, an interferon with, as yet, unknown impact on viral control. In acute HCV infection, individuals with an unfavorable IL28B genotype, (rs12979860 CT or TT alleles), are significantly less likely to clear the acute infection compared to those with a favourable genotype (homozygous for the C allele). Clearance of HCV is a rare event after 6-12 months, and the persistence of HCV virus in the blood of more than 6 months is the definition of chronic infection[58].

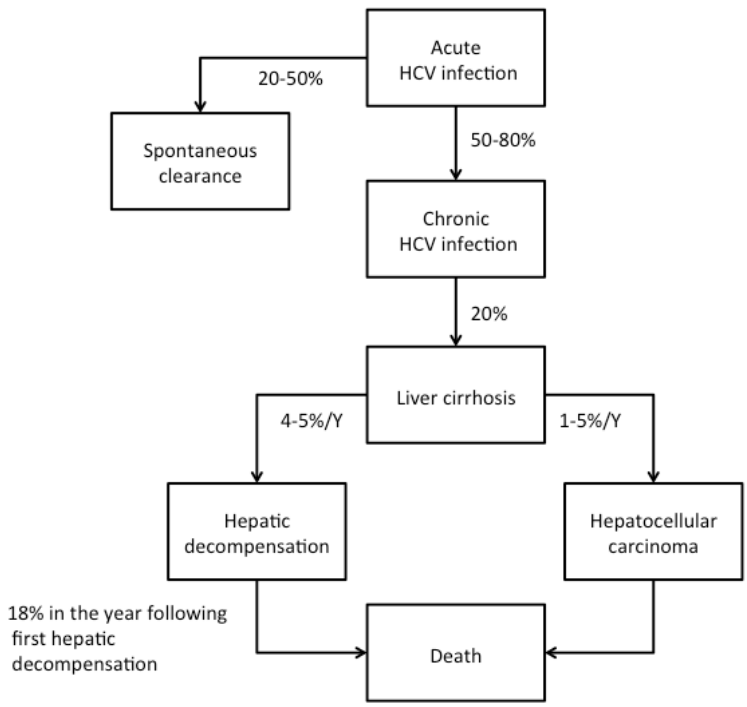

Figure 3. Natural history of HCV infection.

Manifestations and effects of chronic HCV disease

Liver disease

Chronic HCV infection is a slowly progressive disease with activation of the hepatic stellate cells and subsequent accumulation of fibrillar extracellular matrix as the key events in fibrogenesis (Figure 4)[59]. Evolving over decades, this process replaces liver parenchyma with scar tissue and, in its most advanced form, results in liver cirrhosis. It is estimated that up to 20% of chronic HCV patients will develop cirrhosis over 20 years time with an ensuing 1-5% annual risk of decompensation and/or hepatocellular carcinoma (HCC) [6, 60, 61] (Figure 3). The most common clinical sign of decompensation in HCV-related cirrhosis is ascites, followed by gastrointestinal bleeding[62]. The annual mortality rate in cirrhotic patients dramatically increases from 2-4%[10, 63] to 18%[64] after the first significant hepatic decompensation. In contrast to what is seen in chronic hepatitis B, HCC usually does not develop in non-cirrhotic, HCV infected livers. The appearance of HCC can frequently be the first clinical complication of HCV related liver cirrhosis, before evident hepatic decompensation[63].

However, there is a significant interindividual variability in the natural history of chronic HCV infection. The chronic inflammation, inflicted in the liver by HCV, evokes a parallel response of repair and fibrosis formation. Host, viral as well as external factors influence these processes and the net result of liver fibrosis. A number of reports have been published on the natural course of chronic HCV infection[6]. Some studies have shown a benign course over time, for example in young women exposed to HCV contaminated anti-D immunoglobulin where the rate of cirrhosis after 20 years was reported to be as low as 0.8%[65]. In contrast, in hospital based settings the incidence of cirrhosis was estimated above 30%[66]. These seemingly conflicting results may partly be due to selection bias, but also reflect that HCV natural history differs depending on the population studied and also the presence of competing and/or accelerating risk factors in this population. The slowly progressive nature of the fibrosis process also makes observation time an important variable. Difficulty assessing time for acute infection and problems following patients for sufficient lengths of time impedes reliable assessment of the natural course. Fibrosis progression does not seem to follow a linear rate but rather increases exponentially over time. In recent years, an increased understanding of a growing disease burden related to chronic HCV infection has emerged and dramatically rising numbers of deaths attributable to HCV are expected in the coming decades[7, 67].

Extrahepatic disease

Aside from its effect on the liver, HCV can also cause significant morbidity related to other organ systems[68]. In some patients, these extrahepatic manifestations (EHM) are the main features of the clinical picture and will affect both prognosis and treatment decisions.

The exact mechanisms behind these manifestations are not always identified and the causal relationship between HCV and the EHM has not always been established.

HCV has a tropism not only for hepatic cells but also for lymphatic cells[69], which is reflected in some of the EHM. The most common EHM is mixed cryoglobulinemia (MC), a B-lymphoproliferative condition, which is often asymptomatic but can also manifest itself in a number of disease entities, referred to as MC syndrome. Glomerulonephritis, systemic vasculitis, peripheral neuropathy, Raynaud´s syndrome and sicca syndrome can all be manifestations of MC. There is also a malignant potential in MC with up to 11% of patients developing lymphoma[70].

Other diseases with possible relation to HCV infection affect the endocrine system (diabetes mellitus, insulin resistance and thyroid disease), the skin (porphyria cutanea tarda, lichen planus) and joints (arthritis) [68].

Effects on quality of life

A number of studies have shown that chronic hepatitis C may be associated with worse outcome in measurements of health related quality of life (HRQoL)[71] which seems to affect not only patients with advanced liver disease but also individuals without significant liver damage[72-74]. This phenomenon could in part be explained by stigmatization due to HCV diagnosis or co-morbidities conferring poorer HRQoL status, which has been implicated in some studies[72, 75, 76]. Knowledge of the HCV diagnosis has, in itself, been shown to impair HRQoL[77]. However, several studies have demonstrated that HCV positive subjects have a reduction in HRQoL irrespective of their knowledge of HCV virological status[73, 78] and also that HRQoL improved after achievement of sustained virological response following antiviral therapy[79, 80], implicating a potential biological effect of HCV viremia in addition to the effects of comorbidities and psychosocial effects[81].

Effects on mortality

The effect of HCV on mortality in a certain population will depend on various factors. Duration of HCV infection, the presence of risk factors for liver fibrosis development, the presence of competing risk factors for mortality and access to HCV treatment are important aspects to be taken into account. The interplay of these different effectors is especially relevant in the PWID context. The principal disease-specific categories for mortality in HCV carriers are: liver related, drug related, HIV related and other causes[82]. The liver related category includes HCC and liver decompensation, while the drug related category encompasses drug overdoses and suicides. In a nation wide Swedish study of subjects chronically infected with HCV, the proportion of liver related deaths was 19% and drug related mortality 18%[83]. A similar pattern of distribution has been reported in other population-based studies[84-86].

Fibrosis promoting factors such as HIV or HBV co-infection and heavy alcohol use are highly prevalent in the PWID group. Active drug use with ensuing drug related mortality (overdose, violence, accidents and suicide) will overshadow the effects on mortality directly caused by HCV. In addition, uptake of HCV treatment in PWID has hitherto been low. The importance of duration of infection is illustrated by the fact that a high incidence of HCV infections in the 1960:s is now reflected in rising numbers of liver related deaths due to hepatitis C[87]. Projections into the coming decades foresee a substantial rise in HCV related mortality without large-scale diagnostic and therapeutic interventions[88-90].

Methods for the assessment of liver fibrosis

The prognosis of chronic HCV infection is tightly linked with degree of fibrosis; hence fibrosis assessment is a central feature of the diagnostic work up of the HCV patient. With regard to foreseeing prognosis and timing of HCV therapy, ability to define two steps in the fibrosis development process has been critical, those steps being significant fibrosis and cirrhosis. Significant fibrosis is defined histologically as at least portal fibrosis with a few septa on histological examination (Figure 4). Having reached this stage has hitherto been a clear indication for starting treatment. Whether the emergence of new, highly efficient HCV therapies with low toxicity will diminish the need for fibrosis assessment in treatment decision-making remains to be seen. It is most likely that, not least for economical reasons, defining the patients in most urgent need of therapy will be relevant also in the future.

There will also be a continuous need for identifying patients who have developed cirrhosis, and who will need surveillance for cirrhosis complications, in particular HCC, for which the incidence is increased even in subjects who achieve SVR.

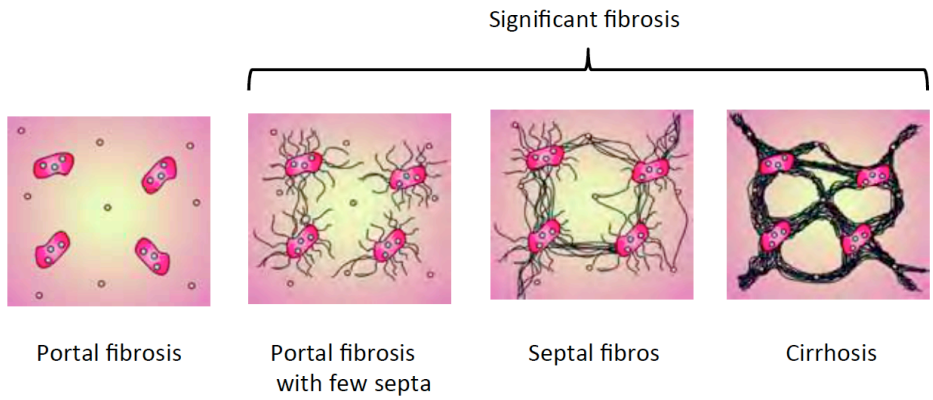

Figure 4. Progression of fibrosis.
Adapted from Asselah T, Bieche I, Sabbagh A, Bedossa P, Moreau R, Valla D, et al. Gene expression and hepatitis C virus infection. Gut 2009;58:846-858.

Liver biopsy

Liver biopsy has traditionally been considered the reference method for liver fibrosis classification. Different scoring systems are used (Ishak-Knodell, Batts-Ludwig, METAVIR) all of them separately assessing both the degree of inflammation (grade) and fibrosis (stage). Although often referred to as the gold standard method, liver biopsy assessment has limitations. The volume of liver represented in a liver biopsy is merely 1/50 000 of the total liver volume. Moreover, pathological liver processes are seldom evenly distributed in the liver parenchyma which confers a risk of sampling error[91]. Biopsy assessment by a pathologist is also subjective and the intra-and interobserver variability can be considerable[92].

The invasive nature of the liver biopsy also makes patient discomfort and risk of complications a clear disadvantage of this assessment method as well as the costs conferred by the need for in-hospital surveillance after the procedure.

Transient elastometry

Transient elastometry (TE) is a non-invasive method for liver fibrosis assessment introduced in 2003[93] and now widely used in routine health care. A mechanical pulse is generated by a transducer, on the skin surface, overlying the right liver lobe. The pulse is propagated through the liver tissue as an elastic shear wave, and the velocity of propagation is translated into a value for liver stiffness expressed in kiloPascal (kPa). With advancing fibrosis, the liver stiffness increases, resulting in a higher shear wave velocity, giving a higher TE value. Ten valid measurements are required for a correct calculation of the median TE value. The variability (interquartile range, IQR) of the measurements should not exceed 30%. For interpretation of results, validated cut-off values for different stages of fibrosis are used. Cut-off values for significant fibrosis range between 5.2-8.9 and for cirrhosis from 10.1-17.6 in studies evaluating patients with chronic HCV infection[93-99]. TE assesses 1/400 of the total liver volume compared to 1/50 000 in liver biopsy. The inter- and intraobserver variability has been shown to be generally low[100] but obesity, liver steatosis, extrahepatic cholestasis, vascular hepatic congestion and ascites are conditions that can result in failure to perform measurements or unreliable results.

AUROC (Area under the receiver operator characteristic curve) values are used to express the reliability of a diagnostic test classifying individuals in two groups; those with and those without a certain condition. The ROC curve is a graphical illustration obtained by plotting the true positive rate (sensitivity) against the false positive rate (1-specificity) at various threshold values. The area under the ROC curve expresses the probability that a randomly chosen individual with the condition will have a higher test value than a randomly chosen individual without the condition. Whereas a perfect test has an AUROC value of 1, a test is considered excellent with an AUROC value of >0.9 and good when this value exceeds 0.8[101]. When assessing TE performance, metaanalyses, while showing AUROC values above 0.8 for the diagnosis of significant fibrosis, have shown AUROC values for the diagnosis of cirrhosis to be above 0.9[102, 103]. Hence, TE performance in diagnosing cirrhosis is superior to that of diagnosing intermediate stages of fibrosis. It has been suggested that for improving the accuracy of assessment of significant fibrosis, TE may be used in conjunction with other methods, such as serum biomarkers or biopsy[102, 103].

Biochemical scoring systems

Another non-invasive mode of assessing liver fibrosis is measurement of serum markers reflecting the stage of hepatic fibrosis. Principally, there are two kinds of biochemical fibrosis markers: direct and indirect. These markers are often used in combinations to improve diagnostic performance.

The direct markers are products directly derived from the metabolism of hepatic extracellular matrix, with hyaluronan, procollagen type III, laminin, collagen type IV and YKL-40 being the most investigated[104]. The use of these markers, though attractive as reflectors of fibrogenesis, is somewhat limited by problems of availability and cost in the routine clinical setting.

The indirect markers are based on combinations of different serum parameters affected by liver damage. Although they do not directly reflect the process of fibrogenesis, there is a statistical association with liver fibrosis stage. Serum parameters such as platelet count, prothrombin-INR, AST and ALT reflect liver function and are checked on a regular routine basis in chronic hepatitis C patients, making these methods an easily accessible and affordable fibrosis assessment method in the routine management of these patients. Among the most commonly used and validated scoring systems are the AST-to-platelet ratio index (APRI)[105] and the FibroTest® (γGT, total bilirubin, haptoglobin, apolipoprotein A1, α2-macroglobulin – adjusted for gender and age)[106].

Combinations of assessment techniques

Much effort has been put in elaborating diagnostic algorithms where non-invasive methods are used in conjunction, with the aim of reaching adequate diagnostic accuracy and reserving liver biopsy for those where non-invasive methods are not sufficient[104]. These algorithms use the separate methods either synchronously or in a sequential manner. As an example, Sebastiani and co-workers by applicating a sequential technique, including two biochemical scores, were able to avoid nearly 50% of liver biopsies for significant fibrosis and 80% for cirrhosis[107]. Castera et al improved diagnostic performance by synchronously combining Fibroscan and a blood biomarker[108], an approach now recommended in the EASL(European Association for the Study of the Liver) guidelines for first line evaluation of patients with chronic HCV infection[109].

HCV treatment

HCV treatment has the aim of eradication of the HCV infection. Eradication is defined as non-detectable HCV-RNA 12 or 24 weeks after treatment cessation (sustained virological response, SVR) and significantly reduces the risk of liver fibrosis progression and end stage liver disease[9, 10]. In non-cirrhotic patients, resolution of liver disease may occur in most cases after SVR has been achieved[110].

Interferon for treatment of HCV infection was first introduced in 1986[111] showing modest SVR rates of 10-20%. With the addition of ribavirin [112, 113], response rates improved. However it was not until the introduction of pegylated interferon in 2001[114, 115] that SVR rates were substantially enhanced, reaching up to 50% for genotype 1 infected patients and up to 80% for non-genotype 1 infected patients. Apart from genotype, there are also other factors affecting SVR rates in interferon-based therapy. Lower baseline viral load, non-black ethnicity, favorable IL28B genotype and absence of cirrhosis are all factors associated with a greater chance for SVR with this treatment. Viral kinetics during interferon-based treatment is also predictive of virological response, with rapid decline in viral load enhancing the chance for SVR.

