



# LUND UNIVERSITY

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

Jerkeman, Anna; Westin, Johan; Lagging, Martin; Norkrans, Gunnar; Lidman, Christer; Frimand, Jan; Simonsberg, Christian; Kakko, Johan; Widell, Anders; Björkman, Per

*Published in:*  
Scandinavian Journal of Infectious Diseases

*DOI:*  
[10.3109/00365548.2013.879994](https://doi.org/10.3109/00365548.2013.879994)

2014

[Link to publication](#)

### *Citation for published version (APA):*

Jerkeman, A., Westin, J., Lagging, M., Norkrans, G., Lidman, C., Frimand, J., Simonsberg, C., Kakko, J., Widell, A., & Björkman, P. (2014). Chronic hepatitis C in Swedish subjects receiving opiate substitution therapy-Factors associated with advanced fibrosis. *Scandinavian Journal of Infectious Diseases*, 46(5), 340-347. <https://doi.org/10.3109/00365548.2013.879994>

*Total number of authors:*  
10

### **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

## **Chronic hepatitis C in Swedish subjects receiving opiate substitution therapy – factors associated with advanced fibrosis**

Anna Jerkeman<sup>1</sup>, Johan Westin<sup>3</sup>, Martin Lagging<sup>3</sup>, Gunnar Norkrans<sup>3</sup>, Christer Lidman<sup>5</sup>, Jan Frimand<sup>2</sup>, Christian Simonsberg<sup>4</sup>, Johan Kakko<sup>6</sup>, Anders Widell<sup>7</sup>, Per Björkman<sup>1</sup>

<sup>1</sup>Department of Clinical Sciences, Section for Infectious Diseases, Malmö, Lund University, SE-205 02 Malmö, Sweden, <sup>2</sup>Addiction Center, Skane University Hospital, SE-205 02 Malmö, Sweden, <sup>3</sup>Department of Infectious Diseases, Institute of Biomedicine, Sahlgrenska Academy, University of Gothenburg, SE-405 30 Gothenburg, Sweden, <sup>4</sup>Addiction Center, Sahlgrenska University Hospital, SE-413 46 Gothenburg, Sweden, <sup>5</sup>Department of Infectious Diseases, Karolinska University Hospital, SE-171 76 Stockholm, Sweden, <sup>6</sup>Stockholm Center for Dependency Disorders, SE-112 38 Stockholm, Sweden, <sup>7</sup>Department of Clinical Microbiology, Skane University Hospital, SE-205 02 Malmö, Sweden

**Key words:** opiate substitution therapy, hepatitis C, liver fibrosis, risk factors

**Running head:** HCV in Swedish patients in opiate substitution treatment

**Declaration of interest:** This study has received financial support from Schering-Plough/MSD and Skåne Regional Council. None of the authors have any conflict of interest related to this work.

### **Corresponding author**

Anna Jerkeman MD

Department of Infectious Diseases

Skane University Hospital, SE-205 02 Malmö, Sweden

Phone +4640337736 Fax +4640337363 e-mail [anna.jerkeman@med.lu.se](mailto:anna.jerkeman@med.lu.se)

## **Abstract**

**Background** Opiate substitution therapy (OST) reduces the risk of death from directly drug related causes in heroin users, allowing other chronic health problems to emerge. People who inject drugs (PWID) are exposed to HCV, with an associated risk of chronic liver disease. We investigated HCV prevalence and liver-related morbidity in a cohort of OST recipients, and analyzed factors associated with significant hepatic fibrosis.

**Methods** All patients registered on April 1<sup>st</sup> 2008 in four clinics providing OST in the three largest cities in Sweden were eligible for inclusion. HCV viremic subjects were evaluated for fibrosis stage by liver biopsy, transient elastometry (TE) and/or a biochemical fibrosis index (Göteborg University Cirrhosis Index; GUCI). Factors associated with severity of fibrosis were determined with logistic regression analysis.

