Mortality, morbidity and treatment uptake related to hepatitis C among people who have injected drugs in Norway

Knut Boe Kielland, MD

Norwegian National Advisory Unit on Concurrent Substance Abuse and Mental Health Disorders (ROP)
Innlandet Hospital Trust

Norwegian Centre for Addiction Research (SERAF)
Institute of Clinical Medicine
Faculty of Medicine
University of Oslo
© Knut Boe Kielland, 2015

Series of dissertations submitted to the
Faculty of Medicine, University of Oslo
No. 2082


All rights reserved. No part of this publication may be
reproduced or transmitted, in any form or by any means, without permission.

Cover: Hanne Baadsgaard Utigard.
Print production: John Grieg AS, Bergen.

Produced in co-operation with Akademika Publishing.
The thesis is produced by Akademika Publishing merely in connection with the
thesis defence. Kindly direct all inquiries regarding the thesis to the copyright
holder or the unit which grants the doctorate.
Contents

Foreword .............................................................................................................................................. 3
Acknowledgements .............................................................................................................................. 5
Summary .............................................................................................................................................. 7
Norsk sammendrag ................................................................................................................................ 9
List of papers ......................................................................................................................................... 11
Errata .................................................................................................................................................. 12
Abbreviations ....................................................................................................................................... 13
Introduction ......................................................................................................................................... 15
Some features of hepatitis C .............................................................................................................. 16
  History of viral hepatitis related to PWID......................................................................................... 16
  Hepatitis A, B and D .......................................................................................................................... 16
  Hepatitis C ....................................................................................................................................... 17
Modes of transmission of HCV ........................................................................................................... 17
Prevalence and incidence ...................................................................................................................... 20
  HCV in the general population......................................................................................................... 20
  HCV among people who inject drugs (PWID) ............................................................................... 32
Natural history of chronic hepatitis C infection (CHC) ....................................................................... 33
  Spontaneous clearance .................................................................................................................... 33
  Liver fibrosis and cirrhosis ............................................................................................................... 34
  End stage liver disease and hepatocellular carcinoma .................................................................... 36
  Extra-hepatic manifestations of HCV ............................................................................................ 38
Mortality ............................................................................................................................................... 40
Treatment uptake, efficacy and mortality after treatment ................................................................... 41
  Total HCV treatment uptake among PWID in Norway ................................................................. 43
Modeling of hepatitis C in different populations .............................................................................. 44
Information on Statens klinikk for narkomane ................................................................................... 46
Objectives .......................................................................................................................................... 49
  Overall research aims ...................................................................................................................... 49
  Objective for each paper .................................................................................................................. 49
Material and methods ......................................................................................................................... 50
  Study designs ................................................................................................................................ 50
Foreword

My work with drug users was initiated accidentally in 1978 as I – just after receiving my authorisation as medical doctor (MD) – was directed to serve civil service as a conscientious objector at “Statens klinikk for narkomane” (SKN) in Hov.

When I started my work at SKN in 1978 most patients were young injecting drug users (see Figure 13, page 47). After finishing civil service in 1979, I began work as a general practitioner in the village of Hov. But I had a never-ending interest for the fate and treatment of drug addicts, and continued as part time MD at SKN during most of the years from 1979 until 2006.

Some of this interest has brought me to the subject of “dual diagnosis” or comorbidity of substance misuse and mental illness, which have been a field for studies and work for several years. But I had a continuous awareness of the somatic problems inherent with all kind of drug abuse. The notion of “triple diagnosis” is often more exact, including substance use dependence as well as mental and somatic illnesses.

For people who inject drugs (PWID) a main somatic health problem have been virus infections due to sharing of needles, syringes and other injection paraphernalia. Hepatitis B was well known many years before I entered the field, and acute hepatitis B was commonly seen among PWID in those days. But only about 5% of HBV-infected adult patients develop chronic disease. Hepatitis A has been a frequent cause for acute hepatitis among PWID, but has not been a major problem because the virus is cleared spontaneously. The first case of human immunodeficiency virus (HIV) at SKN was diagnosed in 1984, followed by a small wave of new cases. But due to better injection hygiene this epidemic was curbed quite efficiently among PWID. Hepatitis C – known from 1989 – is a much greater problem in the long run, due to its high risk of transmission compared to HIV and the great risk of chronicity. Thus, different aspects of hepatitis C are the subject for this thesis.

---

1 The National Clinic for Drug Addicts. The clinic offered residential treatment for drug addicts and was established in 1961. It was an independent unity financed directly by the Norwegian government until 2004 when the institution was integrated into the regional hospital “Innlandet Hospital Trust”.

2 The term “PWID” in this thesis also includes people who have injected drugs earlier and later quitted.
Acknowledgements

The list of persons of importance for this work is long, and I take this opportunity to thank all of them, both in the professional and private networks.

Professionally, the work started in 1992 with establishment of a research register of the patients admitted to Statens klinikk for narkomane (SKN). The director of SKN in those days – Magnar Engeseth – was important because he supported the establishment of the research register, which has been essential for this project (see Introduction page 15). Our main research co-operation was with the Norwegian Institute for Alcohol and Drug Research (SIRUS), especially with Ingeborg Rossow, who inspired and learned me a lot. She may have sown a seed for the future. Among the early research partners was also the late J. Chr. Siebke at the Virologic department of the National Institute for Public Health who had a thorough knowledge about viral hepatitis and the tests to elucidate their course, and who co-authored my first paper on viral hepatitis among drug users, published in the Journal of the Norwegian Medical Association 1991. The idea of studying mortality in anti-HCV positive drug users and compare HCV RNA positive patients with HCV RNA negative ones, matured around 2000, supported persistently by my longtime close friend and colleague Dag Heldal.

The essential supporting person in this work – for whom I have great gratitude – is my main supervisor Olav Dalgard, with whom I had the first contact in 2003. He did understand rapidly that our research register and the frozen sera represented an extraordinary possibility for long term follow-up of hepatitis C among drug users. He inspired and advised, and he has been a trusted and nice friend in the long adventure into this scientific work. My co-supervisors have been Ellen Amundsen at SIRUS and Jørgen Bramness at the Norwegian Centre for Addiction Research (SERAf). Ellen has patiently, friendly and consistently been an excellent advisor on statistical matters and epidemiological questions about injecting drug use in Norway, and Jørgen has always been available for support and advice in spite of his busy position as director of SERAF.

At the Department of Virology, National Institute of Public Health (NIPH) our main co-worker was Kjell Skaug who died all too early, after having completed most of the large work on serum analysis. He has been missed very much. He co-authored Paper I and would have co-authored the other two papers if he had lived. He had a never ending interest in this work until his last days. From NIPH, I would also like to thank Einar Brunvoll who did a great and tedious work finding and testing the old frozen sera, as well as Bjørg Gutigard who did much of this work the last year. Inger Sofie Samdal Vik also has been essential for planning the project and not least by allowing us to employ her staff in order to accomplish this work.
For Study 2 we had a very nice cooperation with the Institute of Forensic Medicine at the University of Oslo, later organized as a department of the Division of Forensic Sciences at the NIPH. The main participants from that institute was the director professor Sidsel Rogde who was interested and seemed to understand the potentials of the work from my first telephone contact with her in 2004, and who with PhD student Gerd JM Delaveris, MD, persistently followed up. Gerd did the pathology work classifying the slides of liver tissues, cooperating with Tor Jacob Eide at the Department of Pathology, Oslo University Hospital Rikshospitalet. I am grateful towards both, and happy to see that our common paper could also be included in Gerd’s PhD.

My formal position during the last years of this work is earned to a scholarship from Innlandet Hospital Trust. Its Department for Research has supported the work in several ways, and I particularly would like to thank the former head of that section, professor Per Farup, who, I think, was essential for this support. The department has also been of great help with practical solutions and mental support all the way. The same is the case with my own present employer National Service for Concurrent Substance Abuse and Mental Disorders (or shortly “The National Centre for Dual Diagnosis”) with its director Lars Lien and research director Anne Landheim with whom I have cooperated during many years on substance use and concurrent mental disorders.

A special thank to Liz Tenold, Trond Pedersen and other co-workers at the Norwegian Social Science Data Service (NSD) who keep our code for linkage to health registers, and who have consistently through many years been expedient and helpful managers of linkage with health registers.

During most of the time for this work I have been active as GP in Hov, which is the main village in the community of Søndre Land. I have had the privilege to be exempted from the obligations to do community health care work which would normally be linked to my position as GP. My gratitude for this is directed both to my colleagues at Hov Medical Centre and to the community of Søndre Land. Without this I would not have been able to do this work.

Last but not least my private network – in obvious front my wife Eva and our three daughters Karen, Ingrid and Marianne – has been supportive all the way, and I am impressed by their wise and enduring patience!

The work has also been dependent on several other persons. When some have been mentioned particularly here, others may duly feel to be forgotten. If that is the case, excuse me!
Summary

Background: Exposure to hepatitis C virus (HCV) implies for 60–80% of the patients a chronic infection which mainly affects the liver. Chronic hepatitis C (CHC) is estimated to affect 130 millions globally. In most of the Western world injecting drug use is the main cause of exposure to HCV. In Scandinavia about 0.5% of people between 15 and 70 years of age are affected, and in Norway that means that about 20,000 persons is estimated to have CHC. The natural course of CHC among PWID – with their high competing risk of death – is not sufficiently known. The aims of these studies were to elucidate both all-cause and liver related mortality, and progression of liver fibrosis among PWID with CHC, as well as to estimate the rate of antiviral treatment uptake in this population and mortality according to treatment uptake.

Methods and patients: The studies were executed within a cohort of 864 patients admitted to Statens klinikkk for narkomane (The National Clinic for Drug Abusers) during the period 1970–1984. Frozen sera from 635 patients were stored at the Department for Virology at the Norwegian Institute of Public Health in Oslo. Of these 535 had been exposed to HCV (anti-HCV positive), and HCV RNA could be analysed with PCR-technique among 523, who comprised the study cohort in Paper 1. The patients were followed-up through register linkage to the Norwegian Causes of death registry, the Cancer registry of Norway, the Nordic Liver Transplantation Registry and the Norwegian Prescription Database. Antiviral treatment before 2004 was explored through linkage to Scandinavian treatment studies which in that period included about half the treated cases. In Paper 1 and Paper 2 the patients with CHC (anti-HCV positive/HCV RNA positive) were compared to those exposed to HCV with spontaneous clearance of the virus (anti-HCV positive/HCV RNA negative).

Paper 1 was a longitudinal study of all-cause mortality and causes of death from the admission to drug abuse treatment in 1970–1984 followed-up until December 31, 2008, as well as of liver related mortality of the same patients from HCV-exposure to the same date. In Paper 2 liver tissue from autopsies were examined at the Institute of Forensic Medicine at the University of Oslo (now Department of Forensic Pathology, Division of Forensic Sciences at NIPH). The stage of liver fibrosis was related to CHC and duration of the infection. In Paper 3 antiviral treatment uptake among the 245 CHC-patients alive in Norway January 1, 1997 was followed up until December 31, 2012. Mortality rate was compared in periods after versus before or without treatment.

Results: Paper 1: Of 523 anti-HCV positive patients 389 (62.7%) had CHC. All-cause mortality rate was 1.85/100 person-years (PY); among males 2.11, and among females 1.39. Mortality rates were not affected by CHC the first 25 years after the admission to SKN. The main causes of death were intoxication (45%), suicide (9%)
and accident (8%). Among patients with CHC 10/134 (7.5%) deaths were liver-related; one had two years before death been liver-transplanted for end-stage liver disease. Among patients dying after 50 years of age, liver-related cause of death was as common as intoxication. Among HCV RNA negative patients 2/86 (2.3%) deaths were liver-related, both of which were associated with chronic hepatitis B.

Paper 2: None of the 26 CHC-patients who were autopsied shorter than 15 years after HCV-exposure had advanced fibrosis (F3) or cirrhosis (F4). Among those who were autopsied 15-25 years after HCV-exposure 4/18 (22%) had F3 or F4, and among those autopsied more than 25 years after exposure 6/17 (35%) had F3 or F4. Among patients without chronic hepatitis there was one death with F4, autopsied 33 years after exposure to HCV.

Paper 3: Of the 245 CHC-patients followed-up from 1997 to 2012 47 (19.2%) had received antiviral treatment. Among the patients alive by December 31, 2012 44/158 (27.2%) had received such treatment. The reason for the different proportions was much higher mortality among those who had not received treatment, mainly due to intoxications. Liver disease was cause of death for 13/81 (16%) of the untreated patients.

Conclusions: CHC had no substantial influence on all-cause mortality among PWID the first 25 years after admission for drug abuse treatment 1974–1984. After 50 years of age liver disease became a major cause of death among PWID with CHC exposed to HCV in their late teens or early 20s. Among those autopsied more than 25 years after HCV-exposure 1/3 had advanced liver fibrosis or cirrhosis. Only 1/5 of the PWID with CHC received antiviral treatment during follow-up 1997–2012. It is of great importance for later liver morbidity and mortality in this group to increase antiviral treatment uptake, particularly among those with advanced fibrosis or cirrhosis.
Norsk sammendrag

Bakgrunn: Smitte av hepatitis C virus (HCV) innebærer for 60–80 % en kronisk livslang infeksjon av leveren. Kronisk hepatitt C antas globalt å ramme omkring 130 millioner mennesker. I den vestlige verden er mennesker som har injisert rusmidler den største gruppen. I Skandinavia antas at omkring 0,5 % av personer mellom 15 og 70 år har kronisk HCV-infeksjon, noe som innebærer omtrent 20 000 mennesker i Norge. Forløpet av kronisk hepatitt C hos mennesker som har injisert rusmidler – med deres høye overdose-dødellighet – er ikke tilstrekkelig kjent. Formålet med disse studiene er dels å undersøke dødelighet og utvikling av leverfibrose hos mennesker som har injisert rusmidler og som har vært smittet med HCV, dels å undersøke hvor mange av de med kronisk infeksjon som har fått antiviral behandling.


Resultater: Studie 1: Av 523 anti-HCV positive hadde 389 (62,7 %) kronisk infeksjon. Mortalitetsraten var 1,85 per 100 personår (PY); hos menn 2,11, hos kvinner 1,39. Mortalitetsraten ble ikke påvirket av kronisk HCV-infeksjon de første 25 årene etter innleggelsen. Viktigste dødsårssaker var forgiftninger (45 %), selvmord (9 %) og ulykker (8 %). Det var 10/134 (7,5 %) leverrelaterte dødsfall innen 2008 blant
pasienter med kronisk hepatitt C, hvorav den ene 2 år før dødsfallet hadde fått utført levertransplantasjon. Blant de HCV RNA negative var 2/86 (2,3 %) av dødsfallene leverrelaterte; begge disse hadde kronisk infeksjon med hepatitt B virus (HBV). Blant HCV RNA positive pasienter som døde mer enn 50 år gamle, var leverdødsfall like hyppig som overdose.


Studie 3: Av de 245 HCV RNA positive pasientene som ble fulgt opp mellom 1997 og 2012 fikk 47 (19,2 %) antiviral behandling. Av de 158 pasientene som fortsatt levde ved utgangen av 2012 utgjorde de behandlede 44 (27,2 %). Årsaken til forskjellen i andel var at de ubehandlede hadde mye høyere dødelighet, spesielt av overdose. Blant de ubehandlede var 13/81 (16 %) av dødsfallene forårsaket av leversykdom.

List of papers


Errata

The Thesis.

- Page 57, concerning Paper 2, first line: “By January 1, 1997 220 of the 523 anti-HCV positive…….” has been corrected to: “By December 31, 2008 220 of the 523 anti-HCV positive…….”
- Page 65 Table 11, line 2: “…recruitment of patients among in the community…” has been corrected to “…recruitment of patients in the community…”

Paper 1.

- In Table 2 the headings of columns HCV RNA (+) and HCV RNA (-) has been interchanged. (The error occurred during editing in the journal, and was not noticed during proof-reading.)

Paper 2.

- In the Abstract, section “Results” is noted: “Of 18 HCV RNA positive subjects autopsied <15 years after HCV exposure none had F3 or F4.” The correct is: “Of 26 HCV RNA positive subjects…..” (This is correctly noted in the result section of the paper.)
Abbreviations

AHC Acute hepatitis C
Anti-HCV Anti hepatitis C antibody
Anti-HBc Anti hepatitis B core antibody
Anti-HBs Anti hepatitis B surface antibody
CHC Chronic hepatitis C
CI 95% confidence interval
CMR Crude mortality rate
DAA Direct acting antiviral
GT Genotype
HBsAg Hepatitis B surface antigen
HAV Hepatitis A virus
HBV Hepatitis B virus
HCV Hepatitis C virus
HE Hepatic encephalopathy
IDU Injecting drug use
IFN Interferon
IR Insulin resistance
MC Mixed cryoglobulinemia
MI Myocardial infarction
MPGN Membranoproliferative glomerulonephritis
MSIS Norwegian Surveillance System for Communicable Diseases
MSM Men who have sex with men
NAFLD Non-alcoholic fatty liver disease
NASH Non-alcoholic steatohepatitis
NDH Norwegian Directorate of Health
NI Nucleos(t)ide HCV NS5B polymerase inhibitors
NI PH Norwegian Institute of Public Health
NNI Non-nucleos(t)ide HCV NS5B polymerase inhibitors
NorPD Norwegian Prescription Database
NSD Norsk samfunnsvitenskapelig datatjeneste (Norwegian Social Science Data Service)
NSP Needle and syringe exchange program
OMT/OST Opioid maintenance treatment/Opioid substitution treatment
PCR Polymerase chain reaction
PegINF Pegylated interferon
PI HCV NS3/4 protease inhibitor
PWID People who inject drugs (the term in this study also includes persons who have injected drugs earlier and later quit)
PWUD People who use drugs
PY Person year
RBV Ribavirin
RCT Randomised controlled trial
RNA Ribonucleic acid
RVR Rapid virologic response
SD Standard deviation

Abbreviations continued
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>SERAF</td>
<td>Senter for rus- og avhengighetsforskning (Norwegian Centre for Addiction Research)</td>
</tr>
<tr>
<td>SIRUS</td>
<td>Statens institutt for rusforskning (Norwegian Institute for Alcohol and Drug Research)</td>
</tr>
<tr>
<td>SKN</td>
<td>Statens klinikk for narkomane (National Clinic for Drug Addicts)</td>
</tr>
<tr>
<td>SMR</td>
<td>Standard mortality rate</td>
</tr>
<tr>
<td>STI</td>
<td>Sexually transmitted infection</td>
</tr>
<tr>
<td>SVR</td>
<td>Sustained virologic response</td>
</tr>
</tbody>
</table>
Introduction

Hepatitis C virus (HCV) was described first time in 1989 and tests for anti-HCV antibodies were rapidly available soon followed by HCV RNA detection through PCR-technique (HCV RNA).