Until 2011, combination therapy based on pegylated interferon and ribavirin and with treatment durations of 24 to 48 weeks, has been the standard of care (SOC) HCV treatment. This regimen has conferred substantial toxicity, sometimes limiting tolerability for patients. Decompensated liver cirrhosis and severe psychiatric disease are examples of contraindications for this treatment. Frequently observed side effects due to pegylated interferon have been of psychiatric nature, for example insomnia, fatigue and depression. Up to 70% of patients treated with pegylated interferon report mild to moderate depressive symptoms and 20% to 40% suffer major depression[116]. Pegylated interferon/ribavirin therapy confers hematological toxicity with anemia, thrombocytopenia and leukopenia, sometimes requiring dose reductions and/or growth factors to be able to continue treatment. Dermatological toxicity is also a common problem associated with pegylated interferon/ribavirin therapy.

Advances in molecular virology have formed the basis for a thorough understanding of the HCV replication cycle and the development of HCV replicons, enabling identification of targets for new HCV drugs. In theory, every step of the HCV replication cycle could serve as a target for these direct acting antivirals (DAA:s). However, the majority of DAA compounds that are currently available on the market or under development, target one of two crucial steps in the HCV life cycle: polypeptide maturation (protease inhibitors) and HCV RNA synthesis. In 2011, the first DAA:s, the protease inhibitors boceprevir and telaprevir, were introduced. By adding these compounds to SOC treatment, the chance of achieving an SVR for treatment naïve genotype 1 patients was raised up to 75%[117-120]. However, efficacy for patients with unfavourable prognostic factors such as previous null response on SOC dual therapy and advanced liver fibrosis was considerably lower[121]. These first generation DAA:s also conferred added toxicity with more frequent and serious skin reactions and more marked anemia, sometimes requiring blood transfusion. Some studies also indicated that for patients with cirrhosis, boceprevir and telaprevir conveyed a risk of decompensation and even fatal outcomes[122]. Other shortcomings to this first generation of triple therapy were activity restricted to genotype 1 only,

unfavourable pharmacodynamics requiring dosing three times a day, and drug-drug interactions.

Since the introduction of the first DAA:s in 2011, a multitude of new DAA:s and also so called host targeting agents (HTA:s) are being evaluated. HTA:s constitute a class of drugs targeting structures in the host cell involved in the HCV life cycle, instead of affecting the virus itself.

These different compounds all share the quality of high antiviral effectiveness but differ in their barrier to resistance and genotypic activity.

Compounds of different classes, including pegylated interferon and/or ribavirin are given in combination to increase efficacy and to avoid selection of resistant strains. Some of these compounds have already been approved for clinical use and many more are expected to reach the market in the near future. Further development of these drugs with the aim of pangenotypic activity and high barrier to resistance is ongoing. Expectations are that more than 90% of infections will be cured with once daily, interferon free, all-oral regimens of short treatment durations. With these new, highly effective regimens, it seems that some pretreatment factors that have been important for predicting response to interferon based regimens, such as IL28B status, ethnicity and viral load, will no longer be predictive of outcome. Whether the presence of cirrhosis will remain a significant negative predictor for response remains to be determined. It is likely that with the broad choice of HCV compounds now coming available, HCV treatment will not only become more efficient but also more complex, challenging care givers to provide the best and most cost-effective regimen for each individual patient. For a list of current agents in use and under development, see Table 1.

Table 1
DAAs and HTAs in clinical use or under development in 2014

Agent class	Generation	Compound
NS3-4A protease inhibitors	First-wave, first-generation	Telaprevir
		Boceprevir
	Second-wave, first-generation	Simeprevir
		Faldaprevir
		Asunaprevir
		ABT-450/r
		Danoprevir/r
		Sovaprevir
		Vedroprevir
		IDX320
		Vaniprevir
	Second-generation	MK-5172
		ACH-2684
Nucleoside/nucleotide analogues	Nucleotide analogues	Sofosbuvir
		VX-135
	Nucleoside analogue	Mericitabine
Non-nucleoside inhibitors of the HCV RdRp	Thumb domain I inhibitors	BMS-791325
		TMC647055
	Thumb domain II inhibitors	Lomibuvir
		GS-9669
	Palm domain I inhibitors	Dasabuvir
		ABT-072
		Setrobuvir
NS5A inhibitors	First-generation	Daclatasvir
		Ledipasvir
		Ombitasvir
		PPI-668
		PPI-461
		ACH-2928
		GSK2336805
		BMS824393
		Samatasvir
	Second-generation	MK-8742
		ACH-3102
		GS-5816
Cyclophilin inhibitors	First-generation	Alisporivir
		SCY-635
Antagonist of miRNA-122	First-generation	Miravirsen

The Swedish drug scene and opiate substitution treatment (OST)

In Sweden, as in many other western countries, there was a substantial increase in the use of narcotic drugs, including opiates, during the later part of the 1960:s. Raw opium and later morphine base entered the illegal drug market in Sweden in the 1960s and heroin was introduced in Sweden in 1974. Currently, it is estimated that approximately 10 000 persons, mainly living in the three metropolitan areas, Stockholm, Gothenburg and Malmö, are heroin users in Sweden. Approximately 75% are men and the mean age in this group increased from 27 years in 1979 to 35 years in 1998[123]. Opioid users have up to 15 times excess mortality and the most common causes of death are directly drug related such as drug overdose, suicide and trauma[23].

In the early 1960s, methadone for treatment of opiate dependence was introduced by Dole and co-workers[124]. Dole and colleagues perceived opiate dependency as a physiological disease characterized by opiate deficiency, that could best be managed by substituting the patients with maintenance therapy with the drug. Later research has formed the notion of opiate dependence as a disease of drug induced, permanent neuronal changes in the brain´s reward and anti-reward systems that can be compensated for by substitution treatment[125]. Only a few years after its global introduction, in 1966, methadone treatment was introduced in Sweden, as one of the first countries in the world. Methadone is a synthetic, full opioid receptor agonist with slow onset and long duration allowing for once daily dosing. Buprenorphine is a combined partial opioid receptor agonist and antagonist also given once daily that was introduced in the late 1990s. Opiate substitution treatment (OST) with either methadone or buprenorphine has been shown to confer reduced drug related mortality, improved social functioning, less criminal behaviour and better quality of life for those who stay in treatment[24-26, 126]. OST has also been considered an important harm reduction measure for preventing transmission of blood borne diseases in people who inject drugs[127, 128].

In an international perspective, Swedish national drug policy has been restrictive, based on the vision of a drug free society[129]. OST has only been offered within acknowledged OST units approved by the Swedish National Board of Health and Welfare (SNBHW). Until 2005, there was an upper limit for the number of eligible patients for each OST unit and the criteria for admission were strict. Subjects receiving maintenance therapy for opiate dependence in Sweden have at least until 2005 had a long history of injecting drug use before inclusion in the OST program.

In 2005, new guidelines for OST were issued from the Swedish National Board of Health and Welfare with less strict admission criteria, resulting in a threefold

increase in the proportion of patients in treatment between 2000 and 2006[130]. A survey study performed by the National Board of Health and Welfare in 2007 showed that still only a minority of subjects with opiate dependence in Sweden were enrolled in OST, and it was estimated that only 30-40% out of 10 000 heroin users in Sweden received OST. A more recent survey, performed in 2012 by the same authorities, showed an increase of OST coverage with more than 5000 individuals in treatment[131] in 114 OST units.

HCV effects on morbidity and mortality in PWID

Injection drug use is linked to a multitude of medical conditions interacting with sociodemographic factors and with strong impact on morbidity and mortality in the PWID group. Both chronic conditions such as blood borne viral infections (in particular hepatitis B, hepatitis C and HIV), alcohol abuse, major psychiatric illnesses, and acute conditions such as sepsis, endocarditis, skin and soft tissue infections contribute to this burden of disease[132]. However, the major causes of death in PWID are still directly drug related ones, such as overdose and violence. A number of studies have shown high rates of death from drug related causes and also a great burden of inpatient care under drug related diagnoses in cohorts with chronic HCV infection, reflecting the close linkage between hepatitis C and injecting drug use[83, 133]. There are also studies showing that low socioeconomic status is associated with increased risk of HCV infection and with poor prognosis in HCV infected subjects[134]. The finding of higher mortality in siblings of HIV/HCV co-infected patients compared to siblings of HIV mono-infected[135] underlines that HCV infection is a marker of socioeconomic factors affecting mortality.

In the era prior to effective antiretroviral therapy (ART), in countries with high HIV prevalence among PWID, HIV infection was a major cause of death and disease, overshadowing the effect of other conditions frequent in PWID populations. With the advent of ART, the spectrum of disease has markedly changed[21]. The concept of competing risks seems equally relevant in PWID with chronic HCV infection. Young active drug users are at greater risk of dying from drug related causes, whereas in PWID who survive the short-term hazards of drug use, chronic conditions such as hepatitis C become more prominent as causes of death. In the aging PWID cohort, many subjects have been chronically HCV infected for several decades. A growing number of reports indicate that liver disease is emerging as an increasingly important determinant of morbidity and mortality in this group[83, 136-138]. Besides duration of the HCV infection, access to HCV care and treatment are factors that may impact the importance of HCV in PWID.

HCV prevention in PWID

Effective preventive measures are crucial to reduce the ongoing transmission and thereby the future burden of HCV related disease and mortality in PWID. Unlike the situation in hepatitis B, there is to date no efficient vaccine against HCV and prospects for a prophylactic or curative vaccine in the near future seem discouraging[139]. The effectiveness of harm reduction measures such as needle exchange programs (NEP) and opiate substitution therapy (OST) in preventing transmission of blood borne viruses (HIV, HCV) has been assessed in a number of studies[140]. While there is scientific evidence to support that NEP and OST can reduce injecting risk behaviour (sharing of needles, syringes and paraphernalia) and HIV transmission, these measures do not seem equally efficient when it comes to HCV. This difference could be attributable to a greater transmissibility of HCV (the per contaminated injecting exposure transmission is 2.5-5% for HCV [141-144] vs. 0.5-2.0% for HIV[143, 145-147]) and to a higher HCV prevalence. The combination of preventive measures of high coverage seems to be the most efficient way of substantially reducing HCV incidence and prevalence[140].

With the advent of new and highly efficient HCV drugs, some researchers have introduced the concept of treatment as HCV prevention. This strategy has been proven effective in preventing HIV transmission [148-150] although the impact on a population level and in certain subpopulations (eg MSM, PWID) remains to be elucidated.

Mathematical modeling has shown that NEP and OST are not alone sufficient to reach significant impact on HCV incidence and prevalence, but must be combined with antiviral treatment of PWID[151, 152]. Compared to HIV treatment in this context, HCV treatment has the advantage of being limited in time and with the goal to cure the infection. However, for the concept of HCV treatment as prevention to be effective, it has to be linked to extensive efforts to identify those PWID with undiagnosed infection and increase their access and willingness to care[153].

HCV treatment in PWID

In developed countries, PWID account for the vast majority of new HCV infections and the majority of chronic HCV infections are attributable to drug use[12]. Although international consensus documents since 2002 have advocated that PWID should be assessed for HCV treatment on a case-by-case basis[154] the uptake of treatment is still low [13-17]. A number of studies have tried to identify

the existing barriers to treatment and have found such barriers on the level of patients, health-care workers and on the system level[18].

For patients, lacking knowledge of their own HCV status and the long time consequences of HCV infection, the asymptomatic nature of the HCV infection, fear of invasive assessment procedures and treatment side effects, and competing priorities have been shown to hamper treatment willingness[18]. Some of these patient related barriers have been successfully addressed through patient education and peer support, most ideally in multidisciplinary settings engaging drug treatment capacity as well as somatic HCV expertise[27]. The emergence of non-invasive techniques for liver fibrosis assessment and less toxic HCV treatment regimens could enhance the rates of HCV evaluation and treatment uptake.

From the health care providers´ perspective, concerns of poor adherence, precipitation of preexisting drug abuse and psychiatric comorbidity and reinfection after viral clearance have been cited as reasons for deferring treatment[155]. However, recent meta-analyses have shown that HCV treatment may be feasible in the PWID context with rates of completion and SVR similar to those seen for non-PWID populations[156-158]. There are, as yet, no reports specifically targeting DAA based treatment in the PWID setting. However, given the benign side effect profile of these new regimens, it seems unlikely that toxicity would be a valid concern when treating PWID with DAA. There is also evidence that the rates of reinfection, in PWID who continue injection practice after achieving an SVR, is low[159].These findings might suggest that post treatment immunity may exist to some extent but also that HCV treatment may impact injection behavior in a favorable manner.

On the system level, lack of HCV guidelines specifically targeting PWID and lack of infrastructure for efficient delivery of HCV assessment and treatment have been examples of major barriers. The International Network on Hepatitis in Substance Users (INHSU) was established in 2009 and focuses specifically on hepatitis C in PWID. In 2013 an expert panel established by INHSU issued the first international recommendations for management of HCV in this group, [160] thereby supplementing existing international guidelines on HCV care by specifically addressing issues related to PWID in this field. A number of studies have described various multidisciplinary models, with HCV care provided within a context of collaboration of clinicians and nurses of different specialties, together with drug and alcohol services, psychiatric care and social support[161]. In meeting the various, and often complex, somatic, psychiatric and social needs of the PWID population, these models have proven successful. A recent meta-analysis has shown that HCV treatment within multidisciplinary teams positively affects the chance of SVR[27].

Methods and data collection

Study setting

Setting study I-II

Patients receiving OST in four public clinics in three metropolitan areas of Sweden (one each in Malmö and Gothenburg, two in Stockholm) on 1 April 2008 were eligible for inclusion in the cross-sectional cohort.

National criteria for OST at the time of inclusion were: at least 2 years of documented opiate abuse, a minimum age of 20 years, a history of several failed attempts of detoxification without substitution therapy, absence of advanced poly-drug abuse, Swedish citizenship and permanent housing.

Setting study III:

The Malmö needle exchange program (MNEP) was established in 1987 with the main aim to prevent HIV transmission in the PWID community. Besides needle exchange, the program offers basic health care and social support, as well as linkage to detoxification and assessment for OST, through close collaboration with representatives of addiction clinics and social services.

Criteria for participation in the MNEP are: age above 20 years, signs of ongoing injection drug use (injection marks), and acceptance of regular HIV testing. At registration, information regarding drug habits is collected. Blood samples for serological markers of HIV, HBV and HCV are drawn at regular intervals. Individuals included in the MNEP between 1987 and 2011, with available national identity numbers (NIN) were eligible for inclusion in this study.

Study design

Study I

Part 1: OST clinics

A structured questionnaire was used by a physician specialized in addiction medicine to interview study subjects on details concerning illicit drug use and OST. Information on alcohol consumption was provided by study subjects as well as by OST clinic staff.

Patients were also interviewed regarding symptoms possibly related to HCV infection and prior investigation and/or treatment of HCV infection.

Blood samples were collected for determination of HCV status. Anti-HCV antibodies were detected using local standard laboratory procedures (different enzyme- or chemiluminescence immunoassays). Seroreactive samples were further tested for HCV RNA by polymerase chain reaction (PCR). HCV genotype was determined for all viremic samples using an in-house nested PCR and sequencing of the NS5B region [162]. Patients with a previous registered positive result for HCV RNA were not retested. Patients with undetectable HCV RNA were re-tested after an interval of at least six months; subjects with at least two negative HCV RNA results were considered to have spontaneously resolved HCV infection.

Part 2: Departments of Infectious diseases

Viremic patients were offered structured assessment for liver disease at departments of infectious diseases including medical history, physical examination, blood sampling and fibrosis assessment.

The degree of fibrosis was assessed using three different techniques: liver biopsy, transient elastometry (TE) or the biochemical fibrosis index GUCI (Göteborg University Cirrhosis Index) score.

Using the Ishak protocol[163], liver biopsies were centrally scored, in a dual consensus fashion, by two experienced hepatopathologists without access to clinical information. Biopsies containing fewer than four portal tracts or measuring less than 1.5 cm were excluded. Significant fibrosis was defined as Ishak stages F3-F6. For statistical analysis of factors associated with fibrosis, Ishak F0-2 was defined as low-grade fibrosis, F3-4 as intermediate and F5-6 as high-grade fibrosis/cirrhosis.

