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## On the path towards universal coverage of hepatitis C treatment among people receiving opioid agonist therapy (OAT) in Norway: a prospective cohort study from 2013 to 2017

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4 **2 opioid agonist therapy (OAT) in Norway: a prospective cohort study from 2013 to 2017**  
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35 **31 Competing interests**

36 I.O. is employed at the Centre for Pharmacoepidemiology, Karolinska Institutet, which receives grants  
37 from several entities (pharmaceutical companies, regulatory authorities, and contract research  
38 organizations) for performance of drug safety and drug utilization studies, unrelated to this work. None  
39 of the other authors have competing interests.  
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## Abstract

### *Objectives*

We aimed to calculate cumulative hepatitis C (HCV) treatment coverage among individuals enrolled in opioid agonist therapy (OAT) in Norway between 2013 and 2017, and to document the treatment transition to direct-acting antiviral agents (DAA). Moreover, we aimed to describe adherence to DAAs in the same cohort.

### *Design:*

Prospective cohort, registry data

### *Setting:*

Specialist health care service (secondary)

### *Participants and outcomes:*

This observational study was based on data from The Norwegian Prescription Database (NorPD). We studied dispensed OAT and HCV treatment annually to calculate the cumulative frequency, and employed secondary sources to calculate prevalence, incidence and HCV treatment coverage from 2013 to 2017, among the OAT population. Factors associated with adherence to DAAs were identified a priori and subject to logistic regression.

### *Results*

10,371 individuals were identified with dispensed OAT, 1,475 individuals of these with dispensed HCV treatment. Annual HCV treatment coverage increased from 3.5% (95% CI: 3.2-4.4) in 2013 to 17% (95% CI: 17-20) in 2017, giving a cumulative HCV coverage among OAT patients in Norway of 38.5%. A complete shift to interferon-free treatment regimens occurred, where DAAs accounting for 32% of HCV treatments in 2013 and 99% in 2017. About two-thirds of OAT patients were considered adherent to their DAA regimens across all genotypes. High-level of OAT continuity was associated with improved adherence to DAAs (aOR 1.4, 95% CI: 1-2, p=0.035).

### *Conclusions*

A large increase in HCV treatment coverage attributed by a complete shift to interferon-free regimens among the Norwegian OAT population has been demonstrated. However, a further substantial scale-up in HCV treatment is required to reach the universal targets of controlling and eradicating the HCV endemic.

## Strengths and limitations - summary

- All dispensed drugs from pharmacies in Norway are registered in the database
- The completeness, precision, and validity of data are high among a hard-to-reach population
- Drugs administered in outpatient clinics are not necessarily captured by NorPD
- Data was not linked on an individual level to diagnosis codes of chronic HCV
- HCV prevalence and incidence data is imprecise

Keywords: Hepatitis C (HCV), treatment uptake, treatment coverage, direct-acting antivirals (DAAs), opioid agonist therapy (OAT), adherence,

## 109 Background

110 The large burden of chronic hepatitis C (HCV) among people who inject drugs (PWID) and recent  
111 developments in HCV medications creates an opportunity to eradicate HCV epidemics. Worldwide,  
112 about 71 million people are chronically infected with the virus and 399.000 died annually from HCV  
113 related complications like liver cirrhosis or hepatocellular carcinoma (1, 2). Despite the low aggregated  
114 HCV prevalence in many countries (1.5-3.5% in Western Europe and <1.5% in North America),  
115 prevalence is much higher among PWID (50%, or more) (3-5). The World Health Organization's Global  
116 Health Sector Strategy aims to eliminate viral hepatitis as a public health treat by 2030 (2). The even  
117 bolder Norwegian HCV strategy aims to reduce national incidence by 90% by 2023 (6). Eliminating  
118 chronic HCV requires a significant effort in terms of increasing uptake of testing, diagnosing, and  
119 linking to care. In addition, other strategies have been proposed alongside increasing antiviral treatment,  
120 such as opioid agonist therapy (OAT) scale-up, safe injection sites and sterile injection equipment to  
121 reach these objectives (2, 7).

122  
123 Injecting drug use and needle sharing is the major driver of HCV incidence (8), however, the coverage  
124 of preventive interventions, such as needle and syringe programs, remains poor among PWIDs (9).  
125 Number of PWIDs in Norway is stable at around 9000 (2.6 per 1 000 inhabitants aged 15-64 years) (10,  
126 11), and opioids and amphetamines are the main injected drugs (11, 12). Modelling studies suggest that  
127 around 7000 former and current PWIDs are living with chronic HCV with an estimated 400 new cases  
128 annually (13, 14). Both HCV-related liver morbidity and mortality are increasing among PWIDs and  
129 are likely to continue to increase until 2022 (14).

130  
131 OAT has been put forward to play a vital role in the management of chronic HCV among people with  
132 opioid dependence and has been shown to reduce the risk of HCV acquisition (15). For these reasons,  
133 OAT may be crucial intervention for achieving large reductions in HCV transmissions by reducing risk  
134 behaviors like injecting use, sharing of injecting equipment and number of sex partners (16). HCV  
135 testing rates have been low in the national OAT program in Norway with great annual and regional  
136 variations (5, 17-20). Only in parts of western Norway, as part of the multicenter INTRO-HCV study,  
137 all patients receiving OAT have been systematically tested and examined with elastography as part of  
138 an annual health assessment since 2017 (21). Even if access to HCV treatment is improving, HCV  
139 treatment coverage remains low (8, 22-25). Globally, the coverage of HCV curative treatment was 13%  
140 by 2016 (26). In Norway, annual HCV treatment coverage among OAT patients was between 1.3% to  
141 2.6% in the period from 2004 to 2013, giving a cumulative HCV coverage for the period of 14% (27).

142  
143 The introduction of direct-acting antiviral (DAAs) medications, with a curation rate of >90%, safer and  
144 better-tolerated than interferon-based therapy, has dramatically changed the treatment of chronic HCV  
145 infections (28, 29). Even if currently expensive, they are considered cost effective from a societal  
146 perspective as universal coverage with antiretroviral treatment could prevent large expenses related to  
147 future complications (30-35). Combining DAAs with the OAT delivery platform may thus prove critical  
148 for achieving reductions in HCV prevalence and incidence (22). A number of treatment barriers exist,  
149 which should in turn be carefully addressed, nevertheless, treatment barriers should not exclude PWIDs  
150 from HCV treatment (8, 36, 37). Both World Health Organization and Norwegian guidelines support  
151 DAA treatment among PWIDs and have also shown good outcomes in systematic reviews (24, 25, 38).

152  
153 The pathway to universal HCV treatment coverage has not been well documented at country levels,  
154 hence, the primary aim of the study was to:

- 155 1) Document HCV treatment uptake annually and cumulatively after the introduction of DAAs  
156 among patients receiving OAT in Norway from 2013-2017 and to calculate HCV treatment  
157 coverage, both annually and cumulatively.
- 158 2) A secondary objective is to document whether there has been a shift or not to interferon-  
159 free treatment regimens.
- 160 3) A third objective is to evaluate adherence to DAAs among OAT patients across all  
161 genotypes in Norway as there are limited studies among this marginalized group of patients.

162

## 163 Methods

164

### 165 Study design and data sources

166 This is an observational study among OAT patients from 2013 to 2017 in Norway. Data were extracted  
 167 from The Norwegian Prescription Database (NorPD) from January 1, 2013 to March 31, 2018. The  
 168 database covers the entire Norwegian population and records all drugs dispensed from pharmacies in  
 169 Norway, hence leaving only over-the-counter drugs and drugs administered at hospitals and nursing  
 170 homes. All drugs are classified according to The Anatomical Therapeutic Chemical (ATC) classification  
 171 system (39). Defined daily doses (DDDs) according to 2018 (40) were employed to quantify the  
 172 dispensed OAT and HCV medications respectively. The DDDs are the assumed average maintenance  
 173 dose per day for a drug used for its main indication (41).

174

175 Data from The Norwegian Centre for Addiction Research were used for estimating the prevalence of  
 176 chronic HCV among OAT patients, whereas incidence data among Norwegian PWIDs was gathered  
 177 from The Norwegian Institute of Public Health and Meijerink et al. (14) The former publish annual  
 178 status reports on prevalence, whereas the latter have demonstrated the incidence in a compartmental  
 179 model for HCV infections from 1973-2030 in Norway. These data were not linked on an individual  
 180 level.

181

### 182 Study population and definitions

183 The study population included all individuals with at least one dispensed prescription of buprenorphine  
 184 (ATC code N07BC01), methadone (N07BC02), buprenorphine-naloxone (N07BC51), and  
 185 levomethadone (N07BC05). Other opioids are very rarely used for OAT in Norway and considered  
 186 outside national guidelines (42). Patients <18 years and with other indications than OAT were excluded  
 187 from the study on the basis of formulation, chronic pain and palliative care reimbursement codes (Figure  
 188 S1).

189

190 Exposure to HCV treatment was defined as being dispensed either pegylated interferon alpha (L03AB05  
 191 and L03AB11) and ribavirin (J05AP01) or DAAs (group J05AP) during the study period. Thus,  
 192 definition of treatment uptake was any individual on OAT who has been dispensed HCV treatment. Any  
 193 individual who died was censored in the calendar year they passed away. Rates were calculated by  
 194 dividing number of individuals with dispensed HCV treatment by individuals on OAT, stratified by each  
 195 calendar year. The cumulative frequency, which is the addition of successive years of treatment uptake,  
 196 was then calculated. HCV treatment was stratified as overall treatment with any chronic HCV  
 197 medication and treatment with solely DAAs.

198

199 HCV treatment coverage was defined as individuals on OAT identified in NorPD annually, adjusted for  
 200 death, HCV prevalence, and new cases of chronic HCV each year, which had received treatment for  
 201 chronic HCV during the study period. Mean prevalence during the study period among patients enrolled  
 202 in OAT ranged from 51% in 2013 to 43% in 2017 (5, 17-20) and proportional prevalence among OAT  
 203 individuals were calculated per calendar year. Incidence was around 400 per year for PWIDs during the  
 204 study period (14). It proved methodologically challenging to estimate the HCV incidence among OAT  
 205 individuals from PWIDs due to lack of reliable evidence from the literature, and for this reason expert  
 206 opinion were obtained from clinicians in addiction medicine and set to 0.70 (70%). We developed the  
 207 following basic model for our coverage calculation:

208

$$209 \quad HCV_{cov} = \frac{t_{HCV}}{p_{HCV} + i_{HCV}} * 100$$

210

211 where HCV cov is HCV coverage,  $t_{HCV}$  = number of OAT patients with dispensed HCV treatment,  
 212  $p_{HCV}$  = number of OAT patients with chronic HCV and  $i_{HCV}$  = number of new cases of chronic  
 213 HCV among OAT patients. Coverage was calculated annually for Norway and by Health County, and  
 214 as cumulative frequencies.



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2  
3 215 We defined adherence to DAA as having collected prescriptions equivalent to three months of treatment  
4 216 or more. DAAs for adults, which in Norway is prescribed only by specialists in either infectious  
5 217 medicine or gastroenterology, are collected for one-month-at-a-time basis where a typical DAA  
6 218 treatment course is 12 weeks, i.e. three dispensed prescriptions and  $\geq 84$  DDDs. The exception is the  
7 219 drug combination ledipasvir/sofosbuvir, which may be prescribed for eight weeks (two collections and  
8 220  $\geq 54$  DDD) for cases of previously untreated genotype 1 infections. This allowed us to examine  
9 221 adherence based on number of dispensed prescriptions and DDDs. Impending factors associated with  
10 222 treatment adherence to DAAs were identified a priori and included gender, age, and OAT continuity,  
11 223 and subject to multivariate analyzes in a step-by-step model.  
12 224

13  
14 225 Finally, OAT continuity was defined according to dispensed DDDs and stratified into three categories,  
15 226 ranging from a high level of OAT continuity in category I ( $>2$  DDD), medium in category II (2-1 DDD),  
16 227 and to a low level of OAT continuity in category III ( $<12$  DDD). One DDD for methadone and  
17 228 buprenorphine is 25mg and 8mg respectively.  
18 229

### 19 230 Statistical analyzes and strategy

20 231 Descriptive data are presented as frequencies, percentages, means, and with corresponding 95%  
21 232 confidence intervals where appropriate. Logistic regression on factors associated with adherence are  
22 233 presented as odds ratio (OR) and adjusted odds ratio (aOR) when adjusted for age, gender and OAT  
23 234 continuity.  
24 235

25 236 The initial processing of the received encrypted file from NorPD was completed in SPSS version 24.  
26 237 Secondly, the file was converted and subsequently analyzed in Stata SE version 15 (StataCorp, TX,  
27 238 USA). Map figures were made in R.  
28 239

### 29 240 Data handling and ethical considerations

30 241 This study was approved by the regional committee for ethics in medical research (no. 2018/939/REK  
31 242 Vest). It was conducted in accordance with the Helsinki Declaration and as an observational study in  
32 243 accordance with international accepted STROBE guidelines (43).  
33 244

### 34 245 Patient and public involvement

35 246 Since all registry data was received pseudo-anonymously from the registry administrator and  
36 247 subsequently analyzed anonymously no written consent was obtained from any of the individuals in the  
37 248 study. No patients were directly involved in this study, however, as part of the bigger INTRO-HCV  
38 249 project patients through user organizations such as Pro-LAR, were involved in the planning process,  
39 250 workshops that included design and recruitment, protocol writing and assessment of the burden of the  
40 251 intervention in the randomized controlled trial.  
41 252

## 42 253 Results

### 43 254 Basic characteristics of study population

44 255 A total of 10,371 individuals were identified in NorPD having received  $\geq 1$  OAT prescriptions during  
45 256 the study period from 2013 to 2017 (Table 1). Almost 70% were male, mean age of 43 years and 45  
46 257 years in 2013 and 2017, respectively. The majority of the OAT patients were treated with  
47 258 buprenorphine-based OAT medication (55% in 2013, 60% in 2017). Over 50% of individuals on OAT  
48 259 had a high level of continuity. Altogether 692 individuals died during the study period.  
49 260

50 261 (insert Table 1)  
51 262

### 52 263 HCV treatment uptake and coverage

#### 53 264 HCV and DAA treatment uptake

54 265 All individuals were stratified according to the year in which they received OAT and HCV treatment.  
55 266 Excluding deaths, this gave a fairly stable OAT population just in excess of 7500 annually. In 2013, 146  
56 267 OAT patients received HCV treatment. Treatment uptake increased over time with 597 patients  
57 268



receiving HCV treatment in 2017. Overall 1475 patients on OAT received HCV treatment during the study period, with an annual HCV treatment uptake increasing from 1.9% (95% CI: 1.6-2.3%) of OAT patients in 2013, to 7.9% (95% CI: 7.3-8.5%) in 2017 (Table S1). By 2017, the cumulative frequency of HCV treatment reached 19% among patients on OAT.

Of the 1475 individuals that received HCV treatment during the study period, 1235 were treated with DAA medications. The annual DAA treatment uptake ranged from 0.6% (95% CI: 0.4-0.8%) in 2013, to 7.8 (95% CI: 7.2-8.4%) in 2017. The proportion of treated individuals receiving DAAs increased over time from 32% of HCV treated OAT patients in 2013 to 99% in 2017.

#### HCV treatment: coverage

We calculated annual HCV coverage among the estimated number of OAT patients that are HCV infected, which ranged from 3.5% (95% CI: 3.2-4.4%) in 2013 to 17% (95% CI: 16.9-19.6%) in 2017. This gave a cumulative frequency that reached 38.5% in 2017 (Table 2). Figure 1 shows cumulative HCV coverage from 2013 to 2017 by the four health counties in Norway (HCV<sub>cov</sub> and data from Table S2 were used for these calculations). There is little variation in treatment coverage across the four health counties.

(insert Figure 1 + Table 2)

#### Adherence to DAAs

Overall, almost 70% of the OAT patients were adherent to their DAA regimen and thought to have finished their DAA treatment course (Table 3). There was no major differences by gender or OAT drug. However, for age, patients in the age group 18-35 were less adherent (42%) compared with older age groups. The drug combination of elbasvir/grazoprevir, commonly used for treatment of genotype 1 infections, had by far the utmost adherence (93%) compared to treatment combinations of sofosbuvir/velpatasvir, and ledipasvir/sofosbuvir, which both were around 70%. However, sometimes ledipasvir/sofosbuvir is prescribed for eight weeks, in which case yields an overall adherence of 78%.

In multivariate analyzes, only adherence to DAAs was associated with OAT continuity (adjusted OR 1.4, 95% CI: 1.0-1.8 p=0.035).

(insert Table 3)

## Discussion

The HCV treatment coverage has increased substantially, yet it seems to low if the ambitious targets of ending the endemic are to be met. Annual treatment uptake increased from 1.9% of all OAT patients in Norway in 2013 to 7.9% in 2017, which gives a cumulative frequency of around 19% over the study period. However, cumulative HCV treatment coverage among OAT patients with assumed chronic HCV in Norway was just above 38%, with annual treatment rates that ranged from 3.5% in 2013 to 17% in 2017. Secondly, we observed a complete shift in the HCV treatment among OAT patients in Norway during the study period, from two-thirds treated with DAAs in 2013, to nearly all in 2017 (99%). Finally, about two-thirds of all OAT patients with chronic HCV were considered adherent to their DAAs regimen, which improved with level of OAT continuity.

Immense advances have been made in chronic HCV treatment since the introduction of DAAs in recent years, however multiple studies have demonstrated continued low treatment uptake among PWIDs and OAT patients midst this marginalized group of patients (23, 27, 44). The marked scale-up and complete shift to DAAs among OAT patients in Norway during the study period is in line with both international recommendations set out by the WHO and national guidelines to offer HCV treatment to both PWIDs and OAT patients (2, 45). Prior to the introduction of DAAs, Midgard et al (2016) showed an annual treatment coverage of 1.3% to 2.6% between 2004 and 2013 among Norwegian OAT patients, giving a cumulative treatment coverage of 14% during the entire study period. Considering there is not in place a national and systematic program for testing and linking to HCV care among PWIDs, nor has the full

effectiveness of integrated treatment combining OAT and HCV treatment been fully demonstrated (46), HCV coverage would probably be substantially higher with a comprehensive model of integrative care where both testing and treatment were provided in OAT outpatient clinics.