From the late 1960s screening for HBsAg and anti-HBs had been part of the standard care at admission to Statens klinik for narkomane (SKN). Sera has been analysed regularly at NIPH. From the first part of the 1970s frozen sera were stored. This was the basis for a cross-sectional study which I performed in cooperation with the late Jens-Christian Siebke at NIPH on the prevalence of markers for HBV, HCV as well as hepatitis A virus (HAV) among patients at SKN [1]. We found the following prevalence of anti-HCV among patients at SKN: 1976 (56%), 1985 (78%) and 1988–89 (73%). Anti-HBs was even more prevalent (this was before HBV-vaccination was used frequently in this population). The prevalence of anti-HAV was also elevated and suggested this was due to parenteral transmission during the viremic phase.

In 1991 I initiated the establishment of a research register with the purpose of exploring mortality among the 1617 patients who had entered into treatment at SKN from the institution was established in 1961 until the end of 1991.

During the ensuing years this register has been linked to several health registries, most importantly to the Causes of death registry (Statistics Norway) several times. This has resulted in a number of publications on different perspectives of mortality among people who use drugs (PWUD) [2-5]. In 1995 we did also submit an article to the Journal of the Norwegian Medical Association on mortality according to anti-HCV, based on the serum analysis performed for the cross-sectional study published in 1991, but this was rejected mainly due to too small sample size for the conclusion which was that HCV did not influence mortality at that time.

The combination of a research register of subjects admitted to the institution and stored sera from most patients opened the possibility for long term follow-up of morbidity and mortality according to chronic hepatitis C (CHC), which is the main theme of this thesis. Such studies had to be based on a much larger cohort than in 1995 as well as longer duration of observation. The project was initiated in 2004 in collaboration with Olav Dalgard and the late Kjell Skaug, head of the Department of Virology, National Institute of Public Health. The work with serologic analyses was performed during the years 2006–2009. Somewhat later Ellen Amundsen at the Norwegian Institute for Alcohol and Drug Research (SIRUS) joined the group with statistics and a thorough knowledge of different perspectives of drug use in Norway as her main formal assets. Later Sidsel Rogde, Gerd Jorunn Møller Delaveris and Tor Jacob Eide were engaged concerning Study 2.
Some features of hepatitis C

History of viral hepatitis related to PWID
Several types of viral hepatitis have been related to PWID, due to parenteral exposure. One of them, hepatitis A (HAV), is mostly transmitted through faecal-oral route. However, it seems certain that HAV may also be transmitted parenterally [1, 6].

The medical history of viral hepatitis is as fascinating as their clinical courses. Epidemic jaundice was mentioned in the Babylonian Talmud in the 5th century AD, and it was also described by Hippocrates in “Of the Epidemics” around year 400 AD [7]. The communicable character of jaundice is attributed to Pope Zacharias in the 8th century. Infective jaundice has been a major problem until the 1950s particularly for soldiers in crowded camps during wartime. Successful experiments were conducted during the second world war for transmission of infective and serologic hepatitis to volunteers [8, 9].

Hepatitis A, B and D
Hepatitis A virus (HAV) has been the main enteric hepatitis in most parts of the world. Until the 1940s it was endemic also in Western Europe, but incidence decreased with better hygienic conditions after the war, somewhat later in southern Europe. During the 1970s and 1980s epidemics of HAV was frequent among PWID, most probably exposed through injections during viremic phases [1, 10]. HAV is never cause of chronic hepatitis.

Phylogenetic evolutionary studies of hepatitis B virus date the origin of this virus in humans in Africa to about 30,000 years BC [11]. Thus, HBV has been evolving together with Homo sapiens sapiens for a very long time. It is also found that, unlike many other viruses adapted to humans from apes, human HBV may be the origin of HBV-infection in apes [12].

Antibody tests for hepatitis B and hepatitis A were developed in 1965 [7, 13, 14] and 1975 [15, 16] respectively. In 1977 a new virus agent was found only among patients with chronic hepatitis B. It was initially denominated “delta” agent, later hepatitis D virus (HDV) [17, 18]. It was quite frequent in the Mediterranean countries, but not in other Western countries. Vertical transmission of HBV is associated with high risk of chronic infection in the new born and remains high after exposure in early childhood explaining the high prevalence in parts of Africa and Asia.

When exposure to HBV occurs in adults chronic hepatitis B (CHB) develops in about 5%, more often if the acute infection is subclinical. HBV exposure was extremely high among PWID globally until the 1990s, but prevalence has been decreasing.
since, partly due to vaccination. Vaccination against HBV is part of the child vaccination program in most countries as is recommended by the World Health Organisation (WHO). UK and the Scandinavian countries are among the few exceptions in Western countries.

Hepatitis C
Infection by HBV explained a large number of cases of post-transfusion hepatitis, but it was experienced that some of these cases of hepatitis could be described as neither hepatitis B nor hepatitis A [19]. They were denominated hepatitis non-A, non-B (HNANB).

Both acute and chronic hepatitis were known to be frequent among PWID. Some could be explained by HBV – or for acute cases also by HAV – but not all. They obviously had HNANB.

In 1989 HCV was described, and antibody tests were developed [20-22]. Phylogenetic evolutionary studies have concluded that the most recent common ancestor of HCV genotype 1 in Western Africa may be around the 14th century and for genotype 2 in the first part of the 18th century [23]. This is probably the oldest ancestors of HCV, which is then a much younger human pathogen than HBV. In Japan genotype 1b prevails and was probably introduced in the late 19th century, with exponential growth since 1920 until the last years possibly due to treatment of schistosomiasis and other medical procedures, as well as exposure though injecting use of amphetamine during the second world war [24].

In the Western world most cases of HNANB were proven to be caused by HCV as soon as serologic tests were available.

Treatment of HNANB with interferon had already been introduced in 1986 [25]. With the supplement of ribavirin in 1998 and introduction of pegylated interferon (PegINF) in 2001 the sustained virologic response (SVR) reached 40% for genotype 1 (GT1) and 60–80 % for GT2 and GT3. After 2011 the addition of direct-acting antivirals (DAAs) has further increased the rate of SVR. Combination of DAAs now allow for >90% SVR with all-oral regimens – without interferon and its serious side-effects [26].

Effective tests for blood donors to eliminate transmission of HBV and HCV were introduced around 1971 and 1990 respectively, reducing blood products as source of hepatic virus transmission to a very large degree in the Western world; somewhat less in some other parts of the globe.

Modes of transmission of HCV
The dominating route of HCV transmission is through percutaneous exposure. Until efficient screening of blood products was implemented shortly after 1990, many
transmissions even in developed countries were iatrogenic, mostly through transfusion of blood products.

In countries with low or middle income reuse of syringes and/or needles in medical treatment may have been a major route of transmission. The prevalence of HCV in different countries mirrors historically the quantity of parenteral procedures as well as the hygienic quality of those procedures. Even if tests for HCV were not available before 1990, the risk of transfusion-associated hepatitis in some countries was minimized through testing for anti-HBV, liver enzymes, and by not paying donors. Japan has a high prevalence of HCV in the older part of the population and Figure 1 illustrates some of the reasons. Until the beginning of the 1960s more than 50% of transfusions were affected. The risk decreased first by using voluntary blood donors who were not paid, then by screening for HBsAg and later for HCV.

Figure 1 Risk of post-transfusion hepatitis in Japan. From Chung et al [27]

After 1992 injection drug use has been the most important route of transmission in most countries; in most of the Western world also before 1992. HCV keeps viability in syringes for several weeks, dependent on the quantity of void volume of blood after use. Syringes with detachable needles retain blood in the syringe and in the needle and the void volume of blood will be higher than in syringes with fixed needles. In syringes with detachable needles viable HCV has been demonstrated experimentally for up to 63 days in both 4°C, 22°C and 37°C, with quantity of HCV inversely proportional with temperature up to 37°C [28]. In syringes with fixed needles viable HCV survives for a much shorter period because of smaller volumes of void blood. Infectivity in dried blood has been demonstrated at least for 16 hours in room temperature [29].

Transmission of HCV in PWID is propagated also through the common use of other injection equipment than syringes and needles, such as spoons, filters and rinse water (injection paraphernalia). This was confirmed in a meta-analysis from 2011 [30]. Among PWID in a needle and syringes exchange program (NSP) in Oslo 2002
there was association by multivariate regression between anti-HCV and syringe sharing, backloading\(^3\), age >34 years, age of first injection <20 years, duration of injecting drug use (IDU) >5 years and injection during incarceration [31]. Users of heroin had higher risk than users of amphetamines. Syringe sharing during lifetime was reported by 76% of the PWID; sharing last four weeks by 18%. In a cross-sectional study in Scotland recent HCV infection (HCVRNA positive/anti-HCV negative) was found in 5.7% of drug users reporting syringe sharing last six months, 2.7% of those sharing paraphernalia only, and 0.7% of those reporting no sharing of both [32]. Sharing of injection equipment seems to be more frequent among younger PWID than among older ones [33]. The risk associated with sharing injection paraphernalia probably has not yet been communicated efficiently to drug users.

High prevalence of HCV also has been found in drug users who report that they do not inject [34]. Snorting of cocaine and amphetamines with sharing of straws is a possible way of transmission in such cases [35-37]. Another possibility may be that some have injected – perhaps just a few times – without admitting it.

Tattooing [38], acupuncture [39], sharing of toothbrushes [40, 41] and razors [41, 42] are other documented ways of transmission although the risk of transmission through tattooing and acupuncture in professional settings actually is low in developed countries. However, tattoos performed in prisons or privately in homes are associated with risk of HCV transmission [43]. Barbers in some countries still pose a risk for transmission of viral hepatitis [42, 44]. Dental procedures have been mode of transmission in many countries [45], and still are in some [46]. A case-control study from France exposes other possible ways of exposure: abortions, some dermatological procedures, outpatient injections, contact sports, beauty treatments, professional pedicure/manicure [47].

Heterosexual transmission of HCV in stable couples has been the subject for much research. When other transmission modes can be excluded, the risk for heterosexual transmission in stable couples is estimated to be 1 in 190,000 sex contacts according to a recent study [48]. A review report the risk to be even less [49]. However, in patients with HIV infection or sexually transmitted infection (STI) there is an increased risk of HCV transmission through heterosexual sexual activity [49].

High numbers of heterosexual partners are associated with increased risk for HCV [50], but it is not established beyond doubt that this is caused by the sexual contact per se or through other unreported risk behaviour [48].

---

\(^3\) Backloading: a way to give shares of drug to other user by squirting drug solution from one syringe into another after removal of the receiving syringe’s plunger
Men who have sex with men (MSM) do not have increased risk of HCV transmission in the absence of HIV according to most studies [51, 52], but transmission seems to be possible [53]. Co-infection with HIV is strongly associated with the transmission of HCV among MSM [54]. HIV positive MSM have had a rapidly increasing incidence of HCV infection during the last decade [55].

The risk of vertical infection from HCV infected mother to child during pregnancy and birth is estimated to be around 5% if the mother has CHC [56, 57]. A Norwegian study showed a transmission rate of 8% [58]. In countries with high prevalence of HCV intra-familial transmission has been demonstrated, especially for children [46, 59], but it is very rare in countries with low HCV prevalence [60, 61]. The exact manner of intra-familial transmission in high-prevalence countries is still enigmatic [62].

**Prevalence and incidence**

**HCV in the general population**

**Global prevalence**
The most recent estimation of global prevalence of HCV was published in 2013 and concluded with a worldwide prevalence of anti-HCV in 2005 of 2.8% (CI 2.6%–3.1%) up from 2.3% (2.1%–2.5%) in 1990 [63], in a world population which in 2005 was 6.5 billions. This corresponds to 184 million individuals. With a clearance rate of 30%, spontaneous or after treatment, this would indicate that about 130 million persons worldwide have a chronic HCV infection (CHC).

However, this last estimation was based on an anti-HCV prevalence in Western Europe of 2.4%, which is substantially higher than expected because the prevalence in the most populated Western European nations, except Italy, clearly is lower [64-68]. This is confirmed in another recent study [69]. In Scandinavia the prevalence is around 0.4-0.5% [70-73].

In Romania and Italy, particularly the southern part, prevalence of HCV is high, especially among the elderly. In Italy anti-HCV prevalence estimates in the general population were obtained through studies conducted in different areas of the country, mostly during the 1990s. In a typical Northern Italian city prevalence of anti-HCV was 3.2% [74]. Three studies from Central and Southern Italy published in 1995–2001 reported rates of anti-HCV in the range between 8.4% and 22.4% [75-77]. The studies demonstrated high rates among older people, and rates <1.0% among those <30 years of age.

It is assumed that there has been important transmission in Italy during the 1950s and 1960s due to medical procedures, razors, barbers, and possible some kind of intra-familial transmission [41]. These ways of transmission have affected the
younger generation to a much lower degree, and this is why prevalence is decreasing as elderly HCV-infected people die [78].

In North-America the estimation of global prevalence is based on anti-HCV prevalence of 1.3% which is in concordance with the most recent cross-sectional study performed on the general population in USA [79].

In Africa prevalence was estimated to 5.3% about 2005, but it varies substantially from high prevalence countries like Egypt, Nigeria, Chad and Guinea with more than 10%, to most parts of East Africa where the prevalence may be below 2% [80]. The prevalence is still not sufficiently explored in some countries, however.

The highest prevalence has been found in rural parts of Egypt due to the fight against schistosomiasis through injecting antimony tartrate. This was an effective medication for the disease, used extensively from the 1950s until the mid-1980s when alternative oral treatment became available [62, 81]. Thus, the success of treatment with antimony tartrate was accomplished with the high price of extensive HCV transmission and a prevalence of CHC in Egypt of more than 20% in the most afflicted rural regions in the Nile delta. Liver cancer is the most prevalent cancer in Egypt with the same regional differences as for HCV [82].

The estimation of the global burden of HCV is also based on anti-HCV prevalence in China of 3.7% [63]. In that country, recent reports downgrade this prevalence, which is now estimated to be approximately 1.0% [83]. The reason for this discrepancy in China is thought to be that incidence since 1990 has been much lower than before 1990. Elderly people with CHC have been dying. It is also indicated that earlier estimates may have been too high, caused by first generation anti-HCV tests of low specificity.

In Japan there was a high prevalence in the older part of the population due to a medical history of widespread use of injections instead of oral medication, early injecting drug use – mainly of methamphetamine before, during and some years after WWII, and high risk of transmission through transfusions by the use of paid donors [27, 84].

The European and particularly the Chinese updates may indicate that the 185 million anti-HCV positive world wide was a too high estimate and that the real number may be lower. However, still we do not have sufficient data to evaluate this with certainty globally. The discrepancies between studies illustrates that it is a difficult task to get secure estimation of the global burden of HCV [85].

Decreasing incidence and prevalence of HCV is also reported from France [45], Japan [27] and USA [86]. Generally, the decrease in prevalence is most important in countries with an important portion of the CHC population consisting of old people. They have usually been exposed through unsafe medical procedures or other forms
of non-IDU transmission in the community. In countries where the main exposure has been through IDU, prevalence may be more stable. Change in CHC prevalence is generally dependent on incidence on one hand, deaths and clearance by treatment on the other.

**Prevalence in Norway**

We do not have precise knowledge on CHC prevalence in Norway. For estimation of CHC prevalence in Norway, we have at least six potential sources:

3. Studies on prevalence among pregnant women 1993 and 2003
5. A study on prevalence of known anti-HCV positive patients in Northern Norway 1998
6. Studies of HCV prevalence among PWID combined with estimations of the number of former and current PWID in Norway

1. Notifications of HCV to The Norwegian Surveillance System for Communicable Diseases (MSIS) have been effected according to changing principles. In 1990–1991 all cases had to be notified. During 1992–2007 only acute cases were notified, and from 2008 again all cases were included by combined data from microbiological laboratories and clinicians. Figure 2 shows the number of notifications, which obviously has been dependent on the principles for notifications. During the years 1992–2007 the number of notifications was small, reflecting the fact that acute hepatitis C rarely was diagnosed. During the years after 2008, the number of notifications has been high, most probably because of a “catching up”-effect of those who had not been notified during the “missing” years. The number has been decreasing, and will probably reach a steady state of about 1000 annually\(^4\). The total number of notifications in Norway until the end of 2014 was 17848 anti-HCV positive persons.

\(^4\) In Sweden where notifications have included all cases from 1990, the number of new HCV notifications since 2005 has been stable with a mean of 2101 anti-HCV positive persons each year. If this corresponds to incidence, an estimate is 2100/9400000 (0.02/100PY). Such an incidence estimate in Norway implies about 1100 new cases each year. However new notifications still most probably include both recently transmitted cases (incidence) and older cases diagnosed recently. Thus incidence may be lower than new notifications implies.
Age distribution of HCV notifications in Norway 2013 is shown in Figure 3. The younger age groups may reflect recently transmitted cases, while the older age groups probably are cases mainly transmitted earlier, but diagnosed or notified for the first time in 2013. Figure 3 can be compared to Figure 5, page 27 which represent age distribution among those who had been exposed to HCV until 2000. The age of anti-HCV positive subjects from the screening in 2000–2001 was lower than for those notified in 2013, possibly reflecting a “cohort-effect” of people transmitted through IDU. During the period 2008–2013 IDU was the mode of HCV transmission in 91% of notified cases where this was reported. However, in half the cases mode of transmission was unknown.