Transient elastometry for measurement of liver stiffness was performed on the right liver lobe through intercostal access. Ten valid measurements with an interquartile range (IQR) less than 30% were required, using the median value for analysis. Significant fibrosis was defined as a stiffness value of ≥8.85 kPa and cirrhosis as a value of ≥10.05 kPa, using threshold levels derived by comparison with Ishak fibrosis staging according to Cross et al [96]. These cut-off values were used to categorize patients into low, intermediate and high-grade fibrosis for statistical analysis.

Göteborg University Cirrhosis Index (GUCI) score, a biochemical fibrosis index shown to be highly correlated to the Ishak fibrosis stage [164, 165] was calculated from the following formula: GUCI = (normalized AST x prothrombin-INR x 100)/platelet count (x 10^9). For GUCI scores, cut-off levels of 0.33 and 1.11 were used to categorize patients into these three categories.

In those subjects where results from several methods were available, liver biopsy was preferred over TE and GUCI score, and TE over GUCI score for categorization.

Factors possibly associated with fibrosis progression were evaluated statistically as per below (Statistical analysis).

Study II

Based on the structured investigation for HCV-related liver disease in study I, patients were eligible for antiviral treatment with pegylated interferon and ribavirin in study II. Exclusion criteria were HIV and/or HBV co-infection and a previous history of anti-HCV treatment.

Indication for antiviral treatment was determined by study investigators (all specialists in infectious diseases) at the respective sites, based mainly on the degree of liver fibrosis. In addition, the presence of other HCV-related disease and the patients' own wish to receive such treatment was considered as potential indications for therapy. Somatic contra-indications for antiviral therapy were also determined by these investigators, and included decompensated cirrhosis, concomitant severe somatic disease and various haematological and biochemical laboratory markers.

Patients were assessed by investigators at the respective addiction clinics (all specialists in addiction medicine and psychiatry) for their psychiatric status and drug abuse situation. No pre-determined criteria were used to define psychiatric contra-indications for antiviral therapy; the possibility to start antiviral therapy with regard to psychiatric and drug use situation was determined at the discretion of the specialist in addiction medicine and psychiatry.

Completion rates, adherence, virological treatment response, adverse events, health-related quality of life, signs of depression and relapse into drug abuse were evaluated at regular scheduled study visits.

For assessment of health related quality of life and depressive symptoms, standardized questionnaires were used (SF-36 and MADRS-s, respectively, see below).

SF-36 for assessment of health related quality of life

In the World Health Organization´s (WHO) definition of health it is stated that health is not only defined as the absence of disease but a state of complete physical, mental and social well-being. In order to address this notion of health as a multidimensional concept, different instruments for assessing health related quality of life (HRQoL) have been developed. These instruments evaluate both biological, psychological as well as social functioning.

The Medical Outcomes Study 36-item short form health survey (SF-36) is one of the most widely used generic HRQoL instruments. It has been used and validated in different populations including HCV and OST patients[166, 167]. The self-administered questionnaire consists of 36 items organized into 8 domains: physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH). The answers are transformed into a score ranging from 0 to 100 for each domain with higher scores indicating better HRQoL. Two comprehensive scores, the physical component summary (PCS) and mental component summary (MCS) are also calculated. Normative values from the Swedish population are available[168].

MADRS-s for evaluation of depressive symptoms

Montgomery Åsberg Depression Rating Scale (MADRS-s) is the self-rating version of the original MADRS instrument constructed for evaluating depressive symptoms. MADRS-s consists of 9 items, each of which is scored from 0 to 6[169]. Although MADRS-s is not a diagnostic instrument for depression, a total MADRS-s score less than 13 is considered to indicate absence of clinically relevant depression[170].

Baseline characteristics and baseline scores for HRQoL (SF-36) and depression (MADRS-s) were assessed in univariate analysis in relation to the study endpoints; completion of treatment, sustained virological response (SVR) and depression during treatment.

Study III

Participants in Malmö NEP (MNEP) who had reported heroin as their main drug of use at program entry were identified as heroin users. Identification of OST receipt for these subjects was made through linkage with data collected from three different data sources; the national register of methadone maintenance treatment (NMMT), the Swedish Prescribed Drug register (SPDR), as well as medical record data.

The NMMT was managed by the Swedish National Board of Health and Welfare (SNBHW) between the years 1989 and 2004. It contains data, including NIN and date for starting and stopping treatment, on patients registered in the OST programs in Sweden.

The SPDR contains data on all dispensed prescriptions in Sweden. Since 2005, data are retrievable for individual patients, through NIN.

Information pertaining to migration was collected from Statistics Sweden and date and cause of death was collected from the Cause of Death Register.

In the Cause of Death Register, causes of death are coded according to the International Classification of Diseases and Related Health Problems (ICD). For deaths occurring between 1987 and 1996 the ninth revision (ICD-9) is used and from 1997 the tenth revision (ICD-10) has been implemented. In this study, liver-related death was defined as death from: viral hepatitis (070 in ICD-9, B15-B19 and B942 in ICD-10), liver disease (570-573 in ICD-9 and K70-K77 in ICD-10) or liver cancer (155 in ICD-9 and C22 in ICD-10).

Statistical analysis

Study I

Differences among groups with regard to categorical variables were compared by the Chi square test, and continuous variables by the Mann-Whitney U test or Kruskal-Wallis 1-way ANOVA. Factors potentially associated with advanced fibrosis and cirrhosis (age, gender, BMI, years since start of injection drug use, cannabis use, smoking, anti-HBc positivity, indicators of problematic alcohol use) were evaluated by trend tests (for continuous variables the Jonckheere-Terpstra test, and for binary variables the linear by linear associations test) and multivariate analysis of factors showing a p-value for trend <0.20 was performed by logistic regression, entering data in a single step. All calculations were performed using the SPSS statistical software package, version 20.0.

Study II

The primary endpoint was completion of treatment, defined as completion of the full, intended treatment course. Patients who interrupted treatment prematurely due to virological stopping rules were also considered to have completed treatment. Secondary endpoints were adherence to treatment (calculated according to the 80/80/80 criteria[171]), SVR and depression during treatment.

Study endpoints were correlated to baseline characteristics (including baseline scores for HRQoL and depression) of the study population in univariate analysis, using Chi-square and Fisher´s exact test for categorical variables and Mann-Whitney U test for continuous variables. In this analysis, genotypes were categorized as genotype 1 versus non-1, fibrosis as low versus medium/high and high versus medium/low. All calculations were performed using the SPSS statistical software package, version 20.0.

Study III

Participants were categorized as non-OST recipients from the date of MNEP registration until the first registered date of OST prescription. Subjects who were identified as having been prescribed OST from any of the data sources mentioned above were onwards categorized as OST recipients (irrespective of the duration of OST). Consequently the same participant could belong to either category at different times during follow-up, depending on OST registration status.

Crude mortality rates (CMR) were calculated as the observed number of deaths divided by the number of person-years of follow-up.

The risk of liver-related mortality in relation to OST exposure was investigated using hazard ratios, calculated by means of Cox regression with OST as a time-dependent variable. Time at risk was calculated from registration in MNEP until death, emigration or 31 December 2011, whichever occurred first. For patients ever starting OST, time-at-risk after OST onset, was calculated from the first date of OST distribution until the end of the study.

Hazard ratios were presented with 95% confidence intervals, and the presence of an effect was tested using the Wald test. P-values below the standard value of 0.05 were considered statistically significant. The proportional hazards assumption was validated using log-log plots as well as goodness of fit tests.

All calculations were performed using the Stata 13 software.

Ethical considerations

All studies were approved by the Regional Ethical Review Board in Lund. Study III was also approved by the Swedish National Board of Health and Welfare. Written informed consent was obtained for all patients in study I-II. In study III, information about the study was advertised in a local free-of-charge newspaper, as well as in OST clinics and MNEP, for patients to be able to opt out from study participation.

Results and Discussion

Prevalence of HCV infection

Out of 524 eligible patients, registered for OST at the participating study sites on 1 April 2008, 277 (53%) consented to inclusion in the first part of study I, including blood sampling for determination of HCV status and a structured interview concerning details on illicit drug use, alcohol consumption, OST and former investigation and treatment for HCV disease (Figure 5). Patients were also asked for symptoms perceived as related to HCV infection before being presented with the results of HCV-antibody and HCV-PCR testing.

One hundred and eighty-seven of those included (68%) were men, and the median age was 44 years (range 22-64).

Seventy-three participants (26%) reported previous investigation for HCV disease, and 18 individuals (6%) had formerly ever initiated HCV treatment. Among 269 individuals tested, 236 (88%) were anti-HCV positive, indicating previous HCV exposure. Anti–HCV negative subjects had a significantly shorter time at risk (i e time in OST subtracted from time since first illicit drug injection) compared to those with positive HCV antibody status (4 vs 13 years, $p<0.0001$). HCV-PCR was performed for 234/236 anti-HCV positive patients, showing chronic HCV infection in 162 (69%). When subtracting the 9 patients who had cleared their infection through treatment, 63 individuals (27%) with spontaneous HCV resolution remained. The chance for spontaneous clearance was significantly greater for women than for men (38% vs 22%, $p=0.02$). The genotype distribution was as follows: genotype 1a 44%, 1b 7%, 2b 13% and 3a 32%.

Symptoms possibly related to HCV-infection were reported by 184/277 (66%) of patients, with fatigue as the most common complaint (132 patients, 48%), however no association between such symptoms and HCV-viremia could be detected.

In our material we found high rates of HCV exposure with anti-HCV antibodies present in almost 90% of tested patients. These figures are higher than the globally estimated midpoint prevalence of anti-HCV antibodies in PWID of 67%[12]. Previous studies have shown that the recruitment setting affects HCV prevalence in PWID, with higher prevalence seen in drug treatment centers, for example OST clinics, in comparison to low-threshold settings like needle exchange programs[172]. This can at least partly be explained by the fact that patients in

drug treatment centers often represent a subset of PWID with drug use of long duration. Longer time in injecting drug use, equivalent to longer time at risk for HCV acquisition, is associated with a higher likelihood of HCV seroconversion[45]. Also in our material, the association between time at risk and HCV status was evident, indicating that early recruitment into OST programs could be an important HCV-preventive measure among others.

A minority of included subjects (26%) reported previous HCV assessment, and even fewer (6%) had former treatment experience. These findings are consistent with those from other countries showing low rates of uptake of HCV treatment in PWID, ranging between 1 and 6%[13, 14, 16] although with a modest increase reaching 10% in recent years in some series[15].

Spontaneous clearance of HCV infection had occurred in 27% of our patients. This was a significantly more frequent event in women compared to men, a phenomenon described by other researchers and possibly attributable to hormonal differences[173, 174]. Higher estrogen levels in women have been proposed as a possible explanation. The fact that premenopausal women respond better than men to peginterferon/ribavirin based HCV therapy[175] and that this difference disappears after menopause[176], also suggests a hormonal effect.

Symptoms frequently reported by patients with chronic HCV infection are, for example, fatigue, myalgia, arthralgia, nausea and abdominal discomfort. These symptoms are unspecific and have not been found to be related to severity of liver disease[62]. In our material, fatigue was a common complaint, reported by two thirds of included patients. However, neither fatigue, nor any of the other reported symptoms showed any relation to the presence of viremia.

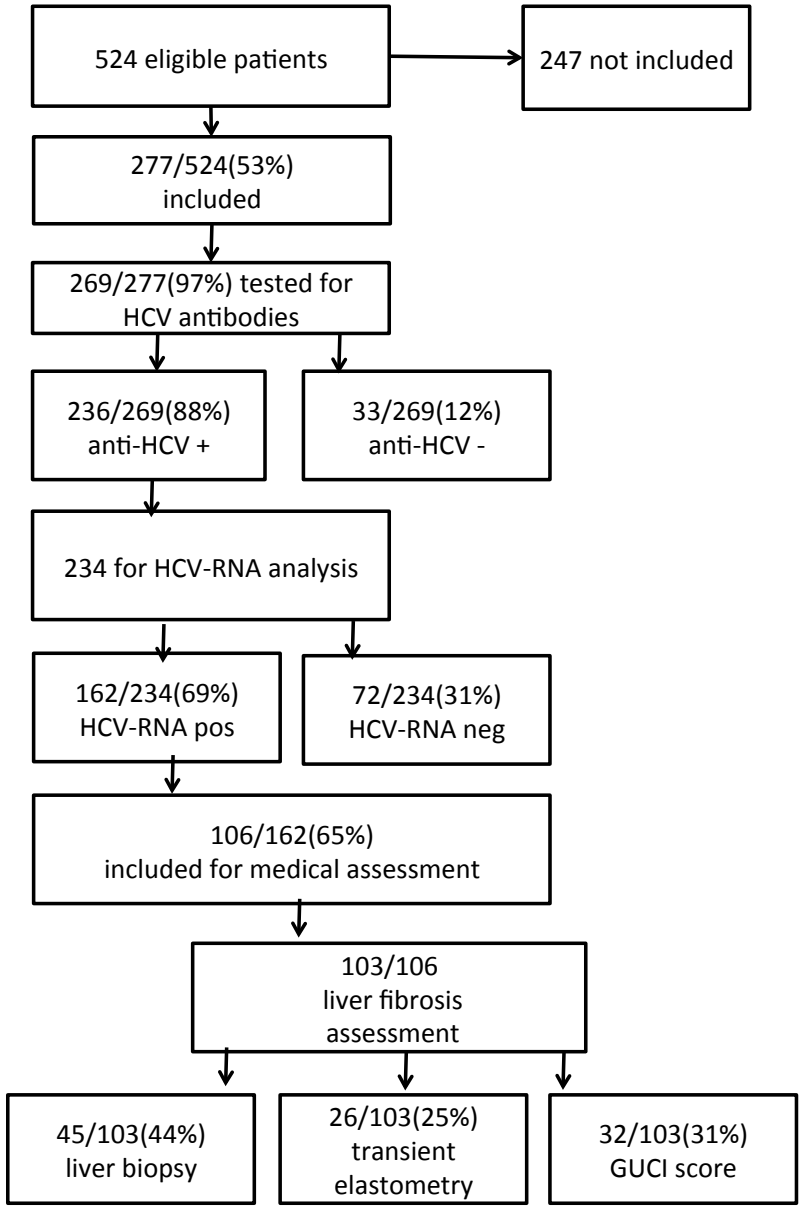

Figure 5.
Overview of study participation, Study I.

Burden and severity of HCV related liver disease in relation to potential risk factors

Among the 162 viremic subjects identified in the first part of study I, 106 consented to further evaluation of liver disease in the second part of study I (Figure 5).

The degree of fibrosis was categorized for 103 patients

Forty-five patients were evaluated with liver biopsy, 26 with TE and 32 with GUCI score. Results are shown in Table 2.

Significant liver fibrosis (defined as Ishak stages F3-F6, TE value ≥ 8.85 kPa or GUCI >0.33) was found in 69 out of 103 (67%) tested viremic patients and was associated with alcohol intake (p=0.03), higher body mass index (BMI; p=0.04) and presence of anti-HBc antibodies (indicating exposure to hepatitis B virus [HBV]; p=0.02).

These findings show a high prevalence of HCV-related liver fibrosis in Swedish OST recipients, and an association with frequently occurring phenomena in the OST setting, such as problematic alcohol use and obesity [177-180].

A number of studies from various countries have found a high prevalence of alcohol use, abuse and dependence in OST receiving subjects, with rates of alcohol-related problems up to 50%[177, 181-183]. However, due to lack of systematic screening and intervention measures for problematic alcohol consumption in OST clinics, this problem may be undetected[184]. Using different approaches to assess alcohol consumption, with information from both patients and clinic staff, we found indications of problematic use in a high proportion of the patients in our study, with for example 23% having been convicted for alcohol related crime, and OST clinic staff reporting problematic use in 17% of patients.

Animal studies indicate that the activation of opiate receptors in certain areas of the CNS is associated with the development of taste for sweet food, which in turn may explain the high rates of overweight and obesity seen in patients in OST[180]. Forty-three percent of the patients in our study were overweight and 24% could be defined as obese, illustrating that the problem of overweight is relevant also in the Swedish OST setting. The association seen in our study, between higher BMI and more advanced fibrosis, has been described in previous research. Progression of liver fibrosis and also increased risk of developing HCC might be mediated by the combination of liver steatosis and insulin resistance[185].