Treatment with DAAs in Norway was until February 1, 2018, limited by strict eligibility criteria based on stage of liver fibrosis. Since then, DAA treatment has been offered to all regardless of genotype and level of liver fibrosis. As a result, treatment demand increased and coverage of curative HCV treatment has amplified, especially among former PWIDs and immigrants (13) being infected prior to the arrival in Norway. Nonetheless, despite high availability of new treatment, access remains low to current PWIDs (13). The Norwegian Hepatitis C policy identifies improved access to treatment, prevention, and surveillance of the endemic as crucial to succeed with HCV eradication (42). Arguably, even with DAA treatment for all, low threshold OAT, needle and syringe programs in place, it is hard to see how this can be achieved unless testing and linkage to care is provided where PWIDs and OAT patients actually are. This opts for decentralized testing and treatment and probably a change in how the specialist health care delivers treatment for current PWIDs. In terms of surveillance, chronic HCV prevalence and incidence data are not readily available for Norway. The infection is regarded as a Group A infectious disease and it has been mandatory to notify The Norwegian Surveillance System for Communicable Diseases (MSIS) since 1990. However, only cases of acute HCV was notifiable initially. Since January 1, 2016 it was changed to merely include HCV RNA and HCV core antigen (13). Thus, it is impossible to tell whether cases before 2016 were acute or chronic, or whether patients achieved sustained virological response (SVR) on their own, or how many cases were actually notified (27).

About two-thirds of all patients were considered adherent to DAAs according to recommendations from the prescribing specialist, across all genotypes. Adherence can be a key predictor for response to DAAs (47). Elbasvir/grazoprevir (93%), clinically associated with genotype 1 and 4, came across as the most adherent drug combination, while the other most encountered combinations of DAAs were around 70%. Our intention was to evaluate to what extent patients initiated and complied to treatment, rather than drawing a comparison between individual DAAs. The main reason for this is varying adherence to drug protocol and guidelines for DAAs during the study period from a prescriber's perspective. A Swedish study found that adherence to drug recommendations varied considerably between genotypes and was only moderate after introduction of DAAs, although it increased markedly after 2015 (48). Adherence to DAAs was associated with OAT continuity, and as such, predicted a higher adherence compared to lower level of OAT continuity in our model. Studies have shown that patients receiving higher doses of OAT, e.g. methadone, above 60mg/day, have better treatment outcomes compared to lower doses (42, 49) and for this reason we set high level of continuity above two DDD. This is in line with previous studies demonstrating that OAT continuity is a factor for HCV treatment (27). Age was not considered statistical significant, however, considerable less adherence was noted in the younger age groups. Although there are few real-life studies measuring adherence among this marginalized group of patients, some studies, for example the SIMPLIFY study, have shown a much higher level of adherence among recent PWIDs (50). Similarly, a Canadian study demonstrated that strong adherence to DAAs is achievable with appropriate support (47). Dissimilarities in methodology and study settings, however, prevent for precise comparisons. Linking these data, on an individual level, to biomarkers of SVR12 was, however, beyond the scope of this paper. In addition, we had no system in place to control whether these patients actually swallowed and metabolized these drugs and as such cannot comment to the extent the medications were actually taken.

## Strengths and limitations

All dispensed drugs in Norway are registered in NorPD. This provide researchers and other stakeholders alike with sound, precise and a near complete database. The main strength of the study is thus it provides a large sample of OAT individuals being treated for chronic HCV, and as such can serve as baseline data for further research, especially decision-modelling for eradicating chronic HCV in Norway or similar countries.

However, as with all observational studies there are several limitations, which should be considered when interpreting both results and conclusions. First, treatment with OAT in Norway is not uniform.

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3 378 Some individuals collect the drugs at pharmacies as dispensed prescriptions while others receive the  
4 379 drugs at OAT outpatient clinics. Drugs administered in outpatient clinics are not necessarily captured  
5 380 by the prescription database (NorPD). Secondly, OAT and HCV treatment administered to hospitalized  
6 381 and institutionalized patients are not recorded in NorPD. Nonetheless, it should be stated that almost all  
7 382 HCV treatment is initiated in outpatient clinics in Norway and hence included in NorPD (27, 51). In  
8 383 addition, some dispensed prescriptions may lack reimbursement codes and medical indication for use,  
9 384 and DDDs does not necessarily reflect the Prescribed Daily Dose (PDD).  
10 385

11 386 Furthermore, data was not linked on an individual level to diagnosis codes of chronic HCV. This is due  
12 387 to the quality of MSIS prior to 2016 is poor and the authors had to employ other data sources when  
13 388 estimating HCV prevalence and incidence rates from a number of different sources, including modelling  
14 389 and expert opinion. For example, when calculating the HCV prevalence, mean population data for  
15 390 Norway was used, rather than more accurate regional data as the latter was not readily available.  
16 391

17 392 When measuring adherence among different age groups we should be careful when interpreting results.  
18 393 Older patients are more likely to have cirrhosis and longer HCV treatment courses compared to younger  
19 394 patients. Finally, PWIDs are a heterogenic group of individuals, and one should be careful not to  
20 395 generalize OAT patients to include all PWIDs.  
21 396

## 22 397 Conclusion

23 398 This is the first population-based study documenting the transition to DAA treatment regimens among  
24 399 Norwegian OAT patients. A marked scale-up in HCV treatment attributed by a complete shift to  
25 400 interferon-free regimens among Norwegian OAT patients has been demonstrated. Adherence to DAAs  
26 401 across all genotypes remained sound, especially for genotype 1 and for high level of OAT continuity.  
27 402 Annual HCV treatment coverage ranged from 3.5% in 2013 to 17% in 2017, giving a cumulative HCV  
28 403 coverage among OAT patients for the study period just above 38%. However, Norway is far from  
29 404 universal coverage of HCV treatment. There is a need to establish more accurate monitoring system and  
30 405 more precision in prevalence and incidence rates of chronic HCV among PWID to get more precise  
31 406 coverage data. Efficacy of health system strategies is needed in order to further scale-up of the most  
32 407 effective HCV policies to this group and for countries to be able to control and eliminate HCV.  
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1  
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3 433 List of abbreviations

4 434 OAT Opioid agonist therapy  
5 435 DAA Direct-acting antivirals  
6 436 HCV Hepatitis C virus  
7 437 PWID People who inject drugs  
8 438 NorPD The Norwegian Prescription Database  
9 439 ATC Anatomical Therapeutic Chemical classification system  
10 440 DDD Defined daily dose  
11 441 PPP Prescribed daily dose  
12 442 NIPH The Norwegian Institute for Public Health  
13 443 SERAF The Norwegian Centre for Addiction Research  
14 444 MSIS The Norwegian Surveillance System for Communicable Diseases  
15 445 Anti-HCV Antibodies to the Hepatitis C virus  
16 446 SVR Sustained virological response  
17 447 INTRO-HCV Integrated treatment of hepatitis C virus infection  
18 448  
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20 449  
21 450 **Declarations**

22 451 *Ethical approval and consent to participate*

23 452 The study was approved by the Regional Ethical Committee (REK Vest) on June 19, 2018.  
24 453

25 454 *Consent for publication*

26 455 Not applicable.  
27 456

28 457 *Availability of data and material*

29 458 Supplemental tables, figure and data sources in this observational study are available in this published  
30 459 article and its additional files.  
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40 468

41 469 *Authors' contributions*

42 470 This observational study was led by CFA in terms of study design, analyzes, drafting and writing the  
43 471 article. SS and JHV was particularly involved with acquisition of data, analyzes and interpretation.  
44 472 Maps were made by JMØ and KAJ. All authors contributed to the conception, writing, and revising  
45 473 the draft(s) critically. All authors have read and approved the version to be published.  
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60 610 List of Tables and Figure  
61 611



612 Table 1:  
613

*Table 1: Basic characteristics of patients receiving OAT in Norway between 2013 and 2017*

Basic characteristics	Total	2013	2014	2015	2016	2017
Individuals >1 OAT	10371	7709	7914	7958	7804	7709
Deaths	692	165	151	138	114	124
Gender, n (%)						
Male	7135 (69)	5221 (69)	5390 (69)	5430 (69)	5354 (70)	5254 (69)
Female	3236 (31)	2323 (31)	2373 (31)	2390 (31)	2336 (30)	2340 (31)
Age, n (%)						
<25		211 (3)	185 (2)	171 (3)	135 (2)	120 (2)
26-40		2813 (37)	2797 (36)	2718 (40)	2574 (33)	2432 (32)
41-60		4289 (57)	4537 (58)	3644 (53)	4627 (60)	4613 (61)
>60		231 (3)	244 (3)	287 (4)	354 (5)	420 (6)
OAT medication, n (%)						
Methadone/Levomethadone		3406 (45)	3264 (42)	3216 (41)	3066 (40)	2981 (39)
Buprenorphine based*		4138 (55)	4499 (58)	4604 (59)	4624 (60)	4604 (61)
Dispensations of HCV drugs**	1475	146	167	243	322	597
OAT continuity category, n (%)						
I: ≥2 DDD	5310 (51)					
II: 1- <2 DDD	3078 (30)					
III: <1 DDD	1983 (19)					

OAT = opioid agonist therapy;  
Source: NorPD = Norwegian Prescription Database  
\* Buprenorphine and buprenorphine/naloxone  
\*\* HCV medications: interferon-based and direct-acting antivirals (DAAs)

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Table 2:

Table 2: Annual and cumulative chronic HCV treatment coverage among OAT patients in Norway between 2013 and 2017

	Source	2013	2014	2015	2016	2017	Total
Chronic HCV treatment n (overall)	NorPD	146	167	243	322	597	1475
DAAAs, n	NorPD	46	95	212	290	592	1235
DAAAs % of HCV		32	57	87	90	99	84
Study population n, yearly incl. deaths	NorPD	7709	7914	7958	7804	7709	10371
Deaths	NorPD	165	151	138	114	124	692
Study population n, yearly, excl. deaths	NorPD	7544	7763	7820	7690	7585	9679
Prevalence chronic HCV, mean %	SERAF	51	52	52	46	43	
Prevalence chronic HCV, n	SERAF	3847	4037	4066	3537	3262	
Incidence chronic HCV among PWIDs n	NIPH, Meijerick et al.	396	388	381	374	366	
Incidence chronic HCV OAT from PWIDs n	Expert opinion	277	272	267	262	256	
<i>Treatment coverage chronic HCV %</i>		3.5	3.9	5.6	8.5	17.0	
<i>Cumulative frequency chronic HCV</i>		3.5	7.4	13.0	21.5	38.5	
95% Confidence interval treatment coverage chronic HCV		3.2-4.4	3.5-4.8	5.3-6.7	8.2-10.1	16.9-19.6	

OAT = opioid agonist therapy, PWID = people who inject drugs, HCV = hepatitis C virus, DAA = direct-acting antivirals, Sources: NorPD = Norwegian Prescription Database, SERAF = The Norwegian Centre for Addiction Research, NIPH = Norwegian Health, Meijerick et al. (2017): Modelling the burden of hepatitis C infection among people who inject drugs in Norway, 1973–2017

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Table 3:

Table 3: Adherence\* to DAAs among OAT patients in Norway between 2013 and 2017

	Adherent	Non-Adherent	Total:
Adherence by gender, n (%):			
Male	551 (67)	191 (67)	742 (67)
Female	277 (33)	92 (33)	369 (33)
Total	828	283	1111
Adherence by age, n (%):			
18-35	119 (58)	85 (42)	204
36-45	259 (68)	122 (32)	381
46-55	302 (70)	128 (30)	430
>56	62 (65)	34 (35)	95
Total	742 (67)	369 (33)	1111
Adherence by OAT medication, n (%):			
Methadone	298 (65)	157 (35)	455
Buprenorphine based	444 (68)	212 (32)	656
Total	742 (67)	369 (33)	1111

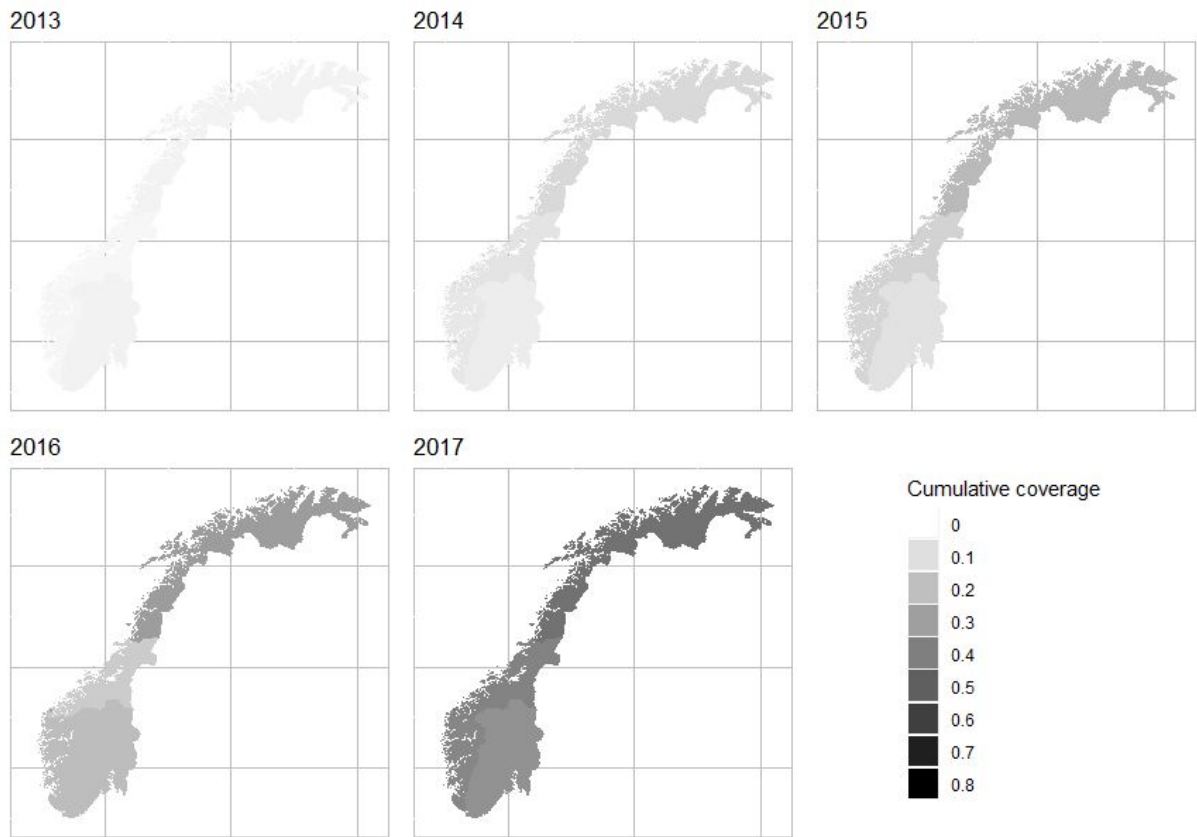
*Logistic regression on factors associated with adherence\**

	aOR (CI 95%)	p-value
Age	0.98 (0.97-1.00)	0.17
Gender		
Male	1.00	
Female	0.92 (0.69-1.23)	0.57
OAT continuity		
Category I: >2 DDD	1.00	
Category II: <2-1 DDD	1.36 (1.02-1.82)	0.035
Category III: <1 DDD	1.36 (0.93-1.99)	0.11

OAT = opioid agonist therapy, DAA = direct-acting antivirals, aOR = adjusted odds ratio, CI = confidence interval  
 Source: NorPD = Norwegian Prescription Database  
 \*Adherence defined as collected  $\geq$ three prescriptions and > 84 DDDs (unless ledipasvir and sofosbuvir which also calculated as  $\geq$ two prescriptions and > 54 DDDs)

Figure 1:

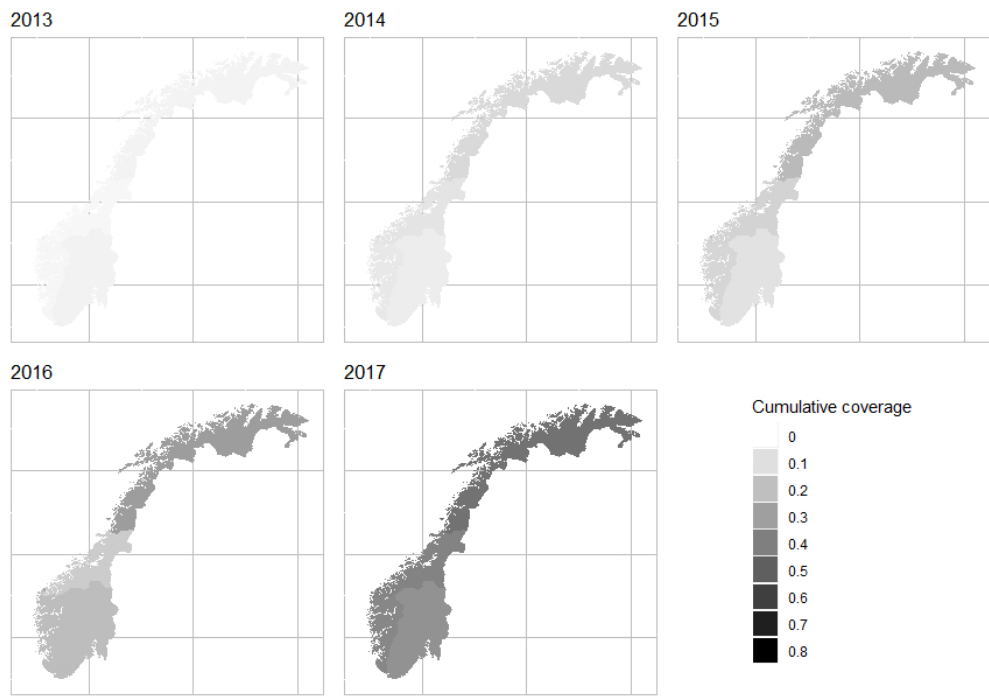
663 *Figure 1: Cumulative chronic HCV treatment coverage among OAT patients in Norway between 2013*  
 664 *and 2017 by Health Counties\**  
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666 OAT = opioid agonist therapy, HCV = hepatitis C virus  
 667 Sources: NorPD = Norwegian Prescription Database, SERAF = The Norwegian Centre for Addiction  
 668 Research, NIPH = Norwegian Institute for Public Health, Meijerink et al. (2017): Modelling the burden  
 669 of hepatitis C infection among people who inject drugs in Norway, 1973–2030, calculations in Table S2  
 670 \*Cumulative coverage in %, the four Health counties: Helse Vest, Helse Midt, Helse Nord and Helse  
 671 Sør-Øst  
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only