**Results** Out of 524 eligible patients, 277 consented to enrolment. 236 subjects (88%) were anti-HCV positive, and 162 of these were viremic (69%). Significant liver fibrosis (defined as Ishak stages F3-F6, TE value  $\geq 8.85$  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];  $p=0.02$ ).

**Conclusions** Significant liver fibrosis was detected in two thirds of HCV viremic OST recipients in this cohort, and was associated with alcohol use, high BMI and exposure to HBV. These findings indicate that management of HCV and associated risk factors should be emphasized in Swedish OST programs.

## Introduction

Chronic hepatitis C is a leading cause of end-stage liver disease in North America and Europe (1, 2). In Sweden, as in most industrialized countries, injection drug use is the predominant route of infection.

Although some studies suggest a marked increase in the incidence of serious liver disease with rising age among people who inject drugs (PWID) (3-7), the natural course of HCV infection and its impact on morbidity and mortality in this population is complex and remains controversial.

Despite high prevalence of HCV infection, the risk of HCV related death among active opiate users is low (10), and the dominant causes of excess mortality are drug overdose, suicide, trauma and in some populations also HIV/AIDS (3, 8-10). However, directly drug related mortality is reduced in patients receiving OST, (11, 12). This might allow for other chronic conditions, such as HCV infection, to emerge as important causes of morbidity and mortality. Yet, factors with a potential influence on the course and outcome of HCV infection are frequent among PWID, irrespective of OST. These factors, such as heavy alcohol intake, co-infection with HIV or HBV and low HCV treatment uptake, might both obscure and aggravate the course of HCV infection in this population..

The emergence of new and more effective antiviral therapies necessitates better understanding of the characteristics of HCV infection among persons infected through injection drug use to enable optimal use of such regimens in this population.

We have investigated the prevalence of HCV infection, the burden of HCV-related chronic liver disease and factors associated with advanced fibrosis among Swedish OST recipients.

## **Methods**

### **Setting**

OST was introduced in Sweden in the 1960s (13). Methadone was the first widely used substance for OST, but since the late 1990s buprenorphine has been used as an alternative. Currently, it is estimated that 30-40% out of 10 000 heroin users in Sweden receive OST(14)

### **Design and study population**

All patients receiving treatment in four public clinics providing OST in three metropolitan areas of Sweden (Stockholm, Gothenburg, Malmö) on April 1<sup>st</sup> 2008 were eligible for inclusion in this cross-sectional study. Visits for inclusion occurred between April 1<sup>st</sup> 2008 and January 29<sup>th</sup> 2010.

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. Written informed consent was obtained (separately for HCV testing and for liver disease investigation). No exclusion criteria were applied.

### **Procedures**

Study subjects were interviewed by a physician specialized in addiction medicine following a structured questionnaire, with details concerning demographics, main drug of use, year of first illicit drug injection, year of OST initiation and type of substitution therapy. In order to estimate alcohol consumption, patients were asked to state their current monthly alcohol consumption by frequency of intake and number of standard units on each occasion. They were also asked for history of conviction for alcohol related crime and admission to facilities

for treatment of alcohol abuse. In addition, addiction clinic staff were asked to provide information on problematic alcohol use following registration in the respective clinics. Lifetime regular use of cannabis for a period greater than one year was recorded. Patients were also interviewed regarding symptoms possibly related to HCV infection and prior investigation and/or treatment of HCV infection. The “time at risk” for HCV acquisition was calculated by subtracting time in OST from time period since first reported illicit drug injection.

Blood samples were collected at this study visit. Anti-HCV antibodies were detected using 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 (15). 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 persistently negative HCV RNA were considered to have spontaneously resolved HCV infection.

Viremic patients were then offered structured assessment for liver disease including medical history, history of alcohol and drug use, details regarding OST, smoking habits and physical examination, performed at departments of infectious diseases. Weight and height were obtained to calculate the body mass index (BMI; weight in kilograms divided by height in square meters). Fibrosis stage was determined using liver biopsy and/or transient elastometry. Blood samples for haematological parameters, liver, renal and metabolic function tests, and markers of HBV (HBsAg, anti-HBc and anti HBs) and HIV infection were collected. The study was approved by the Regional Ethical Review Board in Lund, Sweden.