A majority (61%) of patients in our study showed sign of previous HBV exposure (presence of anti-HBc antibody), although only a minority (2%) had chronic HBV infection. The association found in our material between significant fibrosis and HBV exposure is in accordance with results from other researchers[186]. This

association might be explained by the fact that presence of anti-HBc antibody in some cases is a marker of occult hepatitis B infection, with HBV-DNA being detectable in liver tissue in spite of HBsAg negativity in plasma. Recent reports suggest that occult hepatitis B is a risk factor for progression towards cirrhosis in hepatitis C patients[187]. These findings underline the importance of offering early HBV vaccination in trying to promote liver health in the PWID setting.

Table 2.
Patients in each category of fibrosis by diagnostic method.

	Biopsy n (%)	**TE n (%)**	**GUCI n (%)**	**Total n (%)**
Low	21 (47)	12 (46)	1 (3)	34 (33)
Intermediate	18 (40)	0 (0)	17 (53)	35 (34)
High	6 (13)	14 (54)	14 (44)	34 (33)

Feasibility and efficacy of HCV treatment in the OST setting

Eighty-one HCV viremic patients had completed liver disease investigation in study 1. The main part of these patients (69/81, 85%) had an indication for treatment according to the infectious diseases specialist assessment, and for a majority (46/81, 57%), the indication was liver fibrosis/cirrhosis.

Among 69 patients with an indication for antiviral therapy, 41 (59%) initiated treatment (Figure 6). The reasons for not starting treatment were: HIV-coinfection (one, exclusion criterion for this study), patient's wish to defer treatment (seven), somatic contraindications (five), death prior to scheduled initiation (one). In eight cases the reason was unknown. For six patients, the psychosocial and drug use situation was considered to be too unstable to start antiviral treatment. Thirty-four out of 41 (83%) completed treatment, and 19/41 (46%) achieved SVR according to an intention to treat analysis. Among patients who received the full course of treatment, 19/27 (70%) achieved SVR, 5/8 (62%) for genotype 1 patients and 14/19 (74%) in genotype non-1 patients. Adequate adherence was observed in 29/41 patients (71%). Two serious adverse events occurred, including one death due to liver failure precipitated by gastroenteritis in a patient with previously compensated liver cirrhosis.

The completion rate of 83% in our study is in line with overall completion rates seen in previous studies on HCV treatment, based on peginterferon/ribavirin, in

PWID. In a recent meta-analysis on completion and efficacy of peginterferon/ribavirin-based HCV treatment in PWID, the pooled treatment completion rate was 83.4% (95% C.I 77.1%-88.9%)[27]. The SVR rate in our series of 46% was somewhat lower than the pooled SVR rate of 53% (95% C.I. 49.4%-56.6%) described in the same meta-analysis[27].

In light of the new therapeutic options becoming available in the near future, our figures hold promise of far better SVR rates, as our reported SVR rate reflects the suboptimal efficacy of the peginterferon/ribavirin regimen, rather than a low completion rate. The seven patients who stopped treatment prematurely due to virological non-response, represent a category of patients whose chances of cure will substantially improve with the new treatment options. These are in particular patients with genotype 1, advanced fibrosis/cirrhosis and unfavourable IL-28 genotype.

In seven patients, treatment was stopped prematurely due to adverse events, in five of these cases related to the study medications. Since the new HCV treatment options seem to convey far less toxicity, there is good reason to believe that better tolerability will raise SVR rates even further in this patient group.

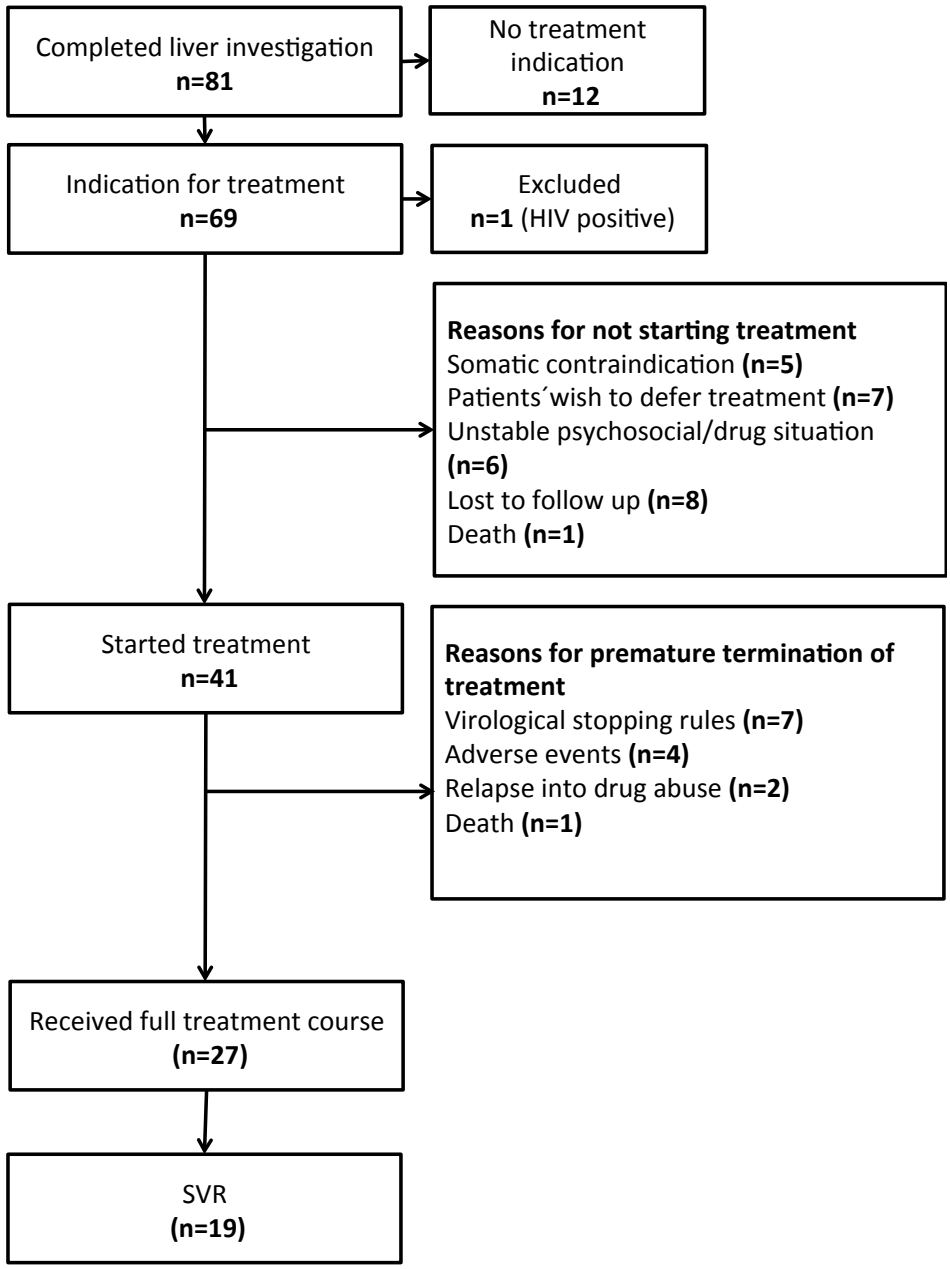

Figure 6.
Overview of study participation, Study II.

Psychiatric status and health-related quality of life

Psychiatric comorbidity was frequent among patients eligible for HCV treatment in our study. Twenty-five percent reported previous psychiatric diagnoses, with depression as the most prevalent.

Baseline scores for all dimensions of self-assessed health, by SF-36, were markedly lower, compared to the Swedish reference population[168], with a significant reduction during HCV treatment (Figure 8).

Thirty-four percent of those who initiated HCV therapy had a MADRS-s score indicating clinically relevant depression already at baseline, and 71% (29/41) fulfilled criteria for clinically significant depression at some time point during treatment (Figure 7). Ten patients were receiving antidepressive therapy already at initiation of HCV treatment, and another six patients commenced such treatment during the HCV therapy course.

There was no significant change in the percentage of positive drug screens during the course of HCV treatment, and a majority (67.5%) showed negative drug screens throughout the treatment period.

Younger age, higher MADRS-s scores and lower SF-36 summary scores for mental health (MCS) at baseline were associated with a significantly higher risk of developing depression during treatment. A low SF-36 score for physical functioning (PF) at baseline was associated with a significantly lower chance of completion.

There is a well-known association between drug use and psychiatric disorders[188, 189]. High rates of psychopathology and reduced quality of life have been described in OST patients[190, 191]. This vulnerable population might therefore be more sensitive to the psychiatric side effects of interferon-based therapy, which could possibly affect rates of treatment completion, relapse into drug abuse and development of depression during treatment. Despite low HRQoL and high occurrence of depression, HCV treatment was feasible and showed satisfactory rates of completion in this cohort of unselected OST recipients. We did not observe any significant change in the percentage of positive drug screens during treatment, indicating that there was no increase in relapses into drug abuse.

These results are concordant with research findings from other groups showing that psychiatric comorbidity is not generally associated with poorer adherence, treatment completion or SVR during peginterferon treatment[192-194]. Our findings of higher MADRS-s scores at baseline being associated with greater risk of developing depression during treatment is supported by previous reports[192].

The limited impact on outcome of pre-existing and evolving psychiatric morbidity in our study could be attributed to the active monitoring of depressive symptoms

and close collaboration between infectious disease specialists and psychiatric expertise. A number of studies in recent years, of various models of interdisciplinary cooperation, support this strategy[27, 195].

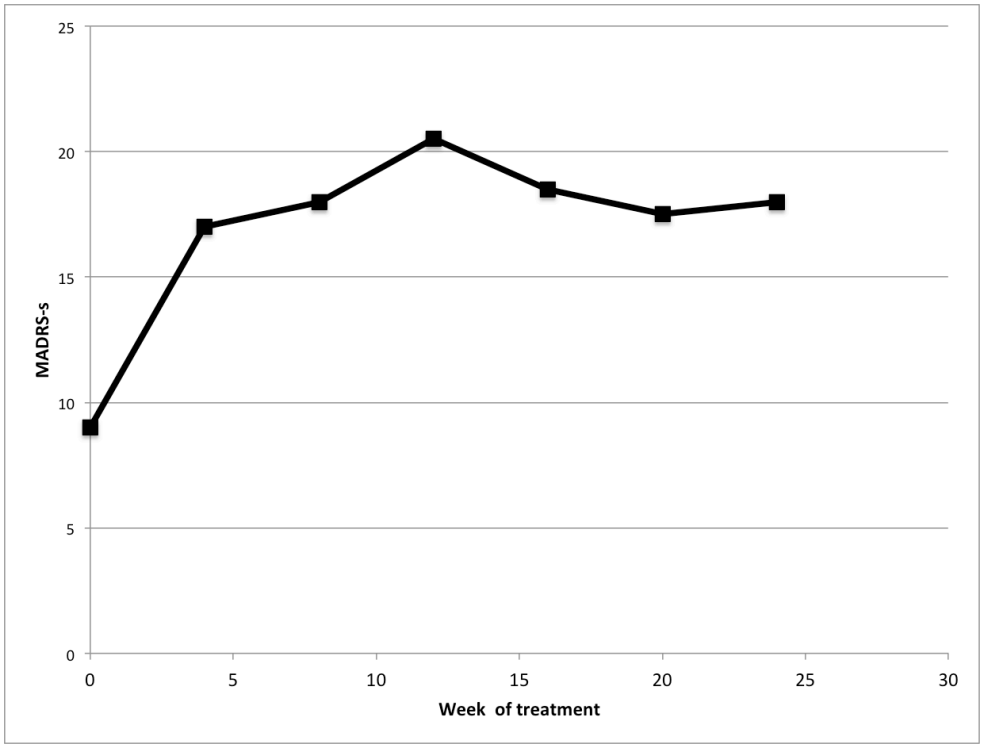

Figure 7.
Median MADRS-s score by week of treatment from baseline until week 24.

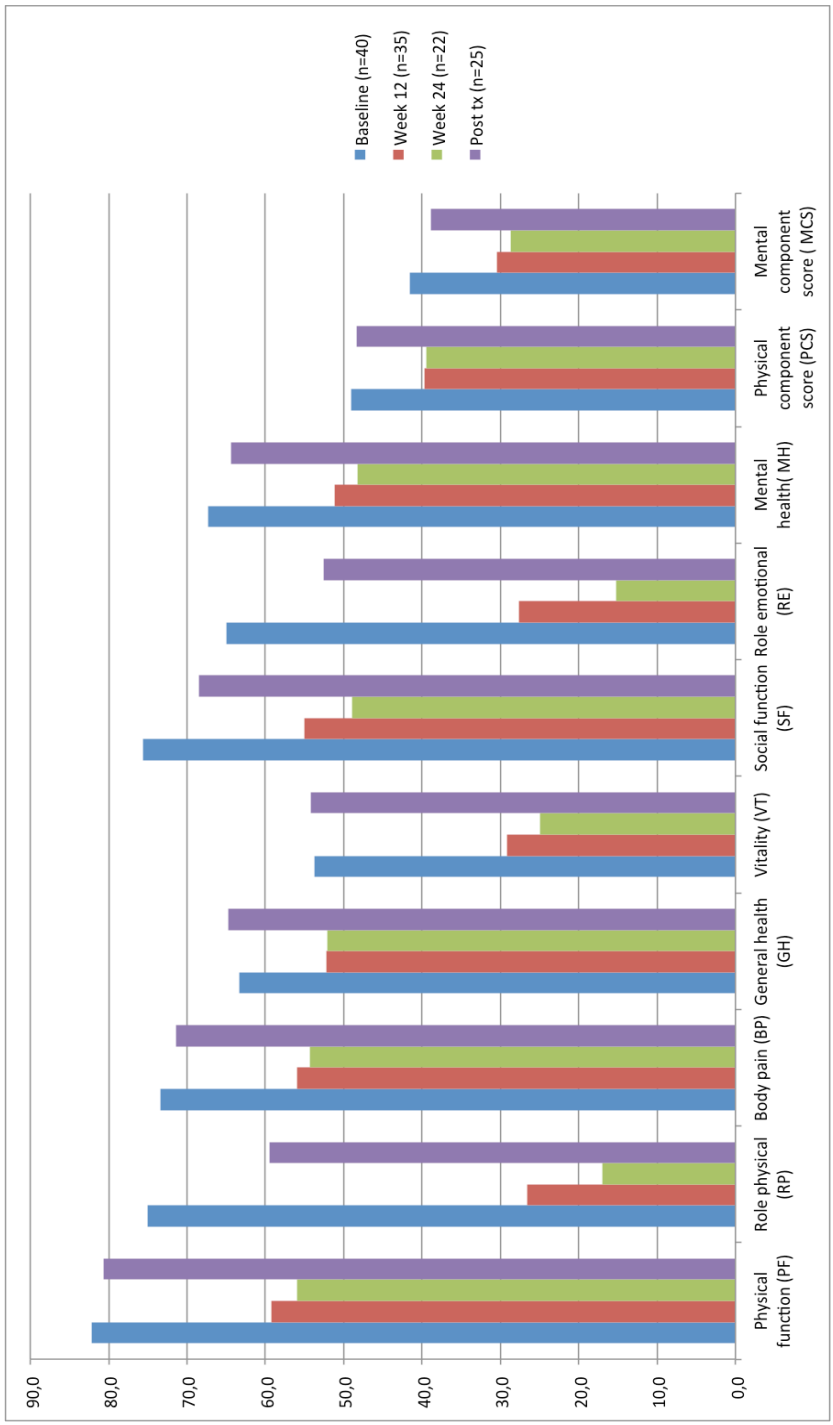

Figure 8.
Mean SF-36 scores for treated patients at baseline, by week of treatment and at follow-up.

Effect of OST on liver related mortality and all cause mortality in heroin users recruited from a needle-exchange program.