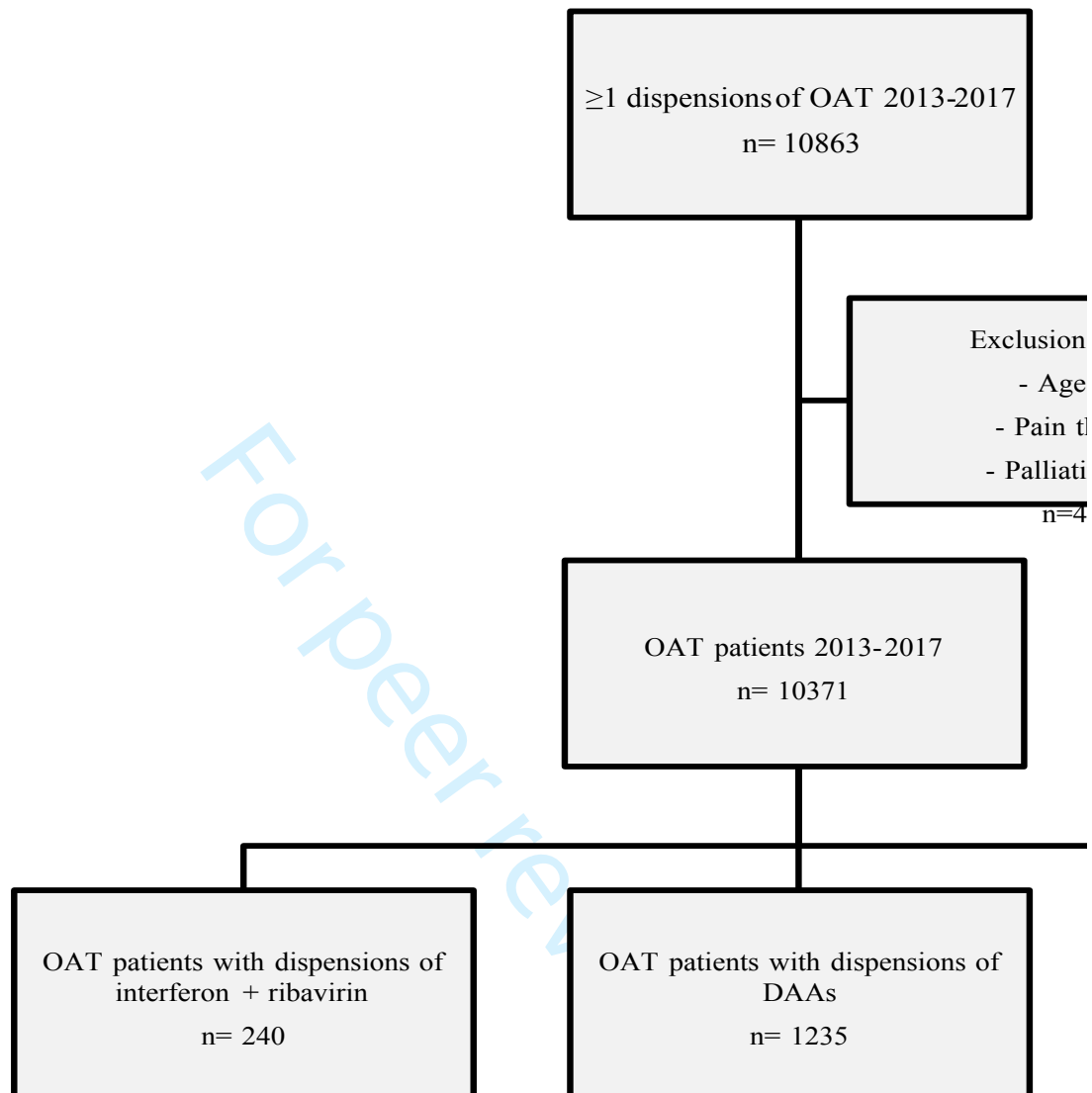
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Cumulative chronic HCV treatment coverage among OAT patients in Norway between 2013 and 2017 by Health Counties

302x213mm (72 x 72 DPI)

Figure S1: Flow chart of study population



OAT = opioid agonist therapy, HCV = hepatitis C virus, DAA = direct-acting antivirals,  
Sources: NorPD = Norwegian Prescription Database



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Criteria:  
Age <18  
No therapy  
No previous care  
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OAT patients with no dispersions of  
interferon, ribavirin or DAAs  
n=8896

For peer review only

Table S1: Annual and cumulative chronic HCV treatment uptake, crude, among OAT patients

	Source	2013	2014	2015
HCV treatment n (overall)	NorPD	146	167	243
DAAAs, n	NorPD	46	95	212
DAAAs % of HCV		32	57	87
Study population n, yearly incl. deaths	NorPD	7709	7914	7958
Deaths	NorPD	165	151	138
Study population n, yearly, excl. deaths	NorPD	7544	7763	7820
Treatment uptake crude %:				
HCV overall		1.9	2.2	3.1
DAAAs		0.6	1.2	2.7
Cumulative frequency HCV overall		1.9	4.1	7.2
Cumulative frequency DAAAs		0.6	1.8	4.5
95% Confidence interval (HCV)		1.6-2.3	1.8-2.5	2.7-3.5
95% Confidence interval (DAAAs)		0.4-0.8	1.0-1.5	2.4-3.1

OAT = opioid agonist therapy, HCV = hepatitis C virus, DAA = direct-acting antivirals,  
Sources: NorPD = Norwegian Prescription Database

*s in Norway between 2013 and 2017*

	<b>2016</b>	<b>2017</b>	<b>Total</b>
	322	597	1475
	290	592	1235
	90	99	84
	7804	7709	10371
	114	124	692
	7690	7585	9679
	4.2	7.9	
	3.8	7.8	
	11.4	19.3	
	8.3	16.1	
	3.7-4.6	7.3-8.5	
	3.4-4.2	7.2-8.4	

Table S2: Annual and cumulative chronic HCV treatment coverage among OAT patients in .

	Source:	2013
Helse Sør-Øst HCV Treatment	NorPD	93
Helse Vest HCV Treatment	NorPD	24
Helse Midt HCV Treatment	NorPD	20
Helse Nord HCV Treatment	NorPD	6
Study population incl death Helse Sør-Øst	NorPD	4553
Study population incl death Helse Vest	NorPD	1889
Study population incl death Helse Midt	NorPD	708
Study population incl death Helse Nord	NorPD	559
Deaths Helse Sør-Øst	NorPD	91
Deaths Helse Vest	NorPD	47
Deaths Helse Midt	NorPD	21
Deaths Helse Nord	NorPD	6
Study population excl death Helse Sør-Øst	NorPD	4462
Study population excl death Helse Vest	NorPD	1842
Study population excl death Helse Midt	NorPD	687
Study population excl death Helse Nord	NorPD	553
Prevalence HCV Helse Sør-Øst, mean %	SERAF	55
Prevalence HCV Helse Vest, mean %	SERAF	43
Prevalence HCV Helse Midt, mean %	SERAF	73
Prevalence HCV Helse Nord, mean %	SERAF	45
Prevalence HCV Helse Sør-Øst, n	SERAF	2454
Prevalence HCV Helse Vest, n	SERAF	792
Prevalence HCV Helse Midt, n	SERAF	502
Prevalence HCV Helse Nord, n	SERAF	238
Incidence HCV Helse Sør-Øst, PWIDs	NIPH, Mejerick et al.	249
Incidence HCV Helse Vest, PWIDs	NIPH, Mejerick et al.	79
Incidence HCV Helse Midt, PWIDs	NIPH, Mejerick et al.	44
Incidence HCV Helse Nord, PWIDs	NIPH, Mejerick et al.	24
Incidence HCV Helse Sør-Øst, OAT, n	NIPH, Mejerick et al.	175
Incidence HCV Helse Vest, OAT, n	NIPH, Mejerick et al.	55
Incidence HCV Helse Midt, OAT, n	NIPH, Mejerick et al.	30
Incidence HCV Helse Nord, OAT, n	NIPH, Mejerick et al.	17
<i>Treatment coverage HCV Helse Sør-Øst %</i>		3.5
<i>Cumulative frequency HCV Helse Sør-Øst</i>		3.5
<i>Treatment coverage HCV Helse Vest %</i>		2.8
<i>Cumulative frequency HCV Helse Vest</i>		2.8
<i>Treatment coverage HCV Helse Midt %</i>		3.8
<i>Cumulative frequency HCV Helse Midt</i>		3.8
<i>Treatment coverage HCV Helse Nord %</i>		2.4
<i>Cumulative frequency HCV Helse Nord</i>		2.4

OAT = opioid agonist therapy, PWID = people who inject drugs, HCV = hepatitis C virus

Sources: NorPD = Norwegian Prescription Database, SERAF = The Norwegian Centre for Addictior  
Meijerink et al. (2017): Modelling the burden of hepatitis C infection among people who inject drugs

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2 *Norway between 2013 and 2017 by Health Regions*  
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4                    2014                    2015                    2016                    2017 Total:  
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6	92	158	196	367	906
7	27	36	64	136	287
8	18	22	27	52	139
9	27	27	20	26	106
10	4636	4609	4575	4580	
11	1971	2000	1833	1735	
12	728	731	742	740	
13	578	616	653	653	
14					
15	82	84	74	74	
16	45	33	29	39	
17	16	10	6	6	
18	8	11	5	5	
19					
20	4554	4525	4501	4506	
21	1926	1967	1804	1696	
22	712	721	736	734	
23	570	605	648	648	
24					
25	53	57	52	45	
26	51	50	47	41	
27	53	52	49	36	
28	48	43	33	28	
29	2414	2579	2341	2028	
30	982	984	848	695	
31	377	375	361	264	
32	274	260	214	181	
33					
34	233	238	236	238	
35	93	91	86	81	
36	39	35	41	33	
37	23	16	11	15	
38	163	167	165	167	
39	65	64	60	56	
40	27	25	29	23	
41	16	11	8	10	
42					
43					
44	3.5	5.7	7.8	16.7	
45	7.1	12.8	20.7	37.4	
46					
47					
48	2.6	3.4	7.0	18.1	
49	5.4	8.8	15.9	34.0	
50					
51					
52	4.4	5.5	6.9	18.1	
53	8.2	13.7	20.6	38.7	
54					
55					
56	9.3	9.9	9.0	13.6	
57	11.7	21.6	30.6	44.2	

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60 n Research, NIPH = Norwegian Institute for Public Health,  
s in Norway, 1973–2030



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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(b) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4, n/a
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	5
		(b) Describe any methods used to examine subgroups and interactions	4/5
		(c) Explain how missing data were addressed	-
		(d) If applicable, explain how loss to follow-up was addressed	n/a
		(e) Describe any sensitivity analyses	-
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	19
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) Summarise follow-up time (eg, average and total amount)	n/a
Outcome data	15*	Report numbers of outcome events or summary measures over time	

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5/6
2			(b) Report category boundaries when continuous variables were categorized	-
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
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9	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
10				
11	<b>Discussion</b>			
12				
13	Key results	18	Summarise key results with reference to study objectives	6
14	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	7/8
15				
16	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7/8
17				
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19	Generalisability	21	Discuss the generalisability (external validity) of the study results	7
20				
21	<b>Other information</b>			
22	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9
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26 \*Give information separately for exposed and unexposed groups.

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28 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and  
29 published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely  
30 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at  
31 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is  
32 available at <http://www.strobe-statement.org>.  
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# BMJ Open

## On the path towards universal coverage of hepatitis C treatment among people receiving opioid agonist therapy (OAT) in Norway: a prospective cohort study from 2013 to 2017

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3 **1 On the path towards universal coverage of hepatitis C treatment among people receiving**  
4 **2 opioid agonist therapy (OAT) in Norway: a prospective cohort study from 2013 to 2017**  
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## Abstract

### *Objectives*

We aimed to calculate cumulative hepatitis C (HCV) treatment coverage among individuals enrolled in opioid agonist therapy (OAT) in Norway between 2013 and 2017, and to document the treatment transition to direct-acting antiviral agents (DAA). Moreover, we aimed to describe adherence to DAAs in the same cohort.

### *Design:*

Prospective cohort, registry data

### *Setting:*

Specialist health care service (secondary)

### *Participants and outcomes:*

This observational study was based on data from The Norwegian Prescription Database (NorPD). We studied dispensed OAT and HCV treatment annually to calculate the cumulative frequency, and employed secondary sources to calculate prevalence, incidence and HCV treatment coverage from 2013 to 2017, among the OAT population. Factors associated with adherence to DAAs were identified a priori and subject to logistic regression.

### *Results*

10,371 individuals were identified with dispensed OAT, 1,475 individuals of these with dispensed HCV treatment. Annual HCV treatment coverage increased from 3.5% (95% CI: 3.2-4.4) in 2013 to 17% (95% CI: 17-20) in 2017, giving a cumulative HCV coverage among OAT patients in Norway of 38.5%. A complete shift to interferon-free treatment regimens occurred, where DAAs accounting for 32% of HCV treatments in 2013 and 99% in 2017. About two-thirds of OAT patients were considered adherent to their DAA regimens across all genotypes. High-level of OAT continuity was associated with improved adherence to DAAs (aOR 1.4, 95% CI: 1-2, p=0.035).

### *Conclusions*

A large increase in HCV treatment coverage attributed by a complete shift to interferon-free regimens among the Norwegian OAT population has been demonstrated. However, treatment coverage is inadmissibly too low and a further substantial scale-up in HCV treatment is required to reach the universal targets of controlling and eliminating the HCV endemic.

## Strengths and limitations - summary

- All dispensed drugs from pharmacies in Norway are registered in the database
- The completeness, precision, and validity of data are high among a hard-to-reach population
- Data was not linked on an individual level to diagnosis codes of chronic HCV
- HCV prevalence and incidence data are imprecise
- Treatment with DAAs were limited during the study period from 2013 to 2017 based on stage of liver fibrosis.

Keywords: Hepatitis C virus (HCV), treatment uptake, treatment coverage, direct-acting antiviral agents (DAAs), opioid agonist therapy (OAT), adherence,

## Background

The large burden of chronic hepatitis C (HCV) among people who inject drugs (PWID) and recent developments in HCV medications creates an opportunity to eliminate HCV epidemics. Worldwide, about 71 million people are chronically infected with the virus and 399,000 died annually from HCV related complications like liver cirrhosis or hepatocellular carcinoma (1, 2). Despite the low aggregated HCV prevalence in many countries (1.5-3.5% in Western Europe and <1.5% in North America), prevalence is much higher among PWID (50%, or more) (3-5). The World Health Organization's Global Health Sector Strategy aims to eliminate viral hepatitis as a public health threat by 2030 (2). The even bolder Norwegian HCV strategy aims to reduce national incidence by 90% by 2023 (6). Eliminating chronic HCV requires a significant effort in terms of increasing uptake of testing, diagnosing, and linking to care. In addition, other strategies have been proposed alongside increasing antiviral treatment, such as opioid agonist therapy (OAT) scale-up, safe injection sites and sterile injection equipment to reach these objectives (2, 7).

Injecting drug use and needle sharing is the major driver of HCV incidence (8), however, the coverage of preventive interventions, such as needle and syringe programs, remains poor among PWIDs (9). Number of people who actively inject drugs in Norway have been stable at around 9000 since 2012 till 2017 (2.6 per 1 000 inhabitants aged 15-64 years) (10, 11), and opioids and amphetamines are the main injected drugs (11, 12). Modelling studies suggest that around 7000 former and current PWIDs are living with chronic HCV with an estimated 400 new cases annually in the same time period (13, 14). Both HCV-related liver morbidity and mortality are increasing among PWIDs and are likely to continue to increase until 2022 (14).

OAT has been put forward to play a vital role in the management of chronic HCV among people with opioid dependence and has been shown to reduce the risk of HCV acquisition (15). For these reasons, OAT may be crucial intervention for achieving large reductions in HCV transmissions by reducing risk behaviors like injecting use and sharing of injecting equipment (16). HCV testing rates have been low in the national OAT program in Norway with great annual and regional variations (5, 17-20). Only in parts of western Norway, as part of the multicenter INTRO-HCV study, all patients receiving OAT have been systematically tested and examined with elastography as part of an annual health assessment since 2017 (21). Even if access to HCV treatment is improving, HCV treatment coverage remains low (8, 22-25). Globally, the coverage of HCV curative treatment was 13% by 2016 (26). In Norway, annual HCV treatment coverage among OAT patients was between 1.3% to 2.6% in the period from 2004 to 2013, giving a cumulative HCV coverage for the period of 14% (27).

The introduction of direct-acting antiviral (DAAs) medications, with a curation rate of approximately 95%, safer and better-tolerated than interferon-based therapy, has dramatically changed the treatment of chronic HCV infections (28, 29). Even if currently expensive, they are considered cost effective from a societal perspective as universal coverage with antiretroviral treatment could prevent large expenses related to future complications (30-35). Combining DAAs with the OAT delivery platform may thus prove critical for achieving reductions in HCV prevalence and incidence (22). A number of treatment barriers exist, which should in turn be carefully addressed, nevertheless, treatment barriers should not exclude PWIDs from HCV treatment (8, 36, 37). Both World Health Organization and Norwegian guidelines support DAA treatment among PWIDs and have also shown good outcomes in systematic reviews (24, 25, 38).

The pathway to universal HCV treatment coverage has not been well documented at country levels, hence, the primary aim of the study was to:

- 1) Document HCV treatment annually and cumulatively after the introduction of DAAs among patients receiving OAT in Norway from 2013-2017 and to calculate HCV treatment coverage, both annually and cumulatively.
- 2) A second objective is to evaluate adherence to DAAs among OAT patients in Norway.