We lack knowledge about persons in Norway having been exposed to HCV without being diagnosed, known cases not notified, notified persons who have later died, and chronically infected persons exposed to antiviral treatment with accomplishment of SVR. A study on OMT-patients indicate that about 25% of the patients who received

---

Figure 2 Number of notifications of anti-HCV in Norway 1990–2013 [87]

Figure 3 Notifications of hepatitis C in Norway 2013 according to gender and age groups [87].
antiviral treatment for CHC 2010—2013 had not been notified to MSIS (Håvard Midgard, personal communication). These patients had known CHC with particular attention because of active treatment, which presumably may have increased probability of notification. The fraction of unnotified HCV-exposed persons can be assumed to be larger among untreated ones. An estimation of possible number of CHC in Norway based on notifications from MSIS and treatment uptake of antiviral medication for CHC from the Norwegian Prescription Database (NorPD) is presented in Table 1. It is based on several assumptions which are far from evident on the fraction of people exposed to HCV who have not been notified, mortality among exposed persons, and clearance after HCV exposure. Furthermore, SVR after antiviral treatment is assumed to be 60% (in a country with high prevalence of GT3) and 80% of CHC is estimated to be caused by IDU.

Table 1 Estimation of prevalence of CHC in Norway based on notifications and treatment uptake. Three alternatives.

<table>
<thead>
<tr>
<th>Anti-HCV positive persons not notified</th>
<th>Alternatives dependent on the size of the unnotified fraction of the anti-HCV positive individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notified for HCV-infection (anti-HCV positive)</td>
<td>17848 17848 17848</td>
</tr>
<tr>
<td>Alternatives 40%, 50% or 60% not notified</td>
<td>/0,6 /0,5 /0,4</td>
</tr>
<tr>
<td>Total number of HCV-exposed (anti-HCV positive)</td>
<td>29747 35696 44620</td>
</tr>
<tr>
<td>Assumed dead 20%</td>
<td>*0,8 *0,8 *0,8</td>
</tr>
<tr>
<td>Prevalence HCV-exposed individuals alive</td>
<td>23797 28557 35696</td>
</tr>
<tr>
<td>Prevalence anti-HCV/100 inhabitants</td>
<td>0.45 0.56 0.69</td>
</tr>
<tr>
<td>Clearance 25%</td>
<td>*0,75 *0,75 *0,75</td>
</tr>
<tr>
<td>Chronic hepatitis C (CHC)</td>
<td>17848 21418 26772</td>
</tr>
<tr>
<td>Antiviral treatment 2004—2014: (SVR 60%)</td>
<td>-3360 -3360 -3360</td>
</tr>
<tr>
<td>Prevalence of CHC in Norway at the end of 2014</td>
<td>14488 18058 23412</td>
</tr>
<tr>
<td>Prevalence CHC/100 inhabitants</td>
<td>0.28 0.35 0.45</td>
</tr>
<tr>
<td>Exposed to HCV through IDU 80%</td>
<td>*0,8 *0,8 *0,8</td>
</tr>
<tr>
<td>Prevalence of CHC caused by IDU</td>
<td>11590 14446 18730</td>
</tr>
</tbody>
</table>

5 Unnotified persons include two groups: Undiagnosed persons and diagnosed ones who have not been notified to MSIS.
6 In Sweden HCV has been notified consistently since 1990, and about 58000 persons have been notified until Dec. 31, 2014. Of these about 20% are dead (AS Duberg, personal communication). We lack this information concerning Norway, and it seems reasonable to extrapolate the Swedish data in this respect.
7 Norwegian population at the end of 2014: 5,166,000.
8 4974 individuals had received ribavirin 2004—2013 according to personal communication from NorPD. We suppose that about 600 had such treatment in 2014. In Norway GT3 is most frequent and also the threshold for entering treatment has been lower for GT3 than for GT1 because of better treatment results with PegINF/ribavirin. Because of the higher SVR for treatment of GT3 than for GT1, it is assumed that SVR has been obtained among 60%.
9 According to the notifications 91% of cases were caused by IDU, when mode of transmission was known. However in about half the cases, mode of transmission was unknown. Possibly the fraction of exposure to HCV through IDU may be lower in that group, why this fraction overall is assumed to constitute 80% of cases.
2. In Oslo persons aged 30, 40, 45, 60 and 75 years were invited to the Oslo Health Study 2000–2001, which included blood testing [71]. Of those invited 43% of men and 50% of women participated. The participation was lowest among 30 year old men (37%) and highest among 60 year old women (59%). In the whole sample 78/11456 (0.7%) were anti-HCV positive and 62 HCV RNA positive (0.5%). Anti-HCV prevalence was 0.8% among men and 0.6% among women. It was highest among men aged 40 and 45 years (1.5%) and very low in the oldest age groups. High risk individuals may have had low participation in the study, which may imply an underestimation of prevalence. On the other hand Oslo probably had a higher prevalence of HCV than the country mean because of higher prevalence of IDU [88].

3. All pregnant women in 11 counties during a period in 1993 were examined as part of a study of toxoplasmosis. Of these, 970 women were selected for a HCV prevalence study. Seven women (0.7%) were anti-HCV positive [72]. In another study of pregnant women recruited in Northern Norway 2003—2004 the rate of CHC was 0.2% [89]. Women have lower risk of HCV than men, which is compensated by the fact that pregnant women represent age groups with higher risk of HCV-infection [71].

4. In a cross-sectional study of 16,756 blood donors in 1990–91, 16 were anti-HCV positive by a second generation ELISA test, 9 (60%) had a history of IDU. 15/16756 (0.09%) were HCV RNA positive [90]. The rate of anti-HCV positive new donors at Ullevål hospital in 1998 (0.13%) was published in Eskild’s study of pregnant women [72]. Donors represent a low-risk group because of the selection procedures of donors.

5. A study of HCV including all anti-HCV positive persons in Northern Norway 1998, based on laboratory information from all patients recognised by primary and secondary health care at that time [91]. Prevalence was 0.24% based on the total population in that area. No screening was performed in this study.

6. Studies of HCV prevalence among PWID combined with studies on the prevalence of IDU. It is recently estimated that the total number of current and former PWID alive in Norway in 2012 was 22,814, of which 8,393 currently use injections; 8,428 had terminated IDU temporarily and 5,993 permanently (Ellen J. Amundsen, SIRUS, personal communication). The numbers reported imply a reduction of the number of current PWID compared to earlier estimations published by the same team at SIRUS [92-94]. A main method for estimation is the “mortality multiplier method” combining knowledge of number of deaths by overdoses in a population with mortality rate in cohorts of PWID. This is supplied by other methods [93]. It is estimated that about ½ of Norwegian PWID have CHC [95, 96], but even if 90% of PWID are anti-HVC positive after 15 years of IDU, the time lag
from first injection to HCV-exposure has increased since the 1980s and 1990s. Consequently this way of counting would result in an estimation of around 11,400 persons in Norway with CHC caused by exposure through IDU.

There is concordance between the estimations based on the lowest alternative in Table 1 and the estimation based on number of former and current PWID in Norway. This indicate somewhat lower prevalence of CHC in Norway in 2014 than may be concluded from the population study in Oslo 2000 conducted by Dalgard et al which indicated a prevalence of about 20,000 in the country at that time. The difference may be explained by decreased prevalence in the period 2000—2014. A prerequisite for this would be that the sum of deaths and obtained SVR has been larger than the incidence of new cases in that period, which is not obvious. Another possibility is that the number of former and current PWID is larger than estimated, and that the fraction of unnotified anti-HCV persons also is larger than 40% (Table 1). Most probably the prevalence of CHC in Norway is between 14,500 and 20,000, or between 0.28% and 0.39%.

**HCV prevalence according to age group**

In countries with high prevalence of HCV, the prevalence usually is higher among older people because the main way of transmission has been medical procedures which later have been changed. The prevalence in different age groups in Romania is shown in Figure 4. The situation is similar in most high-prevalence countries like Italy, Egypt, China and Japan. In such countries the prevalence of HCV will decrease due to natural deaths – as well as deaths by liver disease – among old people.

![Figure 4 Prevalence of anti-HCV in Romania 2006-2008 according to age group](image)

This contrasts the situation in most of Western Europe and North America where the number of subjects exposed to HCV is higher among middle aged people, mostly transmitted through injecting drug use. The situation in Oslo 2000-2001 is a typical example (Figure 5).
Distribution of HCV genotypes

HCV is a RNA-virus with substantial genetic variety, which is the basis for division into genotypes and subtypes. Even if the main characteristics are common, genotypes have different properties particularly concerning response to antiviral treatment based on interferon (INF) and ribavirin (RBV). Small differences also exist concerning development of CHC, with genotype 3 (GT3) characterized with an increased tendency to generate liver steatosis and fibrosis. Genotypes and subtypes also are of great interest for the mapping of the HCV epidemics both geographically and in time.

HCV is currently classified into 7 genotypes and 67 subtypes [98]. Genotypes and subtypes differ about 30% and 20%, respectively, at the nucleotide and amino acid level [99].

GT1b is the most frequent globally. Generally GT1b is linked to transmission through medical procedures, while GT1a is associated to drug use. In North America and most of Northern Europe GT1a is most common, and GT1b dominates in China, Russia, and Japan as well as in Germany and most of southern Europe, especially southern part of Italy. In India and Pakistan GT3a dominates, and this GT is also common in the UK, Russia and the Scandinavian countries, where it is associated with drug use [85]. GT4 prevails in North Africa and the Middle East, and is also found in some European countries where immigrants from those countries have settled. This includes Sweden, but not Norway. GT5 is occurring in Africa, most notably in South-Africa. Also in a region of Central France GT5 occurs among older patients exposed through blood transfusions [100]. GT6 is common in Vietnam as well as in China and Thailand. GT7 originates from Congo.

In Europe genotype also varies with age and manner of exposure. Older patients mostly exposed through transfusion typically have GT1b and GT2, while younger...
patients with IDU as infection route have GT1a and GT3. The latter is increasing in frequency [100].

Traditionally genotypes have been of great importance because the effect of antiviral treatment with PegINF and RBV has depended on them. Genotypes 1, 4 and 6 have had SVR <50%, and genotypes 2 and 3 about 60-80%. Possibly GT5 may be similar in that respect to GT2 and GT3 [101]. GT3 also is associated with increased steatosis and liver fibrosis [102, 103].

The distribution of genotypes in Norway is shown in Figure 6 where results from a population study in Oslo 2000-2001 [71] is compared with results from Department for Virology, NIPH 2008-2012 [104]. The latter had higher proportion of the GT3 – probably associated with IDU – and fewer of the transfusion-related GT1b and GT2. This may be interpreted as an increasing proportion of PWID among anti-HCV positive persons in Norway, which is expected. However, the sample size in the Oslo survey was too small for reliable conclusions [71]. Among PWID in Oslo GT3a is the most frequent [105].

As direct-acting antivirals (DAAs) are introduced, the feasibility of acquiring SVR for genotype 1 – and probably also genotypes 4 and 6 – will increase, and as a consequence the importance of genotypes for treatment success may be decreasing, even if GT3 is less sensitive for some of the DAAs.

**Incidence**

Generally, we know less about incidence than about prevalence concerning HCV, because it is more difficult to estimate. The following methods are possible:
- Notification of new cases of HCV including information – if available – on probable time point of transmission. The ideal situation occurs when all anti-HCV positive persons are already registered.
- Longitudinal follow-up of high risk populations, notably PWID, persons with HIV (particularly MSM), and prisoners.
- Surveillance of low risk populations who have blood tests drawn for other reasons, e.g. blood donors and pregnant women.
- Cross-sectional studies of both HCV RNA and anti-HCV individuals in different populations, e.g. PWID, pregnant women, blood donors or the general population. Anti-HCV negative and HCV RNA positive persons have acute hepatitis C. With known mean time lap from positive test for HCV RNA to positive test for anti-HCV, estimation of incidence is possible.

Comparison of HCV notifications in Sweden and Norway

In Sweden notification of HCV has followed basically unchanged principles since 1991. Both chronic and acute cases have been notified. The number of cases was highest in 1992 and has since decreased until 2006 (Figure 7). Since then the number of HCV notifications in Sweden has been quite stable – around 2100/year.

![Figure 7 Notifications of HCV in Sweden 1990-2006](image)

The number of notifications among subjects <30 years of age has been remarkably unchanged 1998-2013, while notifications of those >30 years has decreased substantially (Figure 8). This may indicate that incidence of HCV in Sweden is stable.
Figure 8 Number of notifications for HCV in Sweden since 1998 according to age and period.

While the principles for notification of HCV in Sweden have included all cases of HCV since 1990, only acute cases were notified in Norway during the years 1992-2007 (Figure 2, page 23. Hence, very few were notified in that period. This was compensated by a large number of notifications the following years when all cases had to be notified again. A comparison between notifications in Norway and Sweden must take this difference into account. The total number of HCV notifications 1990-2014 in Sweden was approximately 58,000, in Norway 17,848. As acute HCV most probably has been notified among young patients, this explains why patients <30 years constitute a larger part of the notifications in Norway than in Sweden during the periods 1998-2005 (Figure 9). With regard to new notifications among patients <30 years representing quite recent infections, such notifications may be a proxy for incidence among PWID. In Sweden an increasing proportion of HCV-notifications have been constituted by such young patients. The number of patients aged 15-29 notified for HCV 2010–2013 in Norway was 1489 (0.0292%), in Sweden 2660 (0.0274%)12. This indicates a similar incidence of HCV in Norway and Sweden, even if there still may be some compensation in the Norwegian number from the lack of notifications before 2008. The findings do not suggest decreasing incidence in this group, contrary to what is estimated in

\[\text{Reference 10 Information from Duberg et al 2008[70] for the period 1990-2006, and from} \]


\[\text{Reference 11 Statens folkehelseinstitutt (SFI), MSIS: http://www.msis.no/}\]

\[\text{Reference 12 The population November 1, 2014 in Norway was 5.16 millions, in Sweden 9.74 millions}\]
Figure 9 HCV-notifications in Sweden and Norway 1998-2013 according to periods and age groups

some other Western countries [106]. With decreasing incidence of IDU in Norway (Ellen Amundsen, personal communication) incidence of HCV is expected to decrease in this country in the near future.

Incidence of HCV in other countries
Incidence of HCV-infection depends on the occurrence of risk behaviours as well as on the prevalence in the population. A study of a rural population in Northern Italy where anti-HCV prevalence was 3.5% in 1986, reported incidence 1986—1996 of 0.05/100PY [41].

In Egypt recent studies still give indications of high incidence of HCV-infection, estimated in different regions between 0.08 and 0.68/100PY [107]. In the general population in Canada where anti-HCV prevalence is 0.78%, incidence is estimated to be 0.026/100PY; 0.034 among males, 0.018 among females [45].

An American study on blood donors 1999-2008 showed much lower incidence in a population with low prevalence 0.003/100PY [108]. Another American combined observational and cross-sectional study concluded with incidence of 0.004/100PY among blood donors (prevalence among new donors 0.34%, repeat donors 0.08%) [109].
In countries where regular notification of HCV – both acute and chronic infections – has been enforced since 1990, new notifications may increasingly represent new cases and thus can indicate incidence. In Sweden the annual number of notifications has been constant at about 2100 persons annually since 2006. Some new infections will be unknown and hence not notified. On the other hand the notifications also include people who have been infected for years. Consequently the quite constant annual number of notifications in Sweden may reflect incidence. If so, the incidence rate of HCV infection would be around 0.02/100PY in the general population of Sweden.

Incidence of HCV-infection among HIV positive MSM (cases/100 PY) seems to have increased strongly during the last years in different parts of the world. From Tokyo is reported an incidence of zero among HIV positive MSM 2005—2006, gradually increased to 2.5/100PY in 2011-2012 [110]. In a study from London and Brighton among HIV-positive MSM, incidence was 0.7/100PY in 2002 and 1.2 in 2006. Incidence increased 20% annually in that population [111].

HCV among people who inject drugs (PWID)

**Prevalence**

During the pre-HIV period which lasted until the mid-1980s in most countries, sharing of syringes and other injection paraphernalia was common. This was partly because drugs were consumed in groups, and partly because supply of syringes and needles was heavily restricted in most countries as a mean to limit the use of drugs for injection. After the frightening perspective of HIV-infection among PWID was acknowledged in the mid-1980s, many countries rapidly liberated the access of syringes and needles for illegal drug use, but behaviour among users changed slowly. HIV was an important problem among PWID in the 1980s and 1990s, but incidence rapidly decreased after 1985 in most Western countries. However, incidence of HCV among PWID decreased more slowly, probably due to the much higher risk of transmission through injection by that virus, perhaps also because of less awareness of HCV than of HIV.

Prevalence of anti-HCV in PWID was found to be between 60% and 90% in a review from 2011 [96]. Most Western countries – including Norway – had prevalence between 70% and 75%. Among Swedish OMT-patients a seroprevalence of 88% was recently reported, of which 69% had CHC. In our cohort (Study 1) 84% (535/635) were anti-HCV positive, while 63% (328/523) were HCV RNA positive. Prevalence of anti-HCV positive subjects tends to increase with duration of IDU and consequently with age [31].

Prevalence in prisons mostly reflects the fact that many prisoners have a history of IDU, but also other risk behaviours like non-professional tattoos and piercing. A
review from 2013 reported that 26% in the general prison population globally were anti-HCV positive, and 64% among those with a history of IDU [112].

