Management of hepatitis C virus infection among people who inject drugs:
Treatment uptake, reinfection and risk behaviours

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Håvard Midgard MD

Akershus University Hospital
Institute of Clinical Medicine, University of Oslo

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The last few years have been a significant time for management of hepatitis C virus (HCV) infection, and during the work with this thesis I have been fortunate to witness an exciting transformational period in modern medicine. In early 2014, the advent of the first direct-acting antiviral drugs for HCV treatment, with cure rates above 90% and minimal side effects, brought new optimism to the field. This important breakthrough provided new opportunities to curb the ‘silent epidemic’ that in many countries disproportionately has affected a marginalised and underprivileged population. Few years later, the body of knowledge has increased and the field of HCV care among people who inject drugs has moved from being a controversial niche to being included in mainstream hepatology, having major impact on international treatment recommendations.

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Summary

Background: Hepatitis C Virus (HCV) infection is a global health problem with 70 million chronically infected individuals and increasing disease burden attributable to liver cirrhosis and hepatocellular carcinoma. In high- and middle-income countries, the majority of incident and prevalent cases are found among people who inject drugs (PWID). As a result of a low treatment uptake in ageing cohorts of PWID, HCV-related liver disease burden continues to rise in this population. In Norway, the total PWID population counts approximately 24 000 individuals, of whom 50% have chronic HCV infection. Current direct-acting antiviral (DAA) treatment now leads to cure, defined as sustained virologic response (SVR), in more than 95% in most populations. This clinical breakthrough provides new opportunities for broadened treatment uptake, reversal of disease burden and HCV elimination. However, HCV treatment for PWID remains controversial given high drug costs, concerns of poor treatment adherence and the risk of reinfection due to ongoing risk behaviours after successful treatment. There are many knowledge gaps that must be addressed in order to provide effective management of HCV infection among PWID and strive for the World Health Organisation goal of HCV elimination within 2030. The overall aim of this thesis was to examine epidemiological and behavioural aspects of HCV infection among PWID related to treatment uptake, reinfection incidence and risk behaviours.

Materials and methods: Study I was a population-based observational study estimating interferon (IFN)-based HCV treatment uptake in Norway between 2004 and 2013 among 3755 individuals who had received opioid substitution treatment (OST) and were notified with HCV infection. The study was based on linked data from the Norwegian Prescription Database and the Norwegian Surveillance System for Communicable Diseases. Study II was a long-term follow-up study assessing the incidence of persistent HCV reinfection among 94 individuals with a history of injecting drug use (IDU) who had achieved SVR in a Scandinavian treatment trial seven years earlier. The reinfection diagnosis was based on post-SVR recurrence of HCV RNA supported by viral sequencing and behavioural data. Study III was an international multicentre study evaluating changes in risk behaviours during and following IFN-based HCV treatment among 93 individuals with ongoing IDU or receiving OST. The study was based on self-reported data on risk behaviours collected longitudinally at each study visit. Study IV was a review article covering HCV epidemiology and the risk of
reinfection after successful treatment in high-risk groups of PWID and men who have sex with men (MSM).

**Results:** Study I demonstrated a cumulative HCV treatment uptake of 14% across all age groups and stable treatment rates during OST (1.3%–2.6% per year). Treatment uptake was associated with duration of active OST, OST continuity and benzodiazepine dispensions. Study II demonstrated an incidence of persistent HCV reinfection of 1.7/100 person-years (PY) among those with a history of IDU and 4.9/100 PY in the subset of individuals who reported IDU after SVR. No baseline factor was associated with reinfection, but relapse to IDU was associated with age < 30 years and low education level. Study III demonstrated a decrease in IDU and hazardous alcohol consumption during treatment and six months of post-treatment follow-up. OST coverage increased modestly during treatment, but no changes were observed in ≥daily injecting, use of non-sterile needles, injecting paraphernalia sharing, or non-injecting drug use. Study IV showed that in studies of IFN-based treatment, the incidence of reinfection ranged from 2–6/100 PY among PWID to 10–15/100 PY among MSM. The pooled reinfection rates calculated from all studies reporting data on PY was 2.1/100 PY among individuals with a history of IDU and 5.6/100 PY among those with post-treatment IDU.

**Conclusions:** HCV treatment uptake among OST patients was low and stable during the last ten years of the IFN treatment era in Norway, contributing to a relatively low proportion of the total number of treatments. Improved treatment uptake in this key population is crucial to achieve the full individual and public health benefits of current DAA treatment. However, high reinfection rates could be a concern over time among individuals with ongoing risk behaviour, compromising individual treatment outcomes and allowing continued HCV transmission. Still, the benefits of HCV treatment may be broader in scope, and favourable changes in drug and alcohol use can be achieved when providing HCV treatment for PWID. Collectively, these findings have important implications for policy and clinical practice in the DAA treatment era and should lead to coordinated efforts to improve the HCV care cascade across different health care arenas for PWID. The results highlight the importance of post-SVR care when providing HCV treatment for people with on-going risk behaviour, informing individual- and population-level strategies to address and prevent reinfection, onwards transmission and liver disease progression. These approaches should be included in a national action plan for HCV elimination in Norway.
List of publications

I. **Midgard H, Bramness JG, Skurtveit S, Haukeland JW, Dalgard O.**

   **Hepatitis C Treatment Uptake among Patients Who Have Received Opioid Substitution Treatment: A Population-Based Study.**

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   **Hepatitis C reinfection after sustained virological response.**


   **Changes in risk behaviours during and following treatment for hepatitis C virus infection among people who inject drugs: The ACTIVATE Study.**


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IV. **Midgard H, Weir A, Palmateer N, Lo Re V III, Pineda JA, Macias J, Dalgard O.**

   **HCV epidemiology in high-risk groups and the risk of reinfection.**

Abbreviations

AASLD American Association for the Study of Liver Disease
AHUS Akershus University Hospital
anti-HCV anti-hepatitis C virus antibody
APRI AST-to-platelet ratio index
ATC Anatomical Therapeutic Chemical
AUDIT-C alcohol use disorders identification test-consumption
CI confidence interval
DAA direct-acting antiviral
DALY disability adjusted life years
DBS dried-blood-spot
DDD defined daily dose
E1 envelope 1
E2 envelope 2
EASL European Association for the Study of the Liver
EHM extrahepatic manifestation
EOT end of treatment
ESLD end-stage liver disease
ETR end of treatment response
GBD global burden of disease
GEE generalized estimating equations
HAV hepatitis A virus
HBV hepatitis B virus
HCV hepatitis C virus
HCC hepatocellular carcinoma
HIV human immunodeficiency virus
HR hazard ratio
HRQL health-related quality of life
HVR1 hypervariable region 1
IDSA Infectious Diseases Society of America
IDU injecting drug use
IFN interferon
INHSU  International Network for Hepatitis in Substance Users
kPa   kiloPascal
LSM   liver stiffness measurement
MSIS  Norwegian Surveillance System for Communicable Diseases
MSM   men who have sex with men
NANBH non-A non-B hepatitis
NIH   National Institutes of Health
NGS   next generation sequencing
NIPH  Norwegian Institute of Public Health
NorPD Norwegian Prescription Database
NSP   needle/syringe provision
OST   opioid substitution treatment
OR    odds ratio
OUS   Oslo University Hospital
PCR   polymerase chain reaction
PoC   point-of-care
PWID  people who inject drugs
PY    person-years
RBV   ribavirin
RCT   randomized controlled trial
REK   regional etisk komité (i.e. regional committee for ethics in medical research)
RNA   ribonucleic acid
RVR   rapid virologic response
SSRI  selective serotonin reuptake inhibitor
SVR   sustained virologic response
TE    transient elastography
TSB   tverrfaglig spesialisert behandling (i.e. multidisciplinary addiction treatment)
WHO   World Health Organisation
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1 Introduction

Hepatitis C Virus (HCV) infection is a global health problem and a major cause of chronic liver disease, hepatocellular carcinoma (HCC) and end-stage liver disease (ESLD). Globally, an estimated 71 million individuals are living with chronic HCV infection and the burden of disease has increased dramatically over the last decades. In high- and middle-income countries, HCV transmission has mainly occurred through injecting drug use (IDU) and the majority of new and existing cases are therefore found among people who inject drugs (PWID). As a result of a high HCV prevalence and low treatment uptake in ageing cohorts of PWID, HCV-related liver disease burden continues to rise in this population.

Over the last three years, the advent of highly efficient direct-acting antiviral (DAA) agents has changed the HCV treatment paradigm. These simple and well-tolerated oral regimens now lead to cure, defined as sustained virologic response (SVR), in more than 95% in most populations. This clinical breakthrough has led to significant therapeutic optimism with new opportunities for broadened treatment uptake, reversal of disease burden and HCV elimination. The World Health Organisation (WHO) aims for eliminating chronic viral hepatitis as a major public health threat within 2030, targeting 90% reduction in incidence and 65% reduction in mortality. However, HCV treatment for PWID may be challenging and remains controversial given high drug costs, concerns of poor treatment adherence and the risk of reinfection due to ongoing risk behaviours after successful treatment. Despite recent advances, there are many remaining knowledge gaps that represent barriers to effective HCV care for PWID.

The overall aim of this thesis was to examine epidemiological and behavioural aspects of HCV infection among PWID related to treatment uptake, reinfection incidence and risk behaviours. In Norway, we currently face a large HCV epidemic among PWID that so far has acquired very little attention. Furthermore, there are substantial uncertainties in local HCV epidemiology that may impede our strategies to manage this epidemic. This thesis therefore represents both an opportunity and obligation to review the literature and provide a reference document for the Norwegian setting. Determining the size of the problem and setting the evidence baseline is required as we move towards HCV elimination in Norway.
Accordingly, Part I of this thesis provides a comprehensive review of the epidemiology and management of HCV infection among PWID. The first half covers epidemiology, natural history of disease and treatment outcomes, while the second half features a more specific background to the main research topics of the thesis: treatment uptake, reinfection and risk behaviours. Particular emphasis is given to Norwegian data while at the same time maintaining a global perspective, and efforts are made to consolidate available data sources and provide the best possible updated local estimates.

Part II of the thesis first summarizes the objectives, methods and results of the four research articles included, followed by a broad discussion of the implications of the findings in light of the evidence previously reviewed. Finally, recommendations for clinical practice and policy are given, including proposed components for a national action plan for HCV elimination.
PART I
EPIDEMIOLOGY AND MANAGEMENT OF HEPATITIS C VIRUS INFECTION AMONG PEOPLE WHO INJECT DRUGS
2 Epidemiology

2.1 History and origins of HCV

In the 1960s, viral hepatitis was categorized into two types, infectious (type A) and serum (type B) hepatitis. Clinical cases were recognised by the onset of jaundice, and distinguished by different circumstances of exposure and different incubation periods. When serological tests for hepatitis A virus (HAV) and hepatitis B virus (HBV) became available in the mid-1970s, a large number of cases of post transfusion hepatitis turned out to be non-reactive. These cases were consequently labelled non-A non-B hepatitis (NANBH) [1]. However, the suspected pathogen could not be isolated and evaded serological diagnosis for more than a decade. When HCV finally was identified in 1989 [2], subsequent serologic tests proved that most NANBH cases were caused by this recently discovered agent [3, 4].

HCV is classified as a member of the genus Hepacivirus within the Flaviviridae family [5]. Phylogenetic analysis has led to identification of seven genotypes that are substantially divergent in sequence, and within these, nearly 70 variants or subtypes [6]. HCV subtypes are also epidemiologically distinct, with differences in geographical distributions and infected risk groups reflecting their recent epidemic spread [7]. For instance, genotypes 1a, 1b, and 3a are more prevalent among PWID in Western countries, while genotype 4a is most frequently found in the Middle East. Genotypes 1b, 2a and 2b are most common in older populations throughout Europe and Asia and are most frequently linked to past blood transfusions. HCV infection is a distinct human disease and there is no clear evidence indicating a zoonotic origin [8].

The origins of HCV has been identified to areas in sub-Saharan Africa and South East Asia where genetically diverse HCV variants appear to have circulated for hundreds of years [8]. The more recent pandemic spread of HCV probably dates back to the 1940s-1950s, preceding the HIV epidemic, but a lack of samples collected before the Second World War has prevented direct confirmation of this theory. However, the fact that HCV transmission primarily occurs by parenteral routes implies that relatively ‘modern’ risk factors (i.e. unsafe medical injections, blood transfusions and IDU) has driven the epidemic [9]. Phylogenetic and epidemiological reconstructions of the modern HCV epidemic have further supported
this narrative. For instance, the spread of genotypes 1a and 1b observed in the United States can be traced back to Japan, where these genotypes were introduced in the late 19th century [10]. Transmission in Japan may later have escalated due to unsafe medical procedures (including parenteral anti-schistosomal therapy) [11] before amphetamine injecting among soldiers during the Second World War brought the virus to the United States.

As IDU increased from the 1960s onwards, it became an increasingly important route for HCV transmission in many Western countries [12-14], overlying existing transfusion-associated transmission. Several reports have confirmed that HCV infection rapidly became prevalent among PWID; in Norway, screening of stored frozen sera from 635 individuals admitted for residential drug treatment between 1970 and 1984 revealed 84% anti-HCV prevalence and 53% HCV ribonucleic acid (RNA) prevalence [15]. After effective screening of blood products was implemented in the early 1990s, eliminating transfusion-associated spread in high-income countries, IDU has remained the primary risk factor for HCV transmission accounting for the majority of incident and prevalent cases in these countries [16-18]. For instance, in the United Kingdom, more than 85% of an estimated 200 000 HCV-infected individuals have acquired it through IDU [19, 20]. Although unsafe medical procedures are still considered a major route of transmission in low- and middle-income countries, HCV epidemics have also emerged among PWID in many of these settings [21].

2.2 Global burden of disease

HCV infection is one of the main causes of chronic liver disease, leading to significant morbidity and mortality as a result of liver cirrhosis complications, including HCC and ESLD. Findings from the 2013 Global Burden of Disease (GBD) Study [22] revealed that annual viral hepatitis (HBV and HCV) deaths had increased from 0.89 to 1.45 million between 1990 and 2013, making viral hepatitis the leading killer among infectious diseases. Deaths from HCV-related liver disease have increased dramatically over the last two decades; between 1990 and 2013 total deaths due to HCV-related cirrhosis more than doubled, with deaths due to HCV-related HCC increasing 3-fold [22]. In many Western countries, HCV infection has been identified as the leading indication for liver transplantation [23-25]. Previous GBD estimates suggested a global anti-HCV prevalence of 2.8% [26], corresponding to 185 million exposed individuals and 130 million HCV RNA positive (chronically infected) individuals. A more recent review [27], critically taking into account
the vast uncertainties of the evidence base, scaled down previous estimates to 80 (64-103) million HCV RNA positive individuals globally. The most recent WHO estimates from 2015 conclude that 71 million are living with chronic HCV infection (1% of the population) [28].

HCV prevalence among PWID is disproportionally high with an estimated 10 million HCV-infected PWID globally, of whom nearly 3 million are living in Europe [16]. Data from the GBD Study confirmed that IDU is a major contributor to the global burden of HCV infection, particularly in high-income countries. Between 1990 and 2013, the proportion of HCV burden attributable to IDU increased from 23% to 39% globally, corresponding to an increase from 2.1 to 7.0 million disability adjusted life years (DALYs) [29]. This increase was most pronounced in in Eastern Europe, where this proportion increased from 32% (73 000 DALYs) to 68% (605 000 DALYs).

According to recent modelling work from The Norwegian Institute of Public Health (NIPH), the estimated number of PWID living with HCV-related cirrhosis in Norway is 1400 and is predicted to increase until peaking at 1530 individuals in 2021 [30]. The same data suggest that in 2015, HCC developed in 24 of these individuals, ten patients needed a liver transplant and 40 died of HCV-related causes.

2.3 Defining populations of PWID

IDU has been characterized as a chronic health problem, with PWID typically experiencing repeated periods of injecting and cessation during their injection careers [31]. Some individuals may overcome their dependency over time [32], often with the aid of harm reduction interventions like OST. Although some individuals will cease injecting after sporadic or short-term injecting, studies of the natural history of drug dependency and IDU are rare [33].

Reflecting their highly heterogeneous nature, defining PWID populations has proven challenging and the term ‘PWID’ is often applied imprecisely in the literature. More recently, efforts have been made to bring structure to this taxonomy in the context of HCV infection [34, 35]. Lifetime PWID refers to people who have ever injected drugs. At the core of this population are recent PWID (with most definitions of ‘recent’ varying from one to twelve months) who may contribute to onwards HCV transmission. The majority of incident HCV
infections occur in this group. At the other end of the spectrum are former PWID, who have ceased injecting and no longer take part in injecting risk behaviours. A large proportion of prevalent HCV infections are found here. However, given the relapsing nature of drug dependency, the ‘recent’ vs. ‘former’ distinction remains very problematic. Finally, among lifetime PWID there is an important population of individuals receiving OST, often referred to as PWID in OST. This is a dynamic and intersecting population of recent and former PWID with on-going opioid dependency and intermittent risk behaviour. Figure 1 illustrates the relationship between different PWID populations.

Understanding definitions of PWID populations is essential to critically evaluate the evidence base and to set future research priorities in this field. However, when referring to these populations, it is important to stress that PWID represent a very heterogeneous group of people, and that defining people by their behaviour only may be valid for academic purposes. Reflections on the power of language are necessary to minimize stigma and discrimination as this field moves forward.

![Figure 1. Relationship between populations of people who inject drugs (A) with estimates of Norwegian population sizes (B). Modified from Grebely et al. 2015 [35].](image)

**2.4 Prevalence of injecting drug use**

Globally, there are an estimated 14 million recent PWID [36] with an estimated 4.5 million recent PWID living in Europe [37]. In Norway, estimates from 2013 suggested that the current population of lifetime PWID counted about 24 000 individuals, of whom 8 000
individuals were recent PWID and 16,000 individuals were former PWID who either temporarily or permanently had ceased IDU [38, 39]. However, the estimated number of recent PWID did not include individuals receiving OST, a population that by the end of 2015 comprised nearly 7,500 individuals [40]. It is widely acknowledged that many OST patients still inject drugs on a regular or occasional basis, but the full extent remains unclear. Self-reported data from Norwegian OST patients have suggested that more than 15% exhibit drug use characterized by dependency [40], while international data have indicated a higher proportion [41]. A plausible estimate of the size of the Norwegian PWID population in which HCV transmission may occur is therefore between 8,000 and 12,000 individuals (Figure 1B).

Encouraging data regarding IDU in Norway has been reported in recent years, with estimated prevalence of injecting declining from 3.0 to 2.4 per 1000 inhabitants between 2008 and 2013 [39]. In Oslo, the incidence of first time injecting significantly decreased from 365 to 164 individuals (63% reduction) between 1985 and 2008 [42]. Extrapolating these estimates to the whole country implies a decreasing incidence from more than 1200 individuals in 2001 to less than 500 individuals in 2012 [personal communication E. J. Amundsen, NIPH].

### 2.5 Prevalence of HCV infection

#### 2.5.1 Global estimates

While the global anti-HCV prevalence in the general population is estimated at 1.6% [27], global antibody prevalence among PWID has been estimated at 67% [16], corresponding to approximately 10 (range 6-15) million anti-HCV positive PWID. In Europe, the recorded midpoint prevalence estimates range from 21% to 91% with approximately half of all countries estimated to have 60% prevalence and above [16]. The total number of anti-HCV positive PWID in Europe is estimated to be 2.7 million, with 2.0 million being chronically infected [37]. In a European systematic review, the estimated viremic prevalence among anti-HCV positive PWID ranged between 53% and 97% with a median of 72% [43].

HCV infection is also common in certain populations of men who have sex with men (MSM). Anti-HCV prevalence is 1-7% among MSM without a history of IDU compared to 25-50% among MSM with a history of IDU, and is higher in MSM with human immunodeficiency virus (HIV) infection (3-39%) than in those without (0-19%) [44-52]. Among HIV-infected MSM registered in a treatment database at Oslo University Hospital
(OUS), 32 of 987 individuals (3%) were anti-HCV positive (personal communication B. M. Bergersen, OUS). Yet, only 22 HCV cases with presumed homosexual acquisition have been notified to the Norwegian Surveillance System for Communicable Diseases (MSIS) [53].

2.5.2 HCV prevalence in the general Norwegian population

There are great uncertainties in the evidence base regarding HCV prevalence in Norway, and population-based data are very limited. A cross-sectional study based on the Oslo Health Study in 2001 [54] that included 11 456 individuals reported anti-HCV prevalence of 0.7% and HCV RNA prevalence of 0.5% in the general adult population. Anti-HCV prevalence was higher among men than among women, highest among men born in 1955 and 1960 (1.5%), and very low among those born before 1950. These results may be underestimates due to a low participation among high-risk individuals. In a study from Northern Norway that included patients tested in primary care in 1998, anti-HCV prevalence was only 0.24% [55]. A study of pregnant women in Eastern Norway reported anti-HCV prevalence of 0.7% [56].

HCV prevalence in Norway can be estimated based on data from MSIS [53]. HCV infection has been subject to mandatory notification since 1990, but notification criteria have changed (Figure 2). Between 1992-2007, only cases of acute HCV infection were registered, while all cases of acute or chronic HCV infection were registered between 1990-1992 and 2008-2015. From 2016, only cases of chronic infection have been registered. Consequently, MSIS cannot discriminate between chronic infection and acute infection with spontaneous clearance.

![Figure 2](image-url)  
*Figure 2. Annual HCV notifications to the Norwegian Surveillance System for Communicable Diseases.*
By March 2017, a total of 20,000 individuals were notified to MSIS with acute or chronic HCV infection. Annual notifications decreased from 3314 cases in 2008 (peak due to a catch-up effect following new routines) to 771 cases in 2016 (chronic infection only). Table 1 shows the estimated number of individuals currently living with chronic HCV infection in Norway. These estimates are indeed uncertain and subject to several assumptions:

- **The number of un-notified HCV cases is not known.** Un-notified cases include both undiagnosed cases and diagnosed cases that have not been notified to MSIS. Study I demonstrated that 43% of all OST patients who received HCV treatment between 2004 and 2013 were not notified, but this proportion decreased to 25% in the final years of the study (Section 10.1.3). While this may infer the proportion of diagnosed cases that remain un-notified, the proportion of undiagnosed cases in Norway is not known. The estimated diagnosed proportion in Sweden is high (80-85%), but lower in Denmark (60%) [23, 57]. As the proportion of un-notified cases will strongly influence the prevalence estimate, the figures in Table 1 are presented according to three scenarios (20%, 30% and 40%).

- **90% of individuals are still alive.** In Sweden, 20% of individuals notified between 1990 and 2010 are diseased [personal communication A. S. Duberg, Örebro University], increasing to 26% among those notified 1990-2015 [58]. In Norway, the majority of notifications are of more recent date, with only 25% of notifications dating prior to 2008. Furthermore, Norwegian data suggest lower mortality; Study I showed that 6% of OST patients notified to MSIS between 2004 and 2013 were diseased (Section 10.1.1).

- **80% of notified cases represent chronic HCV infection.** This estimate is slightly higher than most reported chronicity rates, but it is reasonable to assume that chronic infection has been subject to notification more often than acute infection.

- **7000 individuals have been successfully treated for chronic HCV infection.** This is based on calculations presented in detail later (Section 5.4)

- **80% of HCV infections are attributable to IDU.** This estimate is consistent with data from other high-income countries. Of 730 cases notified to MSIS in 2015 where route of transmission was specified, IDU was the suspected source in 86% [59]. However, about 40% of all notified cases had uncertain route of transmission and in this group, IDU must be assumed to be lower due to a high proportion of immigrants. Among 250 individuals who received DAA treatment at Akershus University Hospital (AHUS) between 2014 and 2016, 25% were immigrants from Pakistan and other endemic countries [data on file].
The resulting HCV prevalence estimates shown in Table 1 (11 000 – 17 000 individuals) are slightly lower than previous figures from 2014, calculating the prevalence of chronic HCV infection in the general Norwegian population between 14 488 and 23 412 individuals [60]. This most likely reflects the fact that in the past few years, the number of successfully treated individuals has exceeded the incidence of new HCV infections (Section 11.4.1; Figure 13).