4494 individuals were registered in MNEP between 1987 and 2011. 1488 opioid users, with unique available NIN, were identified and eligible for further analysis. Prescriptions of OST were identified for 711 persons during the follow-up period. Participants were followed for a total of 15 546 person-years (py) (11 222 py without OST; 4324 py after OST initiation).

During these years of follow-up, 368 deaths occurred among the 1488 opioid users. In 83% of cases, death reports were based on autopsy. Sixteen deaths (4.3%) were caused by liver disease, and ten of these sixteen deaths occurred in OST recipients. When calculating a hazard ratio by Cox regression, we found that OST registration was associated with a significantly increased risk of liver related death (HR 3.08, 95% CI (1.09, 8.68) p=0.03) and this effect seemed more pronounced with longer follow-up time (Table 3).

The risk of all cause mortality did not show a statistically significant difference with regard to OST categorization (HR 1.05, 95%CI (0.83, 1.33).

All causes of death are shown in mutually exclusive categories in Figure 9. The categories applied have previously been described by Randall et al[196] for describing causes of death in PWID.

We hypothesized that OST, through reduction of drug related causes of death, would allow for progression of underlying, oftentimes HCV related, liver disease which in turn would allow for liver related death to become more prominent. The finding of a significantly raised risk of liver related death in relation to OST exposure supports this hypothesis. Interestingly, this elevation of risk in relation to OST could be detected, although the total number of liver related deaths was small. The major causes of death in the MNEP cohort were unnatural causes, with drug related deaths as the most prevalent (Table 4).

Although we did not investigate the prevalence of anti-HCV and HCV viremia in this study, previous data from the MNEP cohort show high levels of HCV exposure [197, 198]. These studies show baseline anti–HCV prevalences of 64% and 91% respectively and with persistently high seroconversion rates during follow up after MNEP inclusion, resulting in an increasing anti-HCV prevalence over time. Hence, it is reasonable to assume that HCV infection is a dominant cause of liver disease in this population. Yet, other etiologies or contributing factors could also be involved. Considering the natural history of chronic HCV, with complications of cirrhosis and end stage liver disease occurring after many decades, the median follow-up time in this study of 25 years, may be considered

too short. There are other studies pointing to the significance of liver disease as an increasingly important cause of death in the PWID setting[137, 138]. With an ageing PWID population, this effect becomes more pronounced. However, the design of these studies differs from ours. While the cited studies focus on subsets of PWID already admitted for drug abuse treatment, we wanted to examine the effect of OST on liver mortality by following a cohort of opioid using PWID, from recruitment from the same NEP, enabling us to assess the effect of OST receipt on liver mortality without the risk of selection bias.

Table 3
Hazard ratios for all cause and liver related mortality, distribution of person-years and crude mortality

Factor	Person years *(In thousands)*		Number of deceased (Crude mortality) Liver related		All	
	Non OST	*OST*	*Non OST*	*OST*	*Non OST*	*OST*
Age (years)[a]						
<30	7.1863	2.3872	2 (0.28)	1 (0.42)	153 (21.3)	47 (19.7)
30-39	3.3145	1.5706	1 (0.30)	4 (2.55)	80 (24.1)	51 (32.5)
40-49	0.6572	0.3344	2 (3.04)	4 (12.0)	23 (35.0)	9 (26.9)
50-59	0.0641	0.0312	1 (15.6)	1 (32.1)	2 (31.2)	3 (96.3)
Sex						
Female	3.4610	1.5990	1 (0.29)	3 (1.88)	41 (11.8)	22 (13.8)
Male	7.7612	2.7244	5 (0.64)	7 (2.57)	217 (28.0)	88 (32.3)
Inclusion year						
1989-	4.3318	1.7653	4 (4.33)	4 (2.27)	94 (21.7)	55 (31.1)
1994-	3.2580	1.1116	0 (0)	3 (2.70)	82 (20.3)	22 (19.8)
1999-	2.6281	0.8511	0 (0)	3 (3.52)	54 (20.5)	15 (17.6)
2004-	1.0041	0.5954	2 (1.99)	0 (0)	28 (27.9)	18 (30.2)
Follow-up time						
(years)						
0-	5.5046	0.9512	2 (0.36)	0 (0)	123 (22.3)	26 (27.3)
5-	3.1926	1.4573	1 (0.31)	4 (2.74)	64 (20.0)	35 (24.0)
10-	1.6809	1.1311	2 (1.19)	2 (1.77)	36 (21.4)	16 (14.1)
15-	0.7304	0.6333	1 (1.37)	4 (6.32)	25 (34.2)	20 (31.6)
20-	0.1135	0.1506	0 (0)	0 (0)	10 (88.1)	13 (86.3)
Total	11.2221	4.3234	6 (0.53)	10 (2.31)	258 (23.0)	110 (25.4)
HR			ref	3.08 (1.09 – 8.68)	ref	1.05 (0.83 – 1.33)
Adjusted HR[b]			ref	3.13 (1.11 – 8.83)	ref	1.07 (0.84 – 1.35)

[a] *Age at MNEP inclusion.* [b] *Adjusted for sex and age at inclusion*

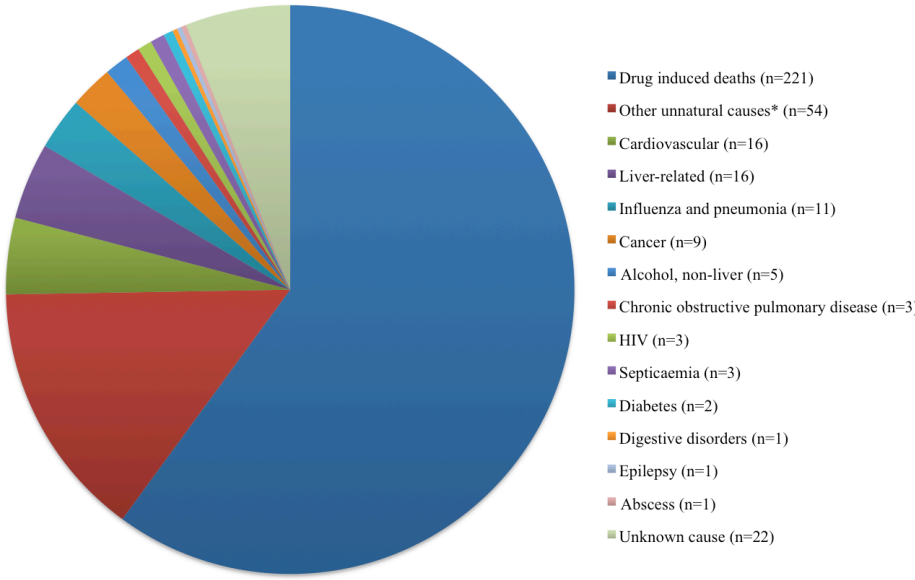

Figure 9.
Causes of death in the Malmö NEP.

*Includes causes related to accidents and violence

Conclusions

I HCV exposure and chronic hepatitis C infection is highly prevalent among Swedish OST recipients, and only a minority has been subject to liver disease assessment and antiviral therapy.

II The majority of Swedish OST recipients with chronic HCV infection show significant liver fibrosis, which is associated with higher alcohol consumption, higher BMI and previous exposure to hepatitis B virus.

III In spite of low baseline scoring for quality of life and high rates of depression, treatment of chronic hepatitis C infection in Swedish OST recipients is feasible in a multidisciplinary setting with acceptable rates of completion and SVR.

IV In heroin users recruited from a needle-exchange program there was a significantly raised risk of liver related death in relation to OST exposure, indicating the increasing proportion of liver disease as a cause of death with longer follow-up.

General discussion

In the Western world, the epidemic of HCV infection is closely linked to the epidemic of injection drug use. This poses challenges when it comes to prevention, detection, assessment and treatment of HCV disease.

This thesis is the first to address hepatitis C in the Swedish OST setting. Our results show high rates of hepatitis C exposure and significant liver fibrosis in a majority of patients. Alcohol consumption, obesity and HBV exposure were associated with severity of fibrosis and found to be common in this patient group. We show that hepatitis C treatment is feasible and with high completion rates, in spite of low HRQoL and high rates of depression. In trying to put into perspective the importance of liver disease for these patients, we show that liver disease affects mortality for OST patients.

The natural history of chronic hepatitis C infection in PWID and its impact on morbidity and mortality has been debated. There are few unselected, prospective studies with sufficient observation time investigating this question. There is a multitude of circumstances with the ability to impact on the natural course, for example competing mortality risks, presence of fibrosis promoting factors and access to HCV treatment. In recent years a growing body of evidence has been compiled, showing that HCV infection is a significant health problem in PWID[82].

In OST treated patients, the risk of directly drug related death is modified, giving chronic HCV infection a greater significance. In the studies forming the basis for this thesis, we have tried to shed light on the importance of HCV in the OST setting in two ways: by studying rates of chronic HCV and significant liver fibrosis in a cohort of OST recipients and by analyzing liver related mortality in NEP participants with and without OST. We conclude that HCV is a highly relevant problem also in the Swedish OST context and calls for greater emphasis on HCV assessment and treatment in Swedish OST clinics. Our results point out some obstacles that need to be addressed in striving for better hepatitis C care for these patients. More than 50% of eligible patients chose not to participate in the initial HCV screening and 24% of patients who initiated liver disease assessment did not complete it. Although we lack information on what grounds patients wished to defer HCV assessment, we could not see any difference in distribution of gender, age or time in OST for these patients. Limited uptake of HCV

assessment reflects multiple barriers on the patient and health care provider level previously described by other researchers[18].

Patient related factors are, for example, the asymptomatic nature of chronic HCV infection, poor knowledge of HCV and its long time consequences, competing priorities and fear of assessment procedures and treatment side effects. We know that referral of PWID to specialized outpatient clinics for HCV assessment has resulted in less than one third of admitted patients appearing for their appointment and even fewer ever starting treatment[13, 199]

For health care professionals, concerns about poor adherence and reinfection after HCV clearance have been put forward as arguments for not treating PWID. In addition, inadequate HCV knowledge among caregivers, for example in primary care and OST clinics has been shown to affect treatment access.

The OST clinic, on the other hand, is an existing infrastructure where HCV care could ideally be integrated. The Swedish model for OST means frequent return visits to the OST clinic with regular surveillance for illicit drug use and relapse into drug abuse. However, in spite of close follow up, since focus has been on addiction care rather than on comprehensive care for somatic as well as psychiatric and social conditions related to addiction, even advanced liver disease related to HCV is frequently not recognized.

Raising hepatitis C awareness in OST clinics could engage measures such as patient and staff education, peer support groups for patients and multidisciplinary approaches with regular presence by infectious diseases specialists. Routine HCV testing, including HCV-RNA for diagnosis of chronic HCV infection should be an integral part of OST care, given the high prevalence of infection in the patient population and limited contact with other care givers who could initiate HCV work up.

New, non-invasive methods for fibrosis assessment such as TE and/or biochemical scoring systems may diminish the need for liver biopsy as part of the assessment procedure and enable initiation of liver disease assessment in the OST clinic.

Given the frequent presence of risk factors for liver fibrosis progression in OST recipients, active management of these factors should be an essential part of HCV care in OST facilities. Moreover, risk factors such as alcohol use, obesity, cigarette smoking and infection with other blood borne viruses (HIV/HBV) are related not only to fibrosis progression but are known risk factors for both cancer and cardiovascular disease, entities that become relevant as well in ageing PWID. Alcohol consumption has a potent synergistic effect on HCV related fibrosis progression. Many studies have shown high rates of problematic use in OST recipients[179], and recently, significant effects of brief interventions in lowering alcohol consumption were reported[184]. Importantly, these studies showed that

delivery of both screening and interventions for problematic alcohol use was feasible in the daily OST setting.

With new treatment options now becoming available, some of the current barriers to treatment are also eliminated and new possibilities arise. More effective and shorter therapies, with better side effect profiles will probably increase treatment willingness among patients, provided that they are informed of this development.

For caregivers, important lessons can be learned from previous studies on HCV treatment in PWID, although these studies were based on peginterferon/ribavirin. Our findings, as well as results from other researchers, show that HCV treatment, provided in a multidisciplinary setting, is feasible in OST patients without jeopardizing OST stability[27, 200]. Thus, the notion among caregivers of poor adherence and completion rates, in this subset of PWID, is not substantiated by our findings. There is reason to believe that with new treatment options, even more patients will follow through on their treatment and a greater part will achieve an SVR with less side effects and increased efficacy of treatment. Our findings of low HRQoL and high rates of former and current psychiatric morbidity, point to important areas for intervention, that would possibly further improve treatment results.

A substantial rise in treatment uptake with new anti HCV agents will confer great costs for society. This will necessitate discussions and decisions on what the aims for these therapeutic efforts are. Efforts at the population level could make elimination of hepatitis C a realistic goal. These efforts would include scaling up measures such as OST and NEP, but also HCV treatment.

With hepatitis C elimination as goal, the crucial group to target with treatment would be active injectors, whose injection behavior makes them the main transmitters. The most active injectors are typically younger individuals, with recent initiation of injection drug use, with shorter duration of their HCV infection and consequently less advanced HCV related liver disease. This group of patients is at substantially greater risk of dying from direct drug-related causes than from hepatitis C. From the individual point of view, treating subjects with more advanced liver disease and therefore at risk for adverse effects on morbidity and mortality may seem more rational. However, these ageing injectors are much less active in their spreading behavior, why treatment focus in this group is not likely to affect HCV incidence.

In aiming for a reduced burden of HCV infections and HCV related liver disease, preventive measures remain a corner stone. The Swedish law regulating NEPs stipulate a minimum age of 20 years before entering these programs. Since the average age of first injection has been shown to be below this limit, young injectors are left at high risk of HCV infection. This is also consistent with reports showing an increasing HCV incidence in young injectors during recent years, in spite of a decreasing trend in the total number of reported HCV cases[49].

Expanding NEP availability for young injectors in combination with lowering thresholds for OST could possibly help prevent HCV spread in the younger age group.

Elaborating innovative models for delivery of HCV care for PWID should be a priority for the caregivers of different disciplines involved. Moreover, national and regional authorities have a responsibility in formulating strategies and providing financial support to catalyze this process. Only through such collaboration can the rapid development in the HCV therapeutic field translate into reduced morbidity and mortality in the PWID population.

Populärvetenskaplig sammanfattning

Hepatit C är idag den ledande orsaken till kronisk leversjukdom i västvärlden och även den vanligaste anledningen till levertransplantation. Sjukdomen orsakas av hepatit C-virus (HCV) och överförs i de flesta fall via blod. Majoriteten av de smittade (50-80%) kommer att utveckla en kronisk HCV-infektion.

Den ständigt pågående inflammation som virusinfektionen orsakar i levern leder, hos vissa patienter, till en tilltagande bindvävsomvandling där friska leverceller ersätts med ärrvävnad. Förloppet av infektionen är ytterst varierande mellan individer. Hos merparten finns inga tecken till allvarlig sjukdom, medan andra får en mer påtaglig leverskada.

Den mest uttalade formen av ärromvandling kallas cirrhos (skrumplever). Hos personer med kronisk HCV infektion kommer upp till 20 % att ha utvecklat cirrhos 20 år efter smittotillfället. Den som väl utvecklat en cirrhos löper sedan hög risk att drabbas av komplikationer som sviktande leverfunktion och levercancer.

Eftersom sjukdomen både i sin akuta och kroniska fas oftast inte ger upphov till några tydliga sjukdomssymptom är många patienter omedvetna om sin HCV infektion.

Diagnostik och behandling av HCV sjukdom har successivt förbättrats under det sista årtiondet. Målet med behandling är utläkning av HCV infektionen vilket medför en markant minskad risk för att drabbas av cirrhos och dess komplikationer.

De behandlingsregimer som hittills varit aktuella har dock medfört långa behandlingstider och ett flertal biverkningar, inte minst av psykisk natur, vilket gjort behandlingen svårtolererad för vissa patienter. De allra senaste årens explosionsartade utveckling på behandlingsområdet gör att vi inom en snar framtid kommer att ha tillgång till högeffektiva HCV läkemedel med korta behandlingstider och färre biverkningar.