## 155 Methods

156

### 157 Study design and data sources

158 This is an observational study among OAT patients from 2013 to 2017 in Norway. Data were  
 159 extracted from The Norwegian Prescription Database (NorPD) from January 1, 2013 to March 31,  
 160 2018. The database covers the entire Norwegian population and records all drugs dispensed from  
 161 pharmacies in Norway, hence leaving only over-the-counter drugs and drugs administered at hospitals  
 162 and nursing homes. All drugs are classified according to The Anatomical Therapeutic Chemical  
 163 (ATC) classification system (39). Defined daily doses (DDDs) according to 2018 (40) were employed  
 164 to quantify the dispensed OAT and HCV medications respectively. The DDDs are the assumed  
 165 average maintenance dose per day for a drug used for its main indication (41).

166

167 Data from The Norwegian Centre for Addiction Research were used for estimating the prevalence of  
 168 chronic HCV among OAT patients, whereas incidence data among Norwegian PWIDs was gathered  
 169 from The Norwegian Institute of Public Health and Meijerink et al. (14)

170

### 171 Study population and definitions

172 The study population included all individuals with at least one dispensed prescription of  
 173 buprenorphine (ATC code N07BC01), methadone (N07BC02), buprenorphine-naloxone (N07BC51),  
 174 and levomethadone (N07BC05). Other opioids are very rarely used for OAT in Norway and  
 175 considered outside national guidelines (42). Patients <18 years and with other indications than OAT  
 176 were excluded from the study on the basis of formulation and route of administration (Figure S1).

177

178 Exposure to HCV treatment was defined as being dispensed either pegylated interferon alpha  
 179 (L03AB05 and L03AB11) and ribavirin (J05AP01) or any of the DAAs (in group J05AP, see Table S1  
 180 for complete list of DAAs by ATC code) during the study period. The first dispensed DAA according  
 181 to ATC code was noted, and to prevent over-counting patients were only counted once at initiation.  
 182 Thus, definition of treatment was any individual on OAT who has been dispensed HCV treatment.  
 183 Any individual who died was censored in the calendar year they passed away. Rates were calculated  
 184 by dividing number of individuals with dispensed HCV treatment by individuals on OAT, stratified by  
 185 each calendar year. The cumulative frequency, which is the addition of successive years of treatment,  
 186 was then calculated. HCV treatment was stratified as overall treatment with any chronic HCV  
 187 medication and treatment with solely DAAs.

188

189 HCV treatment coverage was defined as individuals on OAT identified in NorPD annually, adjusted  
 190 for death, HCV prevalence, and new cases of chronic HCV each year, which had received treatment  
 191 for chronic HCV during the study period. Mean prevalence during the study period among patients  
 192 enrolled in OAT ranged from 51% in 2013 to 43% in 2017 (5, 17-20) and proportional prevalence  
 193 among OAT individuals were calculated per calendar year. Incidence was around 400 per year for  
 194 PWIDs during the study period (14). It proved methodologically challenging to estimate number of  
 195 new cases of chronic HCV among OAT patients. As the OAT coverage among people with opioid  
 196 dependence is between 50 and 60% in Norway (5), OAT patients account for only a proportion of  
 197 overall PWIDs and thus needed to be adjusted for in our calculation. For this reason expert opinion  
 198 were obtained from clinicians in addiction medicine and set to a 0.70 (70%) proportion, giving  
 199 between 277 to 256 new cases annually during the study period. We developed the following basic  
 200 model for our coverage calculation:

$$201 \quad HCV_{cov} = \frac{t_{HCV}}{p_{HCV} + i_{HCV}} * 100$$

202

203 where HCV cov is HCV coverage,  $t_{HCV}$  = number of OAT patients with dispensed HCV treatment,  
 204  $p_{HCV}$  = number of OAT patients with chronic HCV and  $i_{HCV}$  = number of new cases of chronic  
 205 HCV among OAT patients. Coverage was calculated annually for Norway and by Health County, and  
 206 as cumulative frequencies.

207  
208 We defined adherence to DAA as having collected prescriptions equivalent to three months of  
209 treatment or more. DAAs for adults, which in Norway is prescribed only by specialists in either  
210 infectious medicine or gastroenterology, are collected for one-month-at-a-time basis where a typical  
211 DAA treatment course is 12 weeks, i.e. three dispensed prescriptions and  $\geq 84$  DDDs. The exception is  
212 the drug combination ledipasvir/sofosbuvir, which may be prescribed for eight weeks (two collections  
213 and  $\geq 56$  DDD) for cases of previously untreated genotype 1 infections. This allowed us to examine  
214 adherence based on number of dispensed prescriptions and DDDs. Impending factors associated with  
215 treatment adherence to DAAs were identified a priori and included gender, age, and OAT continuity,  
216 and subject to multivariate analyzes in a step-by-step model.

217  
218 Finally, OAT continuity was defined according to dispensed DDDs and stratified into three categories,  
219 ranging from a high level of OAT continuity in category I ( $\geq 2$  DDD), medium in category II (1-2  
220 DDD), and to a low level of OAT continuity in category III ( $< 1$  DDD). One DDD for methadone and  
221 buprenorphine is 25mg and 8mg respectively.

### 222 223 Statistical analyzes and strategy

224 Descriptive data are presented as frequencies, percentages, means, and with corresponding 95%  
225 confidence intervals where appropriate. Logistic regression on factors associated with adherence are  
226 presented as adjusted odds ratio (aOR) when adjusted for age, gender and OAT continuity.

227  
228 The initial processing of the received encrypted file from NorPD was completed in SPSS version 24.  
229 Secondly, the file was converted and subsequently analyzed in Stata SE version 15 (StataCorp, TX,  
230 USA). Map figures were made in R.

### 231 232 Data handling and ethical considerations

233 This study was approved by the regional committee for ethics in medical research (no. 2018/939/REK  
234 Vest). It was conducted in accordance with the Helsinki Declaration and as an observational study in  
235 accordance with international accepted STROBE guidelines (43).

### 236 237 Patient and public involvement

238 Since all registry data was received pseudo-anonymously from the registry administrator and  
239 subsequently analyzed anonymously no written consent was obtained from any of the individuals in  
240 the study. No patients were directly involved in this study, however, as part of the bigger INTRO-  
241 HCV project patients through user organizations such as Pro-LAR, were involved in the planning  
242 process, workshops that included design and recruitment, protocol writing and assessment of the  
243 burden of the intervention in the randomized controlled trial.

## 244 245 Results

### 246 247 Basic characteristics of study population

248 A total of 10,371 individuals were identified in NorPD having received  $\geq 1$  OAT prescriptions during  
249 the study period from 2013 to 2017 (Table 1). Almost 70% were male, mean age of 43 years and 45  
250 years in 2013 and 2017, respectively. The majority of the OAT patients were treated with  
251 buprenorphine-based OAT medication (55% in 2013, 61% in 2017). Over 50% of individuals on OAT  
252 had a high level of continuity. Altogether 692 individuals died during the study period.

253 (insert Table 1)

### 254 255 HCV treatment and coverage

#### 256 257 HCV and DAA treatment

258 All individuals were stratified according to the year in which they received OAT and HCV treatment.  
259 Excluding deaths, this gave a fairly stable OAT population just in excess of 7500 annually. In 2013,  
260 146 OAT patients received HCV treatment. Treatment increased over time with 597 patients receiving



261 HCV treatment in 2017. Overall 1475 patients on OAT received HCV treatment during the study  
262 period, with an annual HCV treatment increasing from 1.9% (95% CI: 1.6-2.3%) of OAT patients in  
263 2013, to 7.9% (95% CI: 7.3-8.5%) in 2017 (Table S2). By 2017, the cumulative frequency of HCV  
264 treatment reached 19% among patients on OAT.

265  
266 Of the 1475 individuals that received HCV treatment during the study period, 1235 were treated with  
267 DAA medications. The annual DAA treatment ranged from 0.6% (95% CI: 0.4-0.8%) in 2013, to 7.8  
268 (95% CI: 7.2-8.4%) in 2017. The proportion of treated individuals receiving DAAs increased over  
269 time from 32% of HCV treated OAT patients in 2013 to 99% in 2017.

#### 270 271 HCV treatment: coverage

272 We calculated annual HCV coverage among the estimated number of OAT patients that are HCV  
273 infected, which ranged from 3.5% (95% CI: 3.2-4.4%) in 2013 to 17% (95% CI: 16.9-19.6%) in 2017.  
274 This gave a cumulative frequency that reached 38.5% in 2017 (Table 2). Figure 1 shows cumulative  
275 HCV coverage from 2013 to 2017 by the four health counties in Norway (HCV<sub>cov</sub> and data from Table  
276 S3 were used for these calculations). There is little variation in treatment coverage across the four  
277 health counties.

278  
279 (insert Figure 1 + Table 2)

#### 280 281 Adherence to DAAs

282 Overall, almost 70% of the OAT patients were adherent to their DAA regimen and considered to have  
283 finished their DAA treatment course (Table 3). There were no major differences by gender or OAT  
284 drug. However, for age, patients in the age group 18-35 were less adherent (42%) compared with older  
285 age groups. The drug combination of elbasvir/grazoprevir, commonly used for treatment of genotype 1  
286 infections, had by far the utmost adherence (93%) compared to treatment combinations of  
287 sofosbuvir/velpatasvir, and ledipasvir/sofosbuvir, which both were around 70%. However, sometimes  
288 ledipasvir/sofosbuvir is prescribed for eight weeks, in which case yields an overall adherence of 78%.

289  
290 In multivariate analyzes, only OAT continuity was associated with adherence to DAAs (adjusted OR  
291 1.4, 95% CI: 1.0-1.8 p=0.035).

292  
293 (insert Table 3)

#### 294 295 Discussion

296 The HCV treatment coverage has increased substantially, yet it seems too low if the ambitious targets  
297 of ending the endemic are to be met. Annual treatment rate increased from 1.9% of all OAT patients in  
298 Norway in 2013 to 7.9% in 2017, which gives a cumulative frequency of around 19% over the study  
299 period. However, cumulative HCV treatment coverage among OAT patients with assumed chronic  
300 HCV in Norway was just above 38%, with annual treatment coverage that ranged from 3.5% in 2013  
301 to 17% in 2017. Secondly, we observed a complete shift in the HCV treatment among OAT patients in  
302 Norway during the study period, from two-thirds treated with DAAs in 2013, to nearly all in 2017.  
303 Finally, about two-thirds of all OAT patients with chronic HCV were considered adherent to their  
304 DAAs regimen, which improved with level of OAT continuity.

305  
306 It can be useful to compare our results at country levels. Immense advances have been made in chronic  
307 HCV treatment since the introduction of DAAs in recent years, however multiple studies have  
308 demonstrated continued low treatment uptake among PWIDs and OAT patients (23, 27, 44), partly  
309 explained by varying and restricted treatment access policies that prevented a widespread scale-up of  
310 DAA treatment during the study period (45). For instance England, saw one of the most restricted  
311 access policies to DAA treatment compared to e.g. France and Germany, which had the least  
312 restrictions (46). Consequently HCV treatment rates varied dramatically across European countries  
313 ranging from 0.6% to 10.2% in 2015 (47). In the same year we found HCV treatment rate of 5.6% in  
314 Norway, which is similar to Sweden, however higher than Denmark that saw treatment rate more in

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3 315 line with the overall 3.7% that year among European countries (47). Prior to the introduction of  
4 316 DAAs, Midgard et al (2016) showed an annual treatment coverage of 1.3% to 2.6% between 2004 and  
5 317 2013 among Norwegian OAT patients, giving a cumulative treatment coverage of 14% during the  
6 318 entire study period. Considering there is not in place a national and systematic program for testing and  
7 319 linking to HCV care among PWIDs, nor has the full effectiveness of integrated treatment combining  
8 320 OAT and HCV treatment been fully demonstrated (48), HCV coverage would probably be  
9 321 substantially higher with a comprehensive model of integrative care where both testing and treatment  
10 322 were provided in OAT outpatient clinics.  
11 323

12 324 The Norwegian Hepatitis C policy identifies improved access to treatment, prevention, and  
13 325 surveillance of the endemic as crucial to succeed with HCV elimination strategies (42). Treatment  
14 326 with DAAs in Norway was until February 1, 2018, limited by eligibility criteria based on stage of liver  
15 327 fibrosis. Since then, DAA treatment has been offered to all regardless of genotype and level of liver  
16 328 fibrosis. As a result, treatment demand increased and coverage of curative HCV treatment has  
17 329 amplified. From 2014 to June 2018, around 5000 patients were treated for chronic HCV in Norway,  
18 330 however, these patients are mostly former PWIDs and immigrants being infected prior to the arrival  
19 331 in Norway (13). It is unclear how many of these patients were on OAT and overlapped with our  
20 332 results. Nonetheless, despite continued falling prices of DAAs, which have made unrestricted  
21 333 treatment possible for all, HCV treatment and coverage remains low among active PWIDs (13), which  
22 334 is in line with our results demonstrating the need for a significant scale-up to improve HCV coverage  
23 335 and being able to plan elimination strategies. It may therefore be crucial to identify other barriers to  
24 336 treatment for this vulnerable patient group. Arguably, even with DAA treatment for all, low threshold  
25 337 OAT, needle and syringe programs in place, it is hard to see how this can be achieved unless testing  
26 338 and linkage to care is provided where PWIDs and OAT patients actually are. This opts for  
27 339 decentralized testing and treatment and probably a change in how the specialist health care delivers  
28 340 treatment for current PWIDs. A substantial scale-up in DAA treatment requires Norway's capacity and  
29 341 health system infrastructure at large, in addition to take place among this group of patients, which have  
30 342 the highest transmission risk in order for treatment-as-prevention strategies to succeed. In terms of  
31 343 surveillance, chronic HCV prevalence and incidence data are not readily available for Norway. The  
32 344 infection is regarded as a Group A infectious disease and it has been mandatory to notify The  
33 345 Norwegian Surveillance System for Communicable Diseases (MSIS) since 1990. However, only cases  
34 346 of acute HCV was notifiable initially. Since January 1, 2016 it was changed to merely include HCV  
35 347 RNA and HCV core antigen (13). Thus, it is impossible to tell whether cases before 2016 were acute  
36 348 or chronic, or whether patients achieved sustained virological response (SVR) on their own, or how  
37 349 many cases were actually notified (27).  
38 350

39 351 About two-thirds of all patients were considered adherent to the DAA regimens. At first this may seem  
40 352 low, however, this may be related to patients being categorized as adherent (100%) and non-adherent  
41 353 (<100%) according to recommendations from the prescribing specialist. For instance, the SIMPLIFY  
42 354 study, while demonstrating that 97% of PWIDs completed DAA treatment, overall 32% were  
43 355 considered non-adherent (<90% adherence) with median adherence at 94% (49). Similar results were  
44 356 reported from another study among PWIDs and OAT patients were 97% completed DAA treatment  
45 357 with a non-adherence of 40% (<90%) and median adherence at 92% (50). Other studies have shown  
46 358 that high adherence to DAAs is achievable with appropriate supportive strategies (51, 52). As such,  
47 359 adherence can be a key predictor for response to DAAs (51). Perhaps the most compelling evidence  
48 360 among PWIDs and OAT patients is a recent systematic review that showed DAA completion rate of  
49 361 above 97% among almost 4500 participants (53). Our intention was to evaluate to what extent patients  
50 362 initiated and complied to treatment, rather than drawing a comparison between individual DAAs. The  
51 363 main reason for this is varying adherence to drug protocol and guidelines for DAAs during the study  
52 364 period from a prescriber's perspective. A Swedish study found that adherence to drug  
53 365 recommendations varied considerably between genotypes and was only moderate after introduction of  
54 366 DAAs, although it increased markedly after 2015 (54). Adherence to DAAs was associated with OAT  
55 367 continuity, and as such, predicted a higher adherence compared to lower level of OAT continuity in  
56 368 our model. Studies have shown that patients receiving higher doses of OAT, e.g. methadone, above  
57 369 60mg/day, have better treatment outcomes compared to lower doses (42, 55) and for this reason we set  
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3 370 high level of continuity above two DDD. This is in line with previous studies demonstrating that OAT  
4 371 continuity is a factor for HCV treatment (27). Age was not considered statistical significant, however,  
5 372 less adherence was noted in the younger age groups. Dissimilarities in methodology and study  
6 373 settings, however, prevent for precise comparisons of adherence, including the above. Linking these  
7 374 data, on an individual level, to biomarkers of SVR12 was, however, beyond the scope of this paper. In  
8 375 addition, we had no system in place to control whether these patients actually swallowed and  
9 376 metabolized these drugs and as such cannot comment to the extent the medications were actually  
10 377 taken.  
11 378

## 12 379 Strengths and limitations

13 380 All dispensed drugs from pharmacies in Norway are registered in NorPD. This provide researchers  
14 381 and other stakeholders alike with sound, precise and a near complete database. The main strength of  
15 382 the study is thus it provides a large sample of OAT individuals being treated for chronic HCV, and as  
16 383 such can serve as baseline data for further research, especially decision-modelling for eliminating  
17 384 chronic HCV in Norway or similar countries.  
18 385

19 386 However, this study has some limitations, which should be considered when interpreting both results  
20 387 and conclusions. Treatment with OAT in Norway is not uniform. It is estimated that NorPD captures  
21 388 around 90% of the patients with dispensed OAT from pharmacies (5). The 10% which is not included  
22 389 in our study could represent OAT patients with more need for follow-up in the OAT outpatient clinics,  
23 390 and as such, can represent patients with higher disease burden and in need of HCV treatment. This  
24 391 could skew our results toward underestimating the HCV treatment coverage as these patients would  
25 392 not be included in our study. On the other hand, our estimates can also be overestimates. OAT patients  
26 393 have successfully entered the health care system and therefore more likely to accept other medical  
27 394 care, including HCV treatment, and thus bias our results toward improved HCV treatment coverage.  
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29 396 OAT and HCV treatment administered to hospitalized and institutionalized patients are not recorded  
30 397 on an individual level in NorPD. Nonetheless, it should be stated that almost all HCV treatment is  
31 398 initiated in outpatient clinics in Norway and hence included in NorPD (27, 56). In addition, some  
32 399 dispensed prescriptions may lack reimbursement codes and medical indication for use, and DDDs does  
33 400 not necessarily reflect the Prescribed Daily Dose (PDD).  
34 401

35 402 Furthermore, data was not linked on an individual level to diagnosis codes of chronic HCV. This is  
36 403 due to the quality of MSIS prior to 2016 is poor and the authors had to employ other data sources  
37 404 when estimating HCV prevalence and incidence rates from a number of different sources, including  
38 405 modelling and expert opinion. This could lead to either over- or underestimating the HCV coverage.  
39 406 We believe, however, that the 0.7 (70%) proportion represents a liberal estimate and the biggest risk is  
40 407 that we overestimated the HCV incidence. When calculating the HCV prevalence, mean population  
41 408 data for Norway was used, rather than more accurate regional data as the latter was not readily  
42 409 available. In addition, treatment with DAAs were limited by stage of liver fibrosis during the study  
43 410 period. Only from February 1, 2018 it was offered universally regardless of level of liver fibrosis.  
44 411 Thus it is likely that younger patients and patients with Metavir F0-F1 score were excluded from DAA  
45 412 treatment during the study period.  
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47 414 When measuring adherence among different age groups we should be careful when interpreting  
48 415 results. Older patients are more likely to have cirrhosis and longer HCV treatment courses compared  
49 416 to younger patients. This could bias our results toward higher adherence among the latter. Finally,  
50 417 PWIDs are a heterogenic group of individuals, and one should be careful not to generalize OAT  
51 418 patients to include all PWIDs.  
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## 53 420 Conclusion

54 421 This is the first population-based study documenting the transition to DAA treatment regimens among  
55 422 Norwegian OAT patients. A marked scale-up in HCV treatment coverage attributed by a complete  
56 423 shift to interferon-free regimens among Norwegian OAT patients has been demonstrated. Adherence

to DAAs across all genotypes remained sound, especially for high level of OAT continuity. Annual HCV treatment coverage ranged from 3.5% in 2013 to 17% in 2017, giving a cumulative HCV coverage among OAT patients for the study period just above 38%. Despite a large increase in treatment, overall HCV coverage is inadmissibly too low in order to meet the ambitious national and WHO targets of controlling and eliminating chronic HCV. . There is a need to establish more accurate monitoring system and more precision in prevalence and incidence rates of chronic HCV among PWID to get more precise coverage data. Efficacy of health system strategies is needed in order to further scale-up of the most effective HCV policies to this group and for countries to be able to control and eliminate HCV.