**Incidence**

In a prospective study of HCV transmission among young PWID in American cities, transmission rate was 17/100PY (55/320PY). 37% of transmissions were estimated to be caused rather by shared injection paraphernalia than by shared needles/syringes [113]. In South Italy around 1994 incidence among PWID was 29/100PY (21/81) [114]. In an American cross-sectional study overall incidence of acute hepatitis C (AHC) among young PWID was 40/100PY, which was compared with an observational study of a similar cohort which reported an incidence of 33/100PY [109]. In France incidence was 11/100PY (12/131PY) among PWID with at least one injection last 6 months, 37/100PY among daily injectors of cocaine, 14/100PY among daily injectors of heroine [115]. There is evidence for decreasing incidence of HCV among PWID in some parts of the world. Among IDUs in Vancouver incidence decreased from 28/100PY in 1996—1999 to 5/100PY in 2006—2012 [106].

In a recent review of HCV epidemiology in PWID populations, incidence among PWID varied with frequency of injections. In studies concerning current PWID median incidence was 26/100PY, (IQR 9-34) [116].

If there are 8400 current PWID in Norway [92, 94] of which 50% have CHC and there are 600 new cases of HCV-infection in this group annually, incidence among PWID would be 600/4200PY or 14/100PY.

**Natural history of chronic hepatitis C infection (CHC)**

**Spontaneous clearance**

A certain proportion of individuals exposed to HCV clear the infection spontaneously. Studies of this are hampered by the lack of symptoms of the acute infection. A recent meta-analysis of 31 studies with a total of 675 subjects with acute hepatitis C concluded with a weighted mean of 26% spontaneous clearance [117]. Individual studies vary in registration of spontaneous clearance, most find between 20% and 40%.

Spontaneous clearance is found positively associated to female gender [117-120], IL28B rs12979860 genotype CC [118, 119, 121, 122], age < 35 years, symptomatic acute HCV infection [123], and HBV co-infection [124-126]. It is also associated with genotype 1 according to the recent study [118], but not in the meta-analysis from 2006 [117]. Clearance is negatively associated with HIV co-infection [124, 127].

Some studies have reported persistence of HCV RNA in liver cells and mononuclear blood cells after spontaneous or treatment-induced clearance, combined with
normal liver enzymes [128]. This has been labelled as occult HCV-infection which also includes anti-HCV negative/serum HCV RNA negative patients with elevated liver enzymes and HCV RNA presence in liver cells or immune cells. The latter may be one cause of cryptogenic liver fibrosis. In some of these patients serum HCV RNA has been detected in sensitive tests for example after ultracentrifugation [129].

Liver fibrosis and cirrhosis
Chronic HCV infection (CHC) causes inflammation in the liver, and induces production of proteins involved in systematic inflammatory responses of significance for other organs, including IL-6 and TNF-alfa. CHC is also associated with insulin resistance and steatosis, the latter most prominent with GT3. There also is an activation of blood monocytes, especially B-cells [130]. These basic mechanisms are of importance both for the development of liver fibrosis and for extra-hepatic effects of CHC.

The detailed mechanism which conducts to fibrosis in the liver has still not been entirely elucidated [131]. There is an activation of hepatic stellate cells in a complicated interaction with natural killer cells (NKC). NKC in the liver initially may be activated, but later in the development of CHC are downgraded and participate in the modulation of inflammation with the effect of decreased fibrosis. The fibrotic tissue originates mainly from the activated stellate cells [132, 133]. A strong immunologic inflammatory response facilitates spontaneous clearance, but is also essential for the development of fibrosis. There is an interaction between CHC and other mechanisms for liver disease, particularly overweight, which is experienced in large parts of the world in epidemic proportions. One of the common factors for non-alcoholic fatty liver disease (NAFLD) and CHC is development of steatosis and insulin resistance.

The rate of fibrosis is dependent on a number of known factors as summarized in Table 2. Of particular interest should be noted higher rate of fibrosis associated with male gender, high age, overweight, genotype 3, HIV co-infection or HBV co-infection, insulin resistance (particularly overt diabetes mellitus type 2) and high consumption of alcohol. It may also be noted that there seems to be an association between non-organ-specific autoimmunoglobulins – like rheumatoid factor (RF), antinuclear antibodies (ANA), smooth muscle antibodies (SMA) – and the rate of liver fibrosis progression. It may also be noticed that the interleukin 28 (IL28) rs12979860 Genotype CC – which is associated with increased clearance of HCV and better IFN/RBV treatment results – also is associated with increased inflammatory activity and fibrosis in HCV GT3 patients, but not in GT1 [134].

In a meta-analysis of the stage-specific fibrosis progression rate (progression of Metavir13 stage/year) in different populations of HCV- patients, the mean

---

13 Metavir is a scoring system for the classification of liver fibrosis in 5 stages and of liver inflammation in 4 grades. The fibrosis scores are:
The progression rate among the IDUs were: F0-F1 0.116, F1-F2 0.085, F2-F3 0.085 and F3-F4 0.130 [135]. This correspond to mean time between F0-F1 of 8.6 years, F1-F2 11.8 years, F2-F3 11.8 years, F3-F4 7.7 years, and mean time from HCV transmission to cirrhosis of about 40 years. However, the rate of fibrosis differs. For probable more than half the patients it is very low, and for at least 1/3 it is much higher.

Table 2 Factors which may be of significance for the development of fibrosis in CHC.

<table>
<thead>
<tr>
<th>Host</th>
<th>References</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>[136-139]</td>
<td>Increased fibrosis</td>
</tr>
<tr>
<td>High age by exposure</td>
<td>[136, 137, 139]</td>
<td>Increased fibrosis</td>
</tr>
<tr>
<td>Co-infection HIV</td>
<td>[136, 140-143]</td>
<td>Increased fibrosis</td>
</tr>
<tr>
<td>Co-infection HBV</td>
<td>[140, 144]</td>
<td>Increased fibrosis</td>
</tr>
<tr>
<td>Schistosomiasis</td>
<td>[62, 145]</td>
<td>Increased fibrosis</td>
</tr>
<tr>
<td>Overweight</td>
<td>[144, 146-149]</td>
<td>Increased fibrosis</td>
</tr>
<tr>
<td>Steatosis</td>
<td>[150, 151]</td>
<td>Increased fibrosis</td>
</tr>
<tr>
<td>Insulin resistance (IR)/metabolic syndrome</td>
<td>[146, 149, 152-154]</td>
<td>Increased fibrosis</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>[152, 155]</td>
<td>Increased fibrosis</td>
</tr>
<tr>
<td>Non-alcoholic steatohepatitis (NASH)</td>
<td>[156]</td>
<td>Increased fibrosis</td>
</tr>
<tr>
<td>High inflammatory activity</td>
<td>[150, 157]</td>
<td>Increased fibrosis</td>
</tr>
<tr>
<td>ALT</td>
<td>[157-161]</td>
<td>Increased fibrosis</td>
</tr>
<tr>
<td>2'-5'-oligoadenylate synthetase 1 (OAS-1).</td>
<td>[162]</td>
<td>Increased fibrosis</td>
</tr>
<tr>
<td>Factor V Leiden genotype (Arg560Gln)</td>
<td>[163]</td>
<td>Increased fibrosis</td>
</tr>
<tr>
<td>Ferritin</td>
<td>[164]</td>
<td>Increased fibrosis</td>
</tr>
<tr>
<td>Serum hepcidin</td>
<td>[165]</td>
<td>Increased fibrosis and inflammatory activity</td>
</tr>
<tr>
<td>IL-10 (-1082) AA genotype and the ATA/ATA and ACC/ACC homozygous haplotypes</td>
<td>[166]</td>
<td>Increased fibrosis</td>
</tr>
<tr>
<td>IL-10 (-1082) GG genotype</td>
<td>[166]</td>
<td>Increased risk for CHC</td>
</tr>
<tr>
<td>IL28B rs12979860 genotype CC</td>
<td>[121, 167, 168]</td>
<td>Increased fibrosis and inflammatory activity in genotype 3</td>
</tr>
<tr>
<td>IL28B SNP rs8099917 genotype TT</td>
<td>[168]</td>
<td>Increased fibrosis (but possibly decreased steatosis)</td>
</tr>
<tr>
<td>MCP-1 (CCL-2)</td>
<td>[169]</td>
<td>Increased fibrosis</td>
</tr>
<tr>
<td>HCV-specific T-cell-derived Transforming GF beta</td>
<td>[170]</td>
<td>Decreased fibrosis</td>
</tr>
<tr>
<td>Homocystein</td>
<td>[171]</td>
<td>Increased steatosis and fibrosis</td>
</tr>
<tr>
<td>Methylene-tetra-hydro-folate reductase (MTHFR) C677T polymorphism TT genotype</td>
<td>[171]</td>
<td>Associated with hyperhomocysteinemia, increased steatosis and fibrosis</td>
</tr>
<tr>
<td>Mixed cryoglobulinemia</td>
<td>[172]</td>
<td>Increased fibrosis</td>
</tr>
<tr>
<td>Non-organ-specific autoantibodies</td>
<td>[173, 174]</td>
<td>Increased fibrosis</td>
</tr>
</tbody>
</table>

F0 = no fibrosis  
F1 = portal fibrosis without septa  
F2 = portal fibrosis with few septa  
F3 = numerous septa without cirrhosis (septal or bridging fibrosis)  
F4 = cirrhosis
Table 2 continued

<table>
<thead>
<tr>
<th>External</th>
<th>References</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heavy alcohol use</td>
<td>[138, 139, 144, 157, 159]</td>
<td>Increased fibrosis</td>
</tr>
<tr>
<td>Heavy tobacco smoking</td>
<td>[147]</td>
<td>Increased steatosis and fibrosis</td>
</tr>
<tr>
<td>Cannabis use</td>
<td>[175]</td>
<td>Increased fibrosis</td>
</tr>
<tr>
<td>High coffee consumption</td>
<td>[176, 177]</td>
<td>Decreased inflammatory activity and fibrosis</td>
</tr>
<tr>
<td>Daily chocolate consumption</td>
<td>[178]</td>
<td>Decreased inflammatory activity and fibrosis</td>
</tr>
<tr>
<td>Virus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotype 3</td>
<td>[102, 103]</td>
<td>Increased steatosis and fibrosis</td>
</tr>
<tr>
<td>Genetic variability</td>
<td>[169]</td>
<td>Increased fibrosis</td>
</tr>
<tr>
<td>HCV RNA quantity</td>
<td>[161]</td>
<td>Increased fibrosis</td>
</tr>
</tbody>
</table>

Based on serial biopsies some studies have demonstrated regression of fibrosis even in patients with ongoing chronic infection [160]. There may still be doubt as to whether this represents real regression or bias due to sampling variability.

End stage liver disease and hepatocellular carcinoma
Histological cirrhosis may be compensated and thus without any symptoms. When symptoms occur, the cirrhosis is uncompensated. Among the main symptoms and signs are: ascites, oesophageal varices, icterus, lowering of blood platelets, and cerebral symptoms due to hepatic encephalopathy, including disturbances of thinking and episodes of confusion.

Hepatic encephalopathy (HE) may be clinically apparent, but exists also in a covert form which is discovered through testing of cognitive functions. Covert HE is associated with increased risk of overt HE, and with increased hospitalisation and mortality [179]. This may indicate a need for more active testing of cognition in patients with cirrhosis for the purpose of adequate treatment of this condition.

When end-stage liver disease (ESLD) occurs, symptoms of decompensated cirrhosis become more accentuated and may include fatigue, nausea, varicose bleedings, icterus, ascites and confusion. Treatment may be liver transplantation. HCV – including CHC with ESLD and HCC secondary to CHC – is the most frequent cause of liver transplantation in many Western countries, including the Nordic countries [180].

Hepatocellular carcinoma (HCC) is a major complication to cirrhosis in CHC. Primary liver cancer (mainly HCC) is worldwide the fifth most common cancer in men and the seventh one in women, with close relationship to chronic infections of HBV and HCV [181]. HCV in itself – unlike HBV – is not a carcinogen, why HCC related to HCV is only occurring with cirrhosis or in some cases of advanced fibrosis.
There is an etiologic link between HCV-related advanced fibrosis/cirrhosis and HCC. The pathologic changes in liver cells typical of fibrosis and cirrhosis destabilise the hepatocytes and make them vulnerable for malign transformation.

An Italian longitudinal study of 214 non-PWID patients with HCV-related compensated cirrhosis (Child-Pugh class A) was followed-up for a mean of 9.5 years (range 1-17 years) during 1986–2003. Few received antiviral treatment. HCC developed in 32%; 23% had ascites, 17% jaundice and 6% oesophageal bleeding. Mortality rate was 4.0/100 PY, 35% of the patients died during follow-up. Cause of death was HCC in 44%, oesophageal bleeding 8%, liver failure 20%, complication to liver transplantation 1%, non-hepatic disease 19% and unknown 8% [182].

In another Italian longitudinal study 352 patients with compensated cirrhosis were followed-up from around 1990 for a mean of 14.4 years (range 0.9-19.5). 194 received IFN monotherapy, but only 28 (14%) had SVR. Of untreated patients and treated ones without SVR the rate of HCC was 2.9/100PY, rate of decompensation 3.7/100PY, and rate of liver-related mortality 2.7/100PY [183].

In Norway adjusted rates of primary liver cancer have increased substantially since the 1960s (Figure 10). Major causes for this may be viral hepatitis, increased alcohol consumption and NASH.

![Figure 10](image)

**Figure 10** Age adjusted rates of incidence of primary liver cancer (C2214) per 100,000 in Norway 1957–2011 (from the Norwegian Cancer Registry)

A Swedish national register based study among patients notified for HCV showed a standardised incidence ratio (SIR) of about 40 for liver cancer >25 years after estimated HCV transmission [184].

---

14 Includes HCC, but also other kinds of liver cancer
Extra-hepatic manifestations of HCV

CHC is associated with several medical problems apart from liver disease. Some of these are scientifically supported by robust evidence, while others are subject for uncertainty and discussions. They are caused either by mixed cryoglobulinemia, general HCV-induced autoimmune response, or possibly by direct virus replication in other organs than the liver [185, 186]. Cryoglobulin complexes have been found in about 1/3 of patients affected by HCV [187]. Studies from Italy indicate that both host genetic factors and HCV genotype may facilitate extra-hepatic manifestations. Genotype 2c is associated to such manifestations in that country [188].

The major extra-hepatic manifestations of HCV are:

- **Skin disease.** Cutaneous manifestations of mixed cryoglobulinemia represent conditions from purpura through necrotizing vasculitis to wide skin ulcers. Symmetrical hyperpigmentation is also a typical feature, secondary to repeated episodes of purpura [189]. HCV has also been linked to porphyria cutanea tarda and increased photosensitivity [190, 191]

- **Renal disease.** HCV has in several studies been associated with immunologic nephropathies [186, 192, 193]. The most common of these is membranoproliferative glomerulonephritis (MPGN) which constitute about 80% of HCV-associated renal disease [185]. Among patients with MPGN in USA 10-20% have CHC. However the proportion of CHC in patients with immunologic renal disease varies, and in a study of 50 patients with immunologic renal disease in Northern Norway, none were anti-HCV positive [194]. A large Swedish register study showed a strongly increased risk of chronic kidney disease associated with CHC, but not of kidney cancer [195].

- **Malignant disease.** The malignant extra-hepatic disorder most consistently related to HCV is B-cell non-Hodkin lymphoma (NHL) which represents a malignant transformation of B-cell clones involved in the production of immunoglobulins related to mixed cryoglobulinemia. The etiology may be that chronic antigenic stimulation by the virus may triggers B-cell proliferation resulting in a wide spectrum of pathology ranging from minor expansion of B-cell populations to an aggressive high-grade lymphoma [185]. NHL is common in countries with high prevalence of HCV, as in Egypt where the prevalence of NHL also follows the same regional trends as HCV [82]. A US register-based case control-study concluded with a 20-30% increased risk of NHL among patients with HCV infection without HIV co-infection, as well as a 3-4 fold increased risk of cryoglobulinemia and Waldenström’s macroglobulinemia, but not of multiple myomas (MM) or other malignancies [196]. A Swedish register-based large case-control study
demonstrated an increased risk for both NHL and MM among anti-HCV positive persons [197]. There has been reported one single case of MM with concurrent HCV infection where antiviral HCV treatment and accomplished SVR resulted in regression and probably cure of MM [198].

- **Metabolic effects.** CHC has been associated with insulin resistance (IR), steatosis and diabetes mellitus type 2 (DB2) according to a number of studies [155, 199-201]. Steatosis is correlated independently to genotype 3, particularly 3a, as well as to overweight and the duration of CHC [202]. The association of CHC with IR is greater than what is seen in chronic liver diseases of other aetiology and is present also without significant liver fibrosis [201, 203]. HCV increases the risk of DM2 particularly in predisposed individuals with other risk factors for that disease [154]. However, the association between HCV and DM2/IR has been seriously disputed in a recent American cross-sectional population based study of high quality [204, 205].

- **Atherosclerosis.** Studies on possible association between HCV and atherosclerosis have shown conflicting results. Several studies from Italy, Japan and China support the associations between HCV and both carotid atherosclerosis and stroke [206-208]. Studies of myocardial infarction (MI) have even more mixed results. Some American studies show an association [209-211], but it seems doubtful if confounding especially with tobacco smoking has been sufficiently avoided in those studies. In countries where IDU is the main source of HCV transmission, it must be expected higher risk of MI due to increased smoking among anti-HCV positive subjects.

- **Cerebral manifestations, fatigue and depression.** Some studies indicate that HCV also may affect the central nervous system (CNS), either directly through viral replication inside CNS or indirectly through immunological influence [212]. A number of studies demonstrate association between CHC and fatigue, depression and cognitive deficit [213-215], but others indicate that this association is not caused by the infection in itself, but indirectly through the awareness and possibly anxiety by the patients of having this chronic infection [216, 217]. In a recent Swedish study OMT-patients reported fatigue (48%), muscular pain (28%), abdominal discomfort (27%), and nausea (21%), but these symptoms were neither associated with HCV viremia nor with fibrosis severity [144]. Brain assessment by magnetic resonance imaging (MRI) and positron emission tomography (PET) seems to give evidence for changes in cerebral perfusion related to HCV, which may strengthen the case for an etiologic association between HCV and mental functions [212, 218].
Mortality

Mortality in populations of CHC depends on the development of liver disease as well as deaths by other causes. The two major groups of patients in Western countries are exposed either through medical procedures or through IDU. The former are usually of more advanced age and their deaths are mainly caused by diseases, some of which are related to HCV, others without such association. The patients who had their HCV through IDU are younger and have higher mortality from external causes, frequently directly drug-related such as overdose. However, as PWIDs who initiated their drug injections during the 1960s, are getting older, they must be expected increasingly to have somatic disease as cause of death.