### *Assessment of liver fibrosis*

Liver biopsies were centrally scored for fibrosis stage by two experienced observers blinded for clinical information (J.W and M.L) according to the Ishak protocol (16) in a dual observer consensus fashion (17, 18). . 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 (TE; Fibroscan®) 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  $\geq 8.85$  kPa and cirrhosis as a value of  $\geq 10.05$  kPa, using threshold levels derived by comparison with Ishak fibrosis staging according to Cross et al (19). 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 (20, 21) was calculated from the following formula:  $GUCI = (\text{normalized AST} \times \text{prothrombin-INR} \times 100) / \text{platelet count} (\times 10^9)$ . Cut-off levels of 0.33 and 1.11 were used to categorize patients into low, intermediate and high-grade fibrosis for statistical analysis.

Patients were categorized into three groups according to their degree of fibrosis defined either by liver biopsy, TE or GUCI score. For this purpose, liver biopsy was preferred over TE and GUCI score, and TE over GUCI score (in case measurements by several methods were available).

Patients with clinical or histological signs of cirrhosis were screened for hepatocellular carcinoma (HCC) using liver ultrasonography.

### **Statistical methods**

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.

## **Results**

### **Patient characteristics**

On April 1<sup>st</sup> 2008, 524 patients were receiving treatment in the four OST clinics. Among these, 277 (53%) consented to inclusion in the first part of the study (Figure 1). Inclusion visits occurred between April 1<sup>st</sup> 2008 and January 29<sup>th</sup> 2010. Characteristics of included subjects are shown in Table I. Among the 247 eligible patients not included, 182 declined participation, 42 had been discharged from treatment, 7 had moved from the uptake area and 16 had died. Median age (45 years) and gender distribution (71% men), as well as duration of OST, did not differ significantly from included subjects.

Previous investigation for HCV-related liver disease was reported by 73 participants (26%); 18 (6%) and 10 (4%) patients respectively reported having started or completed antiviral therapy, respectively.

#### *Drug use details*

Although most patients (264/277; 95%) reported heroin as their main drug of use, use of additional illicit drugs was common; 8 (3%) stated use of cocaine, 71 (26%) amphetamine, 73 (26%) benzodiazepines and 197 (71%) cannabis.

A substantial proportion of the patients had a history of alcohol related problems: 63 (23%) had been convicted for alcohol related crime; OST clinic staff reported excessive use of alcohol in 46 patients (17%) and 18 persons (7%) had received treatment for alcohol abuse. Despite this, most patients (n=179; 66%) claimed their current alcohol consumption to be modest (none or less than once a month). Ninety-five percent were current or former tobacco smokers (84% and 11% respectively).

#### *Concomitant diseases*

Apart from 27 (25%) patients with psychiatric disease (most commonly depression; n=22), few participants reported significant concomitant disease [heart disease (n=16), airway disease (n=16), diabetes (n=5)].

#### **HCV markers**

Among 269 persons tested, anti-HCV was detected in 236 (88%) individuals. Those without HCV antibody had a shorter time at risk of HCV compared to seroreactive participants (4 vs. 13 years, respectively;  $p < 0.0001$ ). There was no significant difference in age and gender distribution between these groups.

HCV PCR was performed for 234 out of 236 anti-HCV-positive subjects; 162 of these (69%) were viremic. Among the 72 (31%) persons without viremia, 9 individuals had received antiviral therapy, and the remaining 63 subjects showed spontaneous HCV resolution.

Spontaneous clearance was significantly more common in women than in men (38% vs. 22%;  $p=0.02$ ).

The distribution of genotypes was: 1a 44%, 1b 7%, 2b 13% and 3a 32%. No mixed infections were detected.