I västvärlden är huvuddelen av HCV fallen relaterade till injektionsmissbruk. Flertalet injektionsmissbrukare smittas med HCV inom de första åren efter att de börjat injicera. Personer med erfarenhet av injektionsmissbruk utgör själva kärnan i HCV epidemin. Trots detta har andelen som behandlats för HCV infektion varit låg. Drogmissbruk är också förknippat med ett flertal andra riskfaktorer, utöver

HCV infektion, som påverkar hälsa och dödlighet. Flertalet dödsfall bland drogmissbrukare är relaterade till akuta konsekvenser av missbruket såsom överdoser, våld och olyckor. Risken för död är kraftigt förhöjd för missbrukare och den mest uttalat förhöjda risken ses hos heroinmissbrukare.

För att bryta ett beroende av heroin och heroinbesläktade droger krävs ofta behandling med läkemedel som ersätter drogen (sk läkemedelsassisterad rehabilitering vid opiatberoende (LARO) med metadon eller buprenorfin) i kombination med andra stödjande insatser. Sådan behandling ges i Sverige inom ramen för särskilda program via beroendevården. Dessa program är starkt reglerade av myndighetsföreskrifter och innebär för patienterna en tät kontakt med mottagningarna för bl a uppföljning av eventuella återfall i missbruk. Det finns ett starkt vetenskapligt stöd för att LARO behandling leder till minskad dödlighet, missbruk och kriminalitet.

Personer som erhåller behandling för heroinberoende har i regel ett mångårigt missbruk bakom sig, och har i de flesta fall också en mångårig kronisk infektion med HCV. Kronisk HCV infektion är en viktig orsak till både sjuklighet och dödlighet bland dessa patienter men hittills har påfallande lite uppmärksamhet ägnats åt att utreda och behandla sjukdomen i denna patientgrupp. Beroendeklinikerna har i första hand fokuserat på patienternas beroendesjukdom och har sällan skickat patienterna vidare till hepatitspecialister. Från hepatitläkarnas sida har man hänvisat till befarad dålig följsamhet och oro för att biverkningar under behandling kunde utlösa återfall i missbruk. Ett strukturerat samarbete kring dessa patienter har saknats.

Resultat från studier i andra delar av världen har visat att goda behandlingsresultat kan uppnås även hos patienter med missbruksbakgrund, i synnerhet i de fall där företrädare för både hepatitspecialiserad vård och beroendevård samarbetat.

I vår studie har vi på fyra utvalda LARO mottagningar i Sverige (Malmö, Stockholm och Göteborg), genom blodprover studerat förekomsten av kronisk HCV infektion. Genom ett nära samarbete mellan Infektionsklinik och Beroendeklinik på varje ort har vi utrett vilka leverskador patienterna har ådragit sig till följd av sin kroniska infektion och vilka riskfaktorer för utveckling av leverskada som finns. Patienterna har erbjudits behandling mot HCV infektionen, och i anslutning till denna behandling har vi med hjälp av skattningsformulär följt livskvalitet och tecken till depression.

För att studera huruvida spektrat av dödsorsaker hos injektionsmissbrukare förändras av LARO behandling har vi studerat dödsorsaker hos en grupp missbrukare som deltagit i ett sprutbytesprogram.

Våra resultat visar att hepatit C är vanligt förekommande i svenska LARO program. 88 % av patienterna hade utsatts för hepatit C smitta och av dessa hade 69 % utvecklat en kronisk HCV infektion. Bland kroniskt infekterade hade många patienter (67 %) utvecklat en betydande leverskada. Graden av leverskada var relaterad till alkoholkonsumtion, BMI och tidigare genomgången infektion med hepatit B.

Vi visar också att patienterna, trots låg skattad livskvalitet och hög andel med depressiva symptom, lyckades genomföra behandlingen i 83 % av fallen. 46 % av patienterna läkte ut sin hepatit C efter behandling.

Vi finner att dödsfall relaterade till leversjukdom får ökad betydelse vid LARO behandling. Risken att dö p g a leversjukdom var mer än tre gånger så stor vid LARO behandling än vid heroinberoende utan sådan behandling.

Våra resultat visar att hepatit C relaterad sjukdom är ett vanligt förekommande, behandlingsbart tillstånd inom svenska LARO program som riskerar att påverka patienternas liv och hälsa. Detta indikerar ett behov av förbättrade system för testning, utredning och behandling av hepatit C för patienter i LARO behandling i Sverige. Med de nya effektiva HCV-behandlingar som inom kort finns tillgängliga kan andelen utläkta med stor sannolikhet ökas påtagligt. Sjukdom och död till följd av hepatit C skulle då i många fall kunna förebyggas. Detta förutsätter dock att andelen LARO behandlade som utreds och behandlas påtagligt ökar vilket ställer oss inför utmaningar som handlar både om ekonomi och förändrade arbetssätt över specialitetsgränser inom vården.

Tack!

Först och främst vill jag tacka mina handledare Per Björkman och Anders Widell.

Per, du är en människa att beundra. Du kombinerar ett knivskarpt intellekt med sann humanism och omsätter detta i praktisk handling på så många sätt. Doktorander, studenter, patienter, kollegor, vänner, alla har vi ynnesten att få en del av dig. Ett Björkmandygn har många timmar! Närvarande även när du i perioder befunnit dig på andra sidan jordklotet. Lagom motvalls och allergisk mot lättköpta sanningar och floskler. Den underskruvade humorn och det karakteristiska skrattet som alltid är nära. Allt detta har varit avgörande ingredienser i detta avhandlingsarbete.

Man ska välja sin handledare med omsorg, och det gjorde jag. Utan dig hade detta projekt varken påbörjats eller lotsats i hamn. Tack, Per!

Anders, din like får man leta efter. Ett möte med dig är alltid spännande, aldrig tråkigt. Likt en cirkusakrobat svingar du dig ut i hisnande resonemang som för den fåkunnige understundom kan verka ha en minst sagt lös anknytning till ämnet för dagen. Efter halsbrytande saltomortaler från italiensk matlagning till radioapparater landar du, via ett inpass om din senaste resa, med stor precision i det aktuella resonemanget. Du har en enastående förmåga att fånga och sammanfatta essenser i talande bilder och därigenom förmedla något av din enorma kunskap inom virologin. Din nyfikenhet på naturvetenskapen och livet i stort är inspirerande. Tack!

Tack till mina kollegor och medförfattare Gunnar Norkrans, Christer Lidman, Jan Frimand, Christian Simonsberg, Johan Kakko och Marianne Alanko som bidragit med era olika kompetenser i denna långa process.

Tack till medförfattarna Johan Westin och Martin Lagging också för ganskning av leverbiopsier.

Tack medförfattare Anders Håkansson för lugn och skärpa samt ovärderlig input från beroendemedicinen.

Tack till Ulla Åkerholm, numera pensionerad forskningssjuksköterska, för fint samarbete och god CRF disciplin.

Tack alla övriga studiemedarbetare på Beroendekliniker och Infektionskliniker i Stockholm, Göteborg och Malmö för att ni oförtrutet arbetat med att lotsa patienterna genom studiernas alla vindlingar. Det här projektet har verkligen inspirerat till mer tvärdisciplinärt samarbete med er.

Tack Liz Jergle Almquist, monitor för de kliniska studierna. En klippa vid min sida. Med ett aldrig sviktande lugn har du tagit oss igenom allt från biobankslagar till apoteksavtal, från SUSAR rapportering till databasbyggande. Vi skulle kunna göra en road movie om vårt kuskande genom landet för prövarmöten och monitoreringar!

Tack Philippe Wagner och Rebecca Rylance samt Jonas Björk för att ni delat med er av ert brinnande intresse för statistik.

Tack Patrik Medstrand och Joakim Esbjörnsson för att ni gläntat på dörren till fylogenetikens underbara värld.

Tack Vilma Molnegren för omsorgsfullt och idogt laboratoriearbete, alltid med ett leende.

Tack professor Inga Odenholt för rappa, handfasta råd på vägen. Alltid redo!

Tack Peter Lanbeck för att du skapat en miljö på Infektionskliniken där forskning får ta plats samtidigt som vi förvaltar vårt adelsmärke: att med glädje och kvalitet bedriva klinisk läkekonst med varje patients bästa för ögonen.

Tack Peter Wiksell, numera min närmsta chef, för att du är en solid och tydlig möjliggörare (inte minst en schema-wizard) med ett oemotståndligt, smittande skratt.

Tack alla kollegor, ur olika yrkeskategorier, på Infektionskliniken för att ni i goda som hårda tider alltid får mig att förstå varför jag kände att jag kommit hem när jag kom till er. Professionalism, nyfikenhet och mycken glädje och humor. Svårslaget!

Tack Shering-Plough/MSD, Gilead och Region Skåne för finansiell stöttning som möjliggjorde detta projekt.

Tack alla vännerna och alldeles speciellt vandrarna/löparna, för värme, skratt, resor, god mat, peppning och visshet om att man duger precis som man är.

Tack mamma Margareta, pappa William för att ni, var och en på sitt sätt, utgjort stöd och fina förebilder. Mamma, du är min hjälte.

Tack alla kära syskon nära och långt borta. Ni gör mig rik. Alldeles särskilt tack till min stora, lilla syster. Vi har varandra.

Tack mina älskade barn, Lovisa, Matilda och Pelle. När jag ibland stretat i motvind har jag alltid kunnat vila i vetskapen om att jag fått förmånen att få vara er mamma. Ni gör mig så stolt, glad och förundrad.

Slutligen tack till mitt livs kärlek, min soulmate, Mats. Den mest nyfikna och fördomsfria människa jag vet. Som ständigt utmanar mig och får mig att våga fast jag inte törs. Med dig har resan inget slut.

References

[1] Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science 1989;244:359-362.

[2] Lavanchy D. Evolving epidemiology of hepatitis C virus. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 2011;17:107-115.

[3] In: Colvin HM, Mitchell AE, editors. Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C. Washington (DC); 2010.

[4] Hatzakis A, Wait S, Bruix J, Buti M, Carballo M, Cavaleri M, et al. The state of hepatitis B and C in Europe: report from the hepatitis B and C summit conference*. J Viral Hepat 2011;18 Suppl 1:1-16.

[5] Bruggmann P, Berg T, Ovrehus AL, Moreno C, Brandao Mello CE, Roudot-Thoraval F, et al. Historical epidemiology of hepatitis C virus (HCV) in selected countries. J Viral Hepat 2014;21 Suppl 1:5-33.

[6] Seeff LB. The history of the "natural history" of hepatitis C (1968-2009). Liver Int 2009;29 Suppl 1:89-99.

[7] Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings LW. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. Gastroenterology 2010;138:513-521, 521 e511-516.

[8] Deuffic-Burban S, Poynard T, Sulkowski MS, Wong JB. Estimating the future health burden of chronic hepatitis C and human immunodeficiency virus infections in the United States. J Viral Hepat 2007;14:107-115.

[9] Morgan TR, Ghany MG, Kim HY, Snow KK, Shiffman ML, De Santo JL, et al. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. Hepatology 2010;52:833-844.

[10] Veldt BJ, Heathcote EJ, Wedemeyer H, Reichen J, Hofmann WP, Zeuzem S, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. Ann Intern Med 2007;147:677-684.

[11] Hagan LM, Schinazi RF. Best strategies for global HCV eradication. Liver Int 2013;33 Suppl 1:68-79.

[12] Nelson PK, Mathers BM, Cowie B, Hagan H, Des Jarlais D, Horyniak D, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. Lancet 2011;378:571-583.

[13] Mehta SH, Genberg BL, Astemborski J, Kavasery R, Kirk GD, Vlahov D, et al. Limited uptake of hepatitis C treatment among injection drug users. Journal of community health 2008;33:126-133.

[14] Grebely J, Raffa JD, Lai C, Krajden M, Kerr T, Fischer B, 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;16:352-358.

[15] Iversen J, Grebely J, Topp L, Wand H, Dore G, Maher L. Uptake of hepatitis C treatment among people who inject drugs attending Needle and Syringe Programs in Australia, 1999-2011. J Viral Hepat 2014;21:198-207.

[16] Strathdee SA, Latka M, Campbell J, O'Driscoll PT, Golub ET, Kapadia F, et al. Factors associated with interest in initiating treatment for hepatitis C Virus (HCV) infection among young HCV-infected injection drug users. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2005;40 Suppl 5:S304-312.

[17] Wiessing L, Ferri M, Grady B, Kantzanou M, Sperle I, Cullen KJ, 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:e103345.

[18] McGowan CE, Fried MW. Barriers to hepatitis C treatment. Liver Int 2012;32 Suppl 1:151-156.

[19] Fugelstad A, Annell A, Rajs J, Agren G. Mortality and causes and manner of death among drug addicts in Stockholm during the period 1981-1992. Acta psychiatrica Scandinavica 1997;96:169-175.

[20] Arendt M, Munk-Jorgensen P, Sher L, Jensen SO. Mortality among individuals with cannabis, cocaine, amphetamine, MDMA, and opioid use disorders: a nationwide follow-up study of Danish substance users in treatment. Drug and alcohol dependence 2011;114:134-139.

[21] Bargagli AM, Hickman M, Davoli M, Perucci CA, Schifano P, Buster M, et al. Drug-related mortality and its impact on adult mortality in eight European countries. European journal of public health 2006;16:198-202.

[22] Merrall EL, Bird SM, Hutchinson SJ. Mortality of those who attended drug services in Scotland 1996-2006: record-linkage study. The International journal on drug policy 2012;23:24-32.

[23] Degenhardt L, Bucello C, Mathers B, Briegleb C, Ali H, Hickman M, et al. Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies. Addiction 2011;106:32-51.

[24] Gibson A, Degenhardt L, Mattick RP, Ali R, White J, O'Brien S. Exposure to opioid maintenance treatment reduces long-term mortality. Addiction 2008;103:462-468.

[25] Gronbladh L, Ohlund LS, Gunne LM. Mortality in heroin addiction: impact of methadone treatment. Acta psychiatrica Scandinavica 1990;82:223-227.

[26] Marsch LA. The efficacy of methadone maintenance interventions in reducing illicit opiate use, HIV risk behavior and criminality: a meta-analysis. Addiction 1998;93:515-532.

[27] Dimova RB, Zeremski M, Jacobson IM, Hagan H, Des Jarlais DC, Talal AH. Determinants of Hepatitis C Virus Treatment Completion and Efficacy in Drug Users Assessed by Meta-analysis. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2012.

[28] Choo QL, Richman KH, Han JH, Berger K, Lee C, Dong C, et al. Genetic organization and diversity of the hepatitis C virus. Proceedings of the National Academy of Sciences of the United States of America 1991;88:2451-2455.

[29] Lindenbach BD. Virion assembly and release. Current topics in microbiology and immunology 2013;369:199-218.

[30] Lohmann V. Hepatitis C virus RNA replication. Current topics in microbiology and immunology 2013;369:167-198.

[31] Niepmann M. Hepatitis C virus RNA translation. Current topics in microbiology and immunology 2013;369:143-166.

[32] Zeisel MB, Felmlee DJ, Baumert TF. Hepatitis C virus entry. Current topics in microbiology and immunology 2013;369:87-112.

[33] Smith DB, Bukh J, Kuiken C, Muerhoff AS, Rice CM, Stapleton JT, et al. Expanded classification of hepatitis C virus into 7 genotypes and 67 subtypes: updated criteria and genotype assignment Web resource. Hepatology 2014;59:318-327.

[34] Pybus OG, Charleston MA, Gupta S, Rambaut A, Holmes EC, Harvey PH. The epidemic behavior of the hepatitis C virus. Science 2001;292:2323-2325.

[35] Simmonds P. Variability of the hepatitis C virus genome. Curr Stud Hematol Blood Transfus 1998:38-63.

[36] Rehermann B. Hepatitis C virus versus innate and adaptive immune responses: a tale of coevolution and coexistence. The Journal of clinical investigation 2009;119:1745-1754.

[37] Thimme R, Binder M, Bartenschlager R. Failure of innate and adaptive immune responses in controlling hepatitis C virus infection. FEMS microbiology reviews 2012;36:663-683.

[38] Colin C, Lanoir D, Touzet S, Meyaud-Kraemer L, Bailly F, Trepo C. Sensitivity and specificity of third-generation hepatitis C virus antibody detection assays: an analysis of the literature. J Viral Hepat 2001;8:87-95.