A meta-analysis from 2011 of mortality related to opioid misuse concludes with a pooled crude mortality rate (CMR) of 2.1/100 PY and a pooled standard mortality rate (SMR) of 14.7 [219]. Men regularly have higher CMR, while women have higher SMR because of their lower mortality in the general population. Overdose was the most common cause of death, but causes varied between studies. CMR rate for overdose was 0.65/100 PY, for suicide 0.12/100 PY, trauma (including homicide) 0.25/100 PY, liver related cause 0.16/100 PY, cardiovascular disease 0.09/100 PY, cancer 0.07/100 PY, respiratory disease 0.03/100 PY. The CMR for liver disease in all types of longitudinal studies of death caused by CHC-induced liver disease obviously are dependent on age of the studied cohorts and on the duration of CHC. Studies of older patients with long duration of IDU and consequently of CHC, must be expected to have higher liver related mortality.

A meta-analysis from 2013 of PWID mortality (which included IDU of stimulants) found a CMR of 2.35/100 PY, higher in low- and middle-income countries. Pooled SMR was 14.7. Overdose and HIV were the most frequent causes of death [220]. A study of mortality in Norwegian opioid users before (waiting list), during and after OMT showed CMR of 2.4, 1.4 and 3.4 deaths per 100 PY respectively. In an “intention to treat” perspective mortality during treatment was 1.8/100PY. A small Norwegian study from Kristiansand demonstrated very high CMR of 5.1/100PY among opioid users without OMT; in a OST programme it was 1.3/100PY, while mortality rate in opioid substitution by general practitioners (GPs) was 0.5/100PY [221]. In another Norwegian study of 501 young drug users admitted to SKN 1981-1991 and followed-up until 2003 CMR was 2.5/100PY, with a SMR of 23.4 [4]. Norwegian studies may show relatively high mortality rates due to a high rate of overdoses, compared to other countries [222]. Two Norwegian longitudinal studies illustrate mortality in patients recruited through known viral hepatitis:

- Gjeruldsen et al followed two cohorts of patients hospitalised for acute parenteral hepatitis (hepatitis B or HNANB) 1972-1976. One cohort had known IDU (n=214), the other (n=193) was infected by other ways. Sera were not available for most of the patients. In the IDU cohort HCV was likely to by prevalent, but this could not be confirmed. During median follow-up of...
23 years the mortality rate in the IDU cohort was 1.5/100 PY. Causes of
death were mainly overdose (56%) and suicide (24%). There were three
(4.4%) deaths by chronic liver disease with a likely alcoholic aetiology.
Possibly concomitant CHC was involved, but this could not be verified [223].
- Kristiansen et al studied a cohort of patients (n=1010) with community-
acquired HCV during a medium of 7 years. At baseline time since estimated
HCV transmission was 11 years. For patients dying before 50 years of age,
drug related causes of death dominated. After 50 years of age, liver related
causes of death were the most prevalent [224].

Another way of studying HCV related mortality in Norway is through the Causes of
death registry, Statistic, Norway. Figure 11 shows that HCV is registered as
underlying cause of death only in few cases, which may be surprising. The number
of deaths from HCC seems to be quite stable since 1996.

![Figure 11](image)

Figure 11 Hepatitis C (B17.1 + B18.2) and hepatocellular carcinoma (C22.0) as
underlying cause of death in Norway 1996-2012 (Causes of Death Registry. Statistics
Norway)

One of the best opportunities to study mortality of HCV has been provided by the
accidental injections of anti-D immunoglobulin contaminated with HCV GT1b to
German [148, 225, 226] and Irish women [227, 228] during the late 1970s. In the
German cohort liver-related mortality among patients with CHC was 3% after 35
years. Information on mortality in the Irish cohort has not been published recently.
The low liver-related mortality is compatible with slower development of liver
fibrosis among women.

**Treatment uptake, efficacy and mortality after treatment**

Treatment for chronic HNANB with interferon-alpha was introduced in the mid-
1980s [25] and continued for CHC after the discovery of that virus in 1989 (see page
Treatment has increasingly included persons who have injected drugs, mainly those who have done that for a limited period. Treatment uptake in Europe varies much between countries. A study from 2008 relating sale of HCV-relevant antivirals until 2006 to known HCV prevalence, concluded that treatment uptake at that time was high in France, Germany and Sweden, low in Finland and Denmark, intermediary in Norway [229], see Figure 12.

![Figure 12 HCV treatment uptake in European countries until 2006 estimated from sales of PegINF and estimated HCV prevalence [229]](image)

There are several barriers to antiviral HCV-treatment which particularly are of significance for PWID [230]. These barriers concern both establishment of the HCV diagnosis, referral to specialist medical care, and treatment initialization.

Table 3 Factors associated with HCV treatment uptake among PWID

<table>
<thead>
<tr>
<th>Decreasing uptake</th>
<th>References</th>
<th>Increasing uptake</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unemployment</td>
<td>[231, 232]</td>
<td>Peer support group</td>
<td>[233]</td>
</tr>
<tr>
<td>Non-attendance &gt;or =1</td>
<td>[231, 232, 234]</td>
<td>Multidisciplinary setting</td>
<td>[233, 235]</td>
</tr>
<tr>
<td>Unstable housing</td>
<td>[235]</td>
<td>Genotypes 2 and3</td>
<td>[232, 234]</td>
</tr>
<tr>
<td>IDU last 6 month</td>
<td>[231, 234, 235]</td>
<td>Male gender</td>
<td>[232, 234, 236]</td>
</tr>
<tr>
<td>Psychiatric illness</td>
<td>[237]</td>
<td>ALT increased</td>
<td>[232]</td>
</tr>
<tr>
<td>Depression</td>
<td>[238]</td>
<td>Advanced fibrosis</td>
<td>[232, 234]</td>
</tr>
<tr>
<td>Excessive alcohol use</td>
<td>[231]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doctor-initiated referral</td>
<td>[231]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotype 1 and 4</td>
<td>[232]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td>[232, 234]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3 continued

<table>
<thead>
<tr>
<th>Liver biopsy not performed</th>
<th>[231, 232]</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV co-infection</td>
<td>[232]</td>
</tr>
<tr>
<td>Aboriginal ethnicity (Canada)</td>
<td>[239]</td>
</tr>
<tr>
<td>ALT normal</td>
<td>[232, 234]</td>
</tr>
<tr>
<td>Metavir stage F0-F1</td>
<td>[232]</td>
</tr>
<tr>
<td>Age &gt;50-56</td>
<td>[231, 232, 240]</td>
</tr>
<tr>
<td>Low age</td>
<td>[234]</td>
</tr>
</tbody>
</table>

In spite of wide spread sceptical views on antiviral treatment for current PWID, treatment is feasible also in this group if it is well designed and multi-professional effort is provided [234, 235, 241-243]. Such treatment seems to result in SVR in the same proportion as treatment for other groups of patients [244]. When treatment is initiated, high adherence is also important. This is possible to obtain among former and current PWID according to a meta-analysis from 2013 [245]. Pooled adherence in that study was 83%. A review of adherence to treatment regimens which included PegINF and RBV suggested increased adherence with HIV co-infection, stable haemoglobin level, and among males. Psychiatric disorder and having to take higher doses of RBV was associated with lower adherence. Use of alcohol and drugs did not consistently influence adherence [246].

**Total HCV treatment uptake among PWID in Norway**

Some Norwegian studies have explored treatment uptake among patients exposed to HCV through IDU.

- Krook et al in a pilot study explored a small number of GT3-patients in an OMT-program including close co-operation between specialists of infection and addictions as well as multidisciplinary support. PegINF was injected at the OMT-centre. All 17 patients completed treatment and SVR was accomplished in 16 (94%) [247].

- Toresen et al examined retrospectively 249 HCV-patients remitted to an outpatient clinic at a tertiary hospital in Bergen. 85% had a history of IDU. The authors documented a high treatment uptake (47%), and that “young age, low degrees of fibrosis, and good patient attendance ensured a high rate of SVR”. SVR was obtained for 44% among GT1 patients, 75% with GT3 [231].

According to the Norwegian Prescription Database (NorPD) the number of individuals having been prescribed ribavirin 2004-2013 was 4,974 (Table 4). Ribavirin has no other medical indication than CHC. If number of CHC in Norway is
considered stable at 20,000, the mean treatment rate during the periods 2004–2008 and 2009–2013 would respectively be 2.3/100PY and 2.7/100PY.

Table 4 Number of persons having received antiviral treatment with ribavirin in Norway 2004-2013

<table>
<thead>
<tr>
<th>Year</th>
<th>HCV-treated each year (NorPD)</th>
<th>HCV-treated each year corrected(^{15})</th>
<th>Corrected Treatment rate if number of CHC in Norway is 20,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>571</td>
<td>390</td>
<td>1.9%</td>
</tr>
<tr>
<td>2005</td>
<td>602</td>
<td>411</td>
<td>2.1%</td>
</tr>
<tr>
<td>2006</td>
<td>662</td>
<td>452</td>
<td>2.3%</td>
</tr>
<tr>
<td>2007</td>
<td>728</td>
<td>497</td>
<td>2.5%</td>
</tr>
<tr>
<td>2008</td>
<td>803</td>
<td>548</td>
<td>2.7%</td>
</tr>
<tr>
<td>2009</td>
<td>770</td>
<td>526</td>
<td>2.6%</td>
</tr>
<tr>
<td>2010</td>
<td>705</td>
<td>481</td>
<td>2.4%</td>
</tr>
<tr>
<td>2011</td>
<td>760</td>
<td>519</td>
<td>2.6%</td>
</tr>
<tr>
<td>2012</td>
<td>900</td>
<td>614</td>
<td>3.1%</td>
</tr>
<tr>
<td>2013</td>
<td>785</td>
<td>536</td>
<td>2.7%</td>
</tr>
<tr>
<td>Total</td>
<td>(7286)</td>
<td>4,974</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

The introduction of new DAAs most probably will make possible both increased treatment uptake and adherence, due to less side effects.

**Modelling of hepatitis C in different populations**

Modelling of disease development in populations is important for planning, evaluation of future treatment expenses and decisions concerning treatment policies. The extensive research on HCV transmission, prevalence, incidence, clearance, natural course, mortality and treatment results make this epidemic suitable for modelling. Several models have been developed in different countries. One of the main research questions related to modelling is: how would increased treatment uptake impact the future burden of the disease?

In several countries are reported that incidence of new HCV transmissions and hence of prevalence is decreasing at the same time as the burden of disease is increasing because more patients are entering into advanced stages of the disease with decompensated cirrhosis, end-stage liver disease (ESLD) or HCC [248]. Obviously increased treatment uptake among patients with advanced fibrosis and compensated cirrhosis would reduce this burden of seriously ill liver patients. Most

---

\(^{15}\) The number of HCV-treated each year is based on those who have been prescribed ribavirin. Number of treated individuals in the whole period was 4974 (NorPD, personal communication). The discrepancy between this number and the sum of individuals each year (7286) is caused by the fact that some individuals had prescriptions during two following years. The original numbers of patients registered each year therefore have been corrected with this factor: 4974/7286=0.68268
studies conclude that high treatment uptake would also have significant impact on later prevalence of CHC [249-251]. Modelling on PWID HCV populations similar to the Norwegian, indicate that high treatment uptake including patients without fibrosis may be cost-effective because of the impact on later prevalence of HCV-infections [252, 253].

Other measures of significance for reduction of later burden of disease would be reduced recruitment to IDU, reduced reuse of injection equipment among PWID, and reduced use of injections among people who use drugs (PWUD). Instrumental for this would be needle and syringe exchange programs (NSP) and opioid maintenance treatment (OMT) [254].
Information on Statens klinikk for narkomane

To better understand the patients in these studies, some information about Statens klinikk for narkomane (SKN) and the drug users admitted during the years 1970–1984, seems appropriate.

The clinic was founded in 1961 offering residential treatment for people who misused drugs from all over the country. During the first years the patients consisted mostly of middle-aged persons using opioids, barbiturates or – somewhat later – benzodiazepines\(^\text{16}\). Their problems with drugs were in most cases initially related to use of subscription-drugs. Concurrent alcohol abuse and mental illness were usual. Some patients injected their drugs, but most did not. Some also had been working as nurses or doctors, and easy availability of drugs may have been part of the aetiology. A large part of these patients had a history of work and independent housing. Many were married and had children, and very few were young (Figure 13). Most had no criminal record. Their drug use was a lonely affair being executed in their homes. In this population few developed viral hepatitis secondary to the use of drugs.

A new wave of young drug users was noticed from the late 1960s. Some of them had been involved in the anti-authoritarian hippie movement, smoking cannabis with friends. Most often the drugs were consumed in groups, sometimes in public areas as for example in the central parts of Oslo. Some came from affluent educated families. Others had more problematic social background. Most terminated their use of recreational drugs after quite a short time, and continued education and later work. But some maintained their use of cannabis, and did also experiment with other drugs, mostly opioids and amphetamines both of which in the late 1960s became available illegally in the large cities or were bought abroad and smuggled home. Intravenous injection became the dominating method for the use of opioids and stimulants.

\(^{16}\) The first benzodiazepine was marketed in Norway in 1960
As young drug users from the late 1960s were received in the clinic, the institution gradually changed. This is illustrated by decreasing mean age of patients from 1966 to 1974 shown in Figure 13. This figure also demonstrates higher mean than median age 1968-1974, which signifies that there was a “tail” of much older patients conducting to a higher mean age, even if most patients were younger and the median age as a consequence lower. In 1971 most patients were <20 years of age. From the late 1970s the older patients disappeared from the institution, conducting mean and medium age to be similar and the age of patients more uniform.

Age at first drug injection decreased slightly during the period of recruitment to the present studies (Table 5). Also the variability of this age was much lower the last periods (lower SD). The patient population became obviously more uniform, with more patients starting injecting at approximately the same age, in their late teens.

<table>
<thead>
<tr>
<th>Table 5 Mean age of first drug injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>1970-74</td>
</tr>
<tr>
<td>1975-79</td>
</tr>
<tr>
<td>1980-84</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

Abbreviation: SD, standard deviation

The proportion that had injected drugs increased during the period 1970 to 1984, as shown in Table 6. During the first periods the younger patients injected more frequently than older ones, but the last period this difference had disappeared.
Table 6 Injection drug use according to period of admission for drug abuse treatment and age at admission to SKN

<table>
<thead>
<tr>
<th>Periods of admission</th>
<th>Admission age &lt;25 years</th>
<th></th>
<th>Admission age &gt;25 years</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All patients</td>
<td>Patients having injected</td>
<td>All patients</td>
<td>Patients having injected</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>1970-74</td>
<td>158</td>
<td>124</td>
<td>78.5%</td>
<td>63</td>
</tr>
<tr>
<td>1975-79</td>
<td>259</td>
<td>225</td>
<td>86.9%</td>
<td>91</td>
</tr>
<tr>
<td>1980-84</td>
<td>197</td>
<td>178</td>
<td>90.4%</td>
<td>92</td>
</tr>
<tr>
<td>Total</td>
<td>614</td>
<td>527</td>
<td>85.8%</td>
<td>246</td>
</tr>
</tbody>
</table>

Most patients initiated injecting before 21 years of age; and during the last periods this was accentuated (Table 7).

Table 7 Age at the time of the first injection episode according to year of admission

<table>
<thead>
<tr>
<th>Age of first drug injection</th>
<th>Admission year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1970-74</td>
</tr>
<tr>
<td>&lt;16</td>
<td>14.80 %</td>
</tr>
<tr>
<td>16-20</td>
<td>65.10 %</td>
</tr>
<tr>
<td>21-30</td>
<td>17.40 %</td>
</tr>
<tr>
<td>&gt;30</td>
<td>2.70 %</td>
</tr>
<tr>
<td>Total</td>
<td>100.00 %</td>
</tr>
</tbody>
</table>
Objectives

Overall research aims
The objective of these studies was to describe the course of HCV-infection among HCV-infected PWID in Norway. This included HCV-related mortality and development of liver fibrosis in the light of antiviral treatment uptake.

Objective for each paper
Paper 1. The main objective was to compare long-term all-cause mortality among past or present PWID who had been exposed to HCV (anti-HCV positive) – with and without persisting HCV infection. We expected that all-cause mortality directly linked to drug abuse would dominate, but would explore if chronic hepatitis C in any way could have an influence on the all-cause mortality when PWID with CHC (HCV RNA positive) were compared to PWID who had been exposed to HCV (anti-HCV positive) and had spontaneous clearance of the virus (HCV RNA negative). Supplementary objectives were to compare causes of death in the same groups as well as to compare long-term liver-related mortality in the same groups.

Paper 2. The objective was to assess the risk of developing fibrosis in PWID with CHC through examination of liver specimens from autopsies. Also in this study all the subjects would have been exposed to HCV (anti-HCV positive), and the subjects chronically infected would be compared to those who had cleared the virus spontaneously.

Paper 3. The main objective was to describe the rate of antiviral HCV treatment uptake among HCV RNA positive PWID who had been admitted to residential drug abuse treatment in 1970-84. Supplementary objective was to describe mortality rate and causes of death among HCV RNA positive PWID who had antiviral HCV treatment compared to patients who had not entered antiviral treatment.
Material and methods

Study designs
The studies were based on cohorts from a research register established in cooperation with SIRUS in 1992, consisting of all 1617 patients admitted first time at SKN during the period 1961-1991. Only information on birth date, gender, national identification number, and date of admission were registered, hence no information on drug use or comorbidities, nor socio-demographic information, was originally available.