Table 1. Estimated HCV prevalence in the general Norwegian population based on data from the Norwegian Surveillance System for Communicable Diseases.

<table>
<thead>
<tr>
<th>Proportion of un-notified cases*</th>
<th>20%</th>
<th>30%</th>
<th>40%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Notified cases</td>
<td>20 000</td>
<td>20 000</td>
<td>20 000</td>
</tr>
<tr>
<td>Adjusted cases*</td>
<td>25 000</td>
<td>28 571</td>
<td>33 333</td>
</tr>
<tr>
<td>Still alive (90%)</td>
<td>22 500</td>
<td>25 714</td>
<td>30 000</td>
</tr>
<tr>
<td>Chronic infection (80%)</td>
<td>18 000</td>
<td>20 571</td>
<td>24 000</td>
</tr>
<tr>
<td>Remaining cases (~7000 successful treatments)</td>
<td>11 000</td>
<td>13 571</td>
<td>17 000</td>
</tr>
<tr>
<td>Cases attributable to injecting drug use (80%)</td>
<td>8 800</td>
<td>10 857</td>
<td>13 600</td>
</tr>
</tbody>
</table>

2.5.3 HCV prevalence among PWID in Norway

HCV prevalence estimates in PWID populations in Norway have been reported in several settings. In a cohort of 635 PWID admitted for residential drug treatment in 1970-1984, antibody prevalence was 84% and viremic prevalence was 53% [15]. HCV testing among 327 users of the needle and syringe exchange in downtown Oslo in 2002 revealed 81% antibody prevalence and 51% viremic prevalence, with 60% viremic prevalence among those who had injected for 5 years or more [61]. Based on results from annual testing activity in this setting, HCV prevalence among recent PWID has been stable during the last decade with 79% anti-HCV prevalence and 46% HCV RNA prevalence reported in 2015 [62]. In 2015, testing was expanded to also include Bergen, showing a slightly higher HCV RNA prevalence of 51% among 121 individuals tested at a low-threshold centre in Bergen [62].

In a probably more selected population of recent PWID who underwent HCV screening at a low-threshold HCV clinic in Oslo between 2013 and 2016 (n=309), anti-HCV prevalence was 89% and HCV RNA prevalence was 69% [63] [data on file]. There is, however, less
accurate data on HCV prevalence in the Norwegian OST population. Here, anti-HCV prevalence has recently been reported as low as 52% [40], but due to low testing activity in some regions and the voluntary nature of testing, these figures are probably substantial underestimates subject to selection bias.

Given a population size of 24,000 lifetime PWID (Figure 1B) and 50% HCV RNA prevalence across all PWID populations, 12,000 individuals may have chronic HCV infection attributable to IDU in Norway. However, many individuals, particularly former PWID, have been successfully treated in recent years. Consequently, this rough approximation is largely in accordance with estimates presented in Table 1 and also consistent with recent modelling estimating that approximately 3700 recent PWID and 5000 former PWID were living with HCV infection in 2013 [30]. Figure 3 consolidates available data sources, showing a plausible distribution of Norwegian HCV patients based on a median estimate of 13,500 individuals living with chronic HCV infection and 80% of cases attributable to IDU.

![Figure 3. Estimated distribution of patients living with chronic HCV infection in Norway (n=13,500).](image)

### 2.6 Incidence of HCV infection

Data on HCV incidence are generally much more scarce than data on prevalence. No pooled global incidence estimate among PWID has been reported, but a number of studies have reported incidence rates in selected PWID populations. A systematic review from 2014, comprising data from nine European countries [43], showed that incidence of primary HCV
infection was highly variable and not easily comparable, ranging from 6.8/100 person-years (PY) in the Netherlands to 38/100 PY in Sweden. The median incidence from 27 studies of lifetime PWID was 13/100 PY, while the median incidence from 11 studies only including recent PWID was 26/100 PY. A review and meta-analysis of HCV in the prison setting found a summary incidence rate of 16.4/100 PY among prisoners with a history of IDU [64].

Unfortunately, no accurate data on HCV incidence are available from Norway, neither in the general population nor in PWID populations. Due to the asymptomatic nature of primary infection as well as low diagnosis and notification rates, no reliable incidence measures can be provided from MSIS. In Sweden, new HCV notifications have been stable at a mean of 2100 anti-HCV positive cases per year since 2007, corresponding to an incidence estimate of approximately 20/100 000 inhabitants [65, 66]. Extrapolating this estimate to the Norwegian population would imply 1100 new cases per year. However, as new notifications include both recent and older cases, incidence is probably lower than new notifications implies. Modelling has estimated a gradual increase in HCV incidence among PWID from the onset of the Norwegian IDU epidemic in 1973, peaking at 780 cases in 2000 and decreasing to 395 cases in 2013 [30]. This decrease could probably be attributed to a decrease in the incidence of IDU and an increase in harm reduction coverage during the same period. According to MSIS, 2109 of 17569 (12%) notified HCV cases (approximately 200 new cases annually in recent years) were acquired outside the country.

2.7 Risk factors for HCV transmission

Sharing of contaminated needles/syringes is acknowledged to be the main route of HCV acquisition among PWID [18]. HCV can maintain viability in needles and syringes for several weeks [67], but the risk of transmission associated with a sharing event depends on a number of factors, such as the quantity of blood injected and the viral load. Importantly, ancillary injecting equipment (spoons/cookers, filters, and water) may also become contaminated with HCV during the process of preparing and injecting, and sharing of such equipment has been associated with an increased risk of HCV in epidemiological studies [68-70]. While the probability of HCV transmission associated with ancillary injecting equipment probably is less than for needle/syringe sharing, the generally higher prevalence of the former may lead to a higher attributable risk and greater contribution to the proportion of new HCV infections. While there is evidence of declining rates of needle/syringe sharing in some
countries [71-77], it remains common for instance in Eastern Europe [78]. In an annual survey among users of NSP in Oslo, reported needle/syringe sharing in the last four weeks decreased from 16% in 2002 to 11% in 2015 [61, 62]. In the 2015 survey, 27% reported recent sharing of ancillary injecting equipment [62].

High HCV prevalence has also been reported among drug users who do not report injecting practices [79]. Permucosal administration of recreational drugs (e.g. cocaine or amphetamine snorting) with sharing of straws is a conceivable way of transmission in such cases [80, 81]. However, under-reporting of former/sporadic IDU or sexual transmission could be other plausible explanations.

While sexual HCV transmission is very rare among heterosexual couples [82], it is considered the predominant route of transmission among MSM, especially in individuals with HIV infection [49, 83]. High-risk traumatic sexual practices [48, 84-89], but also use of mucosally administered recreational drugs [84, 86, 89-91], have been identified as important behavioural risk factors for HCV transmission among MSM. The advent of ‘chemsex’ (i.e. injecting and non-injecting drug use to enhance sexual experience) might further promote HCV transmission among MSM [92], highlighting the important overlap between PWID and MSM populations. Additionally, HIV and ulcerative sexually transmitted infections are important biological risk factors for permucosal HCV transmission [84-86, 89].

In some low- and middle-income countries, iatrogenic transmission due to unsafe medical injections with unsterilized equipment is still highly relevant [17, 18, 93]. Furthermore, unprofessional tattooing/piercing, acupuncture and sharing of toothbrushes or razors are other documented modes of HCV acquisition [94-98]. The risk of vertical transmission from viremic mother to child during pregnancy and birth is approximately 5% [99, 100].

2.8 Prevention of HCV infection

2.8.1 Primary prevention: Harm reduction interventions

Harm reduction is defined as the policies, programmes, and practices that aim to reduce the harms associated with the use of psychoactive drugs among people who are unable or unwilling to stop [101]. The main harm reduction interventions are considered to be methadone- or buprenorphine-based OST and needle/syringe provision (NSP). Both
interventions can reduce HIV transmission, and there is emerging evidence to support the effectiveness of OST and high-coverage NSP (defined as obtaining one or more sterile needle/syringe for each injection) in reducing HCV transmission among PWID [102, 103]. More recently, studies have demonstrated that the combined impact of OST and high-coverage NSP can produce a greater reduction in HCV incidence than either intervention alone [77, 104-106]. Still, data are conflicting, particularly regarding the effect of NSP, but a global systematic Cochrane review is underway [107].

National, regional and international authorities have endorsed harm reduction interventions for the prevention of HCV [108-111]. On a global level, there is generally poor intervention coverage, with OST coverage estimated at 8 OST recipients per 100 PWID and NSP coverage estimated at 22 sterile needles/syringes per PWID per year. The highest OST coverage is in Western Europe (61 OST recipients per 100 PWID) and the highest NSP coverage is in Australia & New Zealand (202 needles/syringes per PWID per year) [112]. The experience of some countries that have achieved high levels of harm reduction coverage is that they can reduce, but not fully control, HCV transmission among PWID [77, 113]. This may be because high coverage needs to be sustained for decades in order to have an impact. Model projections have shown that, in a scenario of 40% viremic prevalence, reducing HCV prevalence by a third would require more than 60% coverage of both OST and high-coverage NSP for 15 years [114]. Experience from Oslo shows that HCV prevalence among recent PWID has remained unchanged during the last decade, despite high harm reduction coverage in the same period [personal communication R. Rykkvin, NIPH].

The Norwegian OST model was implemented in 1998 and is now operated through regional specialized centres. Initially, the program had a high threshold for admission [115], but new national guidelines from 2010 [116] stated opioid dependency as the only absolute criterion and integrated OST into specialist health care as part of a comprehensive treatment and rehabilitation process. While general practitioners can only operate in strict collaboration with specialised drug treatment centres, they prescribe the medication for the majority of clients. The Norwegian OST population has increased steadily and by the end of 2015, nearly 7500 individuals were receiving OST, of whom 40% were receiving methadone and about 57% received a buprenorphine/naloxone combination [40]. There is now a tendency of declining growth with decreases being observed within some regions. Still, the Norwegian
OST population is considered stable, with a retention rate as high as 90% [40]. OST coverage among high-risk opioid users in Norway has recently been estimated at 50% [117].

Although OST is available in all regional health authorities, NSP has been implemented only in Oslo and Bergen. In more rural parts of the country, access to sterile needles and syringes may therefore depend on the users’ ability and willingness to use to the local pharmacy. In 2005, a drug injecting room was established, to great controversy, as a harm reduction measure for PWID in Oslo. A tendency of declining use of this facility has been observed in recent years, possibly reflecting the reported decrease in the incidence of IDU. Between 2013 and 2016, annual supervised injections decreased from 36 138 to 33 140 and registered users decreased from 1339 to 861 individuals [personal communication Ø. Backe, City of Oslo]. As this accounts for a low proportion of the total 1.4 million needles/syringes distributed to 113 000 individual users by NSP in Oslo in 2016 [personal communication K. Hanoa, City of Oslo], the significance of this facility remains uncertain.

2.8.2 Treatment-as-prevention

Although primary prevention through a combination of OST and high-coverage NSP can reduce HCV transmission and avert new HCV infections [104, 105, 114], it is now increasingly acknowledged that substantial reductions in HCV prevalence are unlikely to be achieved without scaling up HCV treatment among PWID. The current availability of highly effective DAA treatment has stimulated a discussion on treatment-as-prevention and its potential for HCV elimination [118]. This perspective is included in the current WHO strategy on viral hepatitis, which aims at 90% reduction of new infections and 65% reduction in mortality by 2030 [119].

In this context, a brief review of the principles of disease elimination may be useful. Twenty years ago, the following hierarchy of public health efforts dealing with infectious diseases was proposed [120]: Control is defined as the reduction of incidence to locally acceptable levels (e.g. diarrhoeal infections); elimination is defined as the reduction to zero incidence in a defined geographical area (e.g. measles, poliomyelitis); eradication is defined as a permanent reduction to zero incidence worldwide (e.g. smallpox); while extinction refers to when an infectious agent no longer exists (e.g. none). In contrast to eradication, continued
interventions to prevent re-establishment of transmission are required in order to sustain control or elimination.

The impact of HCV treatment among PWID is driven by the potential prevention benefit of treating individuals who contribute to onwards HCV transmission. The evidence for this hypothesis derives from theoretical studies based on dynamic transmission models largely calibrated to IFN-based treatment in high-income settings [121-135]. Such models deterministically predict future HCV incidence and prevalence using a compartmental (Markov) model with transitional probabilities, and typically stratify PWID according to HCV infection status, treatment status and OST/NSP status. The dynamic element denotes that susceptible PWID can become infected at a rate proportional to the background viremic prevalence, which decreases as HCV treatment increases. Because changes in prevalence are directly linked to incidence, these models account for both the risk of reinfection and the reduction of transmission risk through averting future infections. Transmission risk is also dependent on risk behaviours, which can be modelled as individual OST/NSP status. However, in model projections the likelihood of reinfection is the same as for primary infection, meaning that successfully treated PWID and uninfected PWID are equally susceptible to HCV infection, independent of any behavioural change as a result of treatment or potential reduced risk due to partial immunity.

There is strong theoretical evidence from dynamic models that scaled-up DAA treatment in combination with high coverage OST/NSP can reduce viremic prevalence and transmission among PWID within 10-15 years, particularly in settings with HCV RNA prevalence below 40% [130, 132, 134]. For instance, substantial reductions in HCV RNA prevalence among PWID have been projected in the United Kingdom and France by switching to DAAs and scaling-up treatment rates [134]. Further, given the potential prevention benefits, both IFN-based and DAA treatment among PWID is shown to be cost-effective [136-139]. A recent economic model demonstrated that treating active PWID with mild and moderate fibrosis was more cost-effective than treating other patient groups with no ongoing transmission risk [140]. Although prioritising people with more severe disease will have an immediate impact on ESLD and HCC, it is unlikely to have any impact on HCV transmission [109, 110]. Another cost-effectiveness model based on Australian epidemiological data concluded that achieving the WHO elimination targets through treatment scale-up is likely to be cost-effective, and that reducing incidence should be a key priority [136].
Despite the availability of high quality theoretical data, there are to date no empirical data supporting the prevention benefit hypothesis. However, data from two clinical trials evaluating treatment-as-prevention are emerging from Australia. The SToP-C study (ClinicalTrials.gov: NCT02064049) evaluates whether a rapid scale-up of DAA treatment can lead to reductions in incidence and prevalence of HCV infection in prisons in New South Wales. The TAP Study (ClinicalTrials.gov: NCT02363517) evaluates whether treatment-as-prevention among PWID in the community through a network-based ‘bring a friend’ approach will lead to reductions in HCV transmission within the injecting network [133]. Important empirical data is also expected to emerge from large-scale elimination programs implemented in Australia, Iceland and Georgia.

### 2.8.3 HCV vaccine development

Prophylactic HCV vaccination for high-risk populations could be another key to control the HCV epidemic, as it potentially would prevent both HCV transmission and liver disease progression. Challenges to vaccine development have been significant due to the marked genetic diversity of HCV, the numerous ways the virus evades the immune response, the lack of immunologically competent model systems and limited culture capacity [141, 142]. Practical barriers to testing a potential vaccine among PWID have also been substantial [143], but results from the first randomized controlled trial (RCT) aimed at preventing chronic HCV infection though vaccination of young HCV-uninfected PWID in San Francisco and Baltimore are highly anticipated (VIP: Vaccine Is Prevention; ClinicalTrials.gov: NCT01436357). In this study, potent T-cell inductors (AdCh3NSmut1 and MVA-NSmut) are administered in two injections at baseline and after 8 weeks [144]. The specific aims are to evaluate safety, HCV-specific immune responses, and the efficacy of preventing chronic HCV infection.
3 Natural history

3.1 Fibrosis progression and liver disease complications

Following HCV exposure, 20-40% spontaneously clear the infection [145], but these estimates are hampered by the often asymptomatic or unspecific onset of acute HCV infection. In a recent meta-analysis of 31 studies of individuals with acute HCV, the mean rate of spontaneous clearance was 26% [146]. Nevertheless, the majority of exposed individuals develop chronic hepatitis with succeeding low-grade inflammation and gradual accumulation of fibrous tissue in the liver. The time from HCV exposure to the establishment of liver cirrhosis remains controversial, but most studies conclude that 10-20% of chronically infected adults develop cirrhosis within 20 years [147, 148]. However, the rate of fibrosis progression is highly variable, much depending on the presence of 1) host factors (male gender, high age at exposure, liver steatosis/steatohepatitis, obesity/metabolic syndrome, type 2 diabetes mellitus/insulin resistance, co-infections), 2) viral factors (genotype 3), or 3) environmental factors (heavy alcohol consumption, tobacco smoking, cannabis use) associated with a more rapid disease progression [147-150].

HCV-related morbidity and mortality can largely be attributed to the development of liver cirrhosis and subsequent complications, which typically arise on the basis of either 1) portal hypertension and circulatory changes (variceal haemorrhage, ascites, hepatorenal syndrome, hepatic encephalopathy, cirrhotic cardiomyopathy), 2) loss of functional liver tissue (disturbed detoxification, disturbed energy metabolism, reduced synthetic function, immunological failure), or 3) carcinogenesis (hepatocellular carcinoma) [151, 152]. Liver cirrhosis can remain a stable condition without complications (i.e. compensated cirrhosis) for several years until liver-related events (i.e. decompensated cirrhosis) occur. Hepatic decompensation is defined as the onset of ascites, variceal bleeding, encephalopathy, hepatorenal syndrome or jaundice.

Among untreated individuals with established HCV-related cirrhosis, the risk of hepatic decompensation is approximately 5% per year [153-155] and the risk of HCC is 2-5% per year [156-159]. Although the incidence of liver-related events in cirrhotic patients decreases following SVR, it still remains significant [160-163] and individuals with decompensated
cirrhosis at baseline may not experience improvements in liver function despite successful HCV treatment [164-166].

In decompensated cirrhosis, prognosis is severe without a liver transplant and mortality can often be attributed to bacterial infections/septicaemia [167]. When symptomatic HCC is present, prognosis is poor with only few months mean survival [168]. HCC surveillance with ultrasound examination every six months improves detection of early stage HCC eligible for curative treatment, but the effect on disease-specific mortality and the cost-benefit of surveillance programs remains controversial [169, 170]. Notably, no RCT has to date confirmed the effect of HCC surveillance in those with HCV-related cirrhosis.

3.2 Liver disease staging

Stage of liver fibrosis can be assessed invasively, with liver biopsy being the traditional gold standard. The most widely used histological scoring system is METAVIR [171-173], which grades necro-inflammatory activity on a four-point scale (A0 to A3) and stages fibrosis on a five-point scale (F0, no fibrosis; F1, mild fibrosis; F2, septal fibrosis; F3, bridging fibrosis; F4, cirrhosis). During the last decade, non-invasive methods employing liver stiffness measurement (LSM) have emerged and largely replaced liver biopsy for staging of viral hepatitis. The most widely used and validated technique is transient elastography (TE), a user-friendly bedside method measuring the velocity of a shear wave propagating through the liver that is directly related to tissue stiffness [174, 175]. The resulting LSMs are expressed in kiloPascals (kPa), ranging from 1.5 to 75 kPa with normal values around 5 kPa and cirrhotic values starting at 12-15 kPa. Because LSMs in the cirrhotic spectrum (12-75 kPa) correlate well with the degree of portal hypertension, the method has major advantages as a prognostic tool for risk stratification and prediction of liver-related events [176, 177].

3.3 Extrahepatic manifestations

There is increasing evidence that HCV infection is associated with a range of extrahepatic manifestations (EHM), theoretically caused either by immune-related mechanisms, HCV induced insulin resistance or viral replication in extrahepatic tissues with subsequent increased cytokine activity [149]. There is a strong causal relationship between HCV and type 2 cryoglobulinemic vasculitis as well as B-cell non-Hodgkin lymphoma, but more than 20 potential EHM have been associated with HCV [178-180]. These EHM include skin
disease (cryovasculitis), renal disease (membranoproliferative glomerulonephritis, membranous nephropathy), immunopathies (Sjögren syndrome, rheumatoid-arthritis like syndrome), malignancies (B-cell lymphoma), cardiovascular disease (atherosclerosis, insulin resistance/type 2 diabetes), and affection of the central nervous system (fatigue, depression, cognitive deficit). However, the relative prevalence, clinical importance and strengths of these associations remain controversial and require further research.

3.4 Natural history of HCV infection among PWID

While the natural history of HCV infection has been extensively studied in general HCV populations, few studies have specifically addressed this among PWID. As a large proportion of PWID populations have been chronically infected for two-three decades or more and given the low historical treatment uptake, many have progressed to advanced fibrosis or cirrhosis. In addition, co-factors for fibrosis progression, including harmful alcohol consumption, overweight/steatosis and HIV co-infection may be more prevalent in this group. However, PWID may have a high competing death risk due to drug related causes (overdose, bacterial infections), suicide, accidents, HIV infection and other medical comorbidities, reducing the burden of disease attributable to HCV in this population [181, 182]. Thus, it is important to understand interactions of risk factors for fibrosis progression, but also the potential impact of competing death risk that may be unique to this population.

In a large meta-analysis of stage-specific fibrosis progression that included 111 studies comprising more than 30 000 individuals with and without a history of IDU [183], the predicted 20- and 30-year cirrhosis probability was 16% and 41%, respectively. Models were specified for different populations; for instance, for a cohort of male PWID with excess alcohol consumption and age at infection of 25 years, the estimated number of years required to progress from HCV exposure to cirrhosis was 35 years with a 20-year cirrhosis probability of 20%. Another meta-analysis [184] included 44 studies representing 6457 individuals who had acquired HCV infection through IDU. The estimated cirrhosis progression rate was 8.1 per 1000 PY, corresponding to a 20-year cirrhosis prevalence of 21%. The most recent systematic review included 21 reports of fibrosis progression among former or recent PWID with chronic HCV infection published between 1990 and 2013 [185]. Here, the pooled incidence rates of cirrhosis, decompensation, and HCC were 6.6, 1.8 and 0.3 per 1000 PY, respectively, leading to an estimated average time from exposure to cirrhosis of 34 years.
Norwegian data has contributed to understanding the relative importance of liver disease among HCV-infected PWID. In a large cohort of HCV RNA positive PWID who were admitted for residential drug treatment in 1970-1984 and prospectively followed for 35 years, liver fibrosis was assessed among diseased individuals who underwent autopsy. Among those, one third had developed advanced liver fibrosis or cirrhosis 25 years or more after HCV exposure [186]. In the same cohort, liver disease was the most important cause of death among individuals above 50 years of age, but competing death risk due to drug overdoses was prevalent in all age groups [15]. Recent cross-sectional data from a low threshold HCV clinic for PWID in Oslo showed that 20% of HCV RNA positive individuals who underwent on-site TE assessment had LSM > 12,5 kPa indicative of liver cirrhosis [187]. Among individuals above 40 years of age, one-quarter had LSM > 12,5 kPa of whom the majority had LSM > 25 kPa suggestive of established portal hypertension.
4 Treatment

4.1 Recent DAA treatment development

Until 2014, HCV treatment was based on weekly injections with pegylated interferon (IFN) and daily ribavirin (RBV) tablets for 3-12 months, depending on the genotype and on-treatment viral kinetics. Overall, these regimens gave SVR in only 50% and led to frequent and sometimes serious IFN-related adverse effects of psychiatric, immunological and haematological nature [188]. This drastically limited the treatment opportunities for many patients, particularly individuals with psychiatric comorbidities (including drug or alcohol addiction) and advanced liver disease. The recent breakthrough in DAA treatment development has changed the HCV treatment paradigm and led to significant therapeutic optimism [189]. The availability of highly effective and tolerable IFN-free oral DAA combinations now provides unique opportunities for broadened treatment uptake with subsequent reductions in liver disease burden and HCV elimination.