### **HBV and HIV markers**

Two patients were HIV-positive (previously known) and 2 patients were HBsAg-positive.

Sixty-five out of 106 patients (61%) were anti-HBc positive; among these 36 (55%) had both anti-HBc and anti-HBs antibodies, whereas 29 of these (45%) did not have detectable anti-HBs(anti-HBc alone). Nineteen patients (18%) had signs of previous HBV vaccination (anti-HBs alone).

### **Liver disease**

#### *Symptoms and clinical findings*

Symptoms potentially related to hepatitis C were reported by 184/277 (66%) subjects before results of anti-HCV testing were released (fatigue 132 [48%], muscular pain 77 [28%], abdominal discomfort 76 [27%] and nausea 57 [21%]), however, the presence of these symptoms was neither associated with HCV viremia nor with fibrosis severity.

Among the 162 viremic patients, 106 (65%) consented to further evaluation of liver disease.

Physical findings suggesting chronic liver disease were detected in a minority of patients (spiders [n=25], palmar erythema [n=11], hepatomegaly [n=6], and splenomegaly [n=1]).

Body mass index (BMI) was determined for 92 (87%) patients. The median BMI was 27 kg/m<sup>2</sup> (range 19-42). Forty patients (43%) were overweight (BMI 25-29.9) and of these 22 (24%) were obese.

### *Liver fibrosis*

The degree of fibrosis could be categorized for 103 patients with any of the three techniques (45 by biopsy, 26 by TE and 32 by GUCI only). The number of patients in each category of fibrosis by diagnostic method is shown in Table II.

Forty-eight patients underwent liver biopsy. Two biopsies were of inadequate size and one biopsy specimen could not be retrieved, leaving 45 biopsies for central scoring.

Twenty-three (51%) patients had significant fibrosis (Ishak stage >F2) and 6 of these (13%) patients had cirrhosis.

TE was performed in 34 participants. The median stiffness value was 10.6 kPa (range 4-75). According to our definitions, 16 (47%) patients had significant fibrosis/cirrhosis. All 16 had a stiffness value >10.5 kPa, which is the cut-off value for cirrhosis recommended by Cross et al and 13 had a stiffness value >12.5 kPa (cut-off value for cirrhosis recommended by Castera et al (22)).

GUCI score could be calculated for 99 patients. The median GUCI score was 0.84 (range 0.19-12.2); 90 (91%) patients had a GUCI score >0.33 and 40 (40%) had a GUCI score >1.11. Since the proportion of advanced fibrosis was higher in patients who were only assessed by GUCI score, we compared the GUCI results in participants who had been investigated with an additional method. There was no significant difference in GUCI score distribution among

patients categorized by biopsy, TE or GUCI, within the categories low, intermediate or high grade fibrosis.

### *Ultrasound*

Abdominal ultrasound was performed in 61 subjects (58%). Twelve patients had splenomegaly, 2 had ascites, and in 4 focal lesions were detected. Further investigations confirmed the diagnosis of hepatocellular carcinoma (HCC) in 2 of these cases.

### *Factors associated with fibrosis/cirrhosis*

There was a trend towards increasing fibrosis severity with increasing age, increasing BMI, presence of anti-HBc antibody and amount of alcohol intake per month (Table III). These factors were tested by logistic regression, with the patients dichotomized as high vs. intermediate/low or low vs. intermediate/high fibrosis stage. When comparing high and intermediate/low fibrosis categories, high stage fibrosis was associated with alcohol intake (HR 0.33,  $p=0.03$ ) and presence of anti-HBc antibody ( $p=0.02$ ). For comparison between low and intermediate/high fibrosis stages, an association was found for increasing BMI and higher stage of fibrosis (HR 1.13,  $p=0.04$ ) (Table III).