#### List of abbreviations

OAT	Opioid agonist therapy
DAA	Direct-acting antivirals
HCV	Hepatitis C virus
PWID	People who inject drugs
NorPD	The Norwegian Prescription Database
ATC	Anatomical Therapeutic Chemical classification system
DDD	Defined daily dose
PPP	Prescribed daily dose
NIPH	The Norwegian Institute for Public Health
SERAF	The Norwegian Centre for Addiction Research
MSIS	The Norwegian Surveillance System for Communicable Diseases
Anti-HCV	Antibodies to the Hepatitis C virus
SVR	Sustained virological response
INTRO-HCV	Integrated treatment of hepatitis C virus infection

#### **Declarations**

##### *Contributorship statement*

This observational study was led by CFA in terms of study design, analyzes, drafting and writing the article. SS and JHV was particularly involved with acquisition of data, analyzes and interpretation. Maps were made by JMØ and KAJ. SS, JHV, IO, FC, JMØ, AL, PV, KAJ and LTF contributed to the conception, writing, and revising the draft(s) critically. All authors have read and approved the version to be published.

##### *Competing interests*

I.O. is employed at the Centre for Pharmacoepidemiology, Karolinska Institutet, which receives grants from several entities (pharmaceutical companies, regulatory authorities, and contract research organizations) for performance of drug safety and drug utilization studies, unrelated to this work. None of the other authors have competing interests.

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##### *Availability of data and material*

Supplemental tables, figure and data sources in this observational study are available in this published article and its additional files.



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List of Tables and Figure

713 Table 1:  
714 *Table 1: Basic characteristics of patients receiving OAT from 2013 to 2017 in Norway*

Basic characteristics	Total	2013	2014	2015	2016	2017
Individuals >1 OAT	10371	7709	7914	7958	7804	7709
Deaths	692	165	151	138	114	124
Gender, n (%)						
Male	7135 (69)	5221 (69)	5390 (69)	5430 (69)	5354 (70)	5254 (69)
Female	3236 (31)	2323 (31)	2373 (31)	2390 (31)	2336 (30)	2340 (31)
Age, n (%)						
<25		211 (3)	185 (2)	171 (3)	135 (2)	120 (2)
26-40		2813 (37)	2797 (36)	2718 (40)	2574 (33)	2432 (32)
41-60		4289 (57)	4537 (58)	3644 (53)	4627 (60)	4613 (61)
>60		231 (3)	244 (3)	287 (4)	354 (5)	420 (6)
OAT medication, n (%)						
Methadone/Levomethadone		3406 (45)	3264 (42)	3216 (41)	3066 (40)	2981 (39)
Buprenorphine based*		4138 (55)	4499 (58)	4604 (59)	4624 (60)	4604 (61)
Dispensations of HCV drugs**	1475	146	167	243	322	597
OAT continuity category, n (%)						
I: ≥2 DDD	5310 (51)					
II: 1-2 DDD	3078 (30)					
III: <1 DDD	1983 (19)					

714 OAT = opioid agonist therapy; DDD = Daily defined Doses  
 715 Source: NorPD = Norwegian Prescription Database  
 716 \* Buprenorphine and buprenorphine/naloxone  
 717 \*\* HCV drugs: interferon-based and direct-acting antivirals (DAAs)

729 Table 2:

730 *Table 2: Annual and cumulative chronic HCV treatment coverage among OAT patients in Norway between 2013 and 2017*

	Source	2013	2014	2015	2016	2017	Total
Chronic HCV treatment n	NorPD	146	167	243	322	597	1475

(overall)							
DAAs, n	NorPD	46	95	212	290	592	1235
DAAs % of HCV		32	57	87	90	99	84
Study population n, yearly incl. deaths	NorPD	7709	7914	7958	7804	7709	10371
Deaths	NorPD	165	151	138	114	124	692
Study population n, yearly, excl. deaths	NorPD	7544	7763	7820	7690	7585	9679
Prevalence chronic HCV, mean %	SERAF	51	52	52	46	43	
Prevalence chronic HCV, n	SERAF	3847	4037	4066	3537	3262	
Incidence chronic HCV among PWIDs n	NIPH, Meijerink et al.	396	388	381	374	366	
Incidence chronic HCV OAT from PWIDs n	Expert opinion	277	272	267	262	256	
<i>Treatment coverage chronic HCV %</i>		3.5	3.9	5.6	8.5	17.0	
<i>Cumulative frequency chronic HCV</i>		3.5	7.4	13.0	21.5	38.5	
95% Confidence interval treatment coverage chronic HCV		3.2-4.4	3.5-4.8	5.3-6.7	8.2-10.1	16.9-19.6	

OAT = opioid agonist therapy, PWID = people who inject drugs, HCV = hepatitis C virus, DAA = direct-acting antivirals,  
 Sources: NorPD = Norwegian Prescription Database, SERAF = The Norwegian Centre for Addiction Research, NIPH = Norwegian Institute for Public Health, Meijerink et al. (2017): Modelling the burden of hepatitis C infection among people who inject drugs in Norway, 1973–2030

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Table 3:

*Table 3: Adherence\* to DAAs among OAT patients in Norway between 2013 and 2017*

	Adherent	Non-Adherent	Total:
Adherence by gender, n (%):			
Male	551 (67)	277 (33)	828
Female	191 (67)	92 (33)	283

Total	742 (67)	369 (33)	1111
Adherence by age, n (%):			
18-35	119 (58)	85 (42)	204
36-45	259 (68)	122 (32)	381
46-55	302 (70)	128 (30)	430
>56	62 (65)	34 (35)	95
Total	742 (67)	369 (33)	1111
Adherence by OAT medication, n (%):			
Methadone/levomethadone	298 (65)	157 (35)	455
Buprenorphine based	444 (68)	212 (32)	656
Total	742 (67)	369 (33)	1111

*Logistic regression on factors associated with adherence\**

	aOR (CI 95%)	p-value
Age	0.98 (0.97-1.00)	0.17
Gender		
Male	1.00	
Female	0.92 (0.69-1.23)	0.57
OAT continuity		
Category I: $\geq 2$ DDD	1.00	
Category II: 1-2 DDD	1.36 (1.02-1.82)	0.035
Category III: $< 1$ DDD	1.36 (0.93-1.99)	0.11

OAT = opioid agonist therapy, DAA = direct-acting antivirals, aOR = adjusted odds ratio, CI = confidence interval, DDD = daily defined doses

Source: NorPD = Norwegian Prescription Database

\*Adherence defined as collected  $\geq$ three prescriptions and  $> 84$  DDDs (unless ledipasvir and sofosbuvir which also calculated as  $\geq$ two prescriptions and  $> 56$  DDDs). Analyses included 1111 patients as inclusion was ceased 01.10.17 to avoid counting treatment initiation after this date non-adherent.

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Figure 1:

*Figure 1: Cumulative chronic HCV treatment coverage among OAT patients in Norway between 2013 and 2017 by Health Counties\**

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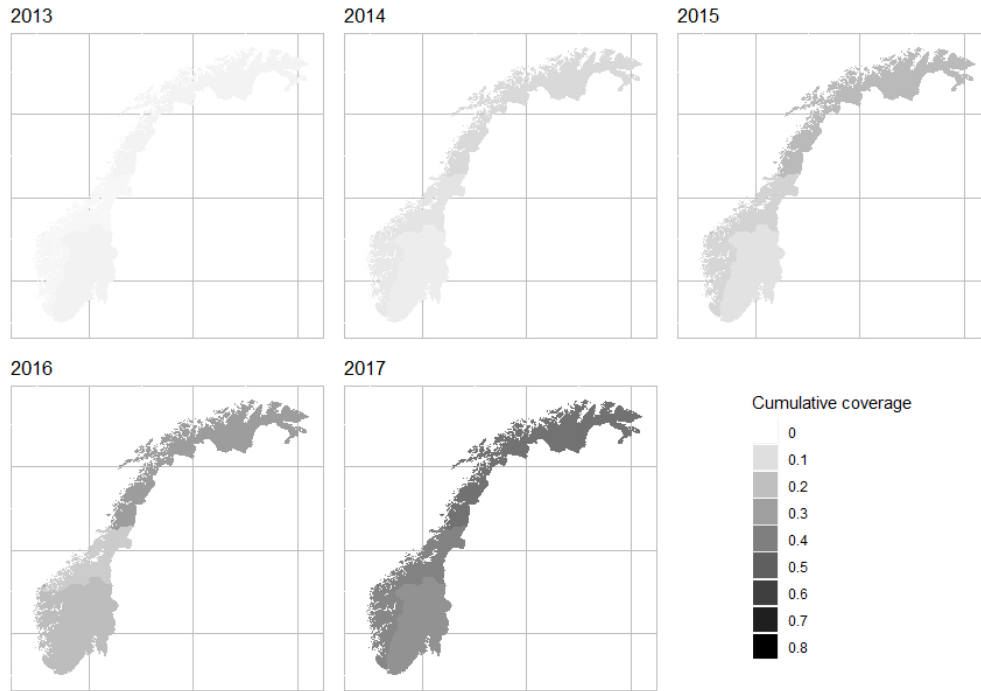
OAT = opioid agonist therapy, HCV = hepatitis C virus

Sources: NorPD = Norwegian Prescription Database, SERAF = The Norwegian Centre for Addiction Research, NIPH = Norwegian Institute for Public Health, Meijerink et al. (2017): Modelling the burden of hepatitis C infection among people who inject drugs in Norway, 1973–2030, calculations in Table S2

\*Cumulative coverage in %, the four Health counties: Helse Vest, Helse Midt, Helse Nord and Helse Sør-Øst

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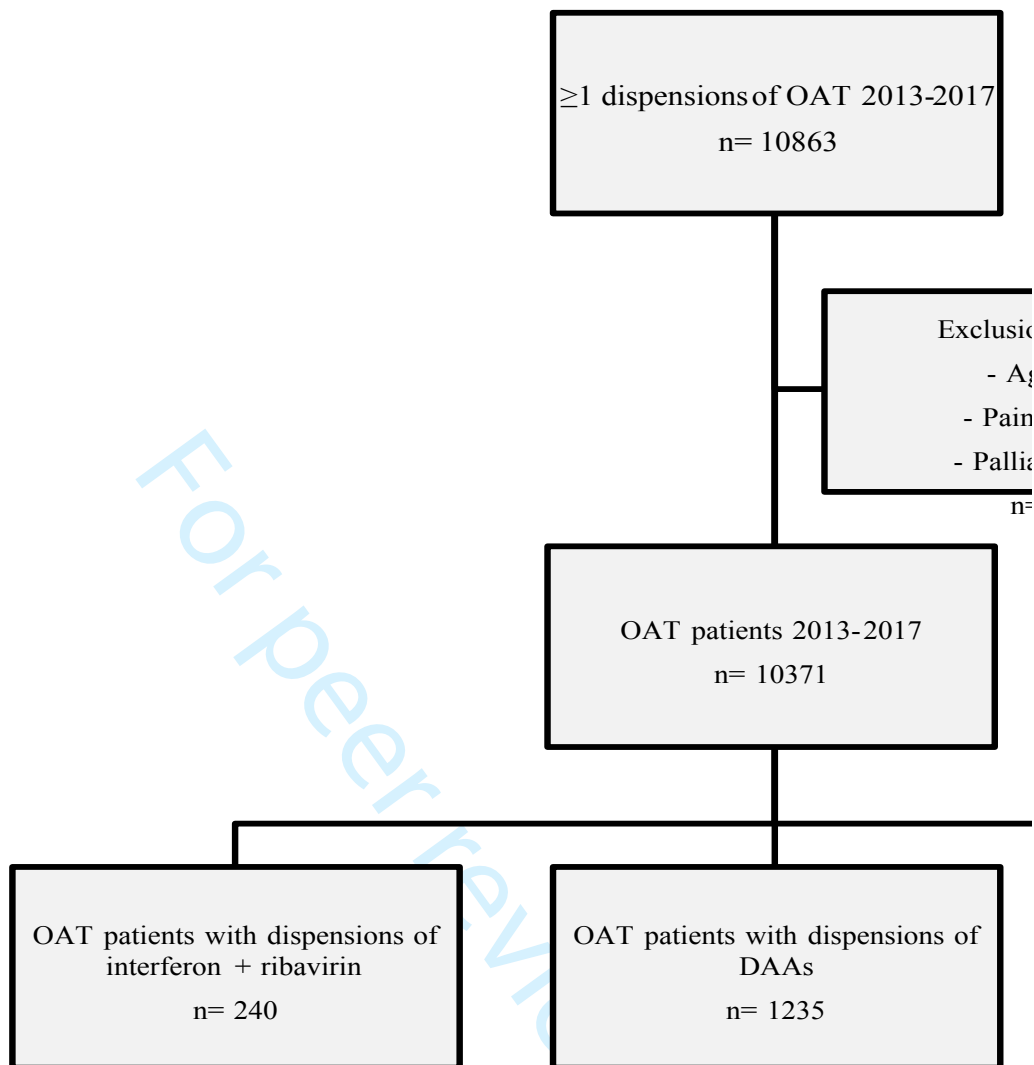




Cumulative chronic HCV treatment coverage among OAT patients in Norway between 2013 and 2017 by Health Counties

302x213mm (72 x 72 DPI)

Figure S1: Flow chart of study population



OAT = opioid agonist therapy, HCV = hepatitis C virus, DAA = direct-acting antivirals,  
Sources: NorPD = Norwegian Prescription Database

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OAT patients with no dispersions of  
interferon, ribavirin or DAAs  
n=8896

Table S1: ATC classification and dispensed DAAs among OAT patients in Norway from 2013 to 2015

Description	ATC code
<b>Anti-infective for systemic use</b>	J
Antivirals for treatment of HCV infection, DAAs	J05AP*
Telaprevir	J05AP02
Boceprevir	J05AP03
Faldaprevir	J05AP04
Simeprevir	J05AP05
Asunaprevir	J05AP06
Daclatasvir	J05AP07
Sofosbuvir	J05AP08
Dasabuvir	J05AP09
Ledipasvir and Sofosbuvir	J05AP51
Dasabuvir, ombitasvir, paritaprevir and ritonavir	J05AP52
Ombitasvir, paritaprevir and ritonavir	J05AP53
Elbasvir and grazoprevir	J05AP54
Sofosbuvir and velpatasvir	J05AP55
Sofosbuvir, velpatasvir, and voxilaprevir	J05AP56
Glecaprevir and pibrentasvir	J05AP57
<b>Most prevalent DAAs dispensed in Norway among OAT patients**</b>	<b>Frequency (%)</b>
Elbasvir and grazoprevir	328 (27)
Sofosbuvir	279 (23)
Ledipasvir and Sofosbuvir	225 (18)
Sofosbuvir and velpatasvir	187 (15)
Ombitasvir, paritaprevir and ritonavir	55 (5)
Daclatasvir	47 (4)
Dasabuvir	34 (3)
Simeprevir	33 (3)
Other	37 (3)
<p>ATC = Anatomical Therapeutic Chemical classification, OAT = opioid agonist therapy, DAA = direct-acting antivirals,  Sources: NorPD = Norwegian Prescription Database  *Excluding Ribavirin J05AP01  **First registered dispensation by ATC. For sofosbuvir, daclatasvir, dasabuvir and simeprevir additional dispensations of other DAA/antivirals may occur.</p>	

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Table S1: Annual and cumulative chronic HCV treatment, crude, among OAT patients in Nor

	Source	2013	2014	2015
HCV treatment n (overall)	NorPD	146	167	243
DAAAs, n	NorPD	46	95	212
DAAAs % of HCV		32	57	87
Study population n, yearly incl. deaths	NorPD	7709	7914	7958
Deaths	NorPD	165	151	138
Study population n, yearly, excl. deaths	NorPD	7544	7763	7820
HCV treatment crude %:				
HCV overall		1.9	2.2	3.1
DAAAs		0.6	1.2	2.7
Cumulative frequency HCV overall		1.9	4.1	7.2
Cumulative frequency DAAAs		0.6	1.8	4.5
95% Confidence interval (HCV)		1.6-2.3	1.8-2.5	2.7-3.5
95% Confidence interval (DAAAs)		0.4-0.8	1.0-1.5	2.4-3.1

OAT = opioid agonist therapy, HCV = hepatitis C virus, DAA = direct-acting antivirals,  
Sources: NorPD = Norwegian Prescription Database

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*Change between 2013 and 2017*

<b>2016</b>	<b>2017</b>	<b>Total</b>
322	597	1475
290	592	1235
90	99	84
7804	7709	10371
114	124	692
7690	7585	9679
4.2	7.9	
3.8	7.8	
11.4	19.3	
8.3	16.1	
3.7-4.6	7.3-8.5	
3.4-4.2	7.2-8.4	

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Table S2: Annual and cumulative chronic HCV treatment coverage among OAT patients in .