Major advances initially came from the development of the HCV replicon system in 2005 [189]. This tool allowed studies of HCV replication in cell culture, thus accelerating the development and testing of new antiviral drugs. To date, inhibition of HCV replication has focused on three viral targets: the NS3 protease, the NS5A protein, and the NS5B RNA polymerase. Since 2014, an increasing number of new agents have been introduced within these three DAA classes. The drugs differ slightly with regards to efficacy and their barrier to resistance, but generally have very few side effects (Table 2).

Current DAA regimens combine agents from 2-3 different classes and yield SVR rates above 95% in most populations after only 8-12 weeks of treatment [190-198]. However, treatment outcomes are still suboptimal in some groups, particularly for patients with genotype 3 infection and decompensated cirrhosis [164]. Pan-genotypic DAA co-formulations are now being introduced [199, 200]. These simple, once-daily regimens give very high SVR rates across all genotypes without addition of RBV, and may prove ideal for HCV treatment in many PWID populations.
Table 2. Characteristics of different classes of direct-acting antiviral drugs currently approved or under review by the European Medicines Agency.

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Genotype coverage</th>
<th>Efficacy</th>
<th>Barrier to resistance</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protease (NS3) inhibitors</td>
<td>1, 4, 6</td>
<td>+++</td>
<td>++</td>
<td>simprevir, paritaprevir, grazoprevir, voxilaprevir, glecaprevir</td>
</tr>
<tr>
<td>NS5A inhibitors</td>
<td>1-6</td>
<td>+++</td>
<td>+</td>
<td>daclatasvir, ledipasvir, velpatasvir, ombitasvir, elbasvir, pibrentasvir</td>
</tr>
<tr>
<td>NS5B polymerase inhibitors (nucleosides)</td>
<td>1-6</td>
<td>++</td>
<td>+++</td>
<td>sofosbuvir</td>
</tr>
<tr>
<td>NS5B polymerase inhibitors (non-nucleosides)</td>
<td>1</td>
<td>++</td>
<td>+</td>
<td>dasabuvir</td>
</tr>
</tbody>
</table>

4.2 Observational and phase 2/3 outcomes among PWID

Observational studies of IFN-based treatment in mixed populations of lifetime PWID and in selected populations of recent PWID have demonstrated similar SVR rates, treatment adherence and safety as in the general population [201-203]. In a systematic review and meta-analysis of 6 studies carried out among recent PWID [202], pooled SVR was 56% for all genotypes, pooled adherence was 82% and pooled treatment discontinuation was 22%. These results are comparable to outcomes in non-PWID populations in large RCTs of IFN-based treatment [204].

Recently, results from the first international multicentre study of IFN-based treatment for genotype 2 or 3 infection among recent PWID or PWID in OST (ACTIVATE) was reported [205]. Efficacy was high (SVR 84%) among those who based on response-guided therapy received short (14 weeks) treatment, but not satisfactory (SVR 38%) among those who received 24 weeks treatment. Recent IDU at baseline or during treatment was not associated with SVR. These results add to previous evidence [206, 207] suggesting that short IFN-based
treatment still could be an affordable option for younger individuals with genotype 2/3 infection and mild fibrosis, irrespective of ongoing IDU.

Despite compelling evidence of similar outcomes from IFN-based treatment, individuals with recent illicit drug use were systematically excluded from phase 2/3 DAA development trials. However, a small number of individuals on stable OST were included. Post-hoc analyses of these large registration trials [208-210] showed no significant differences in SVR rates in OST patients compared to non-OST patients, and ongoing drug use did not affect treatment continuation, adherence or safety. In the ION 1-3 trials (sofosbuvir/ledipasvir), SVR was achieved in 66 of 70 (94%) OST patients, compared to in 1825 of 1882 (97%) non-OST patients [209]. In the ASTRAL 1-3 trials (sofosbuvir/velpatasvir), SVR was achieved in 49 of 51 (96%) OST patients, compared to in 966 of 984 (98%) non-OST patients [208]. In a pooled analysis of the phase 2/3 trials of treatment with ombitasvir/paritaprevir/ritonavir + dasabuvir, SVR was achieved in 54 of 56 (96%) patients who received OST [210]. Finally, in a small phase 2 study of the same DAA combination in stable OST patients, 37 of 38 (97%) participants achieved SVR [211].

A phase 3 study of grazoprevir/elbasvir for patients with treatment naïve genotype 1/4/6 infection [41] so far stands as the lone example of a DAA registration trial specifically aimed at a PWID population. This international RCT included 301 stable OST patients in 13 countries, with 201 and 100 individuals randomized to an immediate and a deferred treatment group, respectively. Individuals with ongoing IDU were not excluded, but at least 80% adherence to OST appointments was required. Median age was 48 years, 76% were male and 21% had liver cirrhosis. Illicit drugs, except cannabis and benzodiazepines, were detected by urine drug screen in one-third of individuals at baseline, highlighting that high levels of drug use (and probably associated risk behaviours) also occur in ‘stable’ OST populations. In intention-to-treat analysis, SVR was achieved in 92% and 90% in the immediate and deferred treatment groups, respectively. Treatment failure could be attributed to relapse in 10 patients, viral breakthrough in 2 patients, discontinuation in 2 patients, and reinfection in 6 patients. In per-protocol analysis, counting reinfecions as successes and excluding treatment discontinuations, SVR was above 95% in both groups. Treatment adherence was measured using electronic blister packs, and ≥ 95% adherence (0-3 missed doses) was measured in 97% in both groups. Neither SVR nor adherence was affected by on-treatment drug use, irrespective of the type of drug detected. These very encouraging results are in line with
results of this DAA combination in the general population [198], but remains to be confirmed also in more marginalised PWID populations.

Preliminary results from the SIMPLIFY trial (ClinicalTrials.gov: NCT02336139) were very recently presented as a conference abstract [212]. This international open-label study included 103 recent PWID (injected in the previous six months) in seven countries (19 sites) across the ACTIVATE network for pan-genotypic treatment with sofosbuvir/velpatasvir. End of treatment response (ETR) was achieved in 99 of 103 (96%) and SVR was achieved in 97 of 103 (94%) participants. No virologic failures were observed, but four participants were lost to follow-up, one died from drug overdose, and one had virologic relapse/reinfection.

There are several ongoing international trials evaluating DAA treatment among PWID. The D3FEAT trial (ClinicalTrials.gov: NCT02498015) included 87 recent PWID and PWID in OST with genotype 1/4 for treatment with paritaprevir/ombitasvir + dasabuvir. The HERO study (ClinicalTrials.gov: NCT02824640) is a RCT evaluating directly observed sofosbuvir/velpatasvir versus patient navigation (public health workers who offer support and education) that aims to include 1000 recent PWID across 8 cities in the United States.

### 4.3 Real-life DAA treatment outcomes among PWID

The real-world efficacy of DAA treatment in PWID populations remains more uncertain, mainly given concerns of non-adherence and loss to follow-up. However, encouraging real-life data from various PWID populations are currently emerging from numerous settings internationally. Outcomes from sofosbuvir-based treatment in a small cohort of PWID at three OST sites in the Bronx, New York, were presented as a conference abstract [213]. Treatment was provided according to local guidelines, and the model of care was individual for 54%, group-based for 25% and directly observed for 21%. Treatment adherence was monitored with electronic blister packs. The mean age was 53 years, 33% had cirrhosis and 74% had psychiatric comorbidities, predominantly depression. Based on urine toxicology, 59% had used illicit drugs within 6 months prior to treatment. SVR was achieved in 60 of 61 (98%) individuals, and one individual became HCV RNA negative but was subsequently lost to follow-up. Daily time frame adherence (defined as medication popped out of the blister pack within the correct day) was 71-77% across all models of care.
In Vancouver, Canada, DAA treatment outcomes were evaluated in a multi-site program for a marginalised inner-city population in the Downtown Eastside region [214]. This area, reportedly with the poorest postal code in the entire Canada, is home to approximately 13 000 PWID with an estimated HCV RNA prevalence as high as 65%. The program was multidisciplinary with group-based HCV treatment delivered by a general practitioner with support from a specialist in infectious diseases and nurses. Treatment was provided though a publically supported program at no cost to low-income residents with fibrosis stage ≥F2 or though compassionate use programs. Median age was 54 years, one-half had liver cirrhosis, 53% received OST and 88% reported recent IDU. SVR was achieved in 139 of 156 (89%) individuals, three patients had virologic failure and 14 were lost to follow-up.

Good results from DAA treatment were also achieved in another cohort of recent PWID in Vancouver treated within a multidisciplinary program at an academic clinic [215]. The mean age was 52 years, 66% were using heroin and 40% received OST. No serious adverse events or treatment-limiting toxicity were observed. Of 50 patients who completed treatment, 44 (88%) achieved SVR, with all six non-SVR cases due to relapse. DAA treatment outcomes from key studies in different PWID populations are summarized in Figure 4.

**Figure 4.** Direct-acting antiviral treatment outcomes from key studies among people who inject drugs.
Encouraging real-life data are also emerging from a primary care-based low-threshold HCV clinic in downtown Oslo [63]. The clinic was established in 2013 as a joint effort between the City of Oslo and AHUS as an effort to reach a highly marginalised population with ongoing IDU. The clinic is located within the premises of the city’s harm reduction services (which also comprises emergency housing, general health clinic, injection room, outreach program and NSP), and is staffed by a general practitioner and two nurses with support from an infectious diseases specialist. The model of care is characterised by flexible staff, ambulant work and broad use of existing networks within relevant low-threshold services and institutions. The nurses draw blood and operate a mobile TE device, enabling efficient on-site or ambulant HCV diagnosis and DAA treatment. To date, 263 individuals have been diagnosed with chronic HCV infection, 222 have been assessed with TE and 90 have initiated treatment [personal communication K. Ulstein, City of Oslo; data on file]. The mean age was 49 years, 78% were male, 90% had injected during treatment and 76% received OST. ETR has been achieved in 95% (59 of 62) of those due for HCV RNA assessment by May 2017. Treatment failure could be attributed to virologic failure in two patients and relapse in one patient. Post-ETR recurrent viremia (relapse or reinfection) has been observed in two patients.

**4.4 International treatment recommendations**

Initial HCV treatment guidelines by the National Institutes of Health (NIH) in 1997 excluded PWID from consideration for therapy, based on concerns about adherence, safety (i.e. increased susceptibility to IFN-related side effects like depression) and reinfection [216]. Following advocacy and improved evidence demonstrating that IFN-based treatment is safe and effective also in this population, the NIH guidelines were revised in 2002 to encourage HCV treatment for PWID [217]. Recent guidelines from the American Association for the Study of Liver Disease (AASLD)/Infectious Diseases Society of America (IDSA) [218], the European Association for the Study of the Liver (EASL) [219], the International Network for Hepatitis in Substance Users (INHSU) [220] and WHO [221] now all recommend HCV treatment for PWID. Although data on DAA treatment in this population still remains limited, the recent emergence of promising results and the obvious feasibility of simpler and more tolerable regimens have reinforced these guidelines.
Although international treatment priorities traditionally have been based on disease severity, prioritizing those with significant liver fibrosis or severe EHMs, current international guidelines signalize a shift in mentality by also taking transmission risks into account. Current 2016 EASL guidelines [219] state that treatment should be considered without delay in individuals at risk of transmitting HCV, including current PWID and MSM with high-risk sexual practices, and further recognize that the prospect of HCV elimination will require unrestricted access to treatment. Current AASLD/IDSA guidelines [218] state that successful HCV treatment of persons at greatest risk for transmission represents a formidable tool to curb transmission and that scaled-up of treatment in PWID is necessary to positively impact the HCV epidemic globally. AASLD/IDSA guidelines further state that drug abstinence requirements should be abandoned, because they create barriers to treatment and potentially exclude populations that are likely to obtain substantial benefit from therapy. The WHO Global Health Sector Strategy on viral hepatitis 2016-2021 [119] aims at 90% reduction in HCV incidence, 80% of viremic patients treated and 65% reduction in HCV-related mortality by 2030. Achieving these ambitious goals will not only require unrestricted treatment access and improved infrastructures for delivery of care, but also implementation of treatment-as-prevention strategies in groups with high transmission risks.

Until 2017, DAA treatment in Norway was restricted to individuals with significant fibrosis or cirrhosis (F2-F4) or severe EHMs [222]. These restrictions were based on the high DAA pricing per se, and no cost-benefit analysis to evaluate the benefit of treating individuals with mild liver disease or high transmission risk has been performed in the Norwegian setting. However, current Norwegian treatment recommendations [223] acknowledge the transmission perspective and encourage HCV treatment in recent PWID to be considered on an individual basis. From February 2017, fibrosis restrictions were repealed for genotype 1 infection as a result of DAA price competition [222], enabling unrestricted treatment for 40% of the Norwegian HCV population.

While traditional ‘old school’ hepatology to a large degree has focused on individual health and management of liver disease complications, modern ‘new school’ hepatology abandons this paradigm and instead acknowledge HCV infection as a transmittable multi-faceted disease with hepatic, extrahepatic, economic, social and patient reported consequences [149]. This new era of hepatology emphasizes the public health perspective and embraces current opportunities for treatment-as-prevention, HCV elimination and social-hepatology.
5 Treatment uptake

5.1 The HCV care cascade

While the high efficacy of current DAA treatment may have great impact at the individual level, substantial population-level benefits are unlikely to be achieved unless diagnosis and treatment rates are markedly lifted. Significant DAA treatment scale-up will therefore require that individuals unaware of their HCV status are diagnosed, and that viremic individuals are linked to care, assessed for liver disease severity and engaged in treatment. The steps along this HCV care continuum, collectively referred to as the ‘HCV care cascade’ (Figure 5), provide a useful framework to discuss strategies for intervention. At each step of the cascade there is opportunity to intervene by addressing existing barriers at patient-, provider- and system-levels.

![Figure 5. The HCV care cascade.](image)

The development of public health strategies to address the epidemic spread and growing disease burden related to HCV infection requires good epidemiological data and insights from mathematical modelling well anchored in the current evidence base. Two key parameters to inform public health policy are the actual rates of diagnosis and treatment.
Recent country-specific mathematical modelling [23, 24] has shown that the combination of enhanced treatment efficacy, diagnosis and treatment uptake can lead to reversal of the projected increase in liver disease burden in most countries. Many countries will also have the potential for marked reductions in HCV RNA prevalence and achieve HCV elimination over the next two decades.

5.2 Testing, diagnosis and linkage to care

The first step of the HCV care cascade refers to the proportion of infected individuals who are actually diagnosed. Globally, HCV testing and diagnosis remains insufficient [224, 225] and recent estimates suggest that the proportion diagnosed with HCV infection varies from less than 20% in low- or middle-income countries like Egypt, Brazil and Turkey to greater than 80% in Australia and Sweden [226]. While the former countries have more generalized epidemics with lower contributions from PWID populations, many high-income countries with major PWID contributions have been able to implement targeted screening of high-risk populations. Nevertheless, a fundamental problem in PWID populations is still that many individuals remain undiagnosed and therefore unlinked to the further steps of the HCV care continuum.

Detection of HCV infection is impeded by its asymptomatic presentation, but also by the challenges of identifying at-risk populations [227]. While OST patients typically are linked to specialist addiction care, more marginalised PWID populations may be harder to reach within conventional health care systems. Also, some former PWID with a history of only sporadic IDU might consider this as an issue of the past of no current relevance. Targeted screening programs may therefore not have reached these individuals. Innovative strategies are therefore needed in order to improve diagnosis and treatment uptake across different populations.

In a systematic review from 2015, evidence-based interventions to enhance HCV assessment and treatment typically fell into interventions addressing testing and case-finding, linkage to care, treatment initiation, or adherence facilitation [228]. A more recent systematic review and meta-analysis included 41 studies on interventions to optimise the HCV care continuum [229]. Here, clinician reminders in the patient file to prompt HCV testing increased HCV testing rates almost four-fold, while coordinated/integrated mental health, substance use and
HCV treatment services increased both HCV treatment uptake, adherence and SVR compared with conventional HCV care. Established targeted testing strategies include interventions based on education and counselling by health professionals with on-site testing [229-233], risk-based assessment through medical chart reminders [229, 234, 235], birth-cohort screening [234], motivational interviewing [236], and simplified HCV diagnostics using dried-blood-spot (DBS) testing [237-240], and point-of-care (PoC) testing [241-243].

New pan-genotypic DAA treatment allows broad simplification of HCV diagnostics that could benefit vulnerable PWID populations [244]. A pioneering cluster-RCT from the United Kingdom in 2008 provided preliminary evidence supporting that DBS could increase HCV testing [237], and this finding was later reproduced after DBS testing was introduced in specialist addiction care in Scotland [239]. A systematic review of the effect of DBS testing in in drug and alcohol clinics, prisons or NSP services concluded that the introduction of DBS testing increased the number of tests, new diagnoses or both [240]. However, as testing is performed in central laboratories, people are required to come back for a second visit to get their result or undergo further diagnostics. Although PoC tests are available, many of these tests only measure anti-HCV antibodies; however, HCV antigen test and novel PoC polymerase chain reaction (PCR) platforms are now under development [244]. Moving forward, the key will be to have rapid, affordable, and highly sensitive and specific HCV RNA assays enabling final diagnosis in a single visit.

Although simplified HCV testing could be effective also in facilitating linkage to care for PWID [241, 243, 245], non-invasive liver disease assessment represents a particularly interesting strategy in this context [246-248]. The increasing availability of TE has simplified liver disease staging and clinical risk stratification considerably and the method is now considered non-invasive standard of care [175]. Much owing to the rapid and painless procedure, immediate results and availability of a mobile device, this tool could easily be disseminated at different levels of health care. An innovative study from 2009 assessed the influence of TE on HCV screening and management among 300 individuals in a street-based outreach setting [246]. All subjects accepted the procedure and more than one-half of HCV RNA positive individuals were linked to follow-up hepatologist consultation. In a more recent Australian study of a liver health promotion campaign that included 256 PWID [248], all participants received TE assessment, DBS testing and educational material. Overall, 95% reported that TE was acceptable and 60% returned for the following clinical visit.
Models of care

HCV infection disproportionately affects individuals marginalized from conventional specialist health care due to ongoing drug and alcohol use, psychiatric comorbidities, health illiteracy or socioeconomic instability that may complicate care delivery. Alternative models of care that effectively can engage such hard-to-reach populations in treatment are therefore fundamental. Acknowledging the notion that ‘one size does not fit all’, common characteristics of these models include a multidisciplinary approach, individually tailored treatment plans and a high degree of flexibility with acceptance of individual life circumstances [249]. In a meta-analysis of IFN-based treatment for PWID, the involvement of multidisciplinary teams was associated with SVR [203].

The most successful models of HCV care adapted for PWID populations have been built upon already existing infrastructures of health services for PWID. As such, the ideal integrated model covers diagnostics and treatment under the same roof with concurrent access to harm reduction services and other relevant health services for PWID. Multidisciplinary models typically include clinician and nursing staff, drug and alcohol support services, psychiatric services, social work, peer support and options for directly observed therapy. Utilizing these principles, HCV treatment for PWID has been successfully delivered in various clinical settings such as OST clinics [213, 236, 250-259], community-based low-threshold services [63, 214, 215, 260-266], general practice [265, 267, 268], and secondary/tertiary hepatology units [269-271]. However, most evidence derives from small observational studies and few RCTs have been conducted.

Experience from Scotland over the last two decades has demonstrated that successful HCV treatment depends on having effective pathways of care and that the introduction of multidisciplinary models in fact can lead to reduced mortality. A large cohort study that included 3122 HCV-infected individuals evaluated different models that had been successively developed between 1994 and 2014 with increasing use of multidisciplinary networks [272]. During this period, the number who accessed treatment services increased from 26% to 73%, the rate of treatment initiations increased from 2% to 16%, SVR improved from 62% to 77%, and all-cause mortality decreased from 34% to 4.5%. Compared to the initial model, the most recent model of care was independently associated with lower mortality, regardless of age, sex, SVR or HIV co-infection.
5.4 Treatment uptake in the general population

At the population-level, HCV treatment uptake can be defined as the proportion of viremic individuals exposed to treatment. This is often referred to as annual or cumulative treatment rates. International data from the IFN-based era has demonstrated a low and stable treatment uptake in the general population; in 2005, estimates from Europe [273] and the United States [274, 275] suggested a cumulative treatment uptake of 3–4% among all people with chronic HCV infection, with annual treatment rates increasing by 0.5% per year. More recent estimates based on epidemiological data collection and expert opinion input from 16 countries demonstrated a broad range of treatment rates between countries [23]; for instance, estimated annual treatment rates in 2013 was 0.5% in Denmark, 1.1% in Egypt, 1.7% in Australia, 2.8% in Sweden, 3.8% in the United Kingdom, and above 5% in France. From this analysis, socio-economic factors would not appear to be the major driver of treatment uptake. Treatment rates were ten-fold lower in Denmark than in France, and Egypt had the highest total number of treated individuals (65 000 individuals), several fold higher than even France or Germany (10-12 000 individuals).

IFN-based treatment uptake in the general population in Norway can be estimated based on data from the Norwegian Prescription Database (NorPD). In contrast to IFN, RBV has no other treatment indication than HCV infection, and can therefore be used as a proxy for HCV treatment. NorPD was established in 2004, and during the ten final years (2004-2013) of the IFN-based treatment era, a total of 7736 RBV treatments (including in individuals without valid Norwegian identify number) were registered in the database. However, as some individuals received prescriptions over two succeeding years, the actual number of unique individuals treated during this period was 5401 [personal communication I. Odsbu, NorPD]. Figure 6 shows the annual number of registered treatments and the estimated number of treated individuals between 2004 and 2013, the latter corrected by a factor of 0.698 (5401/7736), reflecting the discrepancy between the number of unique individuals and the number of registered treatments. These figures suggest a low and quite stable HCV treatment uptake in the general Norwegian population, ranging from 430 individuals in 2004 to 668 individuals in 2012. Given a stable population of 15 000 individuals with chronic HCV in Norway in this period, this corresponds to annual treatment rates between 2.9% and 4.5%. Prior to 2004, approximately 2000 individuals received HCV treatment in Norway, of whom one-half were treated in clinical trials [276] [data on file].
After the introduction of the first IFN-free DAA regimens in Norway in March 2014, HCV treatments have increased moderately. The number of DAA-based treatments initiated between 2014 and 2016 was approximately 2400 (448, 947 and 1007 in 2014, 2015 and 2016, respectively) [personal communication T. Aanes, Sykehusinnkjøp HF] while only 100-200 IFN-based treatments were initiated in the same period [data on file]. The total number of individuals successfully treated for HCV infection can be inferred by incorporating historical average SVR rates to these data. Assuming SVR rates of 50% SVR prior to 2004, 70% between 2004-2013 and 90% between 2014-2016, a total of approximately 7000 individuals (~1000 prior to 2004, ~3780 between 2004-2013 and ~2300 between 2014-2016) must be assumed to have achieved SVR in Norway (Figure 7).
5.5 Treatment uptake among PWID

Despite reports of increasing treatment rates in the general population, treatment uptake probably remains low in most PWID populations. A recent report from the European Monitoring Centre for Drugs and Drug Addiction [277] updated a previous systematic review of treatment outcomes [202] to also include data on treatment uptake. Three cohort studies [264, 266, 268] reported data on treatment uptake among a total of 755 HCV RNA positive lifetime PWID, with an unknown proportion of recent PWID, quoting annual treatment rates of 6.6%, 8.5% and 7.1% respectively. These figures are actually higher than most current population-based estimates from the general population, but given that the study participants were involved in well-established multidisciplinary treatment programs, these studies are likely to overestimate the true treatment uptake among PWID.