## **Discussion**

HCV infection was highly prevalent in this cohort of Swedish PWID receiving OST and a majority of these subjects had significant liver fibrosis. Despite enrolment in OST programs, only a minority of patients had previously been assessed for HCV, a phenomenon that has been described from other countries (23, 24). Subjects without anti-HCV antibodies were characterized by a shorter duration between their first illicit drug injection and OST initiation,

suggesting that early enrolment for OST could contribute to the reduction of HCV infection among injecting heroin users (25).

To our knowledge, this is the first investigation of liver fibrosis in HCV-infected Swedish OST recipients. In most subjects with severe fibrosis this condition had not been recognized previously. How can identification of such patients – who are also in need of antiviral therapy - be improved in OST clinics?

Few of our participants showed signs of liver disease on physical examination. Similarly, the frequency of self-reported “liver related symptoms” did not differ with regard to HCV viremia status or fibrosis severity.

However, GUCI score - a fibrosis index based on simple biochemical markers – indicated advanced fibrosis in 40% of the participants. This method has been validated for non-invasive estimation of fibrosis(26), and could be considered for initial screening in an OST setting to detect subjects in need of further investigation.

Several patients had previously described risk factors for liver fibrosis progression such as obesity(27, 28), use of cannabis(29), smoking(30), exposure to HBV (31) and excessive intake of alcohol(32). We found associations between advanced liver fibrosis and alcohol consumption, increased BMI and the presence of anti-HBc antibodies.

Both alcohol abuse and obesity are important to recognize, especially since these conditions are also linked to other health problems. Using different approaches to estimate alcohol consumption, we found a high prevalence of problematic alcohol use in this cohort, in agreement with earlier studies showing alcohol dependence in 13-31% of OST recipients(33, 34).

Similarly, both overweight and obesity are common in patients on OST(35). In a Swedish autopsy study of 1180 intravenous drug addicts, 43.1% of methadone treated subjects had BMI>25 kg/m<sup>2</sup> (36).

Exposure to HBV was detected in 65 individuals, but only 2 of these fulfilled criteria for chronic hepatitis B. The association between anti-HBc positivity and advanced fibrosis in multivariate analysis could indicate the presence of so-called occult chronic hepatitis B, which has recently been shown to be an independent risk factor for cirrhosis, HCC and mortality(37).

This finding highlights the importance of HBV prevention, which has to target PWID more effectively in countries where HBV immunization is not included in infant vaccination programs.

Most studies on HCV in persons receiving OST have focused on aspects of delivery and outcomes of antiviral therapy. For this study, we chose to include all patients receiving OST on a specific date in order to gather representative information on the burden of HCV and characteristics of liver disease in this population. Furthermore, findings from other regions may not be applicable for Sweden; both due to the restricted access to OST and the low prevalence of HIV co-infection (which has an accelerating impact on fibrosis progression (38, 39)).

There are some limitations to this study. First, only 53% of eligible patients consented to inclusion, and among viremic subjects, 36% did not complete investigation for liver disease. Patients who did not accept participation did not differ from included subjects regarding age and gender distribution or time on substitution therapy. The main reason for non-participation was unstable psycho-social situation; we consider it unlikely that a bias with regard to liver disease severity occurred.

For patients with a prior result indicating HCV viremia we did not repeat PCR testing; they were assumed to have chronic HCV infection. We cannot exclude that some of these cases may have represented acute infection with subsequent spontaneous clearance; this may have led to some overestimation of the proportion of chronic infection in the population.

A further limitation is that we used three different methods for categorization of liver fibrosis. The degree of liver fibrosis can be misclassified by all available techniques. Although liver biopsy is considered to be the gold standard method for staging of liver fibrosis, sampling error can occur, leading to underestimation of cirrhosis (40). In order to compare results of these three methods we used cut-off values validated in previous studies (19, 21). The proportions of patients with significant fibrosis were similar using either biopsy or TE. Among the 32 patients who were only assessed by GUCI score, the proportion was considerably higher (91%). Although overestimation of fibrosis by GUCI score in this group cannot be excluded, GUCI values were similar for each category of fibrosis assessed by biopsy, TE or by GUCI alone.