[39] Mosley JW, Operskalski EA, Tobler LH, Andrews WW, Phelps B, Dockter J, et al. Viral and host factors in early hepatitis C virus infection. Hepatology 2005;42:86-92.

[40] Farci P, Alter HJ, Wong D, Miller RH, Shih JW, Jett B, et al. A long-term study of hepatitis C virus replication in non-A, non-B hepatitis. N Engl J Med 1991;325:98-104.

[41] Averhoff FM, Glass N, Holtzman D. Global burden of hepatitis C: considerations for healthcare providers in the United States. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2012;55 Suppl 1:S10-15.

[42] Hauri AM, Armstrong GL, Hutin YJ. The global burden of disease attributable to contaminated injections given in health care settings. International journal of STD & AIDS 2004;15:7-16.

[43] Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. The Lancet Infectious diseases 2005;5:558-567.

[44] Grebely J, Lima VD, Marshall BD, Milloy MJ, DeBeck K, Montaner J, et al. Declining incidence of hepatitis C virus infection among people who inject drugs in a Canadian setting, 1996-2012. PloS one 2014;9:e97726.

[45] Hagan H, Pouget ER, Des Jarlais DC, Lelutiu-Weinberger C. Meta-regression of hepatitis C virus infection in relation to time since onset of illicit drug injection: the influence of time and place. American journal of epidemiology 2008;168:1099-1109.

[46] Mehta SH, Astemborski J, Kirk GD, Strathdee SA, Nelson KE, Vlahov D, et al. Changes in blood-borne infection risk among injection drug users. The Journal of infectious diseases 2011;203:587-594.

[47] van den Berg CH, Smit C, Bakker M, Geskus RB, Berkhout B, Jurriaans S, et al. Major decline of hepatitis C virus incidence rate over two decades in a cohort of drug users. European journal of epidemiology 2007;22:183-193.

[48] 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. The Medical journal of Australia 2014;201:326-329.

[49] Page K, Morris MD, Hahn JA, Maher L, Prins M. Injection drug use and hepatitis C virus infection in young adult injectors: using evidence to inform comprehensive prevention. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2013;57 Suppl 2:S32-38.

[50] de Waure C, Cefalo C, Chiaradia G, Sferrazza A, Miele L, Gasbarrini G, et al. Intrafamilial transmission of hepatitis C virus in Italy: a systematic review. Journal of epidemiology and community health 2010;64:843-848.

[51] Wejstal R. Sexual transmission of hepatitis C virus. J Hepatol 1999;31 Suppl 1:92-95.

[52] Wandeler G, Gsponer T, Bregenzer A, Gunthard HF, Clerc O, Calmy A, et al. Hepatitis C virus infections in the Swiss HIV Cohort Study: a rapidly evolving epidemic. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2012;55:1408-1416.

[53] Witt MD, Seaberg EC, Darilay A, Young S, Badri S, Rinaldo CR, et al. Incident hepatitis C virus infection in men who have sex with men: a prospective cohort analysis, 1984-2011. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2013;57:77-84.

[54] Yeung CY, Lee HC, Chan WT, Jiang CB, Chang SW, Chuang CK. Vertical transmission of hepatitis C virus: Current knowledge and perspectives. World journal of hepatology 2014;6:643-651.

[55] Wejstal R, Widell A, Mansson AS, Hermodsson S, Norkrans G. Mother-to-infant transmission of hepatitis C virus. Ann Intern Med 1992;117:887-890.

[56] Thomas DL, Astemborski J, Rai RM, Anania FA, Schaeffer M, Galai N, et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. JAMA : the journal of the American Medical Association 2000;284:450-456.

[57] Thomas DL, Thio CL, Martin MP, Qi Y, Ge D, O'Huigin C, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. Nature 2009;461:798-801.

[58] Seeff LB, Hoofnagle JH. National Institutes of Health Consensus Development Conference: management of hepatitis C: 2002. Hepatology 2002;36:S1-2.

[59] Lee UE, Friedman SL. Mechanisms of hepatic fibrogenesis. Best practice & research Clinical gastroenterology 2011;25:195-206.

[60] John-Baptiste A, Krahn M, Heathcote J, Laporte A, Tomlinson G. The natural history of hepatitis C infection acquired through injection drug use: meta-analysis and meta-regression. J Hepatol 2010;53:245-251.

[61] Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology 2008;48:418-431.

[62] Maasoumy B, Wedemeyer H. Natural history of acute and chronic hepatitis C. Best practice & research Clinical gastroenterology 2012;26:401-412.

[63] Sangiovanni A, Prati GM, Fasani P, Ronchi G, Romeo R, Manini M, et al. The natural history of compensated cirrhosis due to hepatitis C virus: A 17-year cohort study of 214 patients. Hepatology 2006;43:1303-1310.

[64] Planas R, Balleste B, Alvarez MA, Rivera M, Montoliu S, Galeras JA, et al. Natural history of decompensated hepatitis C virus-related cirrhosis. A study of 200 patients. J Hepatol 2004;40:823-830.

[65] Wiese M, Berr F, Lafrenz M, Porst H, Oesen U. Low frequency of cirrhosis in a hepatitis C (genotype 1b) single-source outbreak in germany: a 20-year multicenter study. Hepatology 2000;32:91-96.

[66] 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;349:825-832.

[67] Rein DB, Wittenborn JS, Weinbaum CM, Sabin M, Smith BD, Lesesne SB. Forecasting the morbidity and mortality associated with prevalent cases of pre-cirrhotic chronic hepatitis C in the United States. Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver 2011;43:66-72.

[68] Zignego AL, Gragnani L, Giannini C, Laffi G. The hepatitis C virus infection as a systemic disease. Internal and emergency medicine 2012;7 Suppl 3:S201-208.

[69] Zignego AL, Giannini C, Monti M, Gragnani L. Hepatitis C virus lymphotropism: lessons from a decade of studies. Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver 2007;39 Suppl 1:S38-45.

[70] Monti G, Pioltelli P, Saccardo F, Campanini M, Candela M, Cavallero G, et al. Incidence and characteristics of non-Hodgkin lymphomas in a multicenter case file of patients with hepatitis C virus-related symptomatic mixed cryoglobulinemias. Archives of internal medicine 2005;165:101-105.

[71] Strauss E, Dias Teixeira MC. Quality of life in hepatitis C. Liver Int 2006;26:755-765.

[72] Foster GR, Goldin RD, Thomas HC. Chronic hepatitis C virus infection causes a significant reduction in quality of life in the absence of cirrhosis. Hepatology 1998;27:209-212.

[73] Teixeira MC, Ribeiro Mde F, Gayotto LC, Chamone Dde A, Strauss E. Worse quality of life in volunteer blood donors with hepatitis C. Transfusion 2006;46:278-283.

[74] Hsu PC, Federico CA, Krajden M, Yoshida EM, Bremner KE, Anderson FH, et al. Health utilities and psychometric quality of life in patients with early- and late-stage

hepatitis C virus infection. Journal of gastroenterology and hepatology 2012;27:149-157.

[75] Miller ER, Hiller JE, Shaw DR. Quality of life in HCV-infection: lack of association with ALT levels. Australian and New Zealand journal of public health 2001;25:355-361.

[76] Minuk GY, Gutkin A, Wong SG, Kaita KD. Patient concerns regarding chronic hepatitis C infections. J Viral Hepat 2005;12:51-57.

[77] Rodger AJ, Jolley D, Thompson SC, Lanigan A, Crofts N. The impact of diagnosis of hepatitis C virus on quality of life. Hepatology 1999;30:1299-1301.

[78] Strauss E, Porto-Ferreira FA, de Almeida-Neto C, Teixeira MC. Altered quality of life in the early stages of chronic hepatitis C is due to the virus itself. Clinics and research in hepatology and gastroenterology 2014;38:40-45.

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

[80] John-Baptiste AA, Tomlinson G, Hsu PC, Krajden M, Heathcote EJ, Laporte A, et al. Sustained responders have better quality of life and productivity compared with treatment failures long after antiviral therapy for hepatitis C. Am J Gastroenterol 2009;104:2439-2448.

[81] Bokemeyer M, Ding XQ, Goldbecker A, Raab P, Heeren M, Arvanitis D, et al. Evidence for neuroinflammation and neuroprotection in HCV infection-associated encephalopathy. Gut 2011;60:370-377.

[82] Grebely J, Dore GJ. What is killing people with hepatitis C virus infection? Seminars in liver disease 2011;31:331-339.

[83] Duberg AS, Torner A, Davidsdottir L, Aleman S, Blaxhult A, Svensson A, et al. Cause of death in individuals with chronic HBV and/or HCV infection, a nationwide community-based register study. J Viral Hepat 2008;15:538-550.

[84] McDonald SA, Hutchinson SJ, Bird SM, Mills PR, Dillon J, Bloor M, et al. A population-based record linkage study of mortality in hepatitis C-diagnosed persons with or without HIV coinfection in Scotland. Statistical methods in medical research 2009;18:271-283.

[85] Omland LH, Jepsen P, Krarup H, Schonning K, Lind B, Kromann-Andersen H, et al. Increased mortality among persons infected with hepatitis C virus. Clin Gastroenterol Hepatol 2011;9:71-78.

[86] Walter SR, Thein HH, Amin J, Gidding HF, Ward K, Law MG, et al. Trends in mortality after diagnosis of hepatitis B or C infection: 1992-2006. J Hepatol 2011;54:879-886.

[87] McDonald SA, Hutchinson SJ, Bird SM, Robertson C, Mills PR, Graham L, et al. The growing contribution of hepatitis C virus infection to liver-related mortality in Scotland. Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin 2010;15.

[88] Myers RP, Krajden M, Bilodeau M, Kaita K, Marotta P, Peltekian K, et al. Burden of disease and cost of chronic hepatitis C infection in Canada. Canadian journal of gastroenterology & hepatology 2014;28:243-250.

[89] Razavi H, Elkhoury AC, Elbasha E, Estes C, Pasini K, Poynard T, et al. Chronic hepatitis C virus (HCV) disease burden and cost in the United States. Hepatology 2013;57:2164-2170.

[90] Wedemeyer H, Duberg AS, Buti M, Rosenberg WM, Frankova S, Esmat G, et al. Strategies to manage hepatitis C virus (HCV) disease burden. J Viral Hepat 2014;21 Suppl 1:60-89.

[91] Colloredo G, Guido M, Sonzogni A, Leandro G. Impact of liver biopsy size on histological evaluation of chronic viral hepatitis: the smaller the sample, the milder the disease. J Hepatol 2003;39:239-244.

[92] Rousselet MC, Michalak S, Dupre F, Croue A, Bedossa P, Saint-Andre JP, et al. Sources of variability in histological scoring of chronic viral hepatitis. Hepatology 2005;41:257-264.

[93] Sandrin L, Fourquet B, Hasquenoph JM, Yon S, Fournier C, Mal F, et al. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. Ultrasound in medicine & biology 2003;29:1705-1713.

[94] Arena U, Vizzutti F, Abraldes JG, Corti G, Stasi C, Moscarella S, et al. Reliability of transient elastography for the diagnosis of advanced fibrosis in chronic hepatitis C. Gut 2008;57:1288-1293.

[95] Castera L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. Gastroenterology 2005;128:343-350.

[96] Cross TJ, Calvaruso V, Maimone S, Carey I, Chang TP, Pleguezuelo M, et al. Prospective comparison of Fibroscan, King's score and liver biopsy for the assessment of cirrhosis in chronic hepatitis C infection. J Viral Hepat 2010;17:546-554.

[97] Degos F, Perez P, Roche B, Mahmoudi A, Asselineau J, Voitot H, et al. Diagnostic accuracy of FibroScan and comparison to liver fibrosis biomarkers in chronic viral hepatitis: a multicenter prospective study (the FIBROSTIC study). J Hepatol 2010;53:1013-1021.

[98] Kettaneh A, Marcellin P, Douvin C, Poupon R, Ziol M, Beaugrand M, et al. Features associated with success rate and performance of FibroScan measurements for the diagnosis of cirrhosis in HCV patients: a prospective study of 935 patients. J Hepatol 2007;46:628-634.

[99] Ziol M, Handra-Luca A, Kettaneh A, Christidis C, Mal F, Kazemi F, et al. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. Hepatology 2005;41:48-54.

[100] Fraquelli M, Rigamonti C, Casazza G, Conte D, Donato MF, Ronchi G, et al. Reproducibility of transient elastography in the evaluation of liver fibrosis in patients with chronic liver disease. Gut 2007;56:968-973.

[101] Swets JA. Measuring the accuracy of diagnostic systems. Science 1988;240:1285-1293.

[102] Friedrich-Rust M, Ong MF, Martens S, Sarrazin C, Bojunga J, Zeuzem S, et al. Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. Gastroenterology 2008;134:960-974.

[103] 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;102:2589-2600.

[104] Sebastiani G, Alberti A. How far is noninvasive assessment of liver fibrosis from replacing liver biopsy in hepatitis C? J Viral Hepat 2012;19 Suppl 1:18-32.

[105] Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 2003;38:518-526.

[106] Imbert-Bismut F, Ratziu V, Pieroni L, Charlotte F, Benhamou Y, Poynard T. Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. Lancet 2001;357:1069-1075.

[107] Sebastiani G, Halfon P, Castera L, Pol S, Thomas DL, Mangia A, et al. SAFE biopsy: a validated method for large-scale staging of liver fibrosis in chronic hepatitis C. Hepatology 2009;49:1821-1827.

[108] Castera L, Sebastiani G, Le Bail B, de Ledinghen V, Couzigou P, Alberti A. Prospective comparison of two algorithms combining non-invasive methods for staging liver fibrosis in chronic hepatitis C. J Hepatol 2010;52:191-198.

[109] EASL Clinical Practice Guidelines: management of hepatitis C virus infection. J Hepatol 2014;60:392-420.

[110] Shiffman ML, Sterling RK, Contos M, Hubbard S, Long A, Luketic VA, et al. Long term changes in liver histology following treatment of chronic hepatitis C virus. Annals of hepatology 2014;13:340-349.

[111] Hoofnagle JH, Mullen KD, Jones DB, Rustgi V, Di Bisceglie A, Peters M, et al. Treatment of chronic non-A,non-B hepatitis with recombinant human alpha interferon. A preliminary report. N Engl J Med 1986;315:1575-1578.

[112] Poynard T, Marcellin P, Lee SS, Niederau C, Minuk GS, Ideo G, et al. Randomised trial of interferon alpha2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. International Hepatitis Interventional Therapy Group (IHIT). Lancet 1998;352:1426-1432.

[113] Reichard O, Norkrans G, Fryden A, Braconier JH, Sonnerborg A, Weiland O. Randomised, double-blind, placebo-controlled trial of interferon alpha-2b with and without ribavirin for chronic hepatitis C. The Swedish Study Group. Lancet 1998;351:83-87.

[114] Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL, Jr., et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002;347:975-982.

[115] Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet 2001;358:958-965.

[116] Schaefer M, Capuron L, Friebe A, Diez-Quevedo C, Robaeys G, Neri S, et al. Hepatitis C infection, antiviral treatment and mental health: a European expert consensus statement. J Hepatol 2012;57:1379-1390.

[117] Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med 2011;364:2405-2416.

[118] Kwo PY, Lawitz EJ, McCone J, Schiff ER, Vierling JM, Pound D, 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;376:705-716.

[119] McHutchison JG, Everson GT, Gordon SC, Jacobson IM, Sulkowski M, Kauffman R, et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. N Engl J Med 2009;360:1827-1838.

[120] Poordad F, McCone J, Jr., Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med 2011;364:1195-1206.

[121] Welsch C, Jesudian A, Zeuzem S, Jacobson I. New direct-acting antiviral agents for the treatment of hepatitis C virus infection and perspectives. Gut 2012;61 Suppl 1:i36-46.

[122] Hezode C, Fontaine H, Dorival C, Zoulim F, Larrey D, Canva V, et al. Effectiveness of telaprevir or boceprevir in treatment-experienced patients with HCV genotype 1 infection and cirrhosis. Gastroenterology 2014;147:132-142 e134.