Although successful flow of patients through the HCV care cascade has been documented in selected small cohorts of PWID, population-level data on treatment uptake among PWID are scarce. However, low IFN-based treatment rates have been reported in large community-based cohorts in the United States, Australia and Canada. In a cohort of more than 1500 HCV-infected PWID in Baltimore, Maryland, only one individual had received HCV treatment in 1998 [278]. A follow-up study from 2008 [279] evaluated treatment uptake and treatment barriers in the same cohort following enhanced counselling and testing efforts. Of 597 included HCV-infected individuals, 86 (21%) had discussed treatment with a provider and 26 (4%) had initiated treatment. The main treatment barrier in this cohort was lack of the initial referral for treatment evaluation. Individuals who had not discussed treatment with a provider were more likely to report current drug or alcohol use or depression, and were less likely to be knowledgeable of HCV, have health insurance or had a recent non-HCV related outpatient visit.

Self-reported treatment uptake was evaluated in a large cohort of more than 26 000 PWID attending Australian NSPs between 1999 and 2011 [280]. Among 12 000 anti-HCV positive individuals, the proportion reporting current treatment (annual treatment rates) increased from 1.1% to 2.1%, and the proportion reporting ever having received HCV treatment (cumulative treatment rates) increased from 3.4% to 8.6% between 1999 and 2011. Predictors of increased HCV treatment uptake in this cohort included male gender, homosexual identity, older age and history of incarceration.
Canadian data from the CHASE cohort, a cohort of inner city residents consisting mainly of drug users from Vancouver, demonstrated 1% cumulative treatment uptake between 2000 and 2004 with 0.3% annual rates [281]. Serologic HCV status and prescriptions of IFN and RBV were obtained through linkage to provincial data registries. Follow-up data of 1257 anti-HCV positive individuals from this cohort [282] showed that cumulative treatment uptake had increased to 6% (77 of 1257) between 1998 and 2010. There was an increase in treatment rates from 0.2% in 2003 to 1.6% in 2009, but no significant difference between annual treatment rates in the 2003–2006 period (0.65%) compared to the 2007-2009 period (1.04%). In adjusted analysis, aboriginal ethnicity and recent non-injecting crack cocaine use were associated with decreased odds of receiving HCV treatment.

Based on quantitative and qualitative data from various treatment settings and models of care [249, 250, 252, 261, 264, 266, 268, 279-293], barriers to HCV care among PWID typically fall into obstacles either at patient-, provider- or system-levels (Table 3). Historically, the toxicity of IFN-based treatment has probably been the most important barrier in these populations. Moving into the IFN-free treatment era will now allow focusing on remaining system-level barriers related to drug pricing and health care delivery. However, to the best of our knowledge, population-based DAA treatment uptake among PWID remains to be documented.

Table 3. Barriers to HCV treatment among people who inject drugs at patient-, provider- and system-levels.

<table>
<thead>
<tr>
<th>Patient-level</th>
<th>Provider-level</th>
<th>System-level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of knowledge</td>
<td>Lack of knowledge</td>
<td>Lack of models of care</td>
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<tr>
<td>Lack of symptoms</td>
<td>Concerns of side effects</td>
<td>Lack of infrastructures</td>
</tr>
<tr>
<td>Experienced stigma</td>
<td>Concerns of non-adherence</td>
<td>Lack of strategy plans</td>
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<tr>
<td>Mistrust in health care</td>
<td>Concerns of reinfection</td>
<td>High DAA pricing</td>
</tr>
<tr>
<td>Fear of side effects</td>
<td>Concerns of viral resistance</td>
<td>Fibrosis restrictions</td>
</tr>
<tr>
<td>Psychiatric comorbidities</td>
<td>Competing death risk</td>
<td>Drug use restrictions</td>
</tr>
<tr>
<td>Ongoing substance use</td>
<td>Reproduced stigma</td>
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<tr>
<td>Socioeconomic instability</td>
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</table>
5.6 Treatment uptake among PWID in Norway

In Norway, HCV treatment has traditionally been delivered by hospital-based infectious diseases or gastroenterology outpatient clinics, and has not been integrated in specialist addiction care or primary care settings. Although hospital-based clinics have been largely nurse-driven, the model has rarely allowed the nurses to perform ambulant work. In the OST setting, HCV testing activity has been low and routines for specialist referral have not been systematically implemented [294]. This probably reflects traditional treatment restrictions (national guidelines until recently recommended at least 6 months of abstinence from IDU before consideration for treatment) and a common reluctance to provide potentially toxic IFN-based treatment even for ‘stable’ OST patients. Furthermore, the majority of OST in Norway are prescribed by general practitioners. Thus, implementing new guidelines on HCV testing and treatment may be challenging.

Data on HCV treatment uptake among PWID in Norway is limited and population-level data is lacking. A retrospective study examined treatment uptake and outcomes among patients referred to an outpatient clinic at a tertiary hospital in Bergen between 2007 and 2010 [295]. Among 249 HCV RNA positive individuals, of whom 85% were lifetime PWID, cumulative treatment uptake was 47%. SVR was associated with young age, low fibrosis stage, and good patient attendance. In a cohort study of 245 HCV RNA positive PWID who previously had been admitted for residential drug dependency treatment, cumulative treatment uptake was 19% during a 16 years observation period between 1997-2012 [276].

With the introduction of efficient and tolerable DAAs there is now increasing interest in Norway to provide HCV treatment for recent PWID. As described earlier (section 4.3), a low threshold HCV clinic was established in Oslo in 2013 as an effort to reach the most marginalised PWID populations. Preliminary results [data on file] indicate that this model of care is feasible (Figure 8). By early March 2017 (prior to new national treatment guidelines), the clinic had tested 392 individuals, of whom 253 (65%) had chronic HCV infection. 217 of 253 (86%) HCV RNA positive individuals were subsequently assessed with TE, and of those, 101 (47%) had LSM >7 kPa. Of 101 treatment eligible patients according to Norwegian guidelines at the time, 85 (84%) had initiated treatment. Linkage to care was high, and the relatively low overall treatment uptake of 34% (85 of 253) could largely be attributed to national fibrosis restrictions, which contributed to the highest step in the care cascade. From
March 2017, unrestricted treatment for HCV genotype 1 infection was commenced in Norway, potentially eliminating this treatment barrier for 40% of the HCV population. To date, very few patients have lost contact with the clinic and a substantial number are waiting to initiate treatment. It remains to be seen how this change of treatment guidelines will influence the care cascade.

Figure 8. The HCV care cascade among people who inject drugs attending a primary care-based low-threshold treatment setting in Oslo.
6 Reinfection

6.1 The lack of protective immunity

As neither spontaneous nor treatment-induced clearance of the virus confers immunity, ongoing risk behaviours can lead to HCV reinfection. The presumed high risk of reinfection following successful treatment has been reported as a major provider-level treatment barrier and has fuelled debates concerning rational prioritizing and approaches to DAA treatment in high-risk groups. The potential impact of reinfection is of considerable clinical and public health interest as it could compromise both individual- and population-level treatment benefits [118, 296-299]. High levels of reinfection might challenge the cost/benefit of expensive DAAs and would also question the efficacy of existing HCV prevention strategies.

HCV reinfection after spontaneous clearance of the virus has been observed in chimpanzees [300, 301] and in humans [302-315]. These studies have provided insight into factors important for protection against persistent infection by demonstrating evidence of an augmented HCV-specific immune response following reinfection compared to after primary infection [316]. For instance, reinfection after spontaneous clearance has been associated with strong HCV-specific T-cell responses [300, 301], lower peak viral loads and shorter duration of viremia than in primary infection [308, 312, 315], and high levels of re-clearance (i.e. spontaneous clearance of reinfection) with proportions between 30-100% reported [311, 312, 317]. These observations have suggested that some immunological control may develop after repeated exposure to the virus, but only when exposed to homologous HCV strains. Thus, one can at best hope for an acquired partial, but no protective, immunity against reinfection in clinical practice.

The lack of protective immunity has also been evident in efforts to develop HCV vaccines, which so far have been complicated by the great genetic diversity of HCV, complex immunological responses to the virus, and the limited availability of animal models and at-risk cohorts [141, 142]. However, results from the first HCV vaccine trial among PWID are underway (VIP: Vaccine Is Prevention; ClinicalTrials.gov: NCT01436357).
6.2 Overview of reinfection incidence estimates

Reinfection after successful IFN-based treatment has over the last 10-15 years been documented in several studies in populations of former and recent PWID [260, 315, 318-325], prisoners [326, 327] and MSM [313, 314, 328-331]. Also, one study [41] has evaluated reinfection following DAA treatment among PWID in OST. Tables 4 and 5 summarize study populations, designs and reported reinfection incidence estimates from these studies.

Table 4. Overview of studies evaluating HCV reinfection after successful treatment.

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Design</th>
<th>Population</th>
<th>HIV</th>
<th>OST</th>
<th>IDU at baseline</th>
<th>Method</th>
<th>Testing intervals, yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalgard et al 2002</td>
<td>Norway</td>
<td>Retrospective</td>
<td>Former PWID</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>Genotyping</td>
<td>1-7</td>
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<tr>
<td></td>
<td></td>
<td>follow-up</td>
<td></td>
<td></td>
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<td></td>
<td>Risk factors</td>
<td></td>
</tr>
<tr>
<td>Backmund et al 2004</td>
<td>Germany</td>
<td>Prospective</td>
<td>Former and recent PWID</td>
<td>NR</td>
<td>39%</td>
<td>NR</td>
<td>Genotyping</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Risk factors</td>
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</tr>
<tr>
<td>Currie et al 2008</td>
<td>United States</td>
<td>Prospective</td>
<td>Former and recent PWID</td>
<td>56%</td>
<td>NR</td>
<td>0%</td>
<td>HCV RNA</td>
<td>0.5</td>
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<tr>
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<td>cohort</td>
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<td></td>
<td>Risk factors</td>
<td></td>
</tr>
<tr>
<td>Grebely et al 2010</td>
<td>Canada</td>
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<td>Former and recent PWID</td>
<td>6%</td>
<td>43%</td>
<td>54%</td>
<td>Genotyping</td>
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</tr>
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<td></td>
</tr>
<tr>
<td>Grady et al 2012</td>
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<td>Recent PWID</td>
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<td>93%</td>
<td>100%</td>
<td>Sequencing</td>
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<td>Risk factors</td>
<td></td>
</tr>
<tr>
<td>Grebely et al 2012</td>
<td>Australia</td>
<td>Prospective</td>
<td>Recent HCV</td>
<td>33%</td>
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<td>35%</td>
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<td></td>
<td></td>
<td></td>
<td>Risk factors</td>
<td></td>
</tr>
<tr>
<td>Hilsden et al 2013</td>
<td>Canada</td>
<td>Prospective/</td>
<td>Recent PWID</td>
<td>0%</td>
<td>27%</td>
<td>85%</td>
<td>HCV RNA</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Risk factors</td>
<td></td>
</tr>
<tr>
<td>Pineda et al 2015</td>
<td>Spain</td>
<td>Retrospective</td>
<td>Former PWID</td>
<td>100%</td>
<td>24%</td>
<td>NR</td>
<td>Sequencing</td>
<td>0.5</td>
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<td></td>
<td></td>
<td></td>
<td>Risk factors</td>
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<tr>
<td>Weir et al 2016</td>
<td>Scotland</td>
<td>Retrospective</td>
<td>Former and recent PWID</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Genotyping</td>
<td>NR</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Dore et al. 2016</td>
<td>Internat.</td>
<td>RCT</td>
<td>PWID in OST</td>
<td>7%</td>
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<td>NR</td>
<td>Sequencing</td>
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<td>Marco et al 2013</td>
<td>Spain</td>
<td>Prospective-retropective</td>
<td>Prisoners</td>
<td>15%</td>
<td>100%</td>
<td>20%</td>
<td>Genotyping</td>
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<tr>
<td>Lambers et al 2011</td>
<td>Netherlands</td>
<td>Prospective-retropective</td>
<td>MSM</td>
<td>100%</td>
<td>NA</td>
<td>NR</td>
<td>Sequencing</td>
<td>0.25</td>
</tr>
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<td></td>
<td>Risk factors</td>
<td></td>
</tr>
<tr>
<td>Martin et al 2013</td>
<td>United Kingdom</td>
<td>Retrospective</td>
<td>MSM</td>
<td>100%</td>
<td>NA</td>
<td>NR</td>
<td>HCV RNA</td>
<td>NR</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>Risk factors</td>
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<tr>
<td>Vanhommervig et al</td>
<td>Netherlands</td>
<td>Retrospective</td>
<td>MSM</td>
<td>100%</td>
<td>NA</td>
<td>NR</td>
<td>Sequencing</td>
<td>0.5</td>
</tr>
</tbody>
</table>

PWID, people who inject drugs; MSM, men who have sex with men; OST, opioid substitution treatment; IDU, injecting drug use; RCT, randomized controlled trial; NR, not reported; NA, not applicable
Reinfection incidence varies across study populations and most estimates are hampered with uncertainty due to small sample sizes and methodological problems. Most reported rates among PWID are below 5/100 PY, but are typically higher in subpopulations with ongoing IDU and may exceed 10/100 PY among HIV-infected MSM. There are, however, a number of considerations to be made when interpreting these incidence rates. Variations and uncertainties of reported estimates reflect three factors: 1) inter- and intra-study heterogeneity of study populations, 2) variations in sample sizes and study designs, and 3) virological methods. Collectively, these aspects have made generalizability and comparisons between studies challenging.

### Table 5. Overview of reinfection incidence estimates (per 100 person-years) and relevant background data.

<table>
<thead>
<tr>
<th>Study</th>
<th>SVR, n</th>
<th>FU, mean</th>
<th>PYFU (total)</th>
<th>PYFU (IDU post-SVR)</th>
<th>Events, n</th>
<th>Incidence (overall)</th>
<th>Incidence (IDU post-SVR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalgard et al 2002 [318]</td>
<td>27</td>
<td>5.4</td>
<td>118</td>
<td>40</td>
<td>1</td>
<td>0.8</td>
<td>2.5</td>
</tr>
<tr>
<td>Backmund et al 2004 [319]</td>
<td>18</td>
<td>2.8</td>
<td>51</td>
<td>24</td>
<td>2</td>
<td>3.9</td>
<td>8.4</td>
</tr>
<tr>
<td>Currie et al 2008 [320]</td>
<td>9</td>
<td>3.6</td>
<td>38</td>
<td>3.5</td>
<td>1</td>
<td>0.6</td>
<td>1.9</td>
</tr>
<tr>
<td>Grebely et al 2010 [321]</td>
<td>35</td>
<td>2.0</td>
<td>63</td>
<td>38</td>
<td>2</td>
<td>3.2</td>
<td>5.3</td>
</tr>
<tr>
<td>Grady et al 2012 [322]</td>
<td>42</td>
<td>2.5</td>
<td>132</td>
<td>32</td>
<td>1</td>
<td>0.8</td>
<td>3.4</td>
</tr>
<tr>
<td>Grebely et al 2012 [315]</td>
<td>67</td>
<td>1.1</td>
<td>140</td>
<td>56</td>
<td>5</td>
<td>12.3</td>
<td>7.3</td>
</tr>
<tr>
<td>Hilsden et al 2013 [260]</td>
<td>23</td>
<td>1.8</td>
<td>36</td>
<td>NR</td>
<td>1</td>
<td>2.8</td>
<td>NR</td>
</tr>
<tr>
<td>Pineda et al 2015 [323]</td>
<td>84</td>
<td>2.8</td>
<td>330</td>
<td>NR</td>
<td>4</td>
<td>1.2</td>
<td>8.7</td>
</tr>
<tr>
<td>Weir et al 2016 [325]</td>
<td>277</td>
<td>4.5</td>
<td>410</td>
<td>NR</td>
<td>7</td>
<td>1.7</td>
<td>5.7</td>
</tr>
<tr>
<td>Dore et al. 2016 [41]</td>
<td>296*</td>
<td>NR</td>
<td>131</td>
<td>NR</td>
<td>6</td>
<td>4.6</td>
<td>NR</td>
</tr>
<tr>
<td>Marco et al 2013 [327]</td>
<td>119</td>
<td>1.4</td>
<td>171</td>
<td>NR</td>
<td>9</td>
<td>5.3</td>
<td>NR</td>
</tr>
<tr>
<td>Lambers et al 2011 [328]</td>
<td>55</td>
<td>1.3</td>
<td>72</td>
<td>NR</td>
<td>11</td>
<td>15.2</td>
<td>NR</td>
</tr>
<tr>
<td>Martin et al 2013 [313]</td>
<td>114</td>
<td>1.6</td>
<td>224</td>
<td>NR</td>
<td>27</td>
<td>9.6</td>
<td>NR</td>
</tr>
<tr>
<td>Vanhommegem et al 2014 [329]</td>
<td>31</td>
<td>4.0</td>
<td>NR</td>
<td>NR</td>
<td>8</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

SVR, sustained virologic response; IDU, injecting drug use; FU, follow-up; PYFU, person-years of follow-up; NR, not reported; *end of treatment response
6.3 Methodological considerations

6.3.1 Study populations

Most studies of reinfection have been carried out in mixed populations of former and recent PWID treated for chronic HCV infection, often including individuals who have been infected for decades and no longer take part in risk behaviours. Baseline levels of injecting risk behaviours reported in these studies have ranged from 0% to 100%, reflecting variations in PWID definitions. The overall incidence rates from such studies therefore tend to be low (<5/100 PY), but when considering subsets of individuals who reported continued IDU after treatment, incidence rates are higher, often exceeding 5/100 PY. The latter might, however, be an underestimate subject to selection bias, as one would expect higher loss to follow-up among PWID with on-going risk behaviours than among those who have stopped injecting.

Still, most reported reinfection rates among recent PWID are lower than rates of primary HCV infection reported in PWID outside the treatment setting [316]. The highest reinfection rates among PWID are reported from studies carried out among people treated for recent HCV infection [315, 332], reflecting populations with high levels of on-going risk behaviours. This is particularly true for MSM, who may have multiple risk factors for HCV transmission.

The level of harm reduction coverage in a given population would intuitively influence reinfection risk among PWID. While there is evidence supporting the effectiveness of OST and NSP in reducing primary HCV incidence, such data are largely lacking in the setting of reinfection prevention. Reinfection estimates from studies with high baseline OST coverage are indeed variable and NSP coverage is rarely reported. A recent study of DAA treatment among OST patients [41], in which a high proportion of participants still engaged in drug use, reported a reinfection incidence rate of 4.6/100 PY, much in line with results from studies of recent PWID populations. The forces of reinfection would also depend on the background viremic prevalence. While this may theoretically have influenced the incidence rates, most studies among PWID have been carried out in settings with similar viremic prevalence.

6.3.2 Sample sizes and study designs

Major limitations of most reinfection studies are small sample sizes and short longitudinal follow-up, generating very modest numbers of person-years of follow-up, particularly in subsets of PWID with post-treatment risk behaviours. Combined with the small numbers of
reinfections detected, this has resulted in a high degree of statistical uncertainty and wide confidence intervals surrounding most estimates. Given that existing estimates are based on short follow-up time, the actual long-term risk of reinfection remains uncertain.

Varied definitions of time at risk for reinfection may also affect incidence estimates; studies calculating time at risk from SVR may not be directly comparable to studies calculating time at risk from end of treatment (EOT). While the latter definition is more robust and formally more correct, it requires correct discrimination between relapse and reinfection (see below). Estimates may also have been biased by retrospective study designs, particularly due to recall bias among participants or insufficient risk factor assessment inherent to the study design. While this may not have affected overall incidence rates, it has certainly influenced the reliability of subgroup analyses. Furthermore, selection bias due to potentially higher levels of loss to follow-up among high-risk individuals may have affected both prospective and retrospective studies.

6.3.3 Virological methods

Finally, differences in the applied methods for virologic assessments may also have biased reinfection estimates and accounted for some of the variation observed between studies. This can be explained by two factors, namely HCV testing intervals (‘the more often you look’) and methods for viral sequencing (‘the closer you look’).

Some of the inter-study variability in reinfection estimates could be explained by differences in HCV RNA testing intervals [333]. Observational data have demonstrated that reinfections may have a transient course with high rates of spontaneous clearance [311, 312, 317]. Thus, the event has probably generally been underestimated, as reinfection episodes with spontaneous clearance most likely will remain undetected unless HCV RNA is tested very frequently. Studies with wide testing intervals will therefore mainly capture those reinfections that have become persistent.

Recurrence of HCV RNA after SVR could result from one of three possible scenarios: 1) late relapse of the pre-treatment majority variant, 2) persistence/re-emergence of a pre-existing treatment-insensitive minority variant (detected or undetected), or 3) reinfection with a new viral strain not present at baseline [334, 335] (Figure 9). This is an important distinction of
both clinical and academic relevance, but correct classification is challenging and requires sensitive sequencing methods and robust phylogenetic analysis [336]. So far, there has been no standardisation of such methods, and studies employing insensitive techniques [260, 313, 319-321, 325-327, 337] may thus have had a potential to misclassify cases of late relapse as reinfection. On the other hand, among individuals with apparent relapse, it is very difficult to exclude the possibility of reinfection from the same source as the initial infection.

Figure 9. Recurrence of HCV RNA after sustained virologic response could result from either (A) late relapse of a majority variant, (B) persistence/re-emergence of a pre-existing minority variant, or (C) reinfection. TW0, treatment week 0; EOT, end of treatment; SVR, sustained virologic response; LOD, level of detection.

The relapse/reinfection distinction rests upon the detection of potential minority variants present in pre-treatment samples. This is relevant for individuals with on-going risk behaviour, who might harbour mixed infections resulting from either co-infections or superinfections due to repeated exposure to HCV [335]. Conventional line probe assays are widely used, but have poor sensitivity for detection of minority variants that constitute <20% of the total virus population [338-342]. When using more sensitive methods [310, 343, 344], the reported prevalence of mixed infection in populations of PWID increases from <5% to 20-40%. In a study of MSM with HIV co-infection who had failed to respond to interferon-based HCV treatment, 15 of 15 participants had evidence of mixed infection when next generation sequencing (NGS) was performed [345]. Although the presence of mixed infection at baseline may compromise IFN-based HCV treatment outcomes [315, 346], its clinical significance remains controversial.

Most sequencing-based reinfection studies have applied majority population sequencing using the Sanger method [314, 315, 322, 323, 328], but NGS is emerging as the state-of-the-art method [345, 347]. Compared to population-based sequencing, NGS offers high throughput analysis with superior sensitivity, but at the same time generates large amounts of
data that require costly bioinformatics and phylogenetic analysis. However, unless the whole genome is analysed, the choice of region to be sequenced and the exact design of PCR primers may influence the analysis and ultimately lead to misclassification bias [334, 335].

In studies of low-risk populations, the reported risk of late relapse (i.e. recurrence of HCV RNA more than 12 weeks after EOT) is very low, with 5- and 10-year cumulative estimates of <1% [348]. However, recent data based on deep sequencing may shed new light on this dilemma. Of 3004 patients who achieved SVR in the phase 3 studies of sofosbuvir [349], which notably excluded patients with recent illicit drug use or OST, 12 (0.4%) cases of recurrence of HCV RNA were identified more than 3 months after EOT. Based on results from deep sequencing of the NS5B segment, 7 of 12 cases represented reinfection while 5 of 12 cases represented late relapse. No behavioural data was reported. These findings suggest that among cases with HCV recurrence post-SVR, most can be attributed to reinfection even in presumed low-risk populations. Consequently, in the presence of on-going risk behaviour, post-SVR recurrence of HCV RNA therefore most likely represents reinfection. In the absence of a virological gold standard to confirm a ‘true’ reinfection diagnosis, a pragmatic approach would be to take post-treatment risk factors thoroughly into account.