Chronic hepatitis C is a frequent but hitherto largely neglected health problem among Swedish OST recipients. We show that the burden of advanced liver disease in this population is high. In the current era of improving antiviral therapy, management of HCV needs to be integrated within OST programs. Systematic testing with routine referral for further hepatologic assessment of viremic individuals could result in earlier identification of patients with significant liver disease, who should be prioritized for antiviral therapy.

## **Acknowledgements**

The authors would like to thank the following persons for their valuable contribution to the realization of this study: Ulla Åkerholm, Aida Pileram, Anna Vallgård, Annkie Fridström, Katarina Rosén, Joachim von Wachenfeldt, Angelina Enqvist, Irina Komarova, Martin Kåberg, Olof Wisén (deceased) and Liz Jergle Almquist.

We would also like to thank Anders Håkansson for constructive comments during the preparation of this manuscript and Jonas Björk for advice on statistical analysis.

## References

1. Adam R, Karam V, Delvart V, O'Grady J, Mirza D, Klempnauer J, et al. Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR). *J Hepatol.* 2012;57(3):675-88.
2. Wiesner RH, Sorrell M, Villamil F. Report of the first International Liver Transplantation Society expert panel consensus conference on liver transplantation and hepatitis C. *Liver Transplant.* 2003;9(11):S1-9.
3. Gibson A, Randall D, Degenhardt L. The increasing mortality burden of liver disease among opioid-dependent people: cohort study. *Addiction.* 2011;106(12):2186-92.
4. 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(1):31-7.
5. Darke S, Kaye S, Duflou J. Systemic disease among cases of fatal opioid toxicity. *Addiction.* 2006;101(9):1299-305.
6. 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(2):245-51.
7. Kirk GD, Mehta SH, Astemborski J, Galai N, Washington J, Higgins Y, et al. HIV, age, and the severity of hepatitis C virus-related liver disease: a cohort study. *Ann Intern Med.* 2013;158(9):658-66.
8. Copeland L, Budd J, Robertson JR, Elton RA. Changing patterns in causes of death in a cohort of injecting drug users, 1980-2001. *Arch Intern Med.* 2004;164(11):1214-20.
9. 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 Psychiatr Scand.* 1997;96(3):169-75.
10. Larney S, Randall D, Gibson A, Degenhardt L. The contributions of viral hepatitis and alcohol to liver-related deaths in opioid-dependent people. *Drug Alcohol Depend.* 2013;131(3):252-7.
11. 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(3):462-8.
12. Gronbladh L, Ohlund LS, Gunne LM. Mortality in heroin addiction: impact of methadone treatment. *Acta Psychiatr Scand.* 1990;82(3):223-7.
13. Gunne LM, Gronbladh L. The Swedish methadone maintenance program: a controlled study. *Drug and alcohol dependence.* 1981;7(3):249-56. Epub 1981/06/01.
14. Larsson G. Bättre insatser vid missbruk och beroende, SOU 2011:35. Slutbetänkande Missbruksutredningen 2011.
15. 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. *J Gen Virol.* 2007;88(Pt 5):1526-31.
16. 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(6):696-9.
17. Zeuzem S, Pawlotsky JM, Lukasiewicz E, von Wagner M, Goulis I, Lurie Y, et al. International, multicenter, randomized, controlled study comparing dynamically individualized versus standard treatment in patients with chronic hepatitis C. *J Hepatol.* 2005;43(2):250-7.
18. Lagging M, Langeland N, Pedersen C, Farkkila M, Buhl MR, Morch K, et al. Weight-adjusted dosing of ribavirin and importance of hepatitis C virus RNA below 1000

IU/mL by day 7 in short-term peginterferon therapy for chronic genotype 2/3 hepatitis C virus infection. *Hepatology*. 2008;48(2):695.