All three studies were longitudinal cohort studies with a combined retrospective-prospective design. The cohorts were selected from the 864 patients who had their first admission at SKN during the years 1970–1984. Follow-up in Study 1 and Study 2 was until the end of 2008, while it was until the end of 2012 in Study 3.

Participants
Of the 864 patients admitted to SKN 1970–1984, serum was available for 635, of whom 535 (84.1%) were anti-HCV positive. It was possible to analyse HCV RNA with polymerase chain reaction (PCR) technique in the serum of 523/535 subjects. HCV RNA could not be analysed in 12 cases for technical and logistical reasons.

Study 1 included all 523 patients with available serum who were anti-HCV positive and for whom HCV RNA could be tested. Study 2 included all 102 subjects included in Study 1 who were autopsied and had available liver specimens suitable for evaluation of fibrosis. In Study 3 the cohort consisted of the 245 HCV RNA positive patients from Study 1 who were alive in Norway January 1, 1997. This time point was chosen because the first antiviral HCV treatment in this population was registered in 1997 (for details, see Figure 14).

In Study a total of 138 subjects had been autopsied. We managed to apprehend liver tissue from 106, but four specimens were damaged by autolysis to a degree that made staging of fibrosis impossible. Eighty-one liver specimens were found at the Institute of Forensic Medicine at the University of Oslo, 21 were transferred from other laboratories.
SKN was the main institution for residential drug abuse treatment in Norway during most of the period 1970–1984, and the patients in that period consisted to a large extent of young, opiate-dependent PWID.

**Virologic assessment**

During admittance to SKN 1970–1984 the great majority of patients had serum specimens drawn at SKN and analysed for HBV infection at the Virologic Department of the NIPH. Sera have since been stored at -20 °C at NIPH and never thawed. As the main hepatitis laboratory in Norway, NIPH also received sera obtained from the same patients drawn during later admissions at SKN or at other treatment centres, mostly after – but in some cases also anterior to – the index.
admission at SKN. Of the 864 individuals admitted to SKN during the period 1970–1984, frozen sera could be retraced for 635 patients. The median number of sera available from each patient was four, range 1-30. The median time between first and last serum was 5.8 years (interquartile range (IQR) 0.7-16.4).

Sera were analysed for HCV by the following algorithm: first, the most recently drawn serum was tested for anti-HCV antibody. Anti-HCV positive sera were analysed for HCV RNA. Then the oldest available sera from the anti-HCV positive patients were tested for anti-HCV to establish the earliest documented time of HCV infection. If the oldest serum was anti-HCV negative, later sera were tested – if available – to find the first anti-HCV positive one. A similar algorithm was followed concerning HBV-infection: the latest available serum was tested for anti-hepatitis B core antibody (anti-HBc). Positive sera were tested for hepatitis B surface antigen (HBsAg). Then the oldest available serum for those positive for anti-HBc was analysed for anti-HBc. Sera were not tested for HIV infection due to our inability to follow-up on those who eventually would test positive.

The medium period of time between estimated HCV-transmission and the blood test for HCV RNA analysis in Study 1 was 10.3 years (IQR 4.6-22.1), in Study 2: 7.1 years (IQR 4.2-13.7), and in Study 3: 16.8 years (IQR 7.5-25.8 years).

Serum specimens were examined for anti-HCV (Ortho-Clinical Diagnostics HCV 3.0 Elisa), HBsAg, and anti-HBc (Bio-Rad Monolisa HBsAg Ultra and anti- HBc PLUS). HCV RNA was analysed by an “in-house” PCR to detect viral RNA (detection limit 500 virus copies per ml corresponding to 100 IU per ml). Since reinfection was a possibility in those who were initially found HCV RNA negative, we traced more recently drawn sera at Oslo University Hospital, retested them for HCV RNA and found that 5/23 (22%) were HCV RNA positive. In our analyses, those five have been categorised as HCV RNA positive. Their time of HCV transmission is set at the estimated time of reinfection. Information on possible reinfection lacks for most of the HCV RNA negative subjects.

**Time point of HCV transmission**

As acute HCV infection was not registered in any of the patients, the time point of HCV transmission had to be estimated. All patient case records at SKN were examined by the author to establish age of the first drug injection. Case records for most patients contained direct information about this, and, for most of the others, it was possible to establish the age of first injection with reasonable certainty through circumstantial information. The time point of HCV transmission was estimated mainly based on the year of first drug injection (Table 8). HCV transmission was estimated to have occurred after two years following initiation of drug injection for 82% of the cohort in Study 1.
Table 8 Estimation of time point for HCV transmission

<table>
<thead>
<tr>
<th>Time point of HCV transmission</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Two years after first drug injection if first blood sample afterwards was anti-HCV positive.</td>
<td>428</td>
<td>81.8</td>
</tr>
<tr>
<td>2. Similar to 1, but if first drug injection was before 1968, time point of transmission is set to 1970 because there are reasons to doubt if HCV was endemic among IDUs in Norway anterior to 1970.</td>
<td>10</td>
<td>1.9</td>
</tr>
<tr>
<td>3. If an anti-HCV negative serum sample is available after first drug injection and the following anti-HCV positive serum was obtained less than two years later, transmission time is from first anti-HCV positive test</td>
<td>33</td>
<td>6.3</td>
</tr>
<tr>
<td>4. As 3, but if anti-HCV positive serum sample was obtained more than two years later, transmission time is set at two years after last anti-HCV negative sample</td>
<td>38</td>
<td>7.3</td>
</tr>
<tr>
<td>5. If time of first drug injection is unknown, time point of HCV transmission is put identical to first anti-HCV positive test, if this is analysed in serum obtained less than five years after admission to SKN.</td>
<td>7</td>
<td>1.3</td>
</tr>
<tr>
<td>6. As 5, but if first anti-HCV positive test was obtained more than five years after admission, time of transmission is set at five years after admission.</td>
<td>7</td>
<td>1.3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>523</td>
<td>100</td>
</tr>
</tbody>
</table>

Abbreviations: HCV, hepatitis C virus, anti-HCV, anti-hepatitis C antibody; IDU, injecting drug user; SKN, Statens klinikk for narkomane (National Clinic for Drug Abuse in Norway)

Register data and information on antiviral HCV treatment (Study 1 and Study 3)

Data about status of living, including information on emigration, were obtained from the National Registry of Demographic Data and about causes of death from the Causes of Death Registry (Statistics Norway). Information about HCC was supplied by the Cancer Registry of Norway and about liver transplantation by the Nordic Liver Transplant Registry.

Data on HCV antiviral medical treatment after January 1, 2004 were obtained by linkage to The Norwegian Prescription Database (NorPD). NorPD was established in January 2004 and contains information on all prescription drugs dispensed at Norwegian pharmacies to individual patients living outside institutions [255]. Data collected in the database are patients’ unique identifier (encrypted), gender, age, and place of residence, the date of dispensing, and drug information. The reason for the prescription is not recorded, but we used ribavirin as a proxy for HCV treatment since HCV infection is this drug’s only indication. Patients who had received at least one prescription of ribavirin tablets were registered as HCV treated.

Treatments before January 2004 were identified through linkage with Scandinavian HCV treatment trials and information from the Department of Virology at the
Norwegian Institute of Public Health (NIPH), which until the year 2000 was the only laboratory that performed HCV RNA testing in Norway. During the years 1993-2004, several investigator-initiated treatment trials of HCV treatment including 757 subjects were conducted in Norway [236-239]. The databases for these studies were linked to the present study group to identify patients who received HCV treatment before NorPD was established.

Information on SVR was supplied directly from the Scandinavian treatment trials where this information was available or indirectly from the NIPH and the Department of Microbiology, OUH. From NIPH and OUH we had information on serial analysis of HCV RNA during treatment periods. When the final analysis accomplished several months later had a negative result, the patient was classified as having SVR.

In order to estimate the number of possibly unknown treated cases, we acquired information from Schering-Plough and Roche on the quantity of antiviral medication sold in Norway for HCV treatment before the initiation of NorPD in 2004.

Information on sales from the two pharmaceutical companies that supplied interferon for HCV treatment during that period indicate a total number of about 1550 subjects having received antiviral HCV treatment in Norway 1997-2003 (personal information from representatives of Schering-Plough and Roche in Norway). Thus approximately half of the treatment in Norway was administered in treatment trials during that period.

In our cohort, we registered 18 treated cases before 2004, of which 12 were in treatment trials. The latter probably represent approximately half of the treated cases during that period, which would imply that we lost about six treated cases or 11% of those actually treated.

**Evaluation of liver tissue (Study 2)**

Liver tissue was available from all 102 autopsies as tissue blocks fixated in standard 10% neutral formalin and paraffin. They were analysed at the Institute of Forensic Medicine at the University of Oslo (now a division at the NIPH). Three histological sections from each sample were cut to a 4 μm thickness and stained with hematoxylin eosin (HE), acid fuchsin orange G-stain (AFOG) and Perls’ iron stain. The area of sections varied between 0.5 cm² and 3.0 cm². All three sections from each case were examined by two pathologists working independently and blinded for serologic results and anamnestic information. The liver pathology was scored according to the Metavir scales for fibrosis stage (F0-F4) where F0 = no fibrosis, F1 = portal fibrosis without septa, F2 = portal fibrosis with few septa, F3 = septal (or bridging) fibrosis and F4 = cirrhosis. Inflammatory activity, steatosis and autolysis were also graded on four point scales from 0 to 3.
When disagreement in scoring occurred by one stage, the lower score was selected. In four cases the scoring differed by two stages. These cases were reassessed by each pathologist separately, resulting in four scores for each case. The most frequent score was chosen.

**Statistics**

Mortality rates were calculated as number of deaths per 100 person-years (PY). Standard mortality rates were calculated by gender and age groups using death rates in the population by the middle of the follow-up period. The death rates in the population decreased linearly during the whole follow-up period.

In Kaplan-Meier analysis, the 18 individuals (3.4%) who emigrated during follow-up have been censored at the date of emigration. HCV RNA positive cases were censored when antiviral treatment resulted in sustained virologic response. In the analysis of mortality caused by liver disease, the starting point was defined as the time point of estimated HCV-transmission even if in most patients there were no observations during the time from HCV transmission to admission at the residential drug abuse treatment. Log rank tests were used for comparison of mortality trends in Kaplan-Meier analysis, and Fisher’s exact test for comparison of liver mortality rates according to age. Pearson’s Chi-squared test was used for comparison of causes of death in two groups.

In Study 2 rates of advanced fibrosis (F3-F4) were calculated as cases of F3-F4/total cases. In the Kaplan-Meier plot, the end point was death accompanied with advanced fibrosis (F3-F4). Subjects dying without advanced fibrosis were censored. Log rank tests were used for testing significance in Kaplan-Meier analysis. The rate of progression of fibrosis was calculated as Metavir stage/years since HCV-exposure. Pearson’s Chi-squared test was used for comparison of frequencies of ordinal variables.

In Study 3 rate of treatment uptake was calculated as the number of patients treated for the first time per 100 PY, with 95% confidence intervals (CI). Pearson’s Chi-square test was employed in cross-tabulations. Effect of treatment on mortality was estimated using Cox regression with a time-dependent covariate that had the value 0 from January 1, 1997 to the end of treatment and 1 thereafter. Non-treated patients had a value of 0 for the whole observation period. Survival among untreated and treated patients was further illuminated by a survival function plot. Mortality rates were calculated for untreated patients and treated patients before and during treatment versus treated patients after treatment.

In all studies confidence interval (CI) levels were set to 95% and significance at p<0.05. For statistical analysis, the Statistical Package for the Social Sciences (SPSS) version 18.0 and Stata version 11.2 (StataCorp LP) have been employed.
Ethics

No consent was collected from the participants at the time of admission for treatment, and in accordance with the National Committee for Research Ethics no later attempt was made to collect consent from patients or their relatives.

This was in concordance with the original conditions for the establishment of this research register in 1992. The prerequisite had been an exemption from the duty of confidentiality for health workers. This exemption was necessary to link the research register to different kinds of health registries. The exemption had been given repeatedly for new periods until 2008 by the body responsible for such demands which was the Norwegian Directorate of Health (NDH). At that time a new application for extension of the period for exemption was refused by NDH. The reason for this was that the register had existed already for 18 years and that it seemed more like a permanent health register than a research register. And NDH had no competence to give permission to a permanent health register. At the time of the final decision by the NDH, a new law on research ethics and medical research in Norway entered into force July 1, 2009. This law transferred the competence for exemptions for the duty of confidentiality related to research to the Regional Committees for Medical and Health Research Ethics. Appeals should be directed to the National Committee for Medical and Health Research Ethics. Both consented on the conditions for our research register – including the exemption for the duty of confidentiality – and this enabled us to go on with the research work.

At the time of admission to drug abuse treatment for these patients 1970–1984, there were no plans for research, and no consent for this was demanded. However, there was obviously a strong need for research on the destiny of these patients, and this was the reason for the first acceptance of exemption for the duty of confidentiality. For longitudinal studies of mortality there is a need for long term follow-up. This became even more obvious when research on such a slowly developing disease as CHC was planned.

The ethical dilemmas surrounding this were thoroughly discussed with the National Committee for Research Ethics. The possibilities of having consent from patients or their relatives were considered, but both the committees for research ethics and myself concluded that contact in this purpose might represent a serious strain for individuals who might not wish to be reminded of a possibly hidden past. It would also have been extremely difficult to implement.

The study was then approved by the National Committee for Research Ethics and the Norwegian Data Protection Authority. The Director of Public Prosecutions approved the use of tissue material collected at medico-legal autopsies in Study 2, and the studies were also approved by The Norwegian Data Protection Authority.
Results

Characteristics of the cohorts

Paper 1
343/523 (65.6%) subjects were males. Of the 523 anti-HCV positive subjects, 328 (62.7%) were HCV RNA positive, indicating chronic infection, with HCV clearance in 195 individuals (37.3%). Of the anti-HCV positive patients, 435/523 (83.2%) also were anti-HBc positive, of which 419 had been tested for HBsAg. 31/419 (7.4%) were HBsAg positive; 3.8% among HCV RNA positive patients, 13.5% among HCV RNA negative patients (p<0.001). Concordantly, HCV clearance among HBsAg positive patients was 21/31 (68%), among anti-HBV positive/HBsAg negative patients 134/254 (34.5%).

Patient records contained information on drug use in 507/523 (96.9%) cases among whom 495 (97.6%) had injected drugs at least once. Mean time from estimated HCV transmission to admission to SKN was 2.2 years, varying from 11 years before to 14 years after admission at SKN.

Paper 2
By December 31, 2008 220 of the 523 anti-HCV positive patients had died, and liver sections from autopsies were available and of sufficient quality for 102, the study group (Figure 14). These consisted of 61 anti-HCV positive/HCV RNA positive and 41 anti-HCV positive/HCV RNA negative subjects. The 118 anti-HCV positive subjects who died without liver tissue available for analysis, constituted a comparison group for analysis of representativeness.

Paper 3
The study cohort consisted of the 245 HCV RNA positive patients who were alive in Norway by January 1, 1997; 66.5% were males (Figure 14). The mean age was 40.2 years. By the entry into the study they had been chronically infected with HCV for a mean of 20.0 years. The median duration of HCV-infection at the end of 2012 was 36.5 years.

Of the 245 patients 197 (80.4%) were anti-HBc positive of which 5 (2.5 %) were HBsAg positive.

17 This associations between HBsAg and HCV RNA are not described in the journal papers
Main results

Paper 1

**All-cause mortality**
Mean time from admission to SKN until December 31, 2008 was 30.3 years (standard deviation (SD) 3.6) and time from estimated HCV transmission was 32.5 years (SD 3.8). At the end of follow-up, 220 patients (42.1%) were dead, 18 (3.4%) had emigrated, and 285 (54.5%) were still living in Norway. All-cause mortality rate from the admission at SKN until the end of 2008 for males was 2.11 (CI 1.84-2.46) per 100 PY, for females 1.39 (CI 1.07-1.79), overall 1.85 (CI 1.62-2.11). Standard mortality ratio (SMR) for males was 8.7 (CI 7.5-10.1), for females 14.0 (CI 10.8-18.0). Mortality rate for HCV RNA positive patients was 1.75 (CI 1.47-2.07) versus 2.05 (CI 1.66-2.54) for HCV RNA negative patients.

**Causes of death**
Opioid overdose was the most frequent cause of death, followed by violent deaths and suicide. HIV was cause of death in 12/220 (5.5%). Overall, 49.5% of deaths were due to causes directly linked to drug abuse, 19.5% to violent deaths (accident, suicide, homicide), and 28.2% to medical causes. The distributions of causes of death were not significantly different according to the HCV RNA status (Pearson’s Chi-square: p = 0.598).

**Liver-related mortality**
Twelve patients died of liver disease, 10 were HCV RNA positive (including one with HBV/HCV co-infection). Two of the patients were HCV RNA negative, and both were HBsAg positive, indicating chronic HBV infection.

Liver-related deaths among subjects with CHC were 10 out of 134 deaths (7.5%).
HCV-related liver mortality rate was 0.09 per 100 PY (CI 0.05-0.16) in HCV RNA positive subjects. For HCV RNA positive males 9/94 (9.6%) deaths were liver-related and liver mortality rate was 0.16/100PY (CI 0.08-0.31); for females 1/40 (2.5%) deaths were liver-related and the liver mortality rate was 0.04/100PY (CI 0.01-0.26).

Among the 10 HCV RNA positive subjects who died from liver disease, mean age by HCV transmission was 20.4 years and by death or liver transplantation 47.5 years, range 34-54 years. The underlying cause of death was HCV infection in five cases, HCC in one case, and alcoholic liver disease in two cases. One patient had liver transplantation at 52 years of age, but died 2 years later from complications of post-transplantation medication. No cases of HCC were registered at the Cancer Registry except those who were also found in the Causes of Death Registry.