6.4 Reinfection risk in different populations

6.4.1 Lifetime PWID vs. recent PWID

A meta-analysis [202] of the five first reinfection studies published between 2002 and 2012 [318-322] reported a pooled incidence of 2.4/100 PY among lifetime PWID and 6.1/100 PY among individuals with documented post-treatment IDU. The results from this meta-analysis should be interpreted with caution, as it was based on small studies of patients with mixed risk behaviours and relatively short follow-up time. Also, these early studies largely lacked sequencing methods to strengthen the reinfection diagnosis.

Individuals treated for recent HCV infection are high-risk group for HCV transmission due to often on-going risk behaviours, and may therefore represent a key population in the study of reinfection. In an Australian study from 2012 among people treated for acute HCV infection [315], 76% were lifetime PWID, 35% reported recent IDU at enrolment, and 31% were HIV-positive MSM. Among 67 individuals who achieved SVR, 5 cases of reinfection were detected, leading to a higher post-SVR reinfection rate (12.3/100 PY) than reported in
previous studies. This study pioneered sensitive sequencing methods, using subtype-specific real-time PCRs for detecting mixed HCV infection, providing a detailed characterization of the natural history of reinfection and superinfection (i.e. the detection of a HCV strain distinct from the primary strain in those with virological persistence) among treated and untreated individuals. Data from this study was later included in a pooled analysis of four open-label studies carried out in Australia and New Zealand between 2004 and 2015 [332]. The study included 120 individuals with recent HCV infection, and ten cases of HCV reinfection were identified during a total follow-up time at-risk of 135 PY (incidence 7.4/100 PY). The incidence of HCV reinfection was 8.5/100 PY among lifetime PWID, compared to 4.9/100 PY in those who had never injected drugs (predominantly HIV-infected MSM).

6.4.2 PWID in OST

Reinfection was also assessed in aforementioned phase 3 study of the DAA combination elbasvir/grazoprevir among PWID in OST [41]. Given that one-third of the 301 included individuals had detectable illicit drugs (excluding cannabis and benzodiazepines) in urine throughout the study, this population could be considered at high risk of reinfection. Virological failure could be attributed to relapse in ten patients, viral breakthrough in two patients and reinfection in six patients. The reinfection diagnosis was robust, based on deep sequencing and phylogenetic analysis of the NS3 and NS5A segments supported by positive urine drug screening in 4 of 6 individuals. Based on six months post-treatment follow-up, the incidence of reinfection was 4.6/100 PY, much in line with previous estimates following IFN-based treatment among recent PWID. Interestingly, three of six cases were subsequently HCV RNA negative, confirming that an important proportion of reinfections might clear spontaneously also after DAA treatment.

6.4.3 The prison population

HCV infection is common in prison populations worldwide [64]. Although the prison setting may be considered as an opportunity for HCV treatment [350], it may also be an important site for HCV transmission [351] and hence reinfections. A retrospective study from 2010 identified 5 reinfections among 53 Australian prisoners successfully treated for HCV [326], but the incidence rate was not reported. The incidence of reinfection in the prison population has been more thoroughly investigated in an incarcerated cohort in Spain [327] that comprised 81% lifetime PWID and 15% HIV/HCV co-infected. Among 119 prisoners who
obtained SVR, 9 (7.6%) were reinfected after a mean follow-up of 1.4 years, generating an overall incidence of 5.3/100 PY. Self-reported data on risk behaviour were unreliable, as four reinfected individuals reported no risk factors; thus, no reasonable reinfection estimate could be given among those who continued to inject drugs after treatment.

6.4.4 MSM

Data on HCV reinfection among MSM are mainly limited to HIV-infected individuals and most studies have focused on reinfection following treatment of acute HCV infection [313, 314, 328-330]. The reported reinfection incidence rates from these studies are considerably higher (10-15/100 PY) than among PWID, and may even exceed rates of primary HCV infection. However, these results may not be generalizable to HIV-uninfected MSM. Moreover, epidemic outbreaks have been reported only in certain large cities, whereas acute HCV and reinfections continue to be uncommon among MSM in many areas with high prevalence of HIV/HCV co-infection [352]. One could also speculate that health-seeking behaviour is different between MSM and PWID. MSM with the highest risk may be those most likely to seek HCV testing as opposed to high-risk PWID who may have little contact with health care providers.

In a study from Amsterdam [328], 11 of 51 MSM who achieved SVR were reinfected after a median 1.3 years of follow-up, for a reinfection incidence of 15.2/100 PY. Behavioural data were available in 21 individuals and showed that non-injecting drug use was more frequent in reinfected individuals. In a study from London [313], 27 reinfections occurred among 114 individuals with SVR after treatment of acute infection, yielding a reinfection rate of 9.6/100 PY and a 2-year cumulative rate of 25%. In addition, there were six second reinfections occurring after successful treatment of the 13 first reinfections. The pooled reinfection rate for these two studies was 11.4/100 PY [330]. No behavioural data was reported in this study.

6.5 Risk factors for reinfection

Due to small sample sizes, few studies have had sufficient statistical power to identify factors associated with reinfection. The Australian study from 2012 [315] was the first to identify independent risk factors for reinfection among PWID. Here, reinfection or superinfection occurred significantly more often in participants with poorer baseline social functioning and in those who reported methamphetamine injecting compared to opiate injecting during
follow-up. Reinfection was not associated with baseline injecting status, indicating that prediction of reinfection may prove difficult in this population. When data from this study later was included in a pooled analysis of four open-label studies [332], the only factor independently associated with reinfection among PWID was use of unsterile needles/syringes during follow up. Among MSM, IDU post-treatment was reported by 23%, and was the only factor independently associated with HCV reinfection.

Although HIV infection is a biological risk factor for HCV transmission more prevalent among MSM than among PWID, the role of HIV co-infection infection in the context of reinfection remains unclear. In the Spanish prison study [327], reinfection was three times more common in HIV-positive than in HIV-negative subjects (13.4 vs. 4.0/100 PY). Conversely, in another Spanish study of 84 HIV/HCV co-infected individuals [323], a much lower incidence of reinfection (1.2/100 PY) was found. This was an overall low-risk population mainly comprising former PWID or individuals on stable OST, but in the subgroup reporting risk behaviours during follow-up, 3 of 11 were reinfected (incidence 8.7/100 PY). Behavioural risk factors for reinfection among MSM have not been addressed. It is, however, conceivable that they are similar to those reported for primary HCV infection. In particular, the introduction of ‘chemsex’ has probably facilitated HCV transmission in certain sexual networks [92], driving a chain of primary infections and reinfecions.

### 6.6 Long-term risk of reinfection

A comprehensive meta-analysis from 2016 [298] estimated the projected 5-year risk of reinfection in different populations based on pooled incidence rates. The study included 14 articles or conference abstracts of PWID or prisoners, and 4 studies of HIV/HCV co-infected individuals from heterogeneous populations. Among a total of 771 PWID or prisoners, 42 cases of HCV RNA recurrence after SVR were observed. The pooled reinfection incidence was 1.9/100 PY, leading to a projected 5-year risk of 10%. Among HIV/HCV co-infected individuals, the pooled incidence of reinfection was 3.2/100 PY, leading to a projected 5-year risk of 15%. However, given that these projections largely were based on data from small studies, there is considerable uncertainty regarding generalizability and the actual long-term risk of reinfection. A key question is whether reinfection risk remains linear or if a saturation effect occurs with time. Even low rates could be a concern over time, particularly in absence of retreatment and strategies to reduce individual risk.
7 Risk behaviours

7.1 A changing patient population

IFN-free treatment will improve the feasibility of HCV treatment among PWID, including in marginalized populations with a high prevalence of psychiatric comorbidities, ongoing injecting drug use and harmful alcohol consumption. In younger PWID populations, liver disease will tend to be mild and injecting risk behaviours more pronounced. Conversely, in ageing cohorts of treatment naïve PWID, advanced liver disease will be much more common and risk behaviours probably less prominent. With improved treatment uptake in these populations, one must therefore both expect increasing risk of reinfection and liver disease complications following successful treatment. Efforts to minimize post-treatment risk behaviours are therefore of considerable clinical and public health interest. A better understanding of the impact of HCV treatment on risk behaviours is important to inform clinical decision-making, and of particular relevance for the ongoing debate regarding which patient groups to prioritize for treatment [136].

7.2 Harm reduction and behavioural interventions

As reviewed in section 2.7, the strongest risk factor for HCV transmission among PWID is needle and syringe sharing, but there is also a considerable risk attributable to sharing of ancillary injecting equipment. In the absence of a HCV vaccine or systematic implementation of treatment-as-prevention strategies, efforts to reduce transmission risk must therefore focus on either reducing injecting drug use or reducing sharing and contamination of needles and injecting equipment. Current evidence-based primary prevention of HCV transmission is limited to combined OST and NSP, while other harm reduction interventions remain more controversial [103]. Although effective secondary HCV prevention (i.e. prevention of reinfection) have not been evaluated, it is likely that primary prevention strategies also would be effective in this setting.

A recent review of reviews regarding the effectiveness of a range of harm reduction interventions included 12 core reviews and 13 supplementary reviews published between 2000 and 2011 [103]. The interventions considered were OST; NSP and its models of delivery; provision of sterile drug preparation equipment, including smoking foil;
information, education and counselling; and supervised injecting facilities. In addition to considering HIV and HCV transmission, the review also considered self-reported injecting risk behaviour as an outcome. The paper concludes that there is sufficient review-level evidence for OST and NSP, and tentative review-level evidence for the remaining interventions in reducing injecting risk behaviour.

A review from 2012 included six RCTs of peer educator training and counselling interventions directed at reducing injecting risk behaviour [353]. There was a tendency that larger trials observed significant reductions in self-reported injecting risk behaviours in the intervention group compared to the control group, consistent with findings from meta-analyses of the effect of behavioural interventions on HIV risk behaviours [354, 355]. However, the authors were reluctant to draw any conclusions due to the small number of studies and large between-study variations in instruments used to measure the outcome. Further, self-reported data on risk behaviours is subject to information bias and will always be a surrogate end point for HCV transmission.

### 7.3 HCV awareness and risk behaviours

It has been suggested that testing programs combining screening and counselling to enhance HCV awareness could reduce risk behaviours among both uninfected and HCV-infected PWID [356]. However, studies have produced conflicting results, with observed decreases in alcohol use and injection risk behaviours among PWID aware of their positive HCV status reported in some studies [357, 358] but not in others [359-361]. As most studies have been cross-sectional, it remains unclear whether any potential behavioural change would sustain over time.

Some studies, however, have assessed the relationship between HCV awareness and risk behaviours longitudinally. In Baltimore, reductions in syringe sharing were observed for less than a fifth of participants 3–6 months after positive HCV notification [362]. In Melbourne, increased use of new syringes was observed after peer-delivered testing [363]. In a more recent report, receiving a HCV diagnosis was associated with a small decrease in injection frequency over time, but there was no change in injecting equipment borrowing [364]. In San Francisco, HCV notification and counselling among young PWID led to an initial decrease in alcohol and non-injection drug use that were not sustained after 6- or 12-months of follow-up.
In Montreal, however, a linear decrease in syringe sharing was observed after HCV status notification in a population of 208 initially anti-HCV negative PWID followed longitudinally between 2004 and 2011 [356]. Cocaine and heroin injecting decreased by 10% for each 3-months of follow-up among seroconverters, but not among seronegative individuals. No significant changes were observed in alcohol use.

7.4 HCV treatment and risk behaviours

Recent research has investigated whether the benefits of HCV treatment may extend beyond liver-related outcomes to health-related quality of life (HRQL) [149, 366, 367]. Pooled HRQL data from nine phase 3 trials of sofosbuvir-based regimens demonstrated that IFN- and RBV-free regimens led to substantial improvement of HRQL during and following treatment compared to more toxic regimens [366]. It remains to be seen whether this effect could translate into higher treatment adherence or positive behavioural change.

Although there is some evidence to suggest that HCV treatment among PWID could have positive impacts on drug behaviours, data on this relationship is very limited. Some earlier studies of HCV treatment among recent PWID in OST have shown that drug use did not increase during treatment [368, 369]. On the other hand, concern has been raised that side effects of IFN-based treatment could mimic opioid withdrawal symptoms and promote injecting risk behaviours [293, 370]. Yet, it is also conceivable that interaction with health care providers throughout treatment and follow-up could be a transformative process and promote patient empowerment. Having access to regular monitoring and care could create opportunities to receive counselling and discuss behavioural change [356, 364, 371]. Parallel access to multidisciplinary services and support may also play a role; for instance, in a cohort of 467 PWID recruited between 2008 and 2010 in Australia, cessation of IDU was associated with outpatient service use [372].

To date, only one study has specifically evaluated injecting risk behaviours longitudinally during and following HCV treatment [373]. This Australian study included 124 lifetime PWID with recently acquired HCV infection, of whom 84 individuals received IFN-based treatment and 40 participants were untreated controls. Recent IDU was reported at baseline in 47% and 60% of treated and untreated individuals, respectively, and remained relatively stable in both groups throughout 48 weeks of post-enrolment follow-up. Receiving HCV
treatment was not associated with IDU or needle/syringe sharing during follow-up, but was associated with decreased sharing of ancillary injecting equipment. Among the small proportion of treated participants who remained in follow-up, ancillary injecting equipment sharing decreased significantly from 54% at enrolment to 17% at follow-up. Although this study was limited by a substantial loss to follow-up and the inherent bias of self-reported behavioural data, it challenged common concerns that IFN-based treatment may lead to increasing risk behaviours.

The adverse events of IFN have necessitated regular interaction with health care providers, often throughout lengthy courses of treatment. While this may have offered repeated opportunities to discuss behavioural change, for some, IFN itself might also have provided a ‘cathartic’ effect resulting in efforts to protect one’s SVR. One may therefore speculate that the ease of current IFN-free treatment may decrease the potential for behavioural change and lead to increasing risk behaviours, as observed among MSM after the introduction of HIV combination antiretroviral therapy [374]. Emerging data on patterns of drug use during DAA treatment does, however, not support this speculation.

In the recent phase 3 study of elbasvir/grazoprevir for persons receiving OST [41], urine drug screening was conducted at each study visit for amphetamines, cocaine, benzodiazepines, cannabinoids, opioids (methadone, buprenorphine and other opioids), barbiturates, phencyclidine and propoxyphene. Overall, almost 50% of patients had positive results on drug screening for at least one illicit drug (excluding methadone, buprenorphine and cannabinoids) at each study visit, with no important differences observed between the treatment groups or within the individual drugs classes. Non-OST opioids were detected in approximately 20%, cocaine in 10% and amphetamines in 5%. Although no changes in urine drug screens were observed during treatment, data on injecting risk behaviours were not collected. Similarly stable patterns of drug use were also observed in PWID successfully treated with sofosbuvir-based regimens in the Bronx [213]. Illicit drugs were detected in urine in 59% of participants both prior to treatment initiation and during treatment, with no important changes observed between individual drugs. Importantly, on-treatment drug use did neither affect SVR nor treatment adherence in any of these studies.
PART II
OBJECTIVES, METHODS, RESULTS AND DISCUSSION
8 Objectives

8.1 Overall research aims

The overall research aim of these studies was to describe important epidemiological and behavioural aspects of chronic HCV infection among PWID. Based on the current evidence, we identified key knowledge gaps related to treatment uptake, reinfection incidence and risk behaviours. The rationale and specific research aims for these studies are summarized below.

8.2 Rationale

8.2.1 Study I: Hepatitis C treatment uptake among patients who have received opioid substitution treatment: A population-based study

With the current availability of simple, efficient and tolerable DAAs, HCV treatment should become more feasible across different PWID populations. In this context, PWID in OST represent a particularly important target group for several reasons. First, HCV prevalence is high in this population and a substantial proportion of all HCV infections are therefore found here. Second, because permanent or intermittent injecting risk behaviours occur also among individuals receiving OST, this group may contribute to onwards HCV transmission. Third, as OST patients often are enrolled in specialist addiction care, this setting could provide a platform for linkage to HCV care using existing infrastructures.

Documenting treatment uptake and monitoring treatment rates among PWID in OST is therefore a key to guide health policy in this transformative period in the field of HCV. Although there are international data on treatment uptake among PWID derived from community-based cohorts and more selected populations, population-based data among OST patients have not been reported. The high quality of Norwegian health registries provides research opportunities that may be unique in a European context. A priori, we hypothesized that the historical treatment uptake of the IFN-based era had been low, due to the toxicity of IFN, high prevalence of psychiatric comorbidities, low HCV awareness, and lack of models of HCV care adapted for marginalised populations.
8.2.2 Study II: Hepatitis C reinfection after sustained virological response

The potential risk of reinfection after successful treatment is relevant for several reasons. First, due to the lack of protective immunity, reinfection can occur if risk behaviours continue after treatment. Second, increased treatment uptake in more marginalized populations with higher prevalence of high-risk injecting behaviours and health illiteracy may lead to increasing reinfection incidence. Third, a high reinfection incidence could impede potential individual and public health benefits of DAA treatment among PWID and might question the cost-effectiveness of these expensive regimens. Fourth, identifying individuals most at risk could aid the provision of HCV care for this group, informing prioritizing strategies and targeted preventive measures.

Although there are a number of small studies evaluating the incidence of HCV reinfection following IFN-based treatment, existing estimates are uncertain and poorly generalizable due to selected patient populations, small sample sizes, short longitudinal follow-up and methodological limitations. Data on the actual long-term risk of reinfection among PWID are largely lacking. Collecting follow-up data from the Scandinavian treatment trial NORTH-C performed in 2004-2006 [206] provided opportunities to address this question in a real-life context. A priori, we hypothesised that reinfection would be an uncommon event in this population of lifetime PWID who all had been abstinent from IDU at least six months prior to treatment.

8.2.3 Study III: Changes in risk behaviours during and following treatment for hepatitis C virus infection among people who inject drugs:

The ACTIVATE study

As we enter the DAA treatment era, a better understanding of patterns of substance use and risk behaviours among individuals engaged in HCV treatment will be relevant for several reasons. First, increased treatment uptake among PWID will change the typical demographics of the patient populations; in particular, a higher prevalence of ongoing injecting behaviours and harmful alcohol consumption must be expected among treatment eligible individuals. Second, levels of ongoing injecting risk behaviours and alcohol use will have individual and population-level implications for reinfection risk and disease progression following SVR. Third, documenting a beneficial behavioural change among individuals engaged in treatment
could inform treatment recommendations and encourage efforts to improve the HCV care cascade among PWID.

Despite existing evidence of the effectiveness of harm reduction on injecting risk behaviour, there is very limited data on the relationship between HCV treatment and risk behaviours. The ACTIVATE (A Collaborative Trial in Injectors of indiViduAlized Treatment for genotypE 2/3) study [205], the first international multicentre trial of IFN-based treatment for recent PWID, provided a framework to assess self-reported risk behaviours longitudinally in a high-risk population engaged in treatment. A priori, we hypothesised that a positive behavioural change could be observed among individuals engaged in HCV treatment.

8.2.4 Study IV: HCV epidemiology in high-risk groups and the risk of reinfection

Given the rapid advances in HCV treatment, an EASL/AASLD Special Conference entitled *New perspectives in hepatitis C virus infection - The roadmap for cure* was organised in September 2016. The aim of this conference was to summarize the information available, provide a critical review and analysis of the best available data, and discuss unresolved issues requiring further research. Topics covered were epidemiology, pathogenesis and virology, disease assessment, treatment in special patient populations, and HCV eradication strategies. In collaboration with international colleagues, we were invited to submit a review article on HCV epidemiology to coincide with this conference.

8.3 Specific research aims

The primary aim of Study I was to calculate the cumulative HCV treatment uptake among individuals who had received OST in Norway between 2004 and 2013, i.e. the baseline treatment uptake of the IFN-based treatment era. The secondary aims were to estimate and compare annual treatment rates, and to identify factors associated with HCV treatment.

The primary aim of Study II was to calculate the long-term incidence of persistent HCV reinfection among lifetime PWID who had achieved SVR in the NORTH-C trial seven years earlier. The secondary aims were to evaluate the proportion of individuals who had engaged in IDU during the follow-up period, and to identify factors associated with reinfection and relapse to IDU.
The primary aim of Study III was to evaluate changes in recent injecting drug use during and following HCV treatment among participants enrolled in the ACTIVATE study. The secondary aims were to evaluate changes in recent injecting risk behaviours, non-injecting drug use, hazardous alcohol use and OST.

The aim of Study IV was to provide an updated review of the epidemiology of HCV infection in high-risk groups of PWID and MSM, covering prevalence and incidence, risk factors, harm reduction, and reinfection risk. Particular emphasis was given to reinfection, focusing on methodological problems, incidence rates, risk factors and possible preventive strategies.
9 Materials and methods

9.1 Study participants

9.1.1 Linked registry data

Study I was based on linked data from NorPD and MSIS - two central Norwegian health registries administered by NIPD. NorPD was established in January 2004 and contains information on all prescription drugs dispensed at all Norwegian pharmacies to individual patients. This registry therefore has true population-based coverage. For each prescription, the following data are registered: patient’s unique identifier, gender, date of birth and place of residence; prescriber’s unique identifier; date of dispensing; and detailed drug information (Anatomical Therapeutic Chemical [ATC] code, package size, number of packages, defined daily doses [DDDs], reimbursement codes, and price). Although the reason for the prescription is not recorded, the diagnosis can be evident though reimbursement codes and some drug prescriptions can also be considered as proxy for disease. Although data among institutionalized patients in hospitals and other institutions most often are aggregated and recorded at institutional level, OST in such patients has been registered in NorPD at individual level since 2008.

MSIS was established in 1975 as a national surveillance registry for individual cases of communicable diseases. HCV infection has been notified from microbiological laboratories and physicians since 1990. Between 1992 and 2007, only cases of acute HCV infection were registered and notification was not mandatory. Since 2008, all cases of acute or chronic HCV infection has been subject to mandatory notification and registered based on detection of either anti-HCV antibodies or HCV RNA. For each case, registered data include date and method of detection, presumed mode of transmission, place of residence and country of origin. In practice, laboratories notify first (successively or weekly) and send a paper form to the requisitioning physician for clinical data. However, manual notification routines relying on paper forms are vulnerable; experience shows that paper forms often remain uncompleted by the clinician and communication between laboratory and clinician may be suboptimal. Furthermore, some laboratories may fail to notify older infections if they are presumed notified previously. As a result, an important proportion of diagnosed HCV infections (particularly older infections) must be expected to be un-notified, introducing a potential
selection bias to the registry. Furthermore, partly due to the historical change in notification criteria, the registry does not discriminate well between cases of chronic HCV infection and acute HCV infection with spontaneous clearance.

The study population comprised all individuals identified in NorPD between 2004 and 2013 who had received OST and were notified to MSIS with HCV infection during the same period, regardless of the method of detection was an anti-HCV or HCV RNA test. OST patients were defined as individuals who had been dispensed methadone mixture, buprenorphine sublingual tablets or buprenorphine–naloxone combined sublingual tablets at least once during the study period. Individuals receiving methadone tablets or capsules more frequently than methadone mixture were excluded because these formulations are mainly used in pain therapy in Norway. Those who received methadone with reimbursements codes for palliative therapy or malignancies and individuals with age below 18 years or above 70 years were also excluded. Using this inclusion procedure, a total of 3755 OST patients notified with HCV infection were included for the main analysis (Paper I, Figure 1).

9.1.2 Follow-up of the NORTH-C trial

Study II was based on long-term follow up of individuals enrolled in the Scandinavian treatment trial NORTH-C performed in 2004–2006 [206]. NORTH-C was a RCT assessing the effect of short duration (14 weeks) versus standard duration (24 weeks) IFN-based treatment in a typical Scandinavian HCV population dominated by former PWID. The study included 428 mono-infected HCV genotype 2 or 3 patients in Norway, Sweden and Denmark, of whom two-thirds had been classified as lifetime PWID. Reflecting the standard of care at the time, minimum six months of abstinence from drug use was required prior to inclusion but urinary drug screening was not mandatory. OST patients were excluded, as HCV treatment in this population was considered controversial at the time. Participants were not systematically followed prospectively after completion of the study.