	Source:	2013
Helse Sør-Øst HCV Treatment	NorPD	93
Helse Vest HCV Treatment	NorPD	24
Helse Midt HCV Treatment	NorPD	20
Helse Nord HCV Treatment	NorPD	6
Study population incl death Helse Sør-Øst	NorPD	4553
Study population incl death Helse Vest	NorPD	1889
Study population incl death Helse Midt	NorPD	708
Study population incl death Helse Nord	NorPD	559
Deaths Helse Sør-Øst	NorPD	91
Deaths Helse Vest	NorPD	47
Deaths Helse Midt	NorPD	21
Deaths Helse Nord	NorPD	6
Study population excl death Helse Sør-Øst	NorPD	4462
Study population excl death Helse Vest	NorPD	1842
Study population excl death Helse Midt	NorPD	687
Study population excl death Helse Nord	NorPD	553
Prevalence HCV Helse Sør-Øst, mean %	SERAF	55
Prevalence HCV Helse Vest, mean %	SERAF	43
Prevalence HCV Helse Midt, mean %	SERAF	73
Prevalence HCV Helse Nord, mean %	SERAF	45
Prevalence HCV Helse Sør-Øst, n	SERAF	2454
Prevalence HCV Helse Vest, n	SERAF	792
Prevalence HCV Helse Midt, n	SERAF	502
Prevalence HCV Helse Nord, n	SERAF	238
Incidence HCV Helse Sør-Øst, PWIDs	NIPH, Mejerick et al.	249
Incidence HCV Helse Vest, PWIDs	NIPH, Mejerick et al.	79
Incidence HCV Helse Midt, PWIDs	NIPH, Mejerick et al.	44
Incidence HCV Helse Nord, PWIDs	NIPH, Mejerick et al.	24
Incidence HCV Helse Sør-Øst, OAT, n	NIPH, Mejerick et al.	175
Incidence HCV Helse Vest, OAT, n	NIPH, Mejerick et al.	55
Incidence HCV Helse Midt, OAT, n	NIPH, Mejerick et al.	30
Incidence HCV Helse Nord, OAT, n	NIPH, Mejerick et al.	17
<i>Treatment coverage HCV Helse Sør-Øst %</i>		3.5
<i>Cumulative frequency HCV Helse Sør-Øst</i>		3.5
<i>Treatment coverage HCV Helse Vest %</i>		2.8
<i>Cumulative frequency HCV Helse Vest</i>		2.8
<i>Treatment coverage HCV Helse Midt %</i>		3.8
<i>Cumulative frequency HCV Helse Midt</i>		3.8
<i>Treatment coverage HCV Helse Nord %</i>		2.4
<i>Cumulative frequency HCV Helse Nord</i>		2.4

OAT = opioid agonist therapy, PWID = people who inject drugs, HCV = hepatitis C virus

Sources: NorPD = Norwegian Prescription Database, SERAF = The Norwegian Centre for Addictior  
Meijerink et al. (2017): Modelling the burden of hepatitis C infection among people who inject drugs



Norway between 2013 and 2017 by Health Regions

	2014	2015	2016	2017	Total:
	92	158	196	367	906
	27	36	64	136	287
	18	22	27	52	139
	27	27	20	26	106
	4636	4609	4575	4580	
	1971	2000	1833	1735	
	728	731	742	740	
	578	616	653	653	
	82	84	74	74	
	45	33	29	39	
	16	10	6	6	
	8	11	5	5	
	4554	4525	4501	4506	
	1926	1967	1804	1696	
	712	721	736	734	
	570	605	648	648	
	53	57	52	45	
	51	50	47	41	
	53	52	49	36	
	48	43	33	28	
	2414	2579	2341	2028	
	982	984	848	695	
	377	375	361	264	
	274	260	214	181	
	233	238	236	238	
	93	91	86	81	
	39	35	41	33	
	23	16	11	15	
	163	167	165	167	
	65	64	60	56	
	27	25	29	23	
	16	11	8	10	
	3.5	5.7	7.8	16.7	
	7.1	12.8	20.7	37.4	
	2.6	3.4	7.0	18.1	
	5.4	8.8	15.9	34.0	
	4.4	5.5	6.9	18.1	
	8.2	13.7	20.6	38.7	
	9.3	9.9	9.0	13.6	
	11.7	21.6	30.6	44.2	

n Research, NIPH = Norwegian Institute for Public Health,  
s in Norway, 1973–2030

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(b) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4, n/a
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	5
		(b) Describe any methods used to examine subgroups and interactions	4/5
		(c) Explain how missing data were addressed	-
		(d) If applicable, explain how loss to follow-up was addressed	n/a
		(e) Describe any sensitivity analyses	-
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	19
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) Summarise follow-up time (eg, average and total amount)	n/a
Outcome data	15*	Report numbers of outcome events or summary measures over time	

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5/6
2			(b) Report category boundaries when continuous variables were categorized	-
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
4				
5				
6	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
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11	<b>Discussion</b>			
12	Key results	18	Summarise key results with reference to study objectives	6
13	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	7/8
14				
15	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7/8
16				
17	Generalisability	21	Discuss the generalisability (external validity) of the study results	7
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21	<b>Other information</b>			
22	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9
23				
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26 \*Give information separately for exposed and unexposed groups.

27  
28 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and  
29 published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely  
30 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at  
31 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is  
32 available at <http://www.strobe-statement.org>.  
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## On the path towards universal coverage of hepatitis C treatment among people receiving opioid agonist therapy (OAT) in Norway: a prospective cohort study from 2013 to 2017

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## Abstract

### *Objectives*

We aimed to calculate cumulative hepatitis C (HCV) treatment coverage among individuals enrolled in opioid agonist therapy (OAT) in Norway between 2013 and 2017, and to document the treatment transition to direct-acting antiviral agents (DAA). Moreover, we aimed to describe adherence to DAAs in the same cohort.

### *Design:*

Prospective cohort, registry data

### *Setting:*

Specialist health care service (secondary)

### *Participants and outcomes:*

This observational study was based on data from The Norwegian Prescription Database (NorPD). We studied dispensed OAT and HCV treatment annually to calculate the cumulative frequency, and employed secondary sources to calculate prevalence, incidence and HCV treatment coverage from 2013 to 2017, among the OAT population. Factors associated with adherence to DAAs were identified a priori and subject to logistic regression.

### *Results*

10,371 individuals were identified with dispensed OAT, 1,475 individuals of these with dispensed HCV treatment. Annual HCV treatment coverage increased from 3.5% (95% CI: 3.2-4.4) in 2013 to 17% (95% CI: 17-20) in 2017, giving a cumulative HCV coverage among OAT patients in Norway of 38.5%. A complete shift to interferon-free treatment regimens occurred, where DAAs accounting for 32% of HCV treatments in 2013 and 99% in 2017. About two-thirds of OAT patients were considered adherent to their DAA regimens across all genotypes. High-level of OAT continuity was associated with improved adherence to DAAs (aOR 1.4, 95% CI: 1-2, p=0.035).

### *Conclusions*

A large increase in HCV treatment coverage attributed by a complete shift to interferon-free regimens among the Norwegian OAT population has been demonstrated. However, treatment coverage is inadmissibly too low and a further substantial scale-up in HCV treatment is required to reach the universal targets of controlling and eliminating the HCV endemic.

## Strengths and limitations - summary

- All dispensed drugs from pharmacies in Norway are registered in the database
- The completeness, precision, and validity of data are high among a hard-to-reach population
- Data was not linked on an individual level to diagnosis codes of chronic HCV
- HCV prevalence and incidence data are imprecise
- Treatment with DAAs were limited during the study period from 2013 to 2017 based on stage of liver fibrosis.

Keywords: Hepatitis C virus (HCV), treatment uptake, treatment coverage, direct-acting antiviral agents (DAAs), opioid agonist therapy (OAT), adherence,



## Background

The large burden of chronic hepatitis C (HCV) among people who inject drugs (PWID) and recent developments in HCV medications creates an opportunity to eliminate HCV epidemics. Worldwide, about 71 million people are chronically infected with the virus and 399,000 died annually from HCV related complications like liver cirrhosis or hepatocellular carcinoma (1, 2). Despite the low aggregated HCV prevalence in many countries (1.5-3.5% in Western Europe and <1.5% in North America), prevalence is much higher among PWID (50%, or more) (3-5). The World Health Organization's Global Health Sector Strategy aims to eliminate viral hepatitis as a public health threat by 2030 (2). The even bolder Norwegian HCV strategy aims to reduce national incidence by 90% by 2023 (6). Eliminating chronic HCV requires a significant effort in terms of increasing uptake of testing, diagnosing, and linking to care. In addition, other strategies have been proposed alongside increasing antiviral treatment, such as opioid agonist therapy (OAT) scale-up, safe injection sites and sterile injection equipment to reach these objectives (2, 7).

Injecting drug use and needle sharing is the major driver of HCV incidence (8), however, the coverage of preventive interventions, such as needle and syringe programs, remains poor among PWIDs (9). Number of people who actively inject drugs in Norway have been stable at around 9000 since 2012 till 2017 (2.6 per 1 000 inhabitants aged 15-64 years) (10, 11), and opioids and amphetamines are the main injected drugs (11, 12). Modelling studies suggest that around 7000 former and current PWIDs are living with chronic HCV with an estimated 400 new cases annually in the same time period (13, 14). Both HCV-related liver morbidity and mortality are increasing among PWIDs and are likely to continue to increase until 2022 (14).

OAT has been put forward to play a vital role in the management of chronic HCV among people with opioid dependence and has been shown to reduce the risk of HCV acquisition (15). For these reasons, OAT may be crucial intervention for achieving large reductions in HCV transmissions by reducing risk behaviors like injecting use and sharing of injecting equipment (16). HCV testing rates have been low in the national OAT program in Norway with great annual and regional variations (5, 17-20). Only in parts of western Norway, as part of the multicenter INTRO-HCV study, all patients receiving OAT have been systematically tested and examined with elastography as part of an annual health assessment since 2017 (21). Even if access to HCV treatment is improving, HCV treatment coverage remains low (8, 22-25). Globally, the coverage of HCV curative treatment was 13% by 2016 (26). In Norway, annual HCV treatment coverage among OAT patients was between 1.3% to 2.6% in the period from 2004 to 2013, giving a cumulative HCV coverage for the period of 14% (27).

The introduction of direct-acting antiviral (DAAs) medications, with a curation rate of approximately 95%, safer and better-tolerated than interferon-based therapy, has dramatically changed the treatment of chronic HCV infections (28, 29). Even if currently expensive, they are considered cost effective from a societal perspective as universal coverage with antiretroviral treatment could prevent large expenses related to future complications (30-35). Combining DAAs with the OAT delivery platform may thus prove critical for achieving reductions in HCV prevalence and incidence (22). A number of treatment barriers exist, which should in turn be carefully addressed, nevertheless, treatment barriers should not exclude PWIDs from HCV treatment (8, 36, 37). Both World Health Organization and Norwegian guidelines support DAA treatment among PWIDs and have also shown good outcomes in systematic reviews (24, 25, 38).

The pathway to universal HCV treatment coverage has not been well documented at country levels, hence, the primary aim of the study was to:

- 1) Document HCV treatment annually and cumulatively after the introduction of DAAs among patients receiving OAT in Norway from 2013-2017 and to calculate HCV treatment coverage, both annually and cumulatively.
- 2) A second objective is to evaluate adherence to DAAs among OAT patients in Norway.



## 155 Methods

156

### 157 Study design and data sources

158 This is an observational study among OAT patients from 2013 to 2017 in Norway. Data were extracted  
 159 from The Norwegian Prescription Database (NorPD) from January 1, 2013 to March 31, 2018. The  
 160 database covers the entire Norwegian population and records all drugs dispensed from pharmacies in  
 161 Norway. All drugs are classified according to The Anatomical Therapeutic Chemical (ATC)  
 162 classification system (39). Defined daily doses (DDDs) according to 2018 (40) were employed to  
 163 quantify the dispensed OAT and HCV medications respectively. The DDDs are the assumed average  
 164 maintenance dose per day for a drug used for its main indication (41).

165

166 Data from The Norwegian Centre for Addiction Research were used for estimating the prevalence of  
 167 chronic HCV among OAT patients, whereas incidence data among Norwegian PWIDs was gathered  
 168 from The Norwegian Institute of Public Health and Meijerink et al. (14)

169

### 170 Study population and definitions

171 The study population included all individuals with at least one dispensed prescription of buprenorphine  
 172 (ATC code N07BC01), methadone (N07BC02), buprenorphine-naloxone (N07BC51), and  
 173 levomethadone (N07BC05). Patients <18 years and with other indications than OAT were excluded  
 174 from the study on the basis of formulation and route of administration (Figure S1).

175

176 Exposure to HCV treatment was defined as being dispensed either pegylated interferon alpha (L03AB05  
 177 and L03AB11) and ribavirin (J05AP01) or any of the DAAs (in group J05AP, see Table S1 for complete  
 178 list of DAAs by ATC code) during the study period. The first dispensed DAA according to ATC code  
 179 was noted, and to prevent over-counting patients were only counted once at initiation. Thus, definition  
 180 of treatment was any individual on OAT who has been dispensed HCV treatment. Any individual who  
 181 died was censored in the calendar year they passed away. Rates were calculated by dividing number of  
 182 individuals with dispensed HCV treatment by individuals on OAT, stratified by each calendar year. The  
 183 cumulative frequency, which is the addition of successive years of treatment, was then calculated. HCV  
 184 treatment was stratified as overall treatment with any chronic HCV medication and treatment with solely  
 185 DAAs.

186

187 HCV treatment coverage was defined as individuals on OAT identified in NorPD annually, adjusted for  
 188 death, HCV prevalence, and new cases of chronic HCV each year, which had received treatment for  
 189 chronic HCV during the study period. Mean prevalence during the study period among patients enrolled  
 190 in OAT ranged from 51% in 2013 to 43% in 2017 (5, 17-20) and proportional prevalence among OAT  
 191 individuals were calculated per calendar year. Incidence was around 400 per year for PWIDs during the  
 192 study period (14). It proved methodologically challenging to estimate number of new cases of chronic  
 193 HCV among OAT patients. As the OAT coverage among people with opioid dependence is between 50  
 194 and 60% in Norway (5), OAT patients account for only a proportion of overall PWIDs and thus needed  
 195 to be adjusted for in our calculation. For this reason expert opinion were obtained from clinicians in  
 196 addiction medicine and set to a 0.70 (70%) proportion, giving between 277 to 256 new cases annually  
 197 during the study period. We developed the following basic model for our coverage calculation:

198

$$199 \quad HCV_{cov} = \frac{t_{HCV}}{p_{HCV} + i_{HCV}} * 100$$

200

201 where HCV cov is HCV coverage,  $t_{HCV}$  = number of OAT patients with dispensed HCV treatment,  
 202  $p_{HCV}$  = number of OAT patients with chronic HCV and  $i_{HCV}$  = number of new cases of chronic  
 203 HCV among OAT patients. Coverage was calculated annually for Norway and by Health County, and  
 204 as cumulative frequencies.

205

206 We defined adherence to DAA as having collected prescriptions equivalent to three months of treatment.  
 DAAs for adults, which is only prescribed by specialists are collected for one-month-at-a-time basis

207 where a typical DAA treatment course is 12 weeks, i.e. three dispensed prescriptions and  $\geq 84$  DDDs.  
208 The exception is the drug combination ledipasvir/sofosbuvir, which may be prescribed for eight weeks  
209 (two collections and  $\geq 56$  DDD) for cases of previously untreated genotype 1 infections. This allowed  
210 us to examine adherence based on number of dispensed prescriptions and DDDs. Impending factors  
211 associated with treatment adherence to DAAs were identified a priori and included gender, age, and  
212 OAT continuity, and subject to multivariate analyzes in a step-by-step model.

213  
214 Finally, OAT continuity was defined according to dispensed DDDs and stratified into three categories,  
215 ranging from a high level of OAT continuity in category I ( $\geq 2$  DDD), medium in category II (1-2 DDD),  
216 and to a low level of OAT continuity in category III ( $< 1$  DDD). One DDD for methadone and  
217 buprenorphine is 25mg and 8mg respectively.

### 218 219 Statistical analyzes and strategy

220 Descriptive data are presented as frequencies, percentages, means, and with corresponding 95%  
221 confidence intervals where appropriate. Logistic regression on factors associated with adherence are  
222 presented as adjusted odds ratio (aOR) when adjusted for age, gender and OAT continuity.

223  
224 The data was analyzed with SPSS version 24 and Stata SE version 15 (StataCorp, TX, USA). Map  
225 figures were made in R.

### 226 227 Data handling and ethical considerations

228 Since all registry data was received pseudo-anonymously from the registry administrator and  
229 subsequently analyzed anonymously no written consent was obtained from any of the individuals in the  
230 study. This study was approved by the regional committee for ethics in medical research (no.  
231 2018/939/REK Vest). It was conducted in accordance with the Helsinki Declaration and as an  
232 observational study in accordance with international accepted STROBE guidelines (42).