Liver mortality increased strongly with age among patients with CHC. Liver disease constituted 5/17 (29.4%) of HCV RNA positive subjects who died by 50-60 years of age (males 5/13 (38.5%), females 0/4 (0%)).
Cumulative incidence rate of liver-related mortality among patients with CHC before 50 years of age was 0.07/100PY (CI 0.03-0.17) and after 50 years of age 0.91/100PY (CI 0.38-2.18) p <0.001.

Paper 2

**Causes of death**

In this cohort of autopsied subjects 79/102 (77.4%) died of drug related causes, mainly opioid poisoning. Five (4.9%) had committed suicide, while seven (6.9%) had other external causes. Death by liver disease occurred in 3/102 (3.0%); all of which had CHC. One patient died from HIV and seven (6.9%) from other diseases.

**Fibrosis score and rate of fibrosis progression**

We observed cirrhosis (F4) in 8/102, (8%, CI 3%-13%) of autopsied anti-HCV positive PWID. In the group with CHC 7/61, (11%, CI 3%-19%) had cirrhosis compared to 1/41, (2%, CI 0%-7%) among the HCV RNA negative subjects.

The proportion of advanced fibrosis (F3-F4) was 10/61 (16%, CI 7%-26%) among patients with CHC, and 1/41 (2%, CI 0%-7%) among HCV RNA negative subjects (p = 0.026).

The proportion of advanced fibrosis increased according to the time since HCV exposure. Among 26 subjects with CHC autopsied up to 15 years after HCV exposure, none had F3-F4. Among the individuals who died 15-25 years after exposure, 4/18 (22%, CI 3%-41%) had F3-F4, and after more than 25 years since exposure 6/17 (35%, CI 13%-58%) had F3-F4. On the other hand, 16/26 (62%, CI 43%-80%) of subjects with CHC autopsied more than 20 years after exposure had only F0-F1.

The first two cases of advanced fibrosis occurred 17 and 19 years after HCV exposure.

Among HCV RNA positive subjects autopsied at age >45 years 6/16 (38%, CI 14%-62%) had advanced fibrosis/cirrhosis. Among the 41 HCV RNA negative subjects, one male had developed cirrhosis 33 years after HCV exposure, his cause of death was opioid poisoning.

The median rate of fibrosis progression (Metavir units/year) for HCV RNA positive patients was 0.068 (IQR 0.038-0.128, range 0.0-0.63), the mean was 0.097 (SD 0.094).

Only one subject had received antiviral HCV-treatment. She died 27 years after HCV exposure from opioid poisoning, a few months after treatment. Her fibrosis score was F1.
One subject with CHC had HIV as cause of death. At autopsy 14 years after HCV exposure she had F1.

The scoring of fibrosis differed by one stage among the two pathologists in 33 cases, of which 23 were HCV RNA positive. Most discrepancies were between F1 and F2, but in three cases there were discrepancies between F2 and F3.

**Inflammatory activity and steatosis**

There were significant associations between inflammatory activity and fibrosis, and between steatosis and fibrosis.

**Study group compared to comparison group**

The study group of 102 subjects with available liver tissue was compared with the 118 who died in the same period without liver tissue available for assessment of fibrosis.

The study group and the comparison group did not differ concerning gender, mean age at HCV exposure or CHC. However, the groups differed significantly regarding causes of death, with other causes than opioid poisoning significantly more frequent in the comparison group.

**Antiviral HCV treatment**

The first registered antiviral treatment for CHC in the cohort was carried out in 1997. Treatment uptake during the 16 years follow-up was 47/245 (19.2%). Among males treatment uptake was 31/163 (19.0%), and among females 16/82 (19.5%).

After the 16 years follow up at the end of 2012, 158/245 (64.5%) were still alive and living in Norway, three had emigrated, and 84/245 (34.2%) had died. The median age at that time for those alive in Norway was 55.6 years (interquartile range (IQR) 52.9-58.2): for males 56.7 years (IQR 53.7-59.3), and for females 54.6 years (IQR 51.9-56.8).

Three of the treated patients were dead, leaving 44 treated persons alive by the end of 2012. Consequently 44/158 (27.8%) of the cohort still alive in Norway at the end of 2012 had received antiviral treatment: among males 29/99 (29.3%), and among females 15/59 (25.4%), p=0.60. The mean age at treatment was 47.6 years, ranging from 35.6-60.0 years; among males it was 48.7 years; and among females 45.6 years.

The mean rate of treatment uptake was 1.6 per 100 PY with a non-significant trend towards lower rate in the period of 2009-2012 compared to earlier periods.

Virologic result of the treatment was known in 31 cases, of which 21 (68%) had achieved SVR.
Survival after treatment

The crude all-cause mortality rate 1997-2012 was 2.6 per 100 PY (CI 2.1-3.2); among males 2.9 (CI 2.2-3.7), and among females 1.9 (CI 1.3-2.9). Relative hazard of death during observation after treatment versus being untreated was 0.21 (CI 0.07-0.68). Mortality rate after treatment was 0.8 per 100 PY (CI 0.3-2.4) and the untreated rate was 2.8 (CI 2.2-3.5).

Of the three fatalities among treated patients, two occurred among the 10 who did not have SVR, and one among the 21 with SVR (p=0.18). No deaths occurred among the 16 where SVR was unknown.

There were no cases of HCC in addition to those who had died, nor any liver transplantation.

Causes of death

Liver disease was the cause of death in 13 untreated patients. They constitute 13/198 (6.6%) of untreated patients and 13/81 (16.0%) of deaths. Liver disease was also the cause of death in one case among treated patients. The 13 liver-related causes of death among untreated patients included two HCC.

Of other causes of death, those directly associated with substance dependence – mostly opioid overdose – prevailed. They constituted 30/84 (36%) of deaths.
Discussion

Summary of results
These studies indicate that although HCV plays a minor role in the lives of PWID chronically infected with HCV the first two decades after HCV transmission, HCV infection becomes a major health issue after 20-25 years in about 1/3 of those infected. Development of advanced fibrosis including cirrhosis, decompensated cirrhosis and the risk of liver related deaths do increase slowly with age. After the age of 45 years 38% had advanced liver fibrosis and after the age of 50 years 29% of deaths were caused by liver disease among PWID with CHC. Cumulative antiviral HCV treatment uptake was near 20%. Mortality was low among treated patients. It was high among untreated ones, mostly from drug related causes, but also because of liver disease.

Interpretations
As the progression of HCV-related liver disease is slow, it is not surprising that liver disease did not influence all-cause mortality because of the large competing risk of death caused by the substance use per se. One might hypothesize that CHC could influence the rate of other causes of death, for example drug poisoning in the setting of liver cirrhosis, but our results would not lend support to such a hypothesis. However, when the surviving part of the former or current PWID reached the age of 45-50 years, liver disease and liver-related deaths increasingly became important.

In Study 3 mortality was much lower among those who received HCV treatment than among those who remained untreated. Mortality rates were 0.8/100PY and 2.8/100PY respectively. The main reason for this difference was obviously selection of treatment to people who had quit their drug use, or used drugs in a more controlled mode. This caused much less opioid poisoning among the treated patients. However, there were 13 liver-related deaths among the untreated patients, and most of these might have been avoided if treatment had been administered in due time.

The possible decrease in treatment activity observed during the last years (Study 3) may be due to the prospect in the near future of more efficient direct-acting antivirals (DAA) with fewer side effects and shorter treatment duration. Treatment of CHC among PWID has until recently had a high threshold because of the serious side effects to interferon and ribavirin and the need for strict follow-up [236, 239, 256].
Comparison with other studies

Natural course of CHC

Our results can be compared to other longitudinal studies performed among different kinds of patients with CHC. Most researchers followed patients who were particularly selected because of their known CHC, often from secondary or tertiary medical treatment centres. This obviously conducts to a risk of selection bias towards more severely affected patients. Our cohort initially was selected because of injecting drug use, which implies that their CHC had all type of grades, from asymptomatic and without sign of fibrosis during several decades to advanced fibrosis and cirrhosis. A small part of the cohort received antiviral treatment. Thus, our study demonstrates the natural course of HCV-infection among PWID to a high degree. Even if follow-up has been of longer duration than in most others studies, we still lack certain knowledge of the course of CHC when patients reach their 60s and 70s.

Cohorts selected directly for CHC have recruited patients with different characteristics for the manner of HCV-transmission, gender, age both at HCV-transmission and at study end, and the duration of follow-up. The external validity of each of these studies has limits, as is also the case with our studies.

Liver fibrosis and cirrhosis

Freeman et al in 2001 published a review of studies on the development of cirrhosis in CHC-patients [257]. Studies were classified in four groups according to how patients were recruited: liver clinics, post-transfusion, blood donor screening and community based cohorts (Table 9).

Table 9 Cirrhosis after 20 years of CHC in different kinds of studies according to Freeman et al 2001 [257]

<table>
<thead>
<tr>
<th>Study design</th>
<th>Number of studies</th>
<th>Cirrhosis after 20 years¹⁸</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients from liver clinics</td>
<td>Cross-sectional</td>
<td>33</td>
</tr>
<tr>
<td>Post-transfusion cohorts</td>
<td>Longitudinal</td>
<td>5</td>
</tr>
<tr>
<td>Patients from blood donor screening</td>
<td>Cross-sectional</td>
<td>10</td>
</tr>
<tr>
<td>Community based cohorts</td>
<td>Mainly longitudinal</td>
<td>9</td>
</tr>
</tbody>
</table>

Patients from liver clinics probably were selected because of more rapid development of fibrosis, and post-transfusion patients were older at the time of exposure than what has been seen in most other cohorts, which may explain a rapid

¹⁸ Weighted according to study size
development of cirrhosis in this group. Most studies in Freeman’s review had shorter duration of follow-up than 20 years, and the results after 20 years were based on linear extrapolation.

The community based studies in Freeman’s review are compiled in Table 10. Some more recent studies are summarized in Table 11 including our Paper 2.

Table 10 Cirrhosis according to mean duration of HCV infection in different studies with recruitment of patients in the community including PWID. Included in the review of Freeman et al [257].

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Patient recruitment</th>
<th>Population size (anti-HCV positive)</th>
<th>Mean age at follow-up Years</th>
<th>Mean duration of CHC Years</th>
<th>Cirrhosis %</th>
<th>Diagnosis of cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodger 2000 [258]</td>
<td>Acute HNANB, PWID Australia</td>
<td>95</td>
<td>43</td>
<td>23</td>
<td>4.2</td>
<td>Clinical</td>
</tr>
<tr>
<td>Wiese 2000 [226]</td>
<td>Women post-partum Germany</td>
<td>500</td>
<td>44</td>
<td>20</td>
<td>0.8%</td>
<td>Biopsy</td>
</tr>
<tr>
<td>Vogt 1999 [259]</td>
<td>Children after cardiac surgery Germany</td>
<td>67</td>
<td>23</td>
<td>20</td>
<td>4.5%</td>
<td>Biopsy, clinical</td>
</tr>
<tr>
<td>Kenny-Walsh 1999 [228]</td>
<td>Women post-partum Ireland</td>
<td>390</td>
<td>45</td>
<td>17</td>
<td>1.9%</td>
<td>Biopsy</td>
</tr>
<tr>
<td>Bellentani 1994 [260]</td>
<td>Population survey (Dionysos) North Italy</td>
<td>199</td>
<td>50</td>
<td>11.1%</td>
<td>Clinical, ultrasonography or biopsy</td>
<td></td>
</tr>
<tr>
<td>Ohkoshi 1995 [261]</td>
<td>Population survey Japan</td>
<td>63</td>
<td>64</td>
<td>30</td>
<td>10.0%</td>
<td>Clinical, ultrasonography</td>
</tr>
<tr>
<td>Mattsson 1963 [262]</td>
<td>Acute HNANB, PWID and post-transfusion Sweden</td>
<td>24</td>
<td>41</td>
<td>13</td>
<td>8.3%</td>
<td>Clinical</td>
</tr>
<tr>
<td>Thomas 2000 [126]</td>
<td>PWID survey USA (94% black)</td>
<td>1667</td>
<td>71</td>
<td>23</td>
<td>2.3%</td>
<td>Clinical Autopsy</td>
</tr>
<tr>
<td>Alter 1992 [263]</td>
<td>Acute HNANB community USA</td>
<td>106</td>
<td>3</td>
<td>1.0%</td>
<td>Biopsy</td>
<td></td>
</tr>
</tbody>
</table>

In Table 10 and Table 11 percentages of cirrhosis are based on anti-HCV positive patients. The criteria for the diagnosis of cirrhosis varied between studies. In some the diagnosis was based on histology, in others on clinical or laboratory assessment;
one also mainly on ultrasonography. Generally, clinical criteria may have a higher threshold than criteria based on histology [260]. In Table 10 and Table 11 the mean duration of CHC in the studies is the real value, with no extrapolations.

Table 11 Cirrhosis according to mean duration of HCV infection in different studies with recruitment of patients in the community including PWID. Not included in the review of Freeman et al [257].

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Patient recruitment</th>
<th>Population size (anti-HCV positive) N</th>
<th>Mean age at follow-up Years</th>
<th>Mean duration of CHC Years</th>
<th>Cirrhosis %</th>
<th>Diagnosis of cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levine 2006 [160]</td>
<td>Women post-partum Ireland</td>
<td>182</td>
<td>54</td>
<td>27</td>
<td>2.3%</td>
<td>Biopsy</td>
</tr>
<tr>
<td>Bedogni 2008 [264]</td>
<td>Community Dionysos North Italy</td>
<td>139</td>
<td>66</td>
<td>15.8%</td>
<td>Biopsy</td>
<td></td>
</tr>
<tr>
<td>Kristiansen 2010 [265]</td>
<td>Community, mostly PWID Norway</td>
<td>864</td>
<td>40</td>
<td>22</td>
<td>2.1%</td>
<td>Clinical</td>
</tr>
<tr>
<td>Allison 2012 [37]</td>
<td>Blood donors (42% IDU) USA</td>
<td>185</td>
<td>46</td>
<td>25</td>
<td>3.2%</td>
<td>Biopsy</td>
</tr>
<tr>
<td>Jerkeman 2014 [144]</td>
<td>PWID in OMT Sweden</td>
<td>6520</td>
<td>44</td>
<td>22</td>
<td>8.7%</td>
<td>Biopsy</td>
</tr>
<tr>
<td>Kielland 2014 [266]</td>
<td>PWID Norway</td>
<td>102</td>
<td>42</td>
<td>17</td>
<td>7.8%</td>
<td>Autopsy</td>
</tr>
</tbody>
</table>

In Levine’s study from 2006 of Irish women HCV infected post-partum in the late 1970s 3.3% of HCV RNA positive patients had cirrhosis (Ishak stages 5-6) 27 years after HCV-transmission [160]. However, at that time the number with Ishak stages 3 and 4 was 20/167 (12.0%) and 6/167 (3.6%) respectively. Those stages may be compared with stages F2 and F3 in Metavir [267, 268]. Thus there was an important proportion of the patients with moderate or advanced fibrosis in that cohort. The same was the case in Allison’s study of HCV-infected blood donors. After a mean duration of 25 years since HCV-transmission 3.2% had cirrhosis, but 12.4% had Ishak stages 3 or 4 [37].

19 In this study only decompensated liver disease is included. Compensated cirrhosis was not reported.

20 Jerkeman does not report number of anti-HCV positive patients directly here. She reports, however, 45 HCV RNA positive patients who have been assessed by biopsy, and that the HCV RNA positive constitute 69% of anti-HCV positive patients in the whole cohort. From this the number of 65 anti-HCV positive patients in this table is estimated (45 is 69% of 65).
A Danish study based on autopsies of drug related deaths reported that 19% (6/32) of anti-HCV positive subjects had cirrhosis after more than 20 years of drug use [262] compared to 13% (6/46) in our Paper 2. Cirrhosis was observed in 7.8% of our cohort of 102 autopsied anti-HCV positive PWID after a mean of 17 years follow-up until autopsy, mean age at autopsy was 37 years. This is not very different from an Australian autopsy study where 11% of anti-HCV positive autopsy cases of drug-related deaths had cirrhosis, mean age 33 years; duration of the HCV infection was not reported [269].

Comparison of cirrhosis development in the studies exposed in Table 10 shows a surprising variability. The studies of Irish and German females infected post-partum, as well as Allison’s study of blood donors, are in the lower end of a continuum where our study is in the middle. All the studies were from Western countries. IDU most probably was the main cause of HCV transmission in all studies except the Italian ones where the patients had higher mean age. In Kristiansen’s study few had cirrhosis, but as only decompensated cirrhosis was included, the total number of cirrhosis probably was much higher.

The reasons for variability between studies may be differences in a number of factors exposed in Table 2, page 35. Alcohol consumption may be the most important of these factors.

In a meta-analysis of the stage-specific fibrosis progression rate in different populations of HCV-patients, the mean annual progression rate among the PWID were: F0-F1 0.116, F1-F2 0.085, F2-F3 0.085 and F3-F4 0.130 [135]. This corresponds well to the overall mean annual progression rate of 0.097 in our study.

All-cause mortality related to CHC
There has been quite extensive research linked to mortality among cohorts with CHC. The influence from CHC on mortality depends mainly on the duration of the infection and the age of the patients at the time of exposure. In cohorts with young patients and short duration direct influence of CHC tends to be marginal, especially in patients with high competing risk of death, notably related to IDU. Most studied cohorts reflect CHC-populations with mixed mode of transmission and age. In such studies CHC is an important cause of death.

A British study published 2007 by Neal et al of CHC-patients followed-up mainly at secondary medical centres has reported causes of death according to death age in a similar way as we did in Paper 1, figure 3 [270]. Their results indicate that liver disease dominated as early as in the age group 40-49 years, which is earlier than in our cohort (Figure 15). That may be caused by higher alcohol consumption in their cohort, reflecting the higher alcohol consumption in UK compared to Norway21. It is

also noticeable that HCC played an increasing role as cause of death with increasing age in Neal’s study. Younger patients were mainly drug users, while older patients had been exposed to HCV by other ways, which probably is the reason why drug related cause of death played a minor role among patients dying after 50 years of age. Accidents were an important cause of death in our cohort, while it is not obvious were such deaths were coded in Neal’s study.