All patients who had achieved SVR in the NORTH-C trial (n=152) or following subsequent retreatment (n=9) at any Norwegian study site were eligible for inclusion in this follow-up study performed in 2012-2014. All eligible study participants were scheduled for an outpatient consultation at their local study site for clinical assessment, blood samples and questionnaires. Repeated efforts were made to make contact with patients who did not meet
for the initial consultation, a few were interviewed by telephone, but some data were collected retrospectively from the patient files and from microbiological laboratories. Collectively, these efforts yielded high inclusion rates with available follow-up data in 138 of 161 (86%) eligible individuals, including 94 of 106 (89%) lifetime PWID, which constituted the main group of interest for this analysis. For those who had died during the follow-up period, data on cause of death were obtained from the Norwegian Cause of Death Registry.

9.1.3 The ACTIVATE study

Study III was based on data from the international, multicentre open-label study ACTIVATE, performed in 2012-2014 at 17 study sites in Australia (n=5), Canada (n=3), Switzerland (n=3), Belgium (n=2), Germany (n=1), Norway (n=2), and the United Kingdom (n=1) [205]. ACTIVATE was designed to investigate IFN-based HCV treatment outcomes, adherence and risk behaviours among recent PWID. Participants had to be more than 18 years of age, have treatment-naive chronic HCV genotype 2 or 3 infection, and have reported injecting drug use within 24 weeks before enrolment. However, due to slow recruitment, a study protocol amendment was implemented to also include people currently receiving OST with no recent drug use and people who had injected within 24 weeks prior to enrolment. Ultimately, 93 individuals were enrolled, providing data for the present behavioural analyses.

9.2 Pharmacoepidemiological assessments

For Study I, exposure to HCV treatment was defined as the first dispensation of ribavirin (ATC J05AB04) and pegylated IFN alpha (ATC L03AB10 or L03AB11). Considering certain drug dispensations as proxies for psychiatric disease, dispensations and DDDs of benzodiazepines (ATC N05BA, N05CD and N03AE), selective serotonin reuptake inhibitors (SSRIs) (ATC N06AB) and antipsychotics (N05A) were also evaluated. Annual doses were calculated as the total DDDs divided by the individual time of observation (in years). Patients were stratified according to the following categories of benzodiazepine use: no dispensions, moderate use (≤ mean dose) or heavy use (> mean dose). Duration of active OST was calculated as the total number of months with actual dispensions of OST. OST continuity was defined as the duration of active OST divided by the number of months between first and last dispersion (i.e. actual/potential OST duration). Patients were stratified according to OST continuity categories (< 50%, 50–80% or > 80%). Individuals with only one dispensation of OST were considered non-adherent and included in the < 50% category.
9.3 Virological assessments

For Study II, all follow-up blood samples were first tested for HCV RNA locally at each study site using an ‘in-house’ PCR assay (COBAS AmpliPrep/COBAS Amplicor HCV Test v2.0 with limit of detection 20 IU/ml or COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test v2.0 with limit of detection 15 IU/ml). Samples with detectable HCV RNA were either collected from the local study sites or retrieved from microbiological laboratories (in cases of loss to follow-up). All HCV RNA positive samples were then retested/confirmed centrally at the Department of Virology, NIPH, on a quantitative assay (COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test v2.0) and genotyped using a line probe assay (HCV genotype 2.0 Assay (LiPA)). All participants with viral recurrence were evaluated for viral persistence after minimum six months, either by a repeated study visit or through retrospective review of microbiological records.

To discriminate ‘true’ reinfection from potential cases of late post-SVR relapse, viral sequencing and phylogenetic analysis was attempted on all cases of viral recurrence. These analyses were done at the Department of Virology, NIPH. Population-based (Sanger) sequencing was performed on PCR-products from the first available HCV RNA positive sample at follow-up and, if available, on stored frozen baseline samples taken prior to treatment in the NORTH-C trial. First, HCV RNA was extracted and complementary DNA was generated using Superscripts One-Step PCR High Fidelity and Expand High Fidelity PCR system with random hexamers and specific primers. Then, in accordance with methods previously described [375], a ~1500 base-pairs fragment of the HCV genome covering Core, Envelope 1 (E1), hypervariable region 1 (HVR1) and Envelope 2 (E2) was amplified by a nested reverse transcriptase PCR using universal and subtype specific primers. Additional genotype 3a specific primers were designed for improved detection of this prevalent subtype. Finally, sequence alignment and a maximum-likelihood phylogenetic tree of the Core-E2 fragment of all available samples with genotype 3a and a set of reference sequences retrieved from GenBank were constructed using RAxML v.8.1.22 with a General Time Reversible model of nucleotide substitution, gamma model of rate heterogeneity and 100 rapid bootstrap replications. Maximum genetic distance thresholds for HCV reinfection were assessed and defined based on pairwise Core-E2 sequence comparison of reference sequences obtained from GenBank and a local database at NIPH.
9.4 Behavioural assessments

For Study II, participants completed a questionnaire focusing on socio-demographics and risk behaviours prior to treatment and in the follow-up period (injection frequency, sharing of needles/syringes or injecting paraphernalia, and OST). In cases with discrepancy between pre-treatment drug behaviour as reported at follow-up and at baseline in the NORTH-C trial, information favouring drug use was chosen to cover the possibility of under-reporting. For those who did not meet for consultation, data on IDU were collected retrospectively from the patient files where available.

For Study III, participants completed a more comprehensive self-administered questionnaire at all study visits focusing on socio-demographics, drug and alcohol use, and injecting risk behaviours (injection frequency, use of non-sterile needles/syringes and injecting paraphernalia sharing) longitudinally during and following treatment. Alcohol consumption was evaluated using the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C), derived from the first three questions of the full AUDIT. AUDIT-C scores \( \geq 3 \) and \( \geq 4 \) indicate hazardous consumption or active alcohol use disorders among women and men, respectively [376]. Social functioning was measured using the short-form Opioid Treatment Index Social Functioning Scale [377]. Social functioning scores range from 0-18 with higher scores indicating poorer social functioning.

9.5 Liver fibrosis assessments

For Study III, stage of liver fibrosis was assessed either by liver biopsy (METAVIR) [173], LSM using TE, or AST-to-Platelet Ratio Index (APRI). For LSM, the chosen cut-offs for significant liver fibrosis and cirrhosis were 7.1 kPa and 12.5 kPa, respectively [174]. APRI was calculated using aspartate aminotransferase (AST) and platelet count: \([\text{AST (U/L)/upper limit of normal}}/\text{platelet count (10^9/L)}) \times 100. \) APRI >1.5 and >2.0 defined significant liver fibrosis and cirrhosis, respectively [378].

9.6 Statistical analysis

For Study I, cumulative treatment uptake was defined as the proportion of individuals exposed to HCV treatment at some point during the study period. Annual HCV treatment uptake was assessed among all individuals who had been dispensed OST in each calendar
year, and was calculated as the number of treated individuals divided by the number of previously untreated individuals. To evaluate potential changes in annual treatment uptake, Poisson Exact 95% confidence intervals (CIs) for rates were calculated. Logistic regression analysis was used to identify factors associated with ever receiving HCV treatment. Potential predictors were hypothesized a priori and included age, gender, OST specific factors, and dispensations of benzodiazepines, SSRIs and antipsychotics.

For Study II, incidence rates for reinfection (per 100 PY at risk) and corresponding 95% CIs were calculated assuming a Poisson distribution. Factors associated with time to reinfection were evaluated using Cox proportional hazards regression. An alternative model using Poisson regression was also performed and is included in the supplementary materials of the paper. Potential predictors hypothesised to be associated with reinfection were determined a priori and included socio-demographic and behavioural variables. In addition, logistic regression analysis was performed to identify factors associated with relapse to IDU during follow-up.

For Study III, the study outcomes were defined as binary variables (yes vs. no) and included any injecting drug use, ≥daily injecting drug use, use of non-sterile needles, injecting paraphernalia sharing, non-injecting drug use, hazardous alcohol use and OST. Proportions reporting recent (past month) behavioural outcomes were evaluated among individuals present at the following study visits: treatment enrolment, treatment baseline, on-treatment (week 4), end of treatment, and 12 and 24 weeks of post-treatment follow-up. However, given that some participants were lost to follow-up, potentially introducing a selection bias among participants remaining in the study towards the end of follow-up, proportions were also assessed in the subpopulation remaining in 12 weeks of post-treatment follow-up. Finally, to account for the correlated nature of repeated measurements among individual participants, Generalized Estimating Equations (GEE) were used to evaluate the impact of time in the study (defined as incremental study visits) on all outcomes. Alternative models using mixed effects logistic regression were also performed.

For all studies, factors significant at the 0.10 level in unadjusted analysis were included in adjusted multivariate analysis and removed using a stepwise elimination approach. Unadjusted and adjusted odds ratios (OR) or hazards ratios (HR) were reported. All
statistically significant differences were assessed at a two-tailed p < 0.05. Statistical analysis was conducted using SPSS version 22 (Study I) or STATA version 12.0 (Studies II and III).

9.7 Ethics and data handling

Study protocols for all studies were approved by the regional committee for ethics in medical research in Norway (REK), and all studies were conducted according to the Declaration of Helsinki. Data linkage for Study I was performed by a third party (Statistics Norway) as required by the Norwegian law for national health registries, and data was presented in encrypted files providing the confidentiality required. Informed consent from the participants was not collected as all data were analysed anonymously. For Study II, REK initially required that informed consent was given. However, as some patients were lost to follow-up, permission was subsequently given to also collect data retrospectively from hospital patient files and microbiological laboratories without informed consent for patients who were not contactable. For Study III, all participants provided written informed consent prior to enrolment. The study protocol was approved by St. Vincent’s Hospital, Sydney Human Research Ethics Committee, Australia, as well as through local ethics committees at all study sites, including Norway. The Kirby Institute, University of New South Wales, Australia, collected the data and monitored study conduct, while an independent data and safety monitoring board reviewed the progress of the study.

These studies were purely observational and did not contain any intervention (except treatment offered according to standard of care in Study III) and did not involve any risk for the participants. Possible disadvantages were therefore considered minor and limited to the time spent on questionnaires and follow-up visits. The ethical dilemmas regarding supplementary data collection without informed consent for Study II were discussed with REK. In general, retaining PWID in clinical research is often challenging. Individuals may be lost to follow-up for several reasons, including ongoing drug use, psychosocial instability, change of cell phones, change of address, or death. A requirement for informed consent for Study II could therefore introduce a selection bias that would strongly limit the validity of the results. Although this is a vulnerable population, the final decision from REK on this subject could be argued to benefit this group in the future.
10 Results

10.1 Study I

10.1.1 Participant characteristics
From a total of 9919 OST patients identified in NorPD, 3755 individuals notified to MSIS with HCV infection were included as the study population (Paper I, Figure 1 and Table 1). Among those, the mean age at initiation of OST was 36 years, 70% were male and 95% had Norwegian origin. The mean duration of active OST was 3.8 years, 77% had received buprenorphine-based OST and 57% had >80% OST continuity. Benzodiazepines, SSRIs and antipsychotics had been dispensed in 85%, 37% and 55%, respectively. Six percent died during the study period (0.6% per year).

10.1.2 Main findings
The key finding from this study was that 539 of 3755 (14%) OST patients with notified HCV infection had ever received HCV treatment during the study period (cumulative treatment uptake). Cumulative treatment uptake was similar (14-15%) across different age groups. Among treated individuals, 375 (70%) were treated for HCV during OST, 111 (21%) were treated prior to initiation of OST, while 53 (10%) were treated after cessation of OST. Annual treatment uptake during OST ranged between 1.3% (95% CI 0.7–2.2) in 2005 to 2.6% (95% CI 1.9–3.5) in 2008 (Paper I, Table 2 and Figure 2). Although there was a trend towards higher treatment rates during the second half of the study period, there was no significant change over time. In logistic regression analysis, treatment uptake was not associated with age or gender, but associated with duration of active OST, OST continuity and benzodiazepine dispensions (Paper I, Table 1). The odds of HCV treatment increased by 11% for each year of active OST (aOR 1.11; 95% CI 1.07–1.15), were 62% higher among individuals with >80% vs. <50% continuity (aOR 1.62; 95% CI 1.17–2.25), and 35% lower among individuals with heavy vs. no benzodiazepine use (aOR 0.65; 95% CI 0.49–0.87).

10.1.3 Secondary findings
Unexpected findings from this study were related to the validity of MSIS, confirming that a substantial proportion of HCV infections are not notified to MSIS. Overall, 3755 of 9919 (38%) OST patients identified in NorPD were notified with HCV infection, indicating that
MSIS greatly underestimates HCV prevalence in the OST population. Looking at all OST patients, 943 of 9919 had received HCV treatment, of which 43% (404 of 943) in fact were un-notified cases (Paper I, Figure 3). Both among all OST patients (n=9919) and among all treated patients (n=943), un-notified individuals were on average born three years earlier than notified individuals, but other characteristics were similar (Paper I, Supplementary materials).

Figure 10 shows additional data of more local interest that were not included in the paper. In total, 943 OST patients had received treatment during the study period, with the annual number of treatments ranging from 70 to 112. The proportion of treatments initiated before OST were much higher during the first years of the study period (A). The proportion of un-notified treatment cases was highest (>60%) in the first part of the study period, but still remained important (24%) in the final part (2011-2013) (B).

**Figure 10.** Annual number of HCV treatments among individuals who received opioid substitution treatment in Norway between 2004 and 2013 according to time of treatment initiation (A) and notification status (B).

### 10.2 Study II

#### 10.2.1 Participant characteristics

Of 161 eligible patients who had achieved SVR at a Norwegian NORTH-C site, 138 individuals were included for the main analysis (Paper II, Table 1). Of those, 94 were lifetime PWID and 44 had other routes of HCV transmission, predominately iatrogenic transmission in their country of origin (mainly Pakistan). In these two groups, the median age at treatment
was 36 and 39 years and the male proportion was 61% and 57%, respectively. Among lifetime PWID, 80% reported having injected more than 100 times, 48% had lower education level, and 53% were unemployed or received welfare benefits at baseline. The median post-SVR follow-up time was 7.1 years.

10.2.2 Main findings
HCV RNA recurrence during follow-up was identified in 12 of 94 (13%) lifetime PWID, while no cases of recurrence were observed among the 44 individuals without a history of IDU. Persistent viremia was documented in 10 of the 12 cases, one case demonstrated reclearance and one case had uncertain outcome due to loss to follow-up (Paper II, Figure 1 and Table 2). Supported by results from viral sequencing and phylogenetic analysis, the incidence of persistent reinfection was 1.7/100 PY (95% CI 0.8–3.1) among lifetime PWID. Including all twelve cases yielded a slightly higher reinfection incidence of 2.0/100 PY (95% CI 1.0–3.5). The proportion of lifetime PWID who had relapsed to IDU during follow-up was 39% (37 of 94), and all cases of reinfection occurred in this group. The incidence of persistent reinfection in this subgroup was 4.9/100 PY (95% CI 2.3–8.9), increasing to 5.8/100 PY (95% CI 3.0–10.2) when including all twelve cases. In Cox proportional hazards regression analysis, no baseline factor was associated with time to reinfection (Paper II, Table 3). In logistic regression analysis (Paper II, Table 4), relapse to IDU was associated with low education level (aOR 3.64; 95% CI 1.44–9.18) and lower age at treatment, with seven times higher odds of relapse to IDU among individuals below 30 years compared to those 40 years or older (aOR 7.03; 95% CI 1.78–27.8).

10.2.3 Secondary findings
Although OST patients were excluded from the NORTH-C trial, 15 of 94 (16%) lifetime PWID had received OST at some point later, and OST during follow-up was in fact associated with increased hazard of reinfection (HR 7.31; 95% CI 2.35–22.7). This study also shed light on the pitfalls of viral sequencing of old serum samples. Of 24 potential HCV RNA positive samples eligible for viral sequencing (baseline and follow-up samples from 12 individuals), adequate sequence data were obtained only in 10 samples. All samples, except two, had also been genotyped using line probe assays and five cases demonstrated genotype switch at follow-up. No sample showed convincing evidence of mixed infection. Ultimately, based on results from line probe assays, sequencing and phylogenetics, six cases were
considered *confirmed* reinfections, while the remaining six cases were considered *probable* reinfections. Importantly, none of the individuals who presented with reinfection were aware of their current viremia.

Nine of 161 eligible SVR patients had died during the follow-up period (Paper II, Supplementary materials). There were five deaths among lifetime PWID (crude mortality rate 0.70/100 PY [95% CI 0.23-1.63]) and four deaths in the other group (crude mortality rate 1.02/100 PY [95% CI 0.28-2.61]). The causes of death among lifetime PWID were intoxication (two cases), suicide, lung cancer and liver failure. The causes of death in the other group were malignant melanoma, subarachnoid haemorrhage, subdural hematoma/liver failure, and liver failure.

**10.3 Study III**

**10.3.1 Participant characteristics**

Among 93 enrolled participants, the median age was 41 years, 83% were male, 69% had high school or higher education, 15% had part- or full-time employment and 76% had stable housing (Paper III, Table 1). Overall, 59% had injected in the past month before enrolment and among those, 27% had injected on a daily basis or more, 13% had used non-sterile needles and 15% had shared injection paraphernalia. The majority (71%) had received OST in the past month prior to enrolment. Most participants (68%) had no or mild liver fibrosis, but 17% reported hazardous alcohol consumption at enrolment. There was a gradual loss-to follow-up during the study; 87%, 78% and 72% of enrolled participants remained in the study at end of treatment, 12 and 24 weeks of post-treatment follow-up, respectively.

**10.3.2 Main findings**

The key findings from this study were the observations that recent injecting drug use and hazardous alcohol consumption decreased significantly during treatment and follow-up, while injecting risk behaviours remained unchanged (Paper III, Table 2 and Figure 1). In GEE analysis (Paper III, Tables 3 and 4), the odds of any injecting drug use decreased by 11% for each incremental study visit during treatment and follow-up (OR 0.89; 95% CI 0.83-0.95). This effect was most pronounced at end of treatment; here the odds were more than 50% lower compared to at enrolment (OR 0.47; 95% CI 0.33-0.68). The odds of hazardous alcohol use decreased by 44% for each incremental study visit (OR 0.56; 95% CI 0.40-0.77),
an effect that could be attributed to an almost 80% decrease in odds already observed at baseline compared to at enrolment (OR 0.23; 95% CI 0.09-0.61). The odds of OST were 48% higher at end of treatment compared to at enrolment (OR 1.48; 95% CI 1.07-2.04), but this increase did not endure towards end of treatment. No significant changes were found in ≥ daily injecting (OR 0.98; 95% CI 0.89-1.07), use of non-sterile needles (OR 0.94; 95% CI 0.79-1.12), sharing of injecting paraphernalia (OR 0.87; 95% CI 0.70-1.07) or non-injecting drug use (OR 1.01; 95% CI 0.92-1.10).

10.3.3 Secondary findings
Given that individuals gradually were lost to follow-up during the study, proportions reporting the outcomes were also evaluated in the slightly smaller subset of participants still present in the study at 12 weeks of post-treatment follow-up (n=73). Although not tested statistically, the trends in outcomes in this group were very similar to the observations in the main analysis (Paper III, Figure 2). In GEE analysis, no baseline variable was associated with injecting drug use, but poorer social functioning was associated with sharing of injecting paraphernalia, and stable housing was associated with OST (Paper III, Supplementary materials).

10.4 Study IV
This study reviewed reinfection risk among PWID and MSM in light of current knowledge on HCV epidemiology in these groups. Based on existing data from small and heterogeneous studies of IFN-based treatment, the incidence of reinfection after SVR ranged from 2–6/100 PY among PWID to 10–15/100 PY among HIV-infected MSM. These differences mainly reflected heterogeneity in study populations with regards to risk behaviours, but also variations in study designs and applied virological methods. The pooled reinfection rates calculated from all studies reporting data on PY were 2.1/100 PY among lifetime PWID (11 studies; 795 individuals; 43 reinfections; 2082 PY at risk), 5.6/100 PY among the subset of PWID with IDU post treatment (9 studies; 153 individuals; 29 cases; 522 PY at risk), and 12.8/100 PY among HIV-infected MSM (3 studies; 196 individuals; 38 cases; 296 PY at risk). The article concluded by proposing constructive individual- and population level strategies to address and prevent reinfection.
11 Discussion

11.1 Summary of key findings

*Study I* was a population-based observational study evaluating IFN-based HCV treatment uptake in Norway between 2004 and 2013 among OST patients with notified HCV infection. The study demonstrated a cumulative treatment uptake of 14% across all age groups. Annual treatment rates during OST were stable between 1.3% and 2.6%. Treatment uptake was associated with duration of active OST, OST continuity and benzodiazepine dispensations. *Study II* was a clinical follow-up study assessing HCV reinfection incidence among lifetime PWID who had achieved SVR in a Scandinavian treatment trial seven years earlier. The incidence of persistent HCV reinfection was 1.7/100 PY among all lifetime PWID, and 4.9/100 PY in the subset of individuals who had injected drugs after SVR. No baseline factor was associated with reinfection, but relapse to IDU was associated with age < 30 years and low education level. *Study III* was an international multicentre study evaluating risk behaviours among recent PWID longitudinally during and following IFN-based HCV treatment. Injecting drug use and hazardous alcohol consumption decreased during treatment and throughout six months of post-treatment follow-up. OST increased modestly, but no changes were observed in ≥daily injecting, use of non-sterile needles, paraphernalia sharing, or non-injecting drug use. *Study IV* was a review article on HCV epidemiology and reinfection risk in high-risk groups of PWID and MSM. In studies of IFN-based treatment, the incidence of reinfection after SVR ranged from 2–6/100 PY among PWID to 10–15/100 PY among HIV-infected MSM.

Collectively, these studies have highlighted important epidemiological and behavioural aspects of HCV infection among PWID, adding to the existing literature in a field rapidly moving forward. The findings have implications for policy and clinical practice, informing strategies to improve the HCV care cascade among PWID in the current DAA treatment era. While the results emphasize the need for increased screening and linkage to care, they also highlight the importance of post-SVR care for individuals with ongoing risk behaviours.
11.2 Study contributions and implications

11.2.1 Treatment uptake (Study I)

While most previous studies have focused on cohorts of selected PWID, this study is the first to evaluate HCV treatment uptake among OST patients at the population-level. The results are consistent with findings from a Norwegian cohort of PWID who previously had been admitted for residential drug treatment; here 19% of individuals with chronic HCV infection had received HCV treatment during a 16 years observation period between 1997 and 2012 with an overall treatment rate of 1.6/100 PY. In a community-based cohort from Northern Norway [379], cumulative treatment uptake after seven years of observation was higher (28%), probably reflecting a lower proportion of PWID included. The observed treatment rates during OST are actually more in line with the low rates (1-2% per year) reported from community-based cohorts of more marginalised PWID in the United States [279], Australia [280] and Canada [282] and clearly lower than treatment uptake in international studies of PWID engaged in multidisciplinary HCV care (6-9% per year) [264, 266, 268].

The stable and relatively low treatment rates demonstrated might therefore reflect well-documented barriers to IFN-based treatment at patient-, provider- and system-levels [290]. In particular, a low HCV awareness among OST providers and lacking infrastructures for HCV care may have been present despite ongoing expansion of Norwegian OST programs and recent trends to increasingly provide HCV care for recent PWID. A major concern, however, is the observed lack of increase in treatment uptake among older individuals, where advanced liver disease is much more prevalent.