[123] Guttormsson U. Drogutvecklingen i Sverige 2011, Rapport nr 130. Stockholm: Centralförbundet för alkohol- och narkotikaupplysning; 2012.

[124] Dole VP, Nyswander M. A Medical Treatment for Diacetylmorphine (Heroin) Addiction. A Clinical Trial with Methadone Hydrochloride. JAMA : the journal of the American Medical Association 1965;193:646-650.

[125] Kreek MJ, LaForge KS, Butelman E. Pharmacotherapy of addictions. Nature reviews Drug discovery 2002;1:710-726.

[126] Bukten A, Skurtveit S, Gossop M, Waal H, Stangeland P, Havnes I, et al. Engagement with opioid maintenance treatment and reductions in crime: a longitudinal national cohort study. Addiction 2012;107:393-399.

[127] Degenhardt L, Mathers B, Vickerman P, Rhodes T, Latkin C, Hickman M. Prevention of HIV infection for people who inject drugs: why individual, structural, and combination approaches are needed. Lancet 2010;376:285-301.

[128] Hagan H, Pouget ER, Des Jarlais DC. A systematic review and meta-analysis of interventions to prevent hepatitis C virus infection in people who inject drugs. The Journal of infectious diseases 2011;204:74-83.

[129] Larsson G. Bättre insatser vid missbruk och beroende, SOU 2011:35. Slutbetänkande Missbruksutredningen; 2011.

[130] Romelsjo A, Engdahl B, Stenbacka M, Fugelstad A, Davstad I, Leifman A, et al. Were the changes to Sweden's maintenance treatment policy 2000-06 related to changes in opiate-related mortality and morbidity? Addiction 2010;105:1625-1632.

[131] Socialstyrelsen. Kartläggning av läkemedelsassisterad behandling vid opiatberoende; 2012.

[132] Cherubin CE, Sapira JD. The medical complications of drug addiction and the medical assessment of the intravenous drug user: 25 years later. Ann Intern Med 1993;119:1017-1028.

[133] Duberg AS, Pettersson H, Aleman S, Blaxhult A, Daviethsdottir L, Hultcrantz R, et al. The burden of hepatitis C in Sweden: a national study of inpatient care. J Viral Hepat 2011;18:106-118.

[134] Omland LH, Osler M, Jepsen P, Krarup H, Weis N, Christensen PB, et al. Socioeconomic status in HCV infected patients - risk and prognosis. Clinical epidemiology 2013;5:163-172.

[135] Hansen AB, Gerstoft J, Kronborg G, Pedersen C, Sorensen HT, Obel N. Mortality in siblings of patients coinfected with HIV and hepatitis C virus. The Journal of infectious diseases 2007;195:230-235.

[136] El-Kamary SS, Jhaveri R, Shardell MD. All-cause, liver-related, and non-liver-related mortality among HCV-infected individuals in the general US population. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2011;53:150-157.

[137] Gibson A, Randall D, Degenhardt L. The increasing mortality burden of liver disease among opioid-dependent people: cohort study. Addiction 2011;106:2186-2192.

[138] Kielland KB, Skaug K, Amundsen EJ, Dalgard O. All-cause and liver-related mortality in hepatitis C infected drug users followed for 33 years: A controlled study. J Hepatol 2013;58:31-37.

[139] Feinstone SM, Hu DJ, Major ME. Prospects for prophylactic and therapeutic vaccines against hepatitis C virus. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2012;55 Suppl 1:S25-32.

[140] MacArthur GJ, van Velzen E, Palmateer N, Kimber J, Pharris A, Hope V, et al. Interventions to prevent HIV and Hepatitis C in people who inject drugs: a review of reviews to assess evidence of effectiveness. The International journal on drug policy 2014;25:34-52.

[141] Kiyosawa K, Sodeyama T, Tanaka E, Nakano Y, Furuta S, Nishioka K, et al. Hepatitis C in hospital employees with needlestick injuries. Ann Intern Med 1991;115:367-369.

[142] MacDonald M, Crofts N, Kaldor J. Transmission of hepatitis C virus: rates, routes, and cofactors. Epidemiologic reviews 1996;18:137-148.

[143] Moloughney BW. Transmission and postexposure management of bloodborne virus infections in the health care setting: where are we now? CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 2001;165:445-451.

[144] Sodeyama T, Kiyosawa K, Urushihara A, Matsumoto A, Tanaka E, Furuta S, et al. Detection of hepatitis C virus markers and hepatitis C virus genomic-RNA after needlestick accidents. Archives of internal medicine 1993;153:1565-1572.

[145] Henderson DK, Fahey BJ, Willy M, Schmitt JM, Carey K, Koziol DE, et al. Risk for occupational transmission of human immunodeficiency virus type 1 (HIV-1) associated with clinical exposures. A prospective evaluation. Ann Intern Med 1990;113:740-746.

[146] Hudgens MG, Longini IM, Jr., Vanichseni S, Hu DJ, Kitayaporn D, Mock PA, et al. Subtype-specific transmission probabilities for human immunodeficiency virus type 1 among injecting drug users in Bangkok, Thailand. American journal of epidemiology 2002;155:159-168.

[147] Kaplan EH, Heimer R. A model-based estimate of HIV infectivity via needle sharing. J Acquir Immune Defic Syndr 1992;5:1116-1118.

[148] Das M, Chu PL, Santos GM, Scheer S, Vittinghoff E, McFarland W, et al. Decreases in community viral load are accompanied by reductions in new HIV infections in San Francisco. PloS one 2010;5:e11068.

[149] Montaner JS, Lima VD, Barrios R, Yip B, Wood E, Kerr T, et al. Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study. Lancet 2010;376:532-539.

[150] Tanser F, Barnighausen T, Grapsa E, Zaidi J, Newell ML. High coverage of ART associated with decline in risk of HIV acquisition in rural KwaZulu-Natal, South Africa. Science 2013;339:966-971.

[151] Martin NK, Vickerman P, Grebely J, Hellard M, Hutchinson SJ, Lima VD, et al. Hepatitis C virus treatment for prevention among people who inject drugs: Modeling treatment scale-up in the age of direct-acting antivirals. Hepatology 2013;58:1598-1609.

[152] 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. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2013;57 Suppl 2:S39-45.

[153] Grebely J, Matthews GV, Lloyd AR, Dore GJ. Elimination of hepatitis C virus infection among people who inject drugs through treatment as prevention: feasibility and future requirements. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2013;57:1014-1020.

[154] National Institutes of Health Consensus Development Conference Statement: Management of hepatitis C: 2002--June 10-12, 2002. Hepatology 2002;36:S3-20.

[155] Zeremski M, Zibbell JE, Martinez AD, Kritz S, Smith BD, Talal AH. Hepatitis C virus control among persons who inject drugs requires overcoming barriers to care. World journal of gastroenterology : WJG 2013;19:7846-7851.

[156] Hellard M, Sacks-Davis R, Gold J. Hepatitis C treatment for injection drug users: a review of the available evidence. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2009;49:561-573.

[157] Aspinall EJ, Corson S, Doyle JS, Grebely J, Hutchinson SJ, Dore GJ, et al. Treatment of hepatitis C virus infection among people who are actively injecting drugs: a systematic review and meta-analysis. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2013;57 Suppl 2:S80-89.

[158] Zanini B, Lanzini A. Antiviral treatment for chronic hepatitis C in illicit drug users: a systematic review. Antiviral therapy 2009;14:467-479.

[159] Grady BP, Schinkel J, Thomas XV, Dalgard O. Hepatitis C virus reinfection following treatment among people who use drugs. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2013;57 Suppl 2:S105-110.

[160] Robaeys G, Grebely J, Mauss S, Bruggmann P, Moussalli J, De Gottardi A, et al. Recommendations for the management of hepatitis C virus infection among people who inject drugs. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2013;57 Suppl 2:S129-137.

[161] 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. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2013;57 Suppl 2:S56-61.

[162] Abdel-Hamid M, El-Daly M, Molnegren V, El-Kafrawy S, Abdel-Latif S, Esmat G, et al. Genetic diversity in hepatitis C virus in Egypt and possible association with hepatocellular carcinoma. The Journal of general virology 2007;88:1526-1531.

[163] Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, et al. Histological grading and staging of chronic hepatitis. J Hepatol 1995;22:696-699.

[164] Islam S, Antonsson L, Westin J, Lagging M. Cirrhosis in hepatitis C virus-infected patients can be excluded using an index of standard biochemical serum markers. Scand J Gastroenterol 2005;40:867-872.

[165] Westin J, Ydreborg M, Islam S, Alsio A, Dhillon AP, Pawlotsky JM, et al. A non-invasive fibrosis score predicts treatment outcome in chronic hepatitis C virus infection. Scand J Gastroenterol 2008;43:73-80.

[166] Deering D, Frampton C, Horn J, Sellman D, Adamson S, Potiki T. Health status of clients receiving methadone maintenance treatment using the SF-36 health survey questionnaire. Drug Alcohol Rev 2004;23:273-280.

[167] Younossi Z, Kallman J, Kincaid J. The effects of HCV infection and management on health-related quality of life. Hepatology 2007;45:806-816.

[168] Sullivan M KJ, Ware JE. SF-36 Health Survey: Swedish manual and interpretation guide, 2nd ed. . 2002.

[169] Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. The British journal of psychiatry : the journal of mental science 1979;134:382-389.

[170] Schaefer M, Sarkar R, Knop V, Effenberger S, Friebe A, Heinze L, et al. Escitalopram for the prevention of peginterferon-alpha2a-associated depression in hepatitis C virus-infected patients without previous psychiatric disease: a randomized trial. Ann Intern Med 2012;157:94-103.

[171] McHutchison JG, Manns M, Patel K, Poynard T, Lindsay KL, Trepo C, et al. Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. Gastroenterology 2002;123:1061-1069.

[172] Rondy M, Wiessing L, Hutchinson SJ, Mathei C, Mathis F, Mravcik V, et al. Hepatitis C prevalence in injecting drug users in Europe, 1990-2007: impact of study recruitment setting. Epidemiol Infect 2013;141:563-572.

[173] Bakr I, Rekacewicz C, El Hosseiny M, Ismail S, El Daly M, El-Kafrawy S, et al. Higher clearance of hepatitis C virus infection in females compared with males. Gut 2006;55:1183-1187.

[174] Rao HY, Sun DG, Jiang D, Yang RF, Guo F, Wang JH, et al. IL28B genetic variants and gender are associated with spontaneous clearance of hepatitis C virus infection. J Viral Hepat 2012;19:173-181.

[175] Villa E, Karampatou A, Camma C, Di Leo A, Luongo M, Ferrari A, et al. Early menopause is associated with lack of response to antiviral therapy in women with chronic hepatitis C. Gastroenterology 2011;140:818-829.

[176] Hayashi J, Kishihara Y, Ueno K, Yamaji K, Kawakami Y, Furusyo N, et al. Age-related response to interferon alfa treatment in women vs men with chronic hepatitis C virus infection. Archives of internal medicine 1998;158:177-181.

[177] Ryder N, Cullen W, Barry J, Bury G, Keenan E, Smyth BP. Prevalence of problem alcohol use among patients attending primary care for methadone treatment. BMC family practice 2009;10:42.

[178] Hartzler B, Donovan DM, Huang Z. Comparison of opiate-primary treatment seekers with and without alcohol use disorder. Journal of substance abuse treatment 2010;39:114-123.

[179] Srivastava A, Kahan M, Ross S. The effect of methadone maintenance treatment on alcohol consumption: a systematic review. Journal of substance abuse treatment 2008;34:215-223.

[180] Mysels DJ, Sullivan MA. The relationship between opioid and sugar intake: review of evidence and clinical applications. Journal of opioid management 2010;6:445-452.

[181] Stenbacka M, Beck O, Leifman A, Romelsjo A, Helander A. Problem drinking in relation to treatment outcome among opiate addicts in methadone maintenance treatment. Drug Alcohol Rev 2007;26:55-63.

[182] Ottomanelli G. Methadone patients and alcohol abuse. Journal of substance abuse treatment 1999;16:113-121.

[183] Rittmannsberger H, Silberbauer C, Lehner R, Ruschak M. Alcohol consumption during methadone maintenance treatment. European addiction research 2000;6:2-7.

[184] Darker CD, Sweeney BP, El Hassan HO, Smyth BP, Ivers JH, Barry JM. Brief interventions are effective in reducing alcohol consumption in opiate-dependent methadone-maintained patients: results from an implementation study. Drug Alcohol Rev 2012;31:348-356.

[185] Patel A, Harrison SA. Hepatitis C virus infection and nonalcoholic steatohepatitis. Gastroenterology & hepatology 2012;8:305-312.

[186] Mohsen AH. The epidemiology of hepatitis C in a UK health regional population of 5.12 million. Gut 2001;48:707-713.

[187] Squadrito G, Cacciola I, Alibrandi A, Pollicino T, Raimondo G. Impact of occult hepatitis B virus infection on the outcome of chronic hepatitis C. J Hepatol 2013.

[188] Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, et al. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. JAMA : the journal of the American Medical Association 1990;264:2511-2518.

[189] Melchior M, Prokofyeva E, Younes N, Surkan PJ, Martins SS. Treatment for illegal drug use disorders: the role of comorbid mood and anxiety disorders. BMC psychiatry 2014;14:89.

[190] Wittchen HU, Apelt SM, Soyka M, Gastpar M, Backmund M, Golz J, et al. Feasibility and outcome of substitution treatment of heroin-dependent patients in specialized substitution centers and primary care facilities in Germany: a naturalistic study in 2694 patients. Drug and alcohol dependence 2008;95:245-257.

[191] Schafer A, Wittchen HU, Backmund M, Soyka M, Golz J, Siegert J, et al. Psychopathological changes and quality of life in hepatitis C virus-infected, opioid-dependent patients during maintenance therapy. Addiction 2009;104:630-640.

[192] Alavi M, Grebely J, Matthews GV, Petoumenos K, Yeung B, Day C, et al. Effect of pegylated interferon-alpha-2a treatment on mental health during recent hepatitis C virus infection. Journal of gastroenterology and hepatology 2012;27:957-965.

[193] Schaefer M, Hinzpeter A, Mohmand A, Janssen G, Pich M, Schwaiger M, et al. Hepatitis C treatment in "difficult-to-treat" psychiatric patients with pegylated interferon-alpha and ribavirin: response and psychiatric side effects. Hepatology 2007;46:991-998.

[194] Hauser P, Morasco BJ, Linke A, Bjornson D, Ruimy S, Matthews A, et al. Antiviral completion rates and sustained viral response in hepatitis C patients with and without preexisting major depressive disorder. Psychosomatics 2009;50:500-505.

[195] Bonner JE, Barritt ASt, Fried MW, Evon DM. Time to rethink antiviral treatment for hepatitis C in patients with coexisting mental health/substance abuse issues. Digestive diseases and sciences 2012;57:1469-1474.

[196] Randall D, Roxburgh, A., Gibson, A., Degenhardt, L. Mortality among people who use illicit drugs: A toolkit for classifying major causes of death: Sydney: National Drug and Alcohol Research Centre, University of New South Wales; 2009.

[197] Blome MA, Bjorkman P, Flamholc L, Jacobsson H, Molnegren V, Widell A. Minimal transmission of HIV despite persistently high transmission of hepatitis C virus in a Swedish needle exchange program. J Viral Hepat 2011;18:831-839.

[198] Mansson AS, Moestrup T, Nordenfelt E, Widell A. Continued transmission of hepatitis B and C viruses, but no transmission of human immunodeficiency virus among intravenous drug users participating in a syringe/needle exchange program. Scandinavian journal of infectious diseases 2000;32:253-258.

[199] Grebely J, Genoway KA, Raffa JD, Dhadwal G, Rajan T, Showler G, et al. Barriers associated with the treatment of hepatitis C virus infection among illicit drug users. Drug and alcohol dependence 2008;93:141-147.

[200] Mauss S, Berger F, Goelz J, Jacob B, Schmutz G. A prospective controlled study of interferon-based therapy of chronic hepatitis C in patients on methadone maintenance. Hepatology 2004;40:120-124.