19. 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(8):546-54. Epub 2009/10/31.
20. 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(7):867-72.
21. 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(1):73-80.
22. 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(2):343-50.
23. Krook AL, Stokka D, Heger B, Nygaard E. Hepatitis C treatment of opioid dependants receiving maintenance treatment: results of a Norwegian pilot study. *Eur Addict Res*. 2007;13(4):216-21.
24. Grebely J, Bryant J, Hull P, Hopwood M, Lavis Y, Dore GJ, et al. Factors associated with specialist assessment and treatment for hepatitis C virus infection in New South Wales, Australia. *J Viral Hepat*. 2011;18(4):e104-16.
25. Van Den Berg C, Smit C, Van Brussel G, Coutinho R, Prins M. Full participation in harm reduction programmes is associated with decreased risk for human immunodeficiency virus and hepatitis C virus: evidence from the Amsterdam Cohort Studies among drug users. *Addiction*. 2007;102(9):1454-62.
26. Chou R, Wasson N. Blood tests to diagnose fibrosis or cirrhosis in patients with chronic hepatitis C virus infection: a systematic review. *Ann Intern Med*. 2013;158(11):807-20.
27. Ortiz V, Berenguer M, Rayon JM, Carrasco D, Berenguer J. Contribution of obesity to hepatitis C-related fibrosis progression. *Am J Gastroenterol*. 2002;97(9):2408-14.
28. Patel A, Harrison SA. Hepatitis C virus infection and nonalcoholic steatohepatitis. *Gastroenterol Hepatol*. 2012;8(5):305-12.
29. Hezode C, Roudot-Thoraval F, Nguyen S, Grenard P, Julien B, Zafrani ES, et al. Daily cannabis smoking as a risk factor for progression of fibrosis in chronic hepatitis C. *Hepatology*. 2005;42(1):63-71.
30. Hezode C, Lonjon I, Roudot-Thoraval F, Mavrier JP, Pawlotsky JM, Zafrani ES, et al. Impact of smoking on histological liver lesions in chronic hepatitis C. *Gut*. 2003;52(1):126-9.
31. Mohsen AH. The epidemiology of hepatitis C in a UK health regional population of 5.12 million. *Gut*. 2001;48(5):707-13.
32. Hutchinson SJ, Bird SM, Goldberg DJ. Influence of alcohol on the progression of hepatitis C virus infection: a meta-analysis. *Clin Gastroenterol Hepatol*. 2005;3(11):1150-9.
33. Srivastava A, Kahan M, Ross S. The effect of methadone maintenance treatment on alcohol consumption: a systematic review. *J Subst Abuse Treat*. 2008;34(2):215-23.
34. Hartzler B, Donovan DM, Huang Z. Comparison of opiate-primary treatment seekers with and without alcohol use disorder. *J Subst Abuse Treat*. 2010;39(2):114-23.
35. Mysels DJ, Sullivan MA. The relationship between opioid and sugar intake: review of evidence and clinical applications. *J Opioid Manag*. 2010;6(6):445-52.
36. Rajs J, Petersson A, Thiblin I, Olsson-Mortlock C, Fredriksson A, Eksborg S. Nutritional status of deceased illicit drug addicts in Stockholm, Sweden--a longitudinal medicolegal study. *Journal Forensic Sci*. 2004;49(2):320-9.

37. 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.
38. Benhamou Y, Bochet M, Di Martino V, Charlotte F, Azria F, Coutellier A, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfecting patients. The Multivirc Group. *Hepatology.* 1999;30(4):1054-8.
39. Soto B, Sanchez-Quijano A, Rodrigo L, del Olmo JA, Garcia-Bengoechea M, Hernandez-Quero J, et al. Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. *J Hepatol.* 1997;26(1):1-5.
40. Regev A, Berho M, Jeffers LJ, Milikowski C, Molina EG, Pylsopoulos NT, et al. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. *Am J Gastroenterol.* 2002;97(10):2614-8.