The study identified novel pharmacoepidemiological associations between HCV treatment and drug dispensions; the odds of HCV treatment increased for each year of active OST, were higher among individuals with high OST continuity and lower among heavy benzodiazepine users. Benzodiazepine use is common among Norwegian OST patients and is shown to be associated with negative outcomes including poor social functioning and reduced retention in OST programs [380]. These factors may therefore reflect a psychosocial vulnerability specific to a group of OST patients and highlight the need for enhanced treatment uptake also among more marginalised individuals.
This study exposed weaknesses in HCV surveillance in Norway, showing that only 57% of OST patients treated for HCV were notified to MSIS. Although notification rates improved during the study period, it is still a concern that one in four individuals treated for HCV remained un-notified towards the end of the study. Further, only 38% of OST patients were notified with HCV infection. Based on surveys among users of NSP in Norway [61, 62] we would expect that 80-90% were anti-HCV positive. The low notification rate among OST patients may partly reflect a low diagnosis rate due to low testing activity in OST programs, but the low notification rate among treated individuals probably reflects vulnerable notification routines, although some lost notifications must be explained by diagnosis being made prior to 2008 (when notification routines changed) as well as failed linkage between NorPD and MSIS due to missing identity numbers in some individuals.

The study provided insights into the relative contribution of HCV treatments in the OST population compared to the total number of HCV treatments in Norway. Figure 11 illustrates this relationship by combining data from Paper I on annual treatments among OST patients (section 10.1.3; Figure 10) with estimates from NorPD on annual treatments in the general population (section 5.4; Figure 6). Overall, among all 5401 individuals treated for HCV between 2004-2013 (430-668 annually), 943 (17%) had ever received OST (70-112 annually). HCV treatments among individuals ever exposed to OST thus accounted for approximately one-sixth of all HCV treatments in this period. Although clear data are lacking, very few recent PWID not engaged in OST received treatment in this period. Thus,
the large majority (~83%) of HCV treatments have been delivered in the <50% segment of the HCV population comprising former PWID never exposed to OST and individuals exposed to HCV nosocomially (i.e. predominantly immigrants from endemic countries).

The results from this study contributed to a recent collaboration on data collection and mathematic modelling that projected the 10-year impact of existing and scaled-up HCV treatment rates on viremic prevalence and incidence among PWID across eleven country settings in Europe [381]. Data were collected on treatment rates, SVR, PWID prevalence, HCV prevalence, and OST/NSP coverage. Treatment rates among PWID for 2015 varied from less than 0.1% in Finland, to between 0.5-2% in Amsterdam, Hamburg, Norway, Denmark and Sweden, to more than 5% in the Czech Republic and Slovenia. These differences may reflect variations in treatment traditions and the fact that HCV treatment in recent PWID started at different times across countries (ranging from the mid-nineties in Slovenia to only very recently in Finland). Modelling suggested that doubling of current treatment rates in Norway could lead to an observable reduction in HCV RNA prevalence over 10 years, but substantial (~80%) reductions in prevalence would require annual treatment rates to be scaled up to 50 per 1000 PWID (infected or uninfected). An important weakness inherent to this model is that it does not take into account the increasing practical difficulties in reaching the viremic population as HCV prevalence decreases over time.

The main strength of Study I is its population-based approach, providing a large sample of individuals with opiate dependency who had received OST during a ten-year period. The liberal inclusion of individuals who received OST only short-term or intermittently has ensured a study population more representative of a wider PWID population. The study provides important baseline data on HCV treatment uptake in an essential target group for HCV treatment prior to the availability of DAA treatment. Another strength is the identification of novel associations between HCV treatment and OST continuity and benzodiazepine use. The study also highlights important limitations of MSIS.

To summarize, the findings from Study I show that HCV treatment uptake among OST patients was low and stable during the last ten years of the IFN treatment era in Norway, contributing to a relatively low proportion of the total number of treatments in this period. Improved treatment uptake in this key population is critical to realize the potential individual- and population-level benefits of current DAA treatment. The results should inform
coordinated strategies to enhance the steps of the HCV care cascade in a growing population of PWID now being eligible for HCV treatment.

**11.2.2 Reinfection (Studies II and IV)**

Study II was the first to evaluate the risk of HCV reinfection beyond the first few years after SVR. The results are generally in line with findings from previous studies of IFN-based treatment among PWID (Tables 4 and 5). Study IV subsequently reviewed the available data on reinfection risk after successful treatment. The pooled reinfection rates calculated from all studies reporting data on PY was 2.1/100 PY (95% CI 1.5-2.8) among lifetime PWID and 5.6/100 PY (95% CI 3.7-8.0) among the subset of individuals with IDU post treatment (Figure 12). This is a significant risk, but still lower than rates of primary infection reported among PWID outside the treatment setting [316].

![Figure 12. Pooled HCV reinfection rates following successful interferon-based treatment among individuals with a history of injecting drug use and among those who reported injecting after treatment. Points are rates per 100 person-years and lines are corresponding Poisson 95% confidence intervals.](image)

The results are also consistent with two more recent registry-based studies evaluating reinfection retrospectively in larger community-based cohorts. One study assessed reinfection in a Scottish cohort of lifetime PWID who had obtained SVR between 2000-2009 [325]. Among 277 individuals who were tested for HCV RNA after SVR, 7 reinfections (2.5%) were observed after a median of 4.5 years. The reinfection incidence was 1.7/100 PY among all included individuals and 5.7/100 PY among the minority (11%) who were hospitalised for
an opiate- or injection-related cause during follow-up. Another study examined reinfection in a large Canadian population-based cohort that included almost 6000 individuals (42% lifetime PWID) with at least one HCV RNA test available following either spontaneous or treatment induced clearance [382]. Among 2225 individuals with SVR, 50 reinfections (2.2%) were detected during median 5.4 years of follow-up for an overall incidence of 1.9/100 PY. Among those who through registry linkage were identified as PWID (25% of the study population), the incidence was only 1.1/100 PY. However, inherent to these registry-based studies are selection bias. As both studies only included individuals who for some reason were tested for HCV RNA after SVR, they might favour low-risk individuals with health-seeking behaviours. Also, both studies defined PWID populations by linkage to hospitalization codes for drug related diagnoses. The validity of these definitions is questionable, as one would not expect such linkage to capture a representative selection of individuals with ongoing risk behaviours.

Study IV provided a review of reinfection risk also among MSM, calculating a pooled reinfection incidence of 12.8/100 PY among HIV-infected MSM. This is considerably higher than reinfection estimates among PWID, probably reflecting the fundamental differences in epidemiology and risk factors for HCV transmission present in these populations (Table 6). Recently, a large European retrospective multicentre collaboration that included more than 600 MSM reported a slightly lower but still alarming overall reinfection incidence of 7.3/100 PY [383]. In this study, 149 of 606 (25%) individuals with confirmed SVR or spontaneous clearance were reinfected during 3 years of follow-up. Levels of secondary reinfections were very high; thirty of 70 (43%) of those with re-clearance or successful retreatment presented with a second reinfection, 5 with a third, and one with a fourth reinfection.

Figure 13 shows incidence rates of reinfection following successful treatment reported from selected studies carried out in different populations. The overall reinfection rate from Study II is similar to rates reported from other studies of lifetime PWID, but lower than rates reported from studies of individuals with recent HCV infection and HIV co-infected MSM. In contrast to earlier studies, Study II reported persistent reinfection as the main outcome and direct comparison with previously published estimates (which also have included cleared reinfections) may therefore be challenging. However, the incidence of persistent reinfection remains more relevant to inform clinical practice.
Table 6. Differences in HCV epidemiology and reinfection risk among people who inject drugs and men who have sex with men.

<table>
<thead>
<tr>
<th></th>
<th>PWID</th>
<th>MSM</th>
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<tbody>
<tr>
<td>HCV prevalence</td>
<td>High</td>
<td>Low*</td>
</tr>
<tr>
<td>Proportion of total HCV population</td>
<td>Large</td>
<td>Small</td>
</tr>
<tr>
<td>Access to HCV care</td>
<td>Poor</td>
<td>Good</td>
</tr>
<tr>
<td>Health-seeking behaviour</td>
<td>Variable</td>
<td>Common</td>
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<tr>
<td>Treatment of acute HCV infection</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Risk behaviours post-SVR</td>
<td>Variable</td>
<td>Prevalent</td>
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<tr>
<td>Transmission networks</td>
<td>Local</td>
<td>International</td>
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<tr>
<td>Reinfection rates</td>
<td>2-6/100 PY</td>
<td>10-15/100 PY</td>
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*Mainly limited to HIV-infected

Figure 13. Incidence of HCV reinfection following successful treatment from selected studies. Points are rates per 100 person-years and lines are corresponding Poisson 95% confidence intervals.

Identifying those at highest risk of reinfection is essential to aid treatment prioritizing and inform post-treatment HCV care. However, like most previous studies, Study II lacked sufficient statistical power to identify baseline risk factors. A protective effect of OST was documented in the aforementioned Canadian population-based study, in which PWID who
received OST had a 27% lower likelihood of reinfection [382]. In Study II, OST during follow-up was, somewhat contra-intuitively, associated with increased risk of reinfection in unadjusted analysis. However, OST was correlated with relapse to IDU and considering the exclusion of OST patients at baseline, OST is probably a confounder for high-risk behaviour rather than a risk factor for reinfection. Relapse to IDU during follow-up was a common event that occurred in 39% of included PWID and perfectly predicted reinfection. This is a reason for concern, particularly given that all individuals had been abstinent from drug use at least six months prior to inclusion. However, the study population was dominated by young individuals with a history of opiate use but not enrolled in OST at baseline. Given the relapsing nature of opiate dependency and the lack of prospective follow-up, this should not be a surprising finding. Relapse to IDU was associated with lower age and low education level. These are novel findings that may reflect low risk awareness and, possibly, poor social functioning as previously reported [315].

Very little is known of reinfection incidence following DAA treatment. In the setting of IFN-based therapy, there may have been considerable selection bias among individuals considered eligible for, or willing to initiate, treatment. The current therapeutic optimism and ease of DAA treatment will probably change the patient demographics and could also be associated with increasing risk behaviour. To date, only one published study has evaluated the risk of reinfection following DAA treatment, reporting an incidence of 4.6/100 PY among PWID in OST [41], while some preliminary data have been published as abstracts. Collectively, these new data are in much line with previous estimates from studies of IFN-based treatment and do not indicate any dramatic increase.

The main strength of Study II is the high inclusion rate (89%) achieved in a cohort of PWID more than seven years after completion of HCV treatment. This has minimized selection bias and provided the largest-to-date observation time (590 PY at risk) in any clinical study of HCV reinfection. Another strength is the inclusion of a low-risk non-PWID group as controls. Also, the availability of behavioural data has strengthened the reinfection diagnosis in absence of a virological ‘gold standard’, and identified a subset of PWID with ongoing risk behaviours post-SVR. Importantly, all reinfections occurred in this group. Taken together, this has provided robust real-life estimates of reinfection in a well-characterized population that may be more generalizable with regards to long-term risk than most previous reports.
Study II led to the publication of Study IV, a timely paper that represents the most comprehensive review on HCV reinfection to date.

To summarize, the findings from Studies II and IV highlight the fact that HCV care does not always end with an SVR. Although incidence rates of reinfection may be relatively low, high cumulative rates could be a concern over time, particularly in some patient populations. High levels of reinfection might compromise individual long-term treatment benefits and would also allow continued HCV transmission, potentially negating the public health benefits of treatment. Individual- and population-level efforts to address and prevent reinfection should therefore be undertaken when providing HCV care for people with on-going risk behaviour.

11.2.3 Risk behaviours (Study III)

This study is the first study to systematically evaluate risk behaviours among PWID during and following treatment for chronic HCV infection. The results are consistent with previous studies of IFN-based treatment [368, 369, 373] suggesting that drug use and injecting risk behaviours remain relatively stable during HCV treatment. Yet, in contrast to these reports, this study has shown a significant decrease in injecting drug use and hazardous alcohol consumption that sustained throughout 24 weeks of post-treatment follow-up, and also a modest increase in OST during treatment. These findings challenge common concerns that the side effects of IFN-based treatment might escalate risk behaviours among PWID, and instead demonstrate that beneficial behavioural changes could be achieved during HCV treatment. In two recent studies of IFN-free treatment to PWID [41, 213], there was no change in urine drug screens during treatment, but unfortunately, data on risk behaviours were not collected. Further studies are therefore needed to evaluate whether similar behavioural changes also could be observed in the setting of DAA treatment.

The observed changes in injecting, alcohol use and OST are novel and encouraging findings raising the hypothesis that interaction with HCV care providers could enhance patient empowerment and contribute to health-improving behaviour. The decrease in injecting occurred early, was most prominent at end of treatment, but was still present throughout follow-up. Although more than one-quarter of injectors reported \( \geq \) daily injecting throughout the study, concerns of reinfection may not be substantial as long as injection is conducted safely. In fact, injecting risk behaviours remained stable at relatively low levels, with 13%
reporting use of non-sterile needles, 2% reporting receptive needle and syringe sharing, and 15% reporting sharing of injecting paraphernalia at enrolment. Thus, counselling and education on risk reduction could be targeted at a relatively small number of individuals.

The decrease in hazardous alcohol use from 17% to 3% observed early in the study is particularly encouraging and suggests a positive effect of being enrolled in treatment. Although the majority (68%) of included individuals had mild fibrosis, it highlights the importance of minimizing post-SVR liver disease progression in an ageing population of individuals with increasing prevalence of advanced liver disease or cofactors for fibrosis progression. Collectively, these findings therefore holds promise for sustaining individual- and population-level treatment benefits in high-risk populations.

The results are also in line with a recent prospective study from Montreal that included PWID with documented acute HCV infection between 2007 and 2015 and evaluated changes in IDU after one year [384]. Individuals who received HCV treatment or spontaneously cleared their infection reported reduced IDU at follow-up compared to those who did not engage in treatment. The findings suggest that the benefits of HCV care may extend to helping PWID modify their injecting risk behaviour.

The main strength of Study III is the prospective design with longitudinal recording of comprehensive behavioural data during and following HCV treatment. This provided sufficient detail to evaluate a range of outcomes and descriptively analyse patterns of injecting and non-injecting drug use among recent PWID. The development of the international ACTIVATE clinical trial network has also provided important infrastructures for future multicentre collaborations, particularly for trials of DAA treatment for PWID.

To summarize, the findings from Study III add to a growing body of evidence suggesting that the benefits of HCV care are broader in scope and may extend beyond virological cure. The study has shown that favourable changes in drug and alcohol use can be achieved when providing HCV treatment for PWID. Although the results are modest and should be interpreted with caution, they may have important implications for reinfection incidence and post-treatment surveillance among individuals at risk for onwards transmission and liver disease progression.
11.3 Study limitations

The main limitation of Study I is caused by the linkage to MSIS. Although NorPD provides true population-based coverage, the low notification rate in MSIS introduces a potential selection bias to the study population. In fact, by restricting the study population to individuals notified to MSIS, more than 40% of patients actually treated for HCV have been excluded. Although most characteristics were similar between notified and un-notified individuals, un-notified patients were on average three years older than notified individuals. The linkage to MSIS may therefore have led to an age-related selection bias, excluding a group of older HCV infected individuals and underestimating treatment uptake in older age groups. However, this may not have altered the main finding of the study. Cumulative HCV treatment uptake among all OST patients was 9.5% (943 of 9919), and assuming 60% HCV RNA prevalence in the ageing Norwegian OST population [61-63], this finding would correspond to 16% treatment uptake among all individuals with presumed chronic HCV infection. Moreover, sensitivity analysis using logistic regression analysis among all OST patients [data on file] confirmed the same factors being associated with HCV treatment. Finally, as MSIS not adequately discriminates acute from chronic HCV infection, treatment uptake may have been underestimated by including all notified individuals regardless of the method of detection.

Another limitation is related to the quality of NorPD. While HCV treatment has been captured by the registry throughout the study period, OST administered to institutionalized patients was not registered before 2008. This may explain the high proportion of HCV treatments registered prior to initiation of OST during the first years of the study, in a period when HCV treatment for active PWID was quite unusual in Norway. Consequently, annual treatment rates during OST may have been underestimated prior to 2008, reflecting the lower trend in treatment rates observed in this period. This bias may also have undervalued OST duration and OST continuity in some individuals, but cumulative HCV treatment uptake has not been affected. Furthermore, we did not assess treatment uptake according to region of residence, which we now view as an unfortunate limitation. In health authority West, 90% of OST is prescribed by specialists in addiction medicine, compared to only 30% in the other regions [40]. In future research it will be interesting to see if the centralised OST model of the western part of the country more rapidly will adapt to new guidelines and thereby scale up HCV treatment.
Studies II and III included self-reported behavioural data, which are prone to response bias that may promote more socially acceptable responses. In Study II, data collected retrospectively from patient files could be subject to information bias as injecting behaviours might have been underreported. However, that fact that all reinfections occurred among those who reported risk behaviours supports the reliability of the responses. Although very detailed behavioural data was collected in Study III, they are still subject to the same potential bias.

Studies II and III are limited by relatively small sample sizes (n<100), and were not a priori dimensioned to identify risk factors. The failure of detecting factors associated with the outcomes may therefore be attributable to a lack of statistical power (i.e. type II error), which also may have impeded detection of changes for certain outcomes in Study III. In Study II, detailed data on risk behaviours during follow-up were largely lacking. The lack of HIV status at follow-up is particularly unfortunate, but all participants were HIV negative at baseline and HIV/HCV co-infection is very rare among PWID in Norway [61]. Despite the large sample size in of Study I, the lack of relevant clinical data in the registries (e.g. treatment outcomes, genotype distributions, stage of liver fibrosis and comorbidities) has largely limited the analysis to pharmacoepidemiological associations.

The gradual loss to follow-up in Study III may have introduced a selection bias among individuals who remained in the study towards the end of follow-up. As individuals who remain in follow-up are more likely to report favourable outcomes, they may have contributed to the positive behavioural changes observed. However, the main results are supported by similar findings in sub-analysis of individuals present at 12 weeks post-treatment follow-up. Study II is to lesser degree limited by loss to follow-up, as 89% of lifetime PWID and 80% of non-PWID who achieved SVR in NORTH-C were included. Reinfection incidence may still be underestimated, as one would expect higher levels of risk behaviours among individuals lost to follow-up.

Because Study III lacked a control group of individuals not exposed to HCV treatment, the findings could simply reflect natural fluctuations in risk behaviours among PWID. However, the GEE models used in this study are marginal models, implying that any behavioural is an average longitudinal change among individuals who are present. To better take into account individual trajectories over time, alternative models using mixed effect logistic regression were performed [data on file]. Although these models produced similar estimates, they were
not easily interpretable due to much wider confidence intervals, and therefore omitted from the final analysis.

The virological methods in Study II were suboptimal and may have limited the study. First, due to the retrospective approach with long intervals between performed HCV RNA tests, individuals with re-clearance may have been missed. This study therefore underestimates the incidence of all reinfection episodes. However, persistent reinfections are the most clinically significant endpoint and such cases have not been overlooked. Also as a result of long HCV testing intervals, the estimated dates of reinfection are very uncertain. Consequently, it is not possible to determine the slope of the hazard curve, i.e. whether reinfection risk is linear, exponential or subject to saturation. Second, the reinfection/relapse distinction is paramount to studies of reinfection, relying on sensitive methods for detection of mixed infection and careful molecular characterisation. In this study, viral sequencing proved to be challenging and adequate baseline and follow-up sequences were present for only a minority of recurrent cases. This can be explained by several factors, including primer mismatch, low viral loads and degradation of HCV RNA in old baseline samples. As a result, reinfection could be overestimated due to misclassification of cases of late relapse as reinfection. This is unfortunate, but may not be major concern as viral relapse post-SVR24 is a very rare event (<1%) [162, 348]. Also, the reinfection diagnosis is supported by results from line probe assays and robust behavioural data.

Study IV was not a systematic review and literature search was performed much at the discretion of the individual authors. While this may have biased the overview of the general epidemiology, existing reinfection studies are relatively few and have not been missed by the authors. Although the study included pooled estimates of reinfection risk with corresponding Poisson confidence intervals, a proper meta-analysis was not performed.

Finally, as all studies were based on data from the IFN era, their external validity and generalizability to the current treatment era could be questioned. In Study I, the identified factors associated with IFN-based treatment might not be relevant for IFN-free treatment. However, the documented IFN-based treatment rates are fundamental as a baseline for surveillance of future DAA treatment rates. In Study II, included individuals were not engaged in OST at the time of treatment and not monitored after treatment. This might contrast to current practice, where patient and provider awareness for the effects of harm
reduction generally has increased. Studies II and III only included individuals considered eligible for IFN-based treatment, and are therefore inherently subject to selection bias. The ease of new DAA treatment will allow increased treatment in more vulnerable groups with higher prevalence of psychiatric comorbidities and ongoing risk behaviours, and will also permit less interaction with HCV care providers. Although this could result in increasing risk behaviours and subsequent reinfections, the effect of the current transformations in HCV care remains to be seen. Under another viewpoint, one could argue that if a decrease in risk behaviours could be achieved despite the side effects of IFN, such changes are likely to be even stronger under less toxic treatment regimens.

11.4 Recommendations

11.4.1 Strategies to improve treatment uptake among PWID in Norway

Current status in Norway

An increase in HCV treatments has been observed in Norway after the introduction of DAA treatment in 2014. Figure 14 plots the estimated number of successful HCV treatments (section 5.4; Figure 7) along with estimated incidence of injecting drug use [personal communication E. J. Amundsen, NIPH] and estimated incidence of new HCV infections among PWID [30] between 2000 and 2016. The figure demonstrates that by 2014, the annual number of successfully treated individuals had exceeded the incidence of new HCV infections, signalling a very promising epidemiological shift. Between 2014 and 2017, approximately 2300 individuals have achieved SVR, corresponding to approximately 15% of the Norwegian HCV population (section 2.5.2; Figure 1 and section 5.4; Figure 7).

This encouraging development holds promise for future reductions in HCV burden in Norway. However, it is not clear to what degree conventional specialist care have succeeded in reaching PWID. For instance, among 250 individuals who had received DAA treatment at the outpatient infectious diseases clinic at AHUS by January 2017, the majority were former PWID or immigrants from endemic countries, while 21% were receiving OST and only 2% were recent PWID [data on file]. Achieving epidemic control will require treatment to be scaled-up also in groups with ongoing transmission risk. In March 2017, national DAA price competition made it possible to repeal fibrosis restrictions for genotype 1 infection in Norway. It remains to be seen how this will influence treatment uptake among PWID.
Figure 14. Estimates of successful HCV treatments, incidence of injecting drug use, and incidence of HCV infection between 2000 and 2016 in Norway.

Screening and diagnosis

Increasing treatment uptake among PWID will require coordinated efforts to address the steps of the HCV care cascade across different levels of the health care system. The first crucial step is to improve screening and diagnosis. Here, the OST setting could play a key role, representing an existing infrastructure for an important part of the Norwegian PWID population. With current IFN-free treatment, there is no reason to accept continuing low diagnosis rates in this population. Systematic HCV RNA screening should be implemented as a part of initial assessments of all OST patients and at regular intervals for HCV negative individuals with ongoing risk behaviour.

HCV RNA positive individuals should be directly linked to non-invasive liver disease staging. Because TE assessment to date has required referral to specialist in gastroenterology or infectious diseases [223], it may have represented a bottleneck in the system. An alternative approach could therefore be to implement this simple method into the OST setting. A major challenge is the fact that the Norwegian OST model (except in health authority West) is decentralised to primary care (i.e. relying on follow-up from general practitioners). This poses a challenge, as implementing a shift in guidelines may prove difficult in a decentralised system. [40].
Simplified diagnostics is also suitable for reaching more marginalised PWID not enrolled in OST. Finger-prick DPS testing and subsequent TE can provide rapid and complete diagnostic work-up under the same roof [227, 240, 246, 248]. This approach could be included in existing low-threshold services for PWID, in ambulant work towards prisons or residential drug treatment institutions, or through more innovative models such as mobile street clinics/vans [243].