Our results concerning mortality and development of fibrosis can be compared to studies of women exposed to HCV by contaminated anti-D immunoglobulin in 1978-1979 in Germany. Recently follow-up after 35 years has been published by Wiese et al [148]. The duration of observation was about the same as in our studies. However, an important difference is between healthy young women in Wiese’s cohort and drug users with high mortality directly related to drug abuse in our cohort. Development of liver related mortality and liver fibrosis still may be compared, however. Both cohorts have been followed up for approximately 35 years [22].

---

22 The results presented here are based on the register linkage conducted for Study 3. Information on causes of death is updated at the end of 2012.
Comparison of liver-related mortality is shown in Figure 16. Liver-related mortality rate among young, healthy German women and young Norwegian drug using women was very similar, while male drug users had a higher liver-related mortality as could be expected. Because of the high all-cause mortality in the PWID cohorts (Figure 17) a relatively larger part of the observations in this cohort occurred few years after HCV exposure compared to the German female cohort. This may lead to an underestimation of the difference in liver-related mortality per 100PY in the PWID-cohort, compared to the German females where a larger part of the observations occurred in the more risky years several decades after HCV transmission.

![Liver-related crude mortality rates per 100 PY\textsuperscript{23} after 35 years follow-up among German females exposed to HCV through contaminated anti-D immunoglobulin compared to Norwegian females and males exposed to HCV through IDU.](image)

\textsuperscript{23} Person-years in the German cohort have been estimated from data in the published article, where such information was not exposed directly
Figure 17 All-cause crude mortality rates per 100 PY after 35 years follow-up among German females exposed to HCV through contaminated anti-D immunoglobulin compared to Norwegian females and males exposed to HCV through IDU.

**All-cause mortality among PWID**

In our Paper 1 all-cause crude mortality rate (CMR) was 1.85 per 100 PY with a SMR of 8.7 for men, and 14.0 for women. In a global meta-analysis published in 2013 on mortality among PWID CMR was 2.35, in European countries 2.32 [220]. Death by AIDS was a more important cause of death than in our study.

In another similar meta-analysis of opioid users CMR was 2.3/100PY [219]. In that study mortality rate by liver disease was 0.16/100PY, compared to 0.09/100PY in our study. The difference may be caused by higher prevalence of HIV and chronic HBV-infection in the global study.

Two studies on PWUD mortality – both from Sweden – had a follow-up duration comparable to ours [271-273]. Stenbacka et al recruited 1705 illicit drug users from different care centres in Stockholm during 1967. The cohort was followed up until 2003. CMR was 2.1 per 100 PY and SMR 4.4 [220, 272, 273].

The other Swedish study (Nyhlén 2011) recruited 561 PWUD admitted for detoxification 1970-1976 with follow-up until 2006. CMR in that study was 1.3 per 100 PY, SMR 5.9. Liver disease was not specified. Causes of death between Stenbacka’s, Nyhlén’s and our studies are compared in Table 12.
Table 12 Causes of death in three Scandinavian longitudinal cohort studies of drug users with more than 30 years follow-up

<table>
<thead>
<tr>
<th></th>
<th>Stenbacka 2010</th>
<th>Nyhlén 2011</th>
<th>Kielland 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Substance abuse</td>
<td>130</td>
<td>15.1</td>
<td>91</td>
</tr>
<tr>
<td>Violent (suicide included)</td>
<td>277</td>
<td>32.2</td>
<td>54</td>
</tr>
<tr>
<td>Liver disease (HCC included)</td>
<td>118</td>
<td>13.7</td>
<td></td>
</tr>
<tr>
<td>Disease/other disease</td>
<td>287</td>
<td>33.4</td>
<td>59</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>48</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>Total number of deaths</td>
<td>860</td>
<td>100.0</td>
<td>204</td>
</tr>
</tbody>
</table>

As noted, our study (Paper 1) had a CMR between the two Swedish studies, but a much higher SMR, probably reflecting high mortality in young age in our study. Stenbacka’s study was based on a cohort recruited earlier than Nyhlén’s and ours. That cohort had lower substance-related mortality and higher mortality from disease, including liver disease. Even if HCV was not explored in any of the Swedish studies, the higher rate of liver disease in Stenbacka’s study is interesting. The cause of this most probably was that CHC was more advanced because of more advanced age and longer duration of the infection. An alternative explanation is higher alcohol consumption in that cohort.

**Treatment uptake**

Most studies of treatment uptake – as the present study – have been naturalistic, with cohorts of former and/or current PWID followed up during a certain period [239, 256, 274-277]. The treatment uptake in such naturalistic studies tends to be higher in later studies and our cumulated result – 19.8% – is among the highest. Treatment rate per 100 PY, which in our study was 1.6 for the whole period 1997-2012, was 0.28 among anti-HCV positive active PWID in Vancouver 2000-2004 [277], and 1.6 in another study from Vancouver in 2009 [239]. In most studies, treatment rate is not reported. The rate can be deducted in an American study among military veterans [274], where the treatment rate increased sharply during the period 1999-2003 and reached about 4.5/100 PY in 2003, which is clearly higher than in our study.

Other studies describe the results of projects with the explicit aim of increasing treatment uptake among PWID through more intensive counselling and multidisciplinary follow-up. Such studies are usually associated with higher treatment uptake and demonstrate the feasibility of treatment, even among people who are currently injecting drugs [234, 235, 278, 279].
Several studies have demonstrated reduced mortality and liver disease among treated patients obtaining SVR compared to those without SVR [280-284]. In our study, we did not have sufficient power to conclude on this subject.

Treatment uptake has been recorded in a Norwegian study on mortality associated with CHC [224]. After a mean of seven years follow-up, 174 of 626 patients (27.8%) had received anti-HCV treatment. That is higher than in our Study 3, probably due to fewer PWID in the other cohort.

Treatment uptake in our cohort may also be compared to the total treatment uptake in Norway. No study about this has been published. In the period 2004-2013, a total of 4974 persons had treatment which included ribavirin (NorPD, personal communication). The number of HCV RNA positive individuals in Norway is estimated to 20,000 [285]. This corresponds to treatment uptake in Norway around 2.5% per year if prevalence of CHC is considered stable. Thus, the treatment uptake in our cohort of former and current PWID was lower than among other groups of patients with CHC in Norway. This is not unexpected in light of the problems associated with recruitment of PWID to antiviral treatment of CHC.

The indication for antiviral treatment for CHC has mostly been restricted to concern for liver-related morbidity and mortality. However, there is an increasing body of knowledge about extra-hepatic manifestations of HCV. Most intriguing is perhaps the possibility of HCV affection of the brain, conducting to reduced cognitive skills. Thus, extra-hepatic manifestation may become a more important indication for antiviral treatment in the future.

**Strengths**

Our studies had several strengths, which may be summarised as follows:

1. Unselected patients with all degrees of CHC and a long duration of observation. Since patients have been observed since shortly after HCV exposure, no HCV related deaths would be expected in subjects anterior to the inclusion in our cohort

2. Near identical study group and “control group” in Study 1 and 2. The only difference was clearance after HCV exposure in the anti-HCV positive/HCV RNA negative “control groups”. The variables which could be controlled (gender, age at HCV-exposure and at admission to SKN, and prevalence of injecting drug use) did not differ between groups. There are no known reasons to expect differences concerning other factors which could influence neither all-cause nor liver related mortality other than CHC. This gives small possibilities for confounding.

3. Despite the fact that some of the patients received antiviral treatment, the treatment uptake was so limited that Study 1 and Study 2 may be considered to give quite close to a realistic natural course of all-cause
mortality, liver-related mortality and development of liver fibrosis among PWID exposed to HCV during the 1970s. This was accomplished also through censoring after antiviral treatment resulting in SVR.

4. The cohorts were selected in an unbiased manner based on two factors: a) admission to a drug abuse treatment facility and b) selection based on the presence of frozen serum specimens which were anti-HCV positive. The combined retrospective-prospective design did not interfere in a manner that would introduce bias and problems of confounding. The basic cohort was established in 1992 for research on mortality with a retrospective perspective, but the cohort was after that followed-up prospectively.

5. The evaluation of liver fibrosis in Study 2 was based on several microscopic slides from autopsies which were much larger than those obtained by the biopsies used in most studies of fibrosis related to CHC. This strongly reduced the risk of selection bias.

**Limitations**

The most important limitations of our studies may be as follows:

1. We lack information about use of alcohol, more details about the drug use, as well as about socio-demographic factors. This problem is by far most important in Study 3, because of the obvious risk for confounding when mortality after antiviral treatment was analysed in that study. Supplementary information would have made possible more analyses on sub-groups in all the three studies, particularly if the sample size also had been larger.

2. We also lack information of HIV. This has been a repeatedly expressed concern among reviewers and also in an editorial comment in the Journal of Hepatology where Paper 1 and Paper 2 were published [286]. We know about the deaths caused by HIV, and that the prevalence of HIV is low among PWID in Scandinavia compared to PWID in Southern Europe [287]. But still it would have been better to have information on HIV directly. The choice not to include HIV in serum analyses was done for ethical reasons: we knew we would not be able to follow up HIV positive patients and did not feel ourselves comfortable with that. Hence, we did not even ask the National Committee for Research Ethics for permission to include serum analyses of HIV.

3. The sample size might have been larger. Our findings both on liver-related deaths and on development of fibrosis would have been statistically more robust if the cohorts had been larger. Sub-group analyses would also have been possible. However, our cohorts are quite large compared to other long term studies of mortality, morbidity and antiviral HCV treatment uptake among PWID.
4. In the study on fibrosis progression the proportion of deaths caused by overdose was significantly higher in the study group \((p<0.001)\) compared to the comparison group (Paper 2, Table 4). In the comparison group HIV and “other disease” were significantly more frequent; there was also a non-significant trend towards more frequent deaths caused by liver disease in that group \((p=0.127)\). These disparities may imply an underestimation of fibrosis progression in our study.

5. For studies on the effect of antiviral HCV treatment a randomised controlled trial (RCT) obviously would have been the best. Such studies have been accomplished with SVR as endpoint and these have beyond doubt established our knowledge on the efficiency of the combination of PegINF/RBV. Other studies have demonstrated the feasibility of treating both current and former PWID. No RCTs, however, have been performed with PWID as the main group of patients. Thus we do not know if this treatment with its large amount of side effects has other effects on PWID than on other groups of patients. In Paper 3 is reported a large difference in mortality caused by opioid poisoning between treated and untreated PWID with CHC. Is it possible that treatment has changed the drug abuse behaviour in any way, and secondarily contributed to lower mortality? We are not able to answer this important question.

**Methodological considerations**

**Study designs**

The present studies have all been longitudinal cohort studies.

Patients in Study 1 were recruited by the following criteria:

1. Patients had entered drug abuse treatment at SKN 1970–1984. They were part of a research registry created in 1992
2. Serum for evaluation of anti-HCV and HCV RNA was available at the NIPH. Serum was drawn at the time of drug abuse treatment or later, and the analyses were performed 2006-2009.
3. Anti-HCV was positive and serum for analysis of HCV RNA was available

Lack of stored serum and anti-HCV negative result (and for a little group not available serum for HCV RNA-analysis) was the only exclusion criteria. The only difference between study group and controls was spontaneous HCV RNA clearance or no clearance. This did not significantly vary with known variables such as gender, age, frequency of reported IDU, or year of admission for drug abuse treatment. Few variables that might influence the course of HCV infection were known, as for example alcohol exposure, HIV co-infection and HCV genotype. Only a small group was lost to follow-up: those who had emigrated.
A prospective cohort study would have started at the time of admittance, which was not done here. Thus the study was basically a retrospective cohort study. The knowledge on HCV was included later, but the patients were followed-up as if the study were prospective. Thus, Study 1 is not weakened by the usual problems inherent with retrospective cohort studies, like recall bias, biased inclusion criteria, and risk of confounding. We therefore initially denominated the study as a “pseudo-prospective controlled cohort study” meaning that it could be regarded as if it were prospective, and that the HCV RNA negative group could be regarded as a control group. However, one of the reviewers preferred the term “retrospective-prospective controlled cohort design”, which we found acceptable. The retrospective part is the period until the first registration of mortality 1992; the prospective part is the time thereafter. I still think “pseudo-prospective” represent a more precise description of the study. This term has been employed in some other studies in the same sense as we did [288, 289], but it is not extensively used in research literature.

Paper 3 concerned only patients with CHC (HCV RNA positive) and consisted of two parts:

1. A longitudinal cohort follow-up study with antiviral HCV-treatment as end-point.
2. A longitudinal cohort follow-up study with mortality according to HCV treatment as end-point.

The second part of this study implied methodological considerations and problems. Theoretically it was clear that difference in mortality rate might be due to the antiviral HCV-treatment per se, or to other factors related to the selection of patients for such treatment. Those factors might conduct to confounding. Clinical experience as well as other studies gave reason to expect that former PWID much more easily would be selected for antiviral treatment than current PWID. The latter would be expected to have difficulties to accept the side effects and to conform to the strict treatment regimens.

The second part of this study implied methodological considerations and problems. Theoretically it was clear that difference in mortality rate might be due to the antiviral HCV-treatment per se, or to other factors related to the selection of patients for such treatment. Those factors might conduct to confounding. Clinical experience as well as other studies gave reason to expect that former PWID much more easily would be selected for antiviral treatment than current PWID. The latter would be expected to have difficulties to accept the side effects and to conform to the strict treatment regimens.

We first planned to study differences in mortality between treated and untreated patients through creation of an untreated control group. For each HCV-treated patient two controls among the untreated patients were selected based on two criteria: same gender and the closest possible birth date. Time point of observation start was the same as for the treated subject. If controls later were HCV-treated they were censored as controls and established as cases with there own controls. This resulted in Kaplan-Meier analysis with highly significant differences in mortality rates (Log rank test: \(p=0.001\)). However by this method we lost observation of most untreated person-years, why we later changed to another method: comparison by

---

24 A search for the term «pseudo-prospective» in PubMed did not produce more than seven relevant studies
Cox-regression with time-dependent covariate described in the presented article (Paper 3).

**External validity**

The external validity of these studies may be discussed. The studies were based on Norwegian former and current PWID initiating IDU as young people mainly during the late 1960s and the 1970s. Most probably our results concerning both all-cause and liver-related mortality (Paper 1) as well as the development of fibrosis (Paper 2) are valid for this generation of PWID in Scandinavia. Drug-related mortality in the Scandinavian countries – particularly in Norway – has been high compared to most other European countries [290]. In countries with lower drug-related mortality most probably liver-related mortality would play a more important relative role for PWID. However, the rate of development of liver disease is independent of these differences in competing risks of death through the use of Kaplan-Meier survival analysis.

In populations with lower drug related mortality the difference in all-cause mortality between patients with and without accomplished antiviral HCV-treatment (Paper 3) probably would be smaller because of the great impact of drug related deaths among the untreated patients in our study.

We do not possess sufficient information on to which degree people who initiated IDU during later periods share the characteristics concerning preferred drug (opiates or central stimulants), drug related mortality, exposure to HCV, HIV and HBV co-infection, and alcohol consumption, with the PWID of the 1970s and 1980s. In Norway people initiating IDU before 1979 was almost 10 years younger than those initiating after 1995 [92]. Hence, they were also exposed to HCV later. They also have been less exposed to HIV and HBV [104]. However, we know that IDU today also is associated with a high risk of HCV exposure [291].

How mortality associated with CHC will develop depends mainly on efficient prevention, diagnostics, and implementation of antiviral treatment for both former and current PWID. If treatment in the years ahead is accomplished for only a small part of PWID with CHC, the external validity of our studies may be high. From a humanistic point-of-view we must hope that our results will indicate mostly the history of untreated CHC which in the future will not be seen. Hopefully our studies (Papers 1 and 2) will be among the last which convey the natural history of CHC among PWID, because antiviral treatment with DAAs will be employed much more frequently in the future, also among PWID.

The fact that the cohort was recruited from a clinic for residential drug abuse treatment might indicate a selection towards the more severely affected drug users. However, residential treatment has been the mainstay for drug abuse treatment in Norway, and most opioid users have been treated in such facilities, often on several
occasions. The threshold for being accepted to a national residential drug abuse
treatment institution may have been even lower in the 1970s and 1980s than it is
today.
Conclusions

Our studies have revealed that in a cohort of PWID with high competing mortality CHC had no influence on all-cause mortality the first 25 years after HCV exposure. However, after 25 years about 1/3 of the patients with CHC had advanced liver fibrosis. Liver related mortality was a major cause of death among patients dying after 50 years of age. Cumulative treatment uptake was about 20%, but since mortality rate was higher among untreated patients, the situation for surviving individuals in 2013 was that 28% had received antiviral treatment. Median age was then 56 years.

This implies that a large part of former and current PWID with advanced fibrosis remains untreated, and some has also been treated without obtaining SVR. Without antiviral treatment they have a significant risk of developing decompensated cirrhosis or HCC during the years ahead.

For the burden of HCV-related disease in Norway in the near future increased treatment uptake among former and current PWID with advanced fibrosis (F3-F4) – or the prospect of rapid progression of liver disease (F2) – will be of great importance. The future prevalence of CHC among PWID during the years ahead will depend mainly on some few factors which we may influence: incidence of IDU, incidence of CHC among PWID, antiviral treatment resulting in SVR, and mortality among PWID with CHC.
References


91. Kristiansen MG, Gutteberg T, Berg LK, Sjursen H, Mortensen L, Florholmen J. [Hepatitis C in Northern Norway--an 8-
year material], *Tidsskr Nor Laegeforen* 2002; 122(20):1974-1976.


98


224. Kristiansen MG, Lochen ML, Gutteberg TJ, Mortensen L, Eriksen BO, Florholmen J. Total and cause-specific mortality rates in a prospective study of community-