**Table I**

**Characteristics of OST recipients tested for anti-HCV antibodies, and for patients with HCV viremia.**

	<b>All included patients</b>	<b>Viremic patients, assessed for liver fibrosis</b>	<b>Viremic patients, not assessed for liver fibrosis</b>
Number of patients	277*	103	59
Median age in years (range)	44 (22-64)	44 (26-61)	43 (22-58)
Men n, (%)	187 (68)	73 (71)	41 (70)
Median number of years, since first illicit drug injection (range)	20 (1-44)	22 (4-42)	22 (5-43)
Median number of years in OST (range)	5 (0.2-20)	4.9 (0.1-22)	5.9 (0.2-30)
Type of substitution therapy			
Methadone	154 (56%)	57 (55%)	33 (56%)
Buprenorphine	114 (41%)	45 (44%)	24 (41%)
Missing data	9 (3%)	1(1%)	2 (3%)

OST, Opiate substitution treatment. \*Subjects included (269 tested for anti-HCV antibodies; 236 anti-HCV positive)

**Table II****Patients in each category of fibrosis by diagnostic method.**

	<b>Biopsy<sup>1</sup></b>	<b>Transient elastometry<sup>2</sup></b>	<b>GUCI<sup>3</sup></b>	<b>Total</b>
	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>	
Low	21 (47)	12 (46)	1 (3)	34
Intermediate	18 (40)	0 (0)	17 (53)	35
High	6 (13)	14 (54)	14 (44)	34

For categorization of patients, liver biopsy was preferred over TE (transient elastometry) and GUCI (Göteborg University Cirrhosis Index) score, and TE over GUCI score (in case measurements by more than one technique were available). The degree of fibrosis was designated low, intermediate or high and cut off values were defined for each fibrosis assessment technique as below.

1. Low: Ishak F0-F2, Intermediate: F3-F4, High: F5 -F6
2. Low: <8.85 kPa, Intermediate: 8.85 -10.04 kPa, High: ≥10.05 kPa
3. Low: <0.33, Intermediate: 0.33-1.11, High: >1.11

**Table III****Factors associated with degree of liver fibrosis**

	Low grade fibrosis (N=34)	Intermediate grade fibrosis (N=35)	High grade fibrosis (N=34)	Trend (p-value)	Multivariate (Low vs. Intermediate+High)  HR; 95% C. I., (p-value)	Multivariate (Low+Intermediate vs. High)  HR; 95% C. I., (p-value)
Age (years; median)	39.5	44	47	0.02	1.05; 0.96-1.2 (0.3)	1.10; 0.99-1.2 (0.08)
Male gender (%)	21 (62)	25 (71)	27 (79)	0.1	0.94; 0.31-2.9 (0.9)	1.52; 0.44-5.2 (0.5)
BMI (kg/m <sup>2</sup> ; median)	25,2	28.3	28.0	0.05	1.14; 1.01-1.28 (0.04*)	1.05; 0.94-1.2 (0.4)
Interval since first illicit drug injection (years; median)	19	16.5	26.5	0.06	0.95; 0.88-1.0 (0.3)	0.94; 0.87-1.0 (0.2)
Reported use of cannabis N (%)	24 (71)	24 (69)	26 (76)	0.8	-	-
Smoking N (%)	25 (78)	31 (89)	26 (76)	0.5	-	-
Alcohol use less than once monthly N (%)	23 (72)	26 (74)	15 (44)	0.02	0.75; 0.27-2.1 (0.6)	0.33; 0.12-0.92 (0.03*)
Report of alcohol related crime N (%)	7 (21)	9 (26)	10(29)	0.9	-	-
Report of alcohol abuse by OST clinic N (%)	4 (12)	7 (20)	5(15)	0.9	-	-
Previous admission to facility for treatment for alcohol abuse N (%)	1 (3)	2 (6)	2(6)	0.3	-	-
Presence of anti- HBc antibody N (%)	17 (52)	19 (56)	28(82)	0.009	1.98; 0.65-6.1 (0.2)	4.38; 1.2-15.6 (0.02*)

OST, Opiate substitution treatment; HR, hazard ratio

**Figure legends**

**Figure 1**

Overview of study participation