Reaching former PWID no longer engaged in risk behaviours or OST represents a different challenge, as many of these individuals may not be aware of their HCV status. Public campaigns specifically aimed at persons with a history of sporadic drug use or imprisonment should be explored. In this context, general practitioners could play a key role, providing systematic HCV screening for risk groups [223].

Alternative models of care

One of the key obstacles to HCV care among PWID has been attributed to insufficient integration of substance use disorder services in mainstream health-care delivery [249, 385]. PWID are often not able to adhere to the highly structured specialist care settings in which HCV treatment traditionally is provided. Because PWID will be responsible for an increasing burden of HCV-related disease in the future [23, 24, 29, 226, 386], developing treatment models better adapted to this population should be a priority. As reviewed in section 5.3, HCV treatment has been successfully integrated in various multidisciplinary settings across different levels of health care systems. Figure 15 proposes alternative models of HCV care that could be tailored for the Norwegian setting.

Much owing to tradition and the complexity of IFN-based treatment, specialist health care has largely monopolized HCV treatment in most countries, including in Norway. This setting should probably still be the main arena for HCV treatment in Norway, particularly for more complicated cases including patients with advanced liver disease. However, the relative ease of current DAA treatment could permit resource allocation within the frameworks of specialist care. More flexible ambulant models could allow HCV providers/nurses to initiate and follow-up treatments outside the hospital setting, for instance in institutionalized or incarcerated patients. Ambulant teams are already implemented in oncology, paediatrics and psychiatry in Norway and could also be explored for HCV care.
When disseminating HCV treatment beyond conventional specialist models, the OST setting represents a key arena. OST provides a platform for HCV care within the existing infrastructures of addiction medicine, and the feasibility of such models has been documented in several settings internationally [236, 250-254]. In Norway, an integrated OST model has been adopted in Bergen and Stavanger (health authority West), with directly observed administration of OST and regular multidisciplinary follow-up from physicians, nurses, social workers and psychologists [387]. Currently, a RCT comparing the effect of integrated HCV treatment in OST versus standard treatment in specialist outpatient clinics is being performed in Bergen.

Models of care adapted for the most marginalised PWID populations is of particular relevance for the prospect of HCV elimination, which relies heavily on having effective systems capable of reaching the population at the core of the epidemic. Internationally, HCV treatment has been successfully integrated in various community-based settings [63, 214, 215, 260-266]. As discussed in section 11.2.1, mathematic modelling has suggested that 80% reduction in HCV RNA prevalence among PWID in Norway would require annual treatment rates to be scaled up to 50 per 1000 PWID; more precisely, achieving a reduction of HCV incidence to 2 per 100 PY will require annual treatment rates to be scaled up to 46 per 1000
PWID over ten years [381]. Given a PWID population size of 15 000 individuals (recent PWID and PWID in OST) at risk of HCV transmission in Norway, this would correspond to approximately 700 annual treatments. This implies that expansion of HCV care both in OST settings and in community-based settings should be of priority if population-level impact of DAA treatment is to be achieved in Norway. Expanding low-threshold clinics beyond Oslo to the largest Norwegian cities should therefore be a priority. To accomplish this, effective collaboration between specialist and primary health care is essential.

HCV treatment could also be integrated in other primary care settings [265, 267, 268]. Characteristic to Norway is the frequent use of multidisciplinary drug treatment institutions, so called ‘tverrfaglig spesialisert behandling’ (TSB), typically staffed with a general practitioner or a psychiatrist and nurses. In 2015, the number of beds in TSB was 1927, accounting for more than 684 000 bed-days with approximately 90% employed capacity [388]. This setting may hold unrealized potential for multidisciplinary HCV care for broader PWID populations, but HCV epidemiology in TSB has not been investigated. The prison setting is another potential arena for HCV care that has been explored internationally [64, 350, 351]. A recent study on mental health and addiction among inmates in Norway reported a lifetime IDU prevalence of 29% [389], but there is little data on HCV prevalence in Norwegian prisons. A large study aiming to characterize HCV epidemiology in Norwegian and Danish prisons is underway [personal communication K. B. Kielland].

**System-level reforms**

High DAA pricing has represented a health economic rationale for maintaining the traditional liver fibrosis restrictions, and thus also a major treatment barrier in many countries. To address this, a comprehensive system-level reform was implemented in Australia. In March 2016, a government funded ‘access for all’ public health policy was commenced with no cap on number of treatments per year and no liver fibrosis or drug use restrictions [390]. As a result, a massive increase in treatment uptake was experienced with an estimated 31 000 - 34 000 individuals receiving treatment between March and December 2016, corresponding to 13-15% of all individuals living with chronic HCV infection in Australia. This proportion is in fact similar to Norwegian estimates presented above, and may to a large degree reflect a warehousing effect that must be expected to wane. However, during the next decade, the population-level impact of this large-scale elimination program will be revealed.
Similar trends are seen in Norway, where the national collaboration system for purchase of drugs used by the regional health authorities has strongly facilitated DAA price competition. From March 2017, treatment for genotype 1 and 4 infection is available without fibrosis restrictions at one-fifth of the pharmacies’ retail price [222]. It remains to be seen whether this system also can promote similar discounting of emerging pangenotypic DAA regimens. Affordable DAA treatment without fibrosis restrictions for all genotypes is a prerequisite for achieving the WHO eliminations goals. In line with this, a paradigm shift in mentality must be strived for: HCV infection is a transmittable disease that should be diagnosed and treated as early as possible.

The Australian experience highlights the potential of disseminating HCV care across different health care arenas. During the last year in Australia, DAAs were prescribed both by hospital specialists, supervised medical officers and general practitioners. Interestingly, as much as 35% of individuals received their prescriptions from non-specialists, and the proportion of individuals receiving their prescriptions from general practitioners increased from 4% to 19% in few months [390]. In the Norwegian setting, DAA prescription rights could be expanded to specialists in addiction medicine. Furthermore, general practitioners could easily initiate and monitor HCV treatment under specialist supervision. A first step forward would be to implement educational programs targeted for primary care and addiction medicine. As an international organization dedicated to scientific knowledge exchange, knowledge translation and advocacy focused on HCV prevention and care among PWID, INHSU may be a key contributor in this context [391]. INHSU holds an annual scientific symposium, and over the next year the organisation will develop and deliver an education and training program which will be available for health care practitioners in drug and alcohol settings across Europe and North America.

As screening, diagnosis and treatment uptake improves in Norway, national HCV surveillance should be updated to a modern electronic notification system. Efforts should be made to improve and expand this system into a National quality registry, enabling proper surveillance of prevalence, incidence, treatment rates and treatment outcomes including reinfection rates. This could be handled by recording both positive and negative HCV RNA results in to the database. Today, the Norwegian law only permits the collection of data on cure of tuberculosis, and to also allow collection of data on HCV cure would require a change in law [personal communication H. Kløvstad, NIPH].
11.4.2 Strategies to address reinfection and risk behaviours

Long-term impact of reinfection

It must be acknowledged that HCV care among PWID not always ends with an SVR being achieved. Even low reinfection rates could be a concern over time, particularly in absence of retreatment or effective strategies for risk reduction. As shown in Figure 16, reinfection can have a major impact on the proportion of treated individuals remaining HCV RNA negative after five years. For instance, given 90% SVR and 6% reinfection rate per year, only 66% will remain HCV RNA negative after five years if there is no retreatment. Notably, none of those reinfected in Study II were aware of their reinfection prior to inclusion in the study.

The indisputable risk of reinfection offers challenges that require thoughtful clinical and public health responses. Potential strategies to address this fall into individual-level efforts to reduce reinfection risk and population-level efforts to reduce the impact of reinfection in a public health perspective (Table 7).

<table>
<thead>
<tr>
<th>SVR</th>
<th>2%</th>
<th>4%</th>
<th>6%</th>
<th>8%</th>
<th>10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>95%</td>
<td>86%</td>
<td>77%</td>
<td>70%</td>
<td>63%</td>
<td>56%</td>
</tr>
<tr>
<td>90%</td>
<td>81%</td>
<td>73%</td>
<td>66%</td>
<td>59%</td>
<td>53%</td>
</tr>
<tr>
<td>85%</td>
<td>77%</td>
<td>69%</td>
<td>62%</td>
<td>56%</td>
<td>50%</td>
</tr>
<tr>
<td>80%</td>
<td>72%</td>
<td>65%</td>
<td>59%</td>
<td>53%</td>
<td>47%</td>
</tr>
<tr>
<td>75%</td>
<td>68%</td>
<td>61%</td>
<td>55%</td>
<td>49%</td>
<td>44%</td>
</tr>
</tbody>
</table>

Figure 16. Proportion of individuals remaining HCV RNA negative 5 years after successful treatment, according to different scenarios for sustained virologic response (y-axis) and reinfection rates (x-axis). Adapted from J. Grebely, Kirby Institute.
Table 7. Individual- and population-level strategies to address HCV reinfection and risk behaviours among people who inject drugs.

<table>
<thead>
<tr>
<th>Individual-level</th>
<th>Population-level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acknowledgement</td>
<td>Rapid treatment scale-up</td>
</tr>
<tr>
<td>Education and counselling with peer support</td>
<td>Post-SVR HCV RNA surveillance</td>
</tr>
<tr>
<td>Harm reduction optimisation</td>
<td>Rapid access to retreatment</td>
</tr>
<tr>
<td>Regular on- and post-treatment follow-up</td>
<td>Targeted treatment of high-risk transmitters</td>
</tr>
</tbody>
</table>

**Individual-level strategies**

The crucial first step is acknowledgement of the problem without stigma and discrimination; reinfections will occur and simply confirms that a target population of high-risk individuals is being treated. Excluding people from potentially life-saving treatment based on behavioural criteria and concerns of reinfection is unethical and in conflict with current international treatment recommendations. There is no tradition in modern health medicine to emphasize the ‘self-inflicted’ aspect of disease. The analogy to other lifestyle-associated disorders is apparent: One does not withhold anti-diabetic treatment from obese patients, treatment of lung cancer from smokers, or HIV treatment from MSM.

Although an emerging body of data are suggesting that the benefits of HCV treatment may extend beyond virological cure, profound behavioural changes should not be expected. Still, it is reasonable to assume that regular contact with a HCV nurse or physician throughout treatment can provide opportunities for counselling and discussing behavioural change. Although current DAA treatment allows much less interaction with health care providers, regular on-treatment follow-up is strongly recommended for individuals with potentially modifiable risk behaviours. All patients engaged in treatment should be offered information, education and counselling about the risk of reinfection associated with high-risk sexual activity and unsafe injecting practices [103, 353]. Reduction of harmful alcohol consumption should be encouraged, particularly for those with evidence of progressive liver disease. Peer support could be helpful to enhance patient motivation and learning.

Individual-level prevention of reinfection faces the same challenges as prevention of primary infection (section 2.8.1). Although there are little data evaluating the impact of harm reduction on reinfection incidence, it is reasonable to assume that these interventions also
would be effective in this setting. Recent epidemiological data from Canada in fact suggest a protective effect of full harm reduction coverage (OST and NSP including complete injection paraphernalia) on reinfection risk [392]. Combined harm reduction interventions should therefore be optimized for all recent PWID engaged in HCV treatment. Access to multidisciplinary services and support including addiction treatment is essential and may also play a role in influencing behavioural change [103, 249, 393]. Novel behavioural interventions to reduce post-treatment risk behaviours, however, have not been explored.

Certain clinical features of reinfection have to be taken into consideration when discussing its individual-level implications. As reviewed previously (section 6.1), reinfection after spontaneous clearance generally exhibits high rates of rec clearance with lower viral loads and shorter duration of viremia than in primary infection. Reclearence of reinfections after successful treatment may also occur, indicating a benign clinical course also in this setting; for instance, in 3 of 6 reinfections detected in the CO-STAR study [41], viremia were only transient with subsequent undetectable HCV RNA. Moreover, reinfection does not represent virological failure and may therefore generally be easy to treat. However, reinfection occurring in a cirrhotic patient would always be more concerning than in a non-cirrhotic patient, as it could contribute to further liver disease progression. Also, acute reinfection could theoretically represent an insult to the cirrhotic liver resulting in hepatic decompensation. Yet, to the best of our knowledge, no such cases have been described.

**Population-level strategies**

At the population-level, even low reinfection rates could be a concern over time, particularly if there is no treatment scale-up or access to retreatment (Figure 15). A slow or absent treatment scale-up might create an increasing number of susceptible individuals without reduction of the viremic reservoir. As reinfection incidence depends on the viremic prevalence in a given population, this could result in increasing numbers of new infections. Thus, as illustrated by an Australian study [394], a rapid treatment scale-up among PWID is necessary to reduce the impact of reinfection over time. In this study, it was modelled that annual treatment rates of at least 8% would be required to curb an increasing pool of secondary infections within 2030. In this setting, early detection of reinfections and access to retreatment would be essential. Individuals with a high probability of continued high-risk behaviour after SVR should therefore undergo regular HCV RNA screening, preferable
within a multidisciplinary treatment setting, and quickly get access to retreatment if reinfection is detected.

Reinfection incidence will also depend on the level of risk behaviours in the population. As reviewed in section 2.8.2, the prevention benefit hypothesis is derived from dynamic transmission models assuming that reinfection risk equals primary infection risk, with transmission risk being modified by individual harm reduction status. However, reported reinfection incidence is generally lower than primary infection incidence reported among PWID outside the treatment setting [316]. Assuming no protective immunity of importance, it is therefore likely that being engaged in treatment and achieving SVR reduces reinfection risk. If this is the case, transmission models would be much more effective in reducing HCV incidence and prevalence among PWID. A recent modelling study of aggressive treatment among PWID in Norway incorporated this perspective by examining the impact of reducing the probability of reinfection post-SVR [395]. For instance, in a scenario assuming a reinfection probability of 50% of that of the primary infection, the number of new and total viremic infections would fall dramatically, and the proportion of new infections attributable to reinfections would fall from 30% to 15%. Thus, behavioural interventions aimed at reducing reinfection risk can have substantial population-level impact in a large-scale treatment program, and should therefore be explored. The potential role of a prophylactic HCV vaccine in this setting is very intriguing but remains to be evaluated [142, 143].

Targeted HCV treatment for high-risk groups could represent an opportunity for epidemic control [130, 132]. Individuals at high risk of reinfection are probably also the ones most likely to transmit the virus forward. Treatment of high-risk transmitters may therefore have great prevention potential, as these individuals, even if only temporarily, are kept out of the viremic pool. This perspective, based on the prevention benefit hypothesis, is supported by current international treatment guidelines that recommend prioritized treatment for active PWID regardless of fibrosis stage [218, 220, 396]. Targeted HCV treatment for high-risk individuals could be achieved through network-based strategies analogous to the contact tracing methods that have been used for many decades to control sexually transmitted diseases. PWID rarely contribute to international HCV transmission, but instead engage in small local networks of injection partners [131, 397]. In clinical practice, most often single persons within such networks are treated, resulting in a high risk of reinfection. Modelling data have suggested that a feasible approach, both in settings of primary infection and
reinfection, would be to explore and treat whole networks using a ‘bring your friend’-strategy [133]. This innovative model is currently being employed in an ongoing study of community-based treatment-as-prevention (ClinicalTrials.gov: NCT02363517).

**Post-SVR care**

The obvious benefits of achieving SVR are well recognized with important reductions in rates of liver related complications, HCC and mortality, as well as extrahepatic morbidity [149, 160]. That fact that not all individuals will accomplish these benefits underlines the importance of post-SVR counselling and surveillance. Strategies to reduce the risk of liver-related complications for individuals with advanced liver disease are already implemented through HCC surveillance programs [156]. In analogy to this, an extended HCV care continuum to preserve the benefits of SVR among PWID should be considered for individuals with high-risk behaviours. Table 8 proposes a parallel post-SVR care algorithm for individuals at risk of reinfection and individuals at risk of liver related complications. Post-SVR care exemplifies modern ‘new-school’ hepatology, providing a holistic socio-hepatologic approach to HCV infection, maximizing the benefits of SVR for all patient populations [160].

<table>
<thead>
<tr>
<th>Reinfecion</th>
<th>Liver-related complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education and counselling</td>
<td>Education and counselling</td>
</tr>
<tr>
<td>Harm reduction</td>
<td>Harm reduction</td>
</tr>
<tr>
<td>Needle and syringe programs</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Opioid substitution treatment</td>
<td>Obesity</td>
</tr>
<tr>
<td>HCV RNA surveillance</td>
<td>HCC surveillance</td>
</tr>
</tbody>
</table>

**Table 8.** Post-SVR care for individuals at risk of reinfection and liver-related complications.

**11.5 Towards a national action plan for HCV elimination**

Coordinated efforts across different levels of the health care system will be required to achieve the full population-level benefits of DAA treatment and strive for the ambitious WHO goal of HCV elimination within 2030. Potential strategies tailored for the Norwegian setting should be orchestrated in a national action plan. Based on the previous discussions, the following components should be considered:
**Prevention**

- Increase OST coverage in all health regions
- Expand NSP (including complete injection paraphernalia) to all large cities
- Access to complete injection equipment at pharmacies and at different health care arenas for PWID (OST, NSP, TSB, prisons, low-threshold settings, general practice)
- Model robust treatment-as-prevention scenarios calibrated to Norwegian epidemiology

**Diagnosis**

- Increase HCV screening across the different health care arenas for PWID (OST, NSP, TSB, prisons, low-threshold settings, general practice)
- Simplify HCV diagnostics with increased use of DPS testing and PoC diagnostics
- Simplify liver fibrosis assessment with increased use of TE
- Launch public information campaigns aimed at former PWID and immigrants
- Establish NGS to distinguish reinfection from relapse among high-risk individuals

**Treatment and care**

- Integrate HCV treatment in OST, TSB and prisons
- Establish low-threshold HCV clinics in large cities
- Explore ambulant treatment models within specialist health care
- Scale-up treatment dimensioned to curb new infections and reinfections in populations with ongoing transmission
- Targeted treatment of high-risk transmitters including transmission networks
- Establish post-SVR care for individuals at risk of reinfection, enabling routines for harm reduction optimization, HCV RNA surveillance and retreatment

**Surveillance**

- Update MSIS to an electronic surveillance system that expand to also include HCV RNA negative tests in patients who previously tested positive
- Implement a national quality registry for HCV infection administered by NIPH, enabling surveillance of
  - incidence and prevalence at the population level and in high-risk groups
  - treatment uptake at the population level and among PWID populations
  - treatment outcomes (SVR and reinfection rates)
Policy

- Budget the total costs of a elimination program
- Encourage further DAA price competition and negotiations within the national collaboration system for drug purchases
- Repeal fibrosis restrictions for treatment of all genotypes
- Expand DAA prescription rights to also include specialists in addiction medicine
- Implement educational programs and supervised DAA treatment in primary care settings

11.6 Future research priorities

Achieving the WHO elimination targets will require continued research to inform both policy and clinical practice. Current DAA therapies provide the tools, but there are many remaining knowledge gaps that represent barriers to effective prevention and management of HCV infection among PWID globally. A key international research priority now is to document DAA treatment outcomes across different PWID populations. Of particular relevance in more marginalised populations of recent PWID is to evaluate factors associated with non-adherence, non-completion, non-response and reinfection. In this context, novel strategies and treatment models to enhance the steps of the HCV care cascade should be explored. Further, more data is needed to evaluate the efficacy of potential HCV prevention strategies, including harm reduction interventions, vaccines, and treatment-as-prevention programs. Empirical evidence to support the prevention benefit hypothesis is urgently needed to inform HCV eradication strategies. Also, there are still fundamental research needs on HCV epidemiology, including updated estimates for current PWID population sizes, harm reduction coverage, HCV prevalence and incidence, treatment uptake, and reinfection rates.

The following research priorities are highly relevant in a Norwegian context and directly related to the results from this thesis:

- Basic data on HCV epidemiology in Norway is needed, including reliable estimates on prevalence, incidence, diagnosis and notification rates, treatment uptake and SVR. Establishing a new national surveillance system/quality registry at NIPD could provide the key to these data.
- Population-based DAA treatment uptake among Norwegian OST patients should be evaluated and compared with the baseline IFN-based treatment uptake in this population. This could be done by registry linkage using the same method as in Study I, but the
pitfalls of MSIS should be taken into consideration. Treatment uptake among recent PWID in Norway could be documented by linkage of clinical cohorts to national registries.

• Barriers and facilitators to HCV treatment among PWID, including pharmaco-epidemiological associations, should be identified. The hypothesis that OST facilitates HCV treatment should be explored further at the population level.

• DAA treatment outcomes among PWID should be evaluated in clinical trials and real-life settings. The feasibility of models of care tailored for the Norwegian setting (e.g. integrated care in OST, low-threshold clinics, TSB and prison) should be explored, also within controlled studies.

• The incidence of HCV reinfection following DAA treatment should be evaluated carefully as treatment uptake increases among PWID. Sufficient follow-up time and regular testing intervals is crucial to get robust estimates of long-term risk. In such studies, NGS should be the preferred method to distinguish relapse from reinfection, but a more pragmatic approach relying on risk behaviours could also be justified.

• Factors associated with HCV reinfection should be identified, including the effects of OST and NSP. Larger studies are needed to achieve statistical power, and an international collaboration on a pooled analysis has therefore been proposed.

• Patient attitudes towards reinfection and risk avoidance before and after successful HCV treatment should be explored, also using qualitative study designs.

• Drug and alcohol use, and injecting risk behaviours should be evaluated longitudinally during and following DAA treatment within well-dimensioned studies with sufficient follow-up time. Factors associated with behavioural change, including the effect of HCV treatment, as well as the impact of ongoing risk behaviours on treatment outcomes, should be assessed.

• Novel interventions for preventing HCV reinfection should be evaluated, including the impact of on-treatment counselling and post-SVR care. The effect of HCV RNA surveillance on reinfection incidence could be evaluated in controlled trials with individuals being randomized to different follow-up intervals. As reinfection is expected to be a relatively rare event, such studies would require a large sample size and international collaboration.
12 Concluding remarks

The burden of HCV infection among PWID is substantial and continues to increase due to low treatment uptake in ageing cohorts of PWID. Current DAA treatment provides opportunities for reversal of disease burden and epidemic control that may be unprecedented in modern medicine. In Norway, approximately 13 500 individuals are living with chronic HCV infection, and the large majority of these cases are found in PWID populations. Recent Norwegian epidemiological data demonstrate encouraging trends with a decreasing incidence of HCV infection paralleled by an increasing number of successful treatments.

This thesis establishes the baseline as we move towards HCV elimination in Norway, highlighting key challenges that must be addressed if this is to be achieved. The results confirm that treatment uptake among OST patients was low during the last ten years of the IFN treatment era, contributing to a relatively low proportion of the total number of treatments. Furthermore, the findings demonstrate that reinfection may be a concern over time among individuals with ongoing risk behaviour. However, the results also indicate that favourable behavioural changes can be achieved when providing HCV treatment for PWID.

Coordinated efforts across different levels of the health care system are required to optimize the HCV care cascade among PWID and realize the full public health benefits of DAA treatment. In accordance with the WHO targets, a national action plan for HCV elimination should be implemented in Norway. Potential strategies fall into prevention (improved harm reduction coverage), diagnosis (improved screening and assessment), treatment and care (scaled-up integrated treatment and post-SVR care), surveillance (monitoring of incidence, prevalence and treatment outcomes), and policy (budgeting, price negotiations and removal of fibrosis restrictions). Moving forward, there are many remaining knowledge gaps that must be addressed in order to achieve effective prevention and management of HCV infection among PWID.
References


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