### 233 234 Patient and public involvement

235 No patients were directly involved in this study, however, as part of the bigger INTRO-HCV project  
236 patients through user organizations such as Pro-LAR, were involved in the planning process, workshops  
237 that included design and recruitment, protocol writing and assessment of the burden of the intervention  
238 in the randomized controlled trial.

## 239 240 Results

### 241 Basic characteristics of study population

242 A total of 10,371 individuals were identified in NorPD having received  $\geq 1$  OAT prescriptions during  
243 the study period from 2013 to 2017 (Table 1). Almost 70% were male, mean age of 43 years and 45  
244 years in 2013 and 2017, respectively. The majority of the OAT patients were treated with  
245 buprenorphine-based OAT medication (55% in 2013, 61% in 2017). Over 50% of individuals on OAT  
246 had a high level of continuity. Altogether 692 individuals died during the study period.

247  
248 (insert Table 1)

### 249 250 HCV treatment and coverage

#### 251 252 HCV and DAA treatment

253 All individuals were stratified according to the year in which they received OAT and HCV treatment.  
254 Excluding deaths, this gave a fairly stable OAT population just in excess of 7500 annually. In 2013, 146  
255 OAT patients received HCV treatment. Treatment increased over time with 597 patients receiving HCV  
256 treatment in 2017. Overall 1475 patients on OAT received HCV treatment during the study period, with  
257 an annual HCV treatment increasing from 1.9% (95% CI: 1.6-2.3%) in 2013 to 7.9% (95% CI: 7.3-  
258 8.5%) in 2017 (Table S2). By 2017, the cumulative frequency of HCV treatment reached 19% among  
259 patients on OAT.

261 Of the 1475 individuals that received HCV treatment during the study period, 1235 were treated with  
262 DAAs. The annual DAA treatment ranged from 0.6% (95% CI: 0.4-0.8%) in 2013, to 7.8 (95% CI: 7.2-  
263 8.4%) in 2017. The proportion of treated individuals receiving DAAs increased over time from 32% of  
264 HCV treated OAT patients in 2013 to 99% in 2017.

#### 265 266 HCV treatment: coverage

267 We calculated annual HCV coverage among the estimated number of OAT patients that are HCV  
268 infected, which ranged from 3.5% (95% CI: 3.2-4.4%) in 2013 to 17% (95% CI: 16.9-19.6%) in 2017.  
269 This gave a cumulative frequency that reached 38.5% in 2017 (Table 2). Figure 1 shows cumulative  
270 HCV coverage from 2013 to 2017 by the four health counties in Norway (HCV<sub>cov</sub> and data from Table  
271 S3 were used for these calculations). There were little variation in treatment coverage across the four  
272 health counties.

273  
274 (insert Figure 1 + Table 2)

#### 275 276 Adherence to DAAs

277 Overall, almost 70% of the OAT patients were adherent to their DAA regimen and considered to have  
278 finished their DAA treatment course (Table 3). There were no major differences by gender or OAT  
279 drug. However, for age, patients in the age group 18-35 were less adherent (42%) compared with older  
280 age groups. The drug combination of elbasvir/grazoprevir, commonly used for treatment of genotype 1  
281 infections, had by far the utmost adherence (93%) compared to treatment combinations of  
282 sofosbuvir/velpatasvir, and ledipasvir/sofosbuvir, which both were around 70%. However, sometimes  
283 ledipasvir/sofosbuvir is prescribed for eight weeks, in which case yields an overall adherence of 78%.

284  
285 In multivariate analyzes, only OAT continuity was associated with adherence to DAAs (adjusted OR  
286 1.4, 95% CI: 1.0-1.8 p=0.035).

287  
288 (insert Table 3)

#### 289 290 Discussion

291 The HCV treatment coverage has increased substantially, yet it seems too low if the ambitious targets  
292 of ending the endemic are to be met. Annual treatment rate increased from 1.9% of all OAT patients in  
293 Norway in 2013 to 7.9% in 2017, which gives a cumulative frequency of around 19% over the study  
294 period. However, cumulative HCV treatment coverage among OAT patients with assumed chronic HCV  
295 in Norway was just above 38%, with annual treatment coverage that ranged from 3.5% in 2013 to 17%  
296 in 2017. Secondly, we observed a complete shift in the HCV treatment among OAT patients in Norway  
297 during the study period, from two-thirds treated with DAAs in 2013, to nearly all in 2017. Finally, about  
298 two-thirds of all OAT patients with chronic HCV were considered adherent to their DAAs regimen,  
299 which improved with level of OAT continuity.

300  
301 It can be useful to compare our results at country levels. Immense advances have been made in chronic  
302 HCV treatment since the introduction of DAAs in recent years, however multiple studies have  
303 demonstrated continued low treatment uptake among PWIDs and OAT patients (23, 27, 43), partly  
304 explained by varying and restricted treatment access policies that prevented a widespread scale-up of  
305 DAA treatment during the study period (44). For instance England, saw one of the most restricted access  
306 policies to DAA treatment compared to e.g. France and Germany, which had the least restrictions (45).  
307 Consequently HCV treatment rates varied dramatically across European countries ranging from 0.6%  
308 to 10.2% in 2015 (46). In the same year we found HCV treatment rate of 5.6% in Norway, which is  
309 similar to Sweden, however higher than Denmark that saw treatment rate more in line with the overall  
310 3.7% that year among European countries (46). Prior to the introduction of DAAs, Midgard et al (2016)  
311 showed an annual treatment coverage of 1.3% to 2.6% between 2004 and 2013 among Norwegian OAT  
312 patients, giving a cumulative treatment coverage of 14% during the entire study period. Considering  
313 there is not in place a national and systematic program for testing and linking to HCV care among  
314 PWIDs, nor has the full effectiveness of integrated treatment combining OAT and HCV treatment been

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3 315 fully demonstrated (47), HCV coverage would probably be substantially higher with a comprehensive  
4 316 model of integrative care where both testing and treatment were provided in OAT outpatient clinics.  
5 317

6 318 The Norwegian Hepatitis C policy identifies improved access to treatment, prevention, and surveillance  
7 319 of the endemic as crucial to succeed with HCV elimination strategies (48). Treatment with DAAs in  
8 320 Norway was until February 1, 2018, limited by eligibility criteria based on stage of liver fibrosis. Since  
9 321 then, DAA treatment has been offered to all regardless of genotype and level of liver fibrosis. As a  
10 322 result, treatment demand increased and coverage of curative HCV treatment has amplified. From 2014  
11 323 to June 2018, around 5000 patients were treated for chronic HCV in Norway, however, these patients  
12 324 are mostly former PWIDs and immigrants being infected prior to the arrival in Norway (13). It is unclear  
13 325 how many of these patients were on OAT and overlapped with our results. Nonetheless, despite  
14 326 continued falling prices of DAAs, which have made unrestricted treatment possible for all, HCV  
15 327 treatment and coverage remains low among active PWIDs (13), which is in line with our results  
16 328 demonstrating the need for a significant scale-up to improve HCV coverage and being able to plan  
17 329 elimination strategies. It may therefore be crucial to identify other barriers to treatment for this  
18 330 vulnerable patient group. Arguably, even with DAA treatment for all, low threshold OAT, needle and  
19 331 syringe programs in place, it is hard to see how this can be achieved unless testing and linkage to care  
20 332 is provided where PWIDs and OAT patients actually are. This opts for decentralized testing and  
21 333 treatment and probably a change in how the specialist health care delivers treatment for current PWIDs.  
22 334 A substantial scale-up in DAA treatment requires Norway's capacity and health system infrastructure  
23 335 at large, in addition to take place among this group of patients, which have the highest transmission risk  
24 336 in order for treatment-as-prevention strategies to succeed. In terms of surveillance, chronic HCV  
25 337 prevalence and incidence data are not readily available for Norway. The infection is regarded as a Group  
26 338 A infectious disease and it has been mandatory to notify The Norwegian Surveillance System for  
27 339 Communicable Diseases (MSIS) since 1990. However, only cases of acute HCV was notifiable initially.  
28 340 Since January 1, 2016 it was changed to merely include HCV RNA and HCV core antigen (13). Thus,  
29 341 it is impossible to tell whether cases before 2016 were acute or chronic, or whether patients achieved  
30 342 sustained virological response (SVR) on their own, or how many cases were actually notified (27).  
31 343

32 344 About two-thirds of all patients were considered adherent to the DAA regimens. At first this may seem  
33 345 low, however, this may be related to patients being categorized as adherent (100%) and non-adherent  
34 346 (<100%) according to recommendations from the prescribing specialist. For instance, the SIMPLIFY  
35 347 study, while demonstrating that 97% of PWIDs completed DAA treatment, overall 32% were considered  
36 348 non-adherent (<90% adherence) with median adherence at 94% (49). Similar results were reported from  
37 349 another study among PWIDs and OAT patients were 97% completed DAA treatment with a non-  
38 350 adherence of 40% (<90%) and median adherence at 92% (50). Other studies have shown that high  
39 351 adherence to DAAs is achievable with appropriate supportive strategies (51, 52). As such, adherence  
40 352 can be a key predictor for response to DAAs (51). Perhaps the most compelling evidence among PWIDs  
41 353 and OAT patients is a recent systematic review that showed DAA completion rate of above 97% among  
42 354 almost 4500 participants (53). Our intention was to evaluate to what extent patients initiated and  
43 355 complied to treatment, rather than drawing a comparison between individual DAAs. The main reason  
44 356 for this is varying adherence to drug protocol and guidelines for DAAs during the study period from a  
45 357 prescriber's perspective, which was only moderate after introduction of DAAs, although it increased  
46 358 markedly after 2015 (54). In addition, since included patients were only counted once upon DAA  
47 359 initiation, there is some uncertainty whether patients in the non-adherent group had lengthier treatment  
48 360 courses due to for instance awaiting liver transplantation or becoming reinfected with HCV. Rate of  
49 361 reinfection is controversial and less understood, however it seems to be low between 1 to 5% in the  
50 362 interferon era (55). After the introduction of DAAs, a study found six cases of reinfection among 301  
51 363 patients (4.6 reinfections per 100 person-years), with three of those experiencing spontaneous clearance  
52 364 of their reinfection (56).  
53 365

54 366 Adherence to DAAs was associated with OAT continuity, and as such, predicted a higher adherence  
55 367 compared to lower level of OAT continuity in our model. Studies have shown that patients receiving  
56 368 higher doses of OAT, e.g. methadone, above 60mg/day, have better treatment outcomes compared to  
57 369 lower doses (48, 57) and for this reason we set high level of continuity above two DDD. This is in line  
58 369



with previous studies demonstrating that OAT continuity is a factor for HCV treatment (27). Age was not considered statistically significant, however, less adherence was noted in the younger age groups. Dissimilarities in methodology and study settings, however, prevent for precise comparisons of adherence, including the above. Linking these data, on an individual level, to biomarkers of SVR12 was, however, beyond the scope of this paper. In addition, we had no system in place to control whether these patients actually swallowed and metabolized these drugs and as such cannot comment to the extent the medications were actually taken.

### Strengths and limitations

All dispensed drugs from pharmacies in Norway are registered in NorPD. This provide researchers and other stakeholders alike with sound, precise and a near complete database. The main strength of the study is thus it provides a large sample of hard to reach patients being treated for chronic HCV.

However, this study has some limitations, which should be considered when interpreting both results and conclusions. Treatment with OAT in Norway is not uniform. It is estimated that NorPD captures around 90% of the patients with dispensed OAT from pharmacies (5). The 10% which is not included in our study could represent OAT patients with more need for follow-up in the OAT outpatient clinics, and as such, can represent patients with higher disease burden and in need of HCV treatment. This could skew our results toward underestimating the HCV treatment coverage as these patients would not be included in our study. On the other hand, our estimates can also be overestimates. OAT patients have successfully entered the health care system and therefore more likely to accept other medical care, including HCV treatment, and thus bias our results toward improved HCV treatment coverage.

OAT and HCV treatment administered to hospitalized and institutionalized patients are not recorded on an individual level in NorPD. Nonetheless, it should be stated that almost all HCV treatment is initiated in outpatient clinics in Norway and hence included in NorPD (27, 58). In addition, some dispensed prescriptions may lack reimbursement codes and medical indication for use, and DDDs does not necessarily reflect the Prescribed Daily Dose (PDD).

Furthermore, data was not linked on an individual level to diagnosis codes of chronic HCV. This is due to the quality of MSIS prior to 2016 is poor and the authors had to employ other data sources when estimating HCV prevalence and incidence rates from a number of different sources, including modelling and expert opinion. This could lead to either over- or underestimating the HCV coverage. We believe, however, that the 0.7 (70%) proportion represents a liberal estimate and the biggest risk is that we overestimated the HCV incidence. When calculating the HCV prevalence, mean population data for Norway was used, rather than more accurate regional data as the latter was not readily available. In addition, treatment with DAAs were limited by stage of liver fibrosis during the study period. Only from February 1, 2018 it was offered universally regardless of level of liver fibrosis. Thus it is likely that younger patients and patients with Metavir F0-F1 score were excluded from DAA treatment during the study period.

When measuring adherence among different age groups we should be careful when interpreting results. Older patients are more likely to have cirrhosis and longer HCV treatment courses compared to younger patients. This could bias our results toward higher adherence among the latter. Finally, PWIDs are a heterogenic group of individuals, and one should be careful not to generalize OAT patients to include all PWIDs.

### Conclusion

This is the first population-based study documenting the transition to DAA treatment regimens among Norwegian OAT patients. A marked scale-up in HCV treatment coverage attributed by a complete shift to interferon-free regimens among Norwegian OAT patients has been demonstrated. Adherence to DAAs across all genotypes remained sound, especially for high level of OAT continuity. Annual HCV treatment coverage ranged from 3.5% in 2013 to 17% in 2017, giving a cumulative HCV coverage among OAT patients for the study period just above 38%. Despite a large increase in treatment, overall

424 HCV coverage is inadmissibly too low in order to meet the ambitious national and WHO targets of  
 425 controlling and eliminating chronic HCV. . There is a need to establish more accurate monitoring system  
 426 and more precision in prevalence and incidence rates of chronic HCV among PWID to get more precise  
 427 coverage data. Efficacy of health system strategies is needed in order to further scale-up of the most  
 428 effective HCV policies to this group and for countries to be able to control and eliminate HCV.

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#### 432 List of abbreviations

433	OAT	Opioid agonist therapy
434	DAA	Direct-acting antivirals
435	HCV	Hepatitis C virus
436	PWID	People who inject drugs
437	NorPD	The Norwegian Prescription Database
438	ATC	Anatomical Therapeutic Chemical classification system
439	DDD	Defined daily dose
440	PPP	Prescribed daily dose
441	NIPH	The Norwegian Institute for Public Health
442	SERAF	The Norwegian Centre for Addiction Research
443	MSIS	The Norwegian Surveillance System for Communicable Diseases
444	Anti-HCV	Antibodies to the Hepatitis C virus
445	SVR	Sustained virological response
446	INTRO-HCV	Integrated treatment of hepatitis C virus infection

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#### 449 **Declarations**

450

##### 451 *Contributorship statement*

452 This observational study was led by CFA in terms of study design, analyzes, drafting and writing the  
 453 article. SS and JHV was particularly involved with acquisition of data, analyzes and interpretation.  
 454 Maps were made by JMØ and KAJ. SS, JHV, IO, FC, JMØ, AL, PV, KAJ and LTF contributed to the  
 455 conception, writing, and revising the draft(s) critically. All authors have read and approved the version  
 456 to be published.

457

##### 458 *Competing interests*

459 I.O. is employed at the Centre for Pharmacoepidemiology, Karolinska Institutet, which receives grants  
 460 from several entities (pharmaceutical companies, regulatory authorities, and contract research  
 461 organizations) for performance of drug safety and drug utilization studies, unrelated to this work. None  
 462 of the other authors have competing interests.

463

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 466 Council (no. 269855) and the Western Norway Regional Health Authority (“Åpen prosjektstøtte) with  
 467 Department of Addiction Medicine, Haukeland University Hospital as responsible institution. The  
 468 funders had no role in the study design, data collection and analyzes, decision to publish, nor preparation  
 469 of any content in the manuscript. Two of the authors, CFA and JHV, are funded from the above research  
 470 grant, whereas the other authors are funded by their respective affiliations.

471

##### 472 *Availability of data and material*

473 Supplemental tables, figure and data sources in this observational study are available in this published  
 474 article and its additional files.

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List of Tables and Figure

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Table 1:

*Table 1: Basic characteristics of patients receiving OAT from 2013 to 2017 in Norway*

Basic characteristics	Total	2013	2014	2015	2016	2017
Individuals >1 OAT	10371	7709	7914	7958	7804	7709
Deaths	692	165	151	138	114	124
Gender, n (%)						
Male	7135 (69)	5221 (69)	5390 (69)	5430 (69)	5354 (70)	5254 (69)
Female	3236 (31)	2323 (31)	2373 (31)	2390 (31)	2336 (30)	2340 (31)
Age, n (%)						
<25		211 (3)	185 (2)	171 (3)	135 (2)	120 (2)
26-40		2813 (37)	2797 (36)	2718 (40)	2574 (33)	2432 (32)
41-60		4289 (57)	4537 (58)	3644 (53)	4627 (60)	4613 (61)
>60		231 (3)	244 (3)	287 (4)	354 (5)	420 (6)
OAT medication, n (%)						
Methadone/Levomethadone		3406 (45)	3264 (42)	3216 (41)	3066 (40)	2981 (39)
Buprenorphine based*		4138 (55)	4499 (58)	4604 (59)	4624 (60)	4604 (61)
Dispensations of HCV drugs**	1475	146	167	243	322	597
OAT continuity category, n (%)						
I: ≥2 DDD	5310 (51)					
II: 1-2 DDD	3078 (30)					
III: <1 DDD	1983 (19)					

OAT = opioid agonist therapy; DDD = Daily defined Doses  
 Source: NorPD = Norwegian Prescription Database  
 \* Buprenorphine and buprenorphine/naloxone  
 \*\* HCV drugs: interferon-based and direct-acting antivirals (DAAs)

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Table 2:

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Table 2: Annual and cumulative chronic HCV treatment coverage among OAT patients in Norway between 2013 and 2017

	Source	2013	2014	2015	2016	2017	Total
Chronic HCV treatment n (overall)	NorPD	146	167	243	322	597	1475
DAAAs, n	NorPD	46	95	212	290	592	1235
DAAAs % of HCV		32	57	87	90	99	84
Study population n, yearly incl. deaths	NorPD	7709	7914	7958	7804	7709	10371
Deaths	NorPD	165	151	138	114	124	692
Study population n, yearly, excl. deaths	NorPD	7544	7763	7820	7690	7585	9679
Prevalence chronic HCV, mean %	SERAF	51	52	52	46	43	
Prevalence chronic HCV, n	SERAF	3847	4037	4066	3537	3262	
Incidence chronic HCV among PWIDs n	NIPH, Mejerick et al.	396	388	381	374	366	
Incidence chronic HCV OAT from PWIDs n	Expert opinion	277	272	267	262	256	
<i>Treatment coverage chronic HCV %</i>		3.5	3.9	5.6	8.5	17.0	
<i>Cumulative frequency chronic HCV</i>		3.5	7.4	13.0	21.5	38.5	
95% Confidence interval treatment coverage chronic HCV		3.2-4.4	3.5-4.8	5.3-6.7	8.2-10.1	16.9-19.6	

OAT = opioid agonist therapy, PWID = people who inject drugs, HCV = hepatitis C virus, DAA = direct-acting antivirals,  
 Sources: NorPD = Norwegian Prescription Database, SERAF = The Norwegian Centre for Addiction Research, NIPH = Norwegian Institute for Public Health, Mejerick et al. (2017): Modelling the burden of hepatitis C infection among people who inject drugs in Norway, 1973–2030

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Table 3:

Table 3: Adherence\* to DAAs among OAT patients in Norway between 2013 and 2017

	Adherent	Non-Adherent	Total:
Adherence by gender, n (%):			
Male	551 (67)	277 (33)	828
Female	191 (67)	92 (33)	283
Total	742 (67)	369 (33)	1111
Adherence by age, n (%):			
18-35	119 (58)	85 (42)	204
36-45	259 (68)	122 (32)	381
46-55	302 (70)	128 (30)	430
>56	62 (65)	34 (35)	95
Total	742 (67)	369 (33)	1111
Adherence by OAT medication, n (%):			
Methadone/levomethadone	298 (65)	157 (35)	455
Buprenorphine based	444 (68)	212 (32)	656
Total	742 (67)	369 (33)	1111

*Logistic regression on factors associated with adherence\**

	aOR (CI 95%)	p-value
Age	0.98 (0.97-1.00)	0.17
Gender		
Male	1.00	
Female	0.92 (0.69-1.23)	0.57
OAT continuity		
Category I: $\geq 2$ DDD	1.00	
Category II: 1-2 DDD	1.36 (1.02-1.82)	0.035
Category III: $< 1$ DDD	1.36 (0.93-1.99)	0.11

OAT = opioid agonist therapy, DAA = direct-acting antivirals, aOR = adjusted odds ratio, CI = confidence interval, DDD = daily defined doses

Source: NorPD = Norwegian Prescription Database

\*Adherence defined as collected  $\geq$ three prescriptions and  $> 84$  DDDs (unless ledipasvir and sofosbuvir which also calculated as  $\geq$ two prescriptions and  $> 56$  DDDs). Analyses included 1111 patients as inclusion was ceased 01.10.17 to avoid counting treatment initiation after this date non-adherent.

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3 764 Figure 1:  
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5 766 *Figure 1: Cumulative chronic HCV treatment coverage among OAT patients in Norway between 2013*  
6 767 *and 2017 by Health Counties\**  
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OAT = opioid agonist therapy, HCV = hepatitis C virus

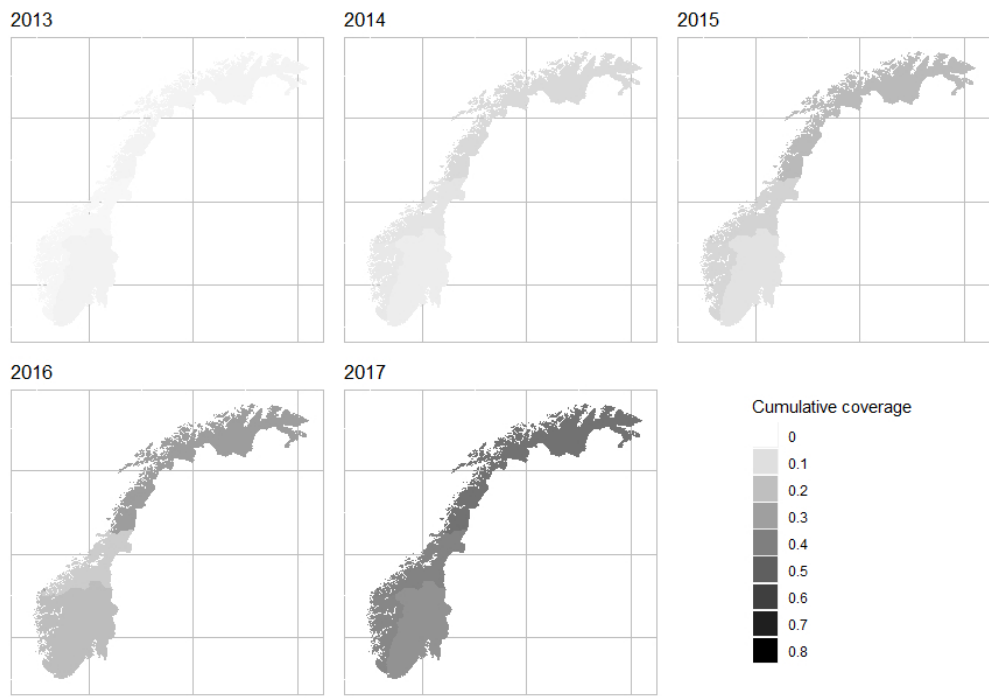
Sources: NorPD = Norwegian Prescription Database, SERAF = The Norwegian Centre for Addiction Research, NIPH = Norwegian Institute for Public Health, Meijerink et al. (2017): Modelling the burden of hepatitis C infection among people who inject drugs in Norway, 1973–2030, calculations in Table S2  
\*Cumulative coverage in %, the four Health counties: Helse Vest, Helse Midt, Helse Nord and Helse Sør-Øst

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Cumulative chronic HCV treatment coverage among OAT patients in Norway between 2013 and 2017 by Health Counties

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Figure S1: Flow chart of study population

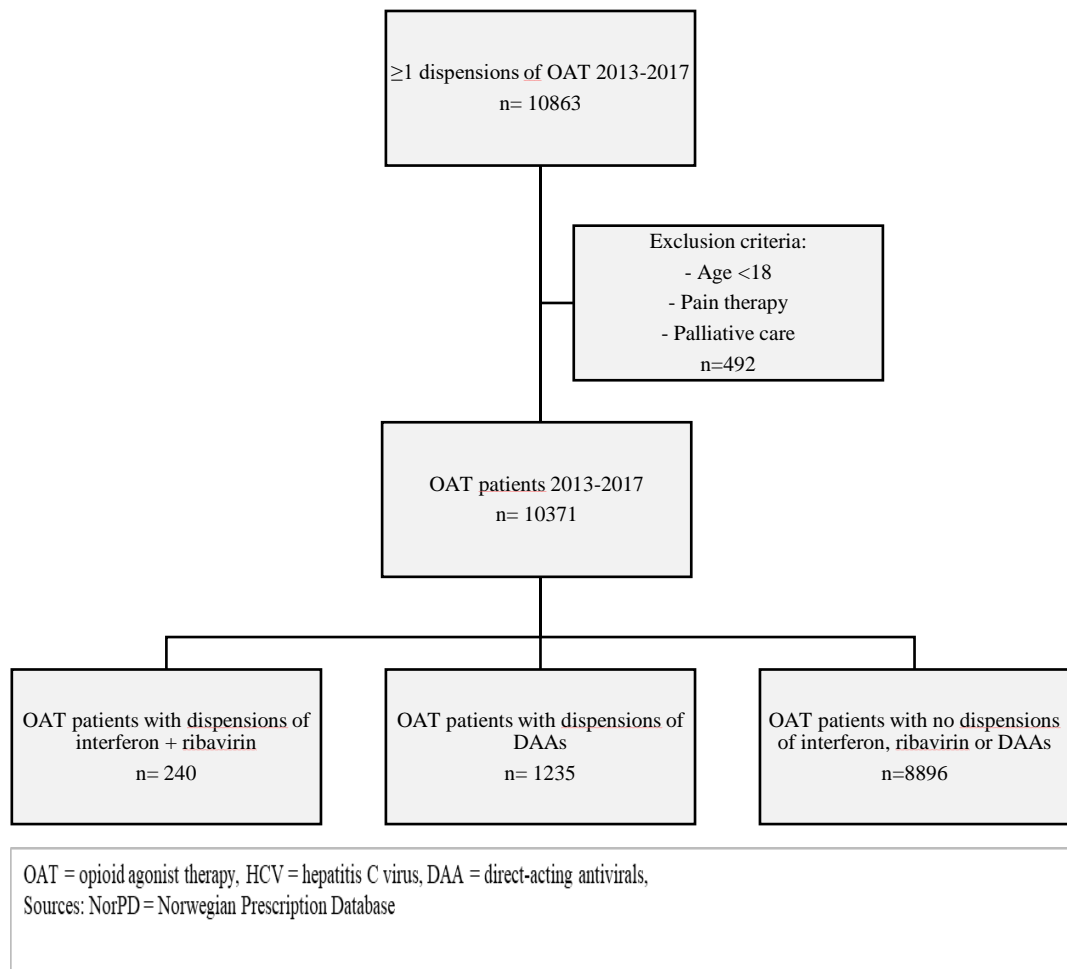


Table S1: ATC classification and dispensed DAAs among OAT patients in Norway from 2013 to 2017

Description	ATC code
<b>Anti-infective for systemic use</b>	J
Antivirals for treatment of HCV infection, DAAs	J05AP*
Telaprevir	J05AP02
Boceprevir	J05AP03
Faldaprevir	J05AP04
Simeprevir	J05AP05
Asunaprevir	J05AP06
Daclatasvir	J05AP07
Sofosbuvir	J05AP08
Dasabuvir	J05AP09
Ledipasvir and Sofosbuvir	J05AP51
Dasabuvir, ombitasvir, paritaprevir and ritonavir	J05AP52
Ombitasvir, paritaprevir and ritonavir	J05AP53
Elbasvir and grazoprevir	J05AP54
Sofosbuvir and velpatasvir	J05AP55
Sofosbuvir, velpatasvir, and voxilaprevir	J05AP56
Glecaprevir and pibrentasvir	J05AP57
<b>Most prevalent DAAs dispensed in Norway among OAT patients**</b>	<b>Frequency (%)</b>
Elbasvir and grazoprevir	328 (27)
Sofosbuvir	279 (23)
Ledipasvir and Sofosbuvir	225 (18)
Sofosbuvir and velpatasvir	187 (15)
Ombitasvir, paritaprevir and ritonavir	55 (5)
Daclatasvir	47 (4)
Dasabuvir	34 (3)
Simeprevir	33 (3)
Other	37 (3)

ATC = Anatomical Therapeutic Chemical classification, OAT = opioid agonist therapy, DAA = direct-acting antivirals

Sources: NorPD = Norwegian Prescription Database

\*Excluding Ribavirin J05AP01

\*\*First registered dispensation by ATC. For sofosbuvir, daclatasvir, dasabuvir and simeprevir additional dispensations of other DAA/antivirals may occur.

*Table S1: Annual and cumulative chronic HCV treatment, crude, among OAT patients in Norway between 2013 and 2017*

	Source	2013	2014	2015	2016	2017	Total
HCV treatment n (overall)	NorPD	146	167	243	322	597	1475
DAA, n	NorPD	46	95	212	290	592	1235
DAA % of HCV		32	57	87	90	99	84
Study population n, yearly incl. deaths	NorPD	7709	7914	7958	7804	7709	10371
Deaths	NorPD	165	151	138	114	124	692
Study population n, yearly, excl. deaths	NorPD	7544	7763	7820	7690	7585	9679
HCV treatment crude %:							
HCV overall		1.9	2.2	3.1	4.2	7.9	
DAA		0.6	1.2	2.7	3.8	7.8	
Cumulative frequency HCV overall		1.9	4.1	7.2	11.4	19.3	
Cumulative frequency DAA		0.6	1.8	4.5	8.3	16.1	
95% Confidence interval (HCV)		1.6-2.3	1.8-2.5	2.7-3.5	3.7-4.6	7.3-8.5	
95% Confidence interval (DAA)		0.4-0.8	1.0-1.5	2.4-3.1	3.4-4.2	7.2-8.4	

OAT = opioid agonist therapy, HCV = hepatitis C virus, DAA = direct-acting antivirals,  
Sources: NorPD = Norwegian Prescription Database

Table S2: Annual and cumulative chronic HCV treatment coverage among OAT patients in Norway between 2013 and 2017 by Health Regions

	Source:	2013	2014	2015	2016	2017	Total:
Helse Sør-Øst HCV Treatment	NorPD	93	92	158	196	367	906
Helse Vest HCV Treatment	NorPD	24	27	36	64	136	287
Helse Midt HCV Treatment	NorPD	20	18	22	27	52	139
Helse Nord HCV Treatment	NorPD	6	27	27	20	26	106
Study population incl death Helse Sør-Øst	NorPD	4553	4636	4609	4575	4580	
Study population incl death Helse Vest	NorPD	1889	1971	2000	1833	1735	
Study population incl death Helse Midt	NorPD	708	728	731	742	740	
Study population incl death Helse Nord	NorPD	559	578	616	653	653	
Deaths Helse Sør-Øst	NorPD	91	82	84	74	74	
Deaths Helse Vest	NorPD	47	45	33	29	39	
Deaths Helse Midt	NorPD	21	16	10	6	6	
Deaths Helse Nord	NorPD	6	8	11	5	5	
Study population excl death Helse Sør-Øst	NorPD	4462	4554	4525	4501	4506	
Study population excl death Helse Vest	NorPD	1842	1926	1967	1804	1696	
Study population excl death Helse Midt	NorPD	687	712	721	736	734	
Study population excl death Helse Nord	NorPD	553	570	605	648	648	
Prevalence HCV Helse Sør-Øst, mean %	SERAF	55	53	57	52	45	
Prevalence HCV Helse Vest, mean %	SERAF	43	51	50	47	41	
Prevalence HCV Helse Midt, mean %	SERAF	73	53	52	49	36	
Prevalence HCV Helse Nord, mean %	SERAF	45	48	43	33	28	
Prevalence HCV Helse Sør-Øst, n	SERAF	2454	2414	2579	2341	2028	
Prevalence HCV Helse Vest, n	SERAF	792	982	984	848	695	
Prevalence HCV Helse Midt, n	SERAF	502	377	375	361	264	
Prevalence HCV Helse Nord, n	SERAF	238	274	260	214	181	
Incidence HCV Helse Sør-Øst, PWIDs	NIPH, Mejierick et al.	249	233	238	236	238	
Incidence HCV Helse Vest, PWIDs	NIPH, Mejierick et al.	79	93	91	86	81	
Incidence HCV Helse Midt, PWIDs	NIPH, Mejierick et al.	44	39	35	41	33	

Incidence HCV Helse Nord, PWIDs	NIPH, Mejerick et al.	24	23	16	11	15
Incidence HCV Helse Sør-Øst, OAT, n	NIPH, Mejerick et al.	175	163	167	165	167
Incidence HCV Helse Vest, OAT, n	NIPH, Mejerick et al.	55	65	64	60	56
Incidence HCV Helse Midt, OAT, n	NIPH, Mejerick et al.	30	27	25	29	23
Incidence HCV Helse Nord, OAT, n	NIPH, Mejerick et al.	17	16	11	8	10
<i>Treatment coverage HCV Helse Sør-Øst %</i>		3.5	3.5	5.7	7.8	16.7
<i>Cumulative frequency HCV Helse Sør-Øst</i>		3.5	7.1	12.8	20.7	37.4
<i>Treatment coverage HCV Helse Vest %</i>		2.8	2.6	3.4	7.0	18.1
<i>Cumulative frequency HCV Helse Vest</i>		2.8	5.4	8.8	15.9	34.0
<i>Treatment coverage HCV Helse Midt %</i>		3.8	4.4	5.5	6.9	18.1
<i>Cumulative frequency HCV Helse Midt</i>		3.8	8.2	13.7	20.6	38.7
<i>Treatment coverage HCV Helse Nord %</i>		2.4	9.3	9.9	9.0	13.6
<i>Cumulative frequency HCV Helse Nord</i>		2.4	11.7	21.6	30.6	44.2

OAT = opioid agonist therapy, PWID = people who inject drugs, HCV = hepatitis C virus

Sources: NorPD = Norwegian Prescription Database, SERAF = The Norwegian Centre for Addiction Research, NIPH = Norwegian Institute for Public Health, Mejerick et al. (2017): Modelling the burden of hepatitis C infection among people who inject drugs in Norway, 1973–2030

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4
		(b) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4, n/a
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	5
		(b) Describe any methods used to examine subgroups and interactions	4/5
		(c) Explain how missing data were addressed	-
		(d) If applicable, explain how loss to follow-up was addressed	n/a
		(e) Describe any sensitivity analyses	-
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	19
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) Summarise follow-up time (eg, average and total amount)	n/a
Outcome data	15*	Report numbers of outcome events or summary measures over time	

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5/6
2			(b) Report category boundaries when continuous variables were categorized	-
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
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6	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
7				
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11	<b>Discussion</b>			
12	Key results	18	Summarise key results with reference to study objectives	6
13	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	7/8
14				
15	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7/8
16				
17	Generalisability	21	Discuss the generalisability (external validity) of the study results	7
18				
19	<b>Other information</b>			
20	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9
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\*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.