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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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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.

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,

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 eradicate 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 treat 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 PWIDs in Norway is stable at around 9000 (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 (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, sharing of injecting equipment and number of sex partners (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 >90%, 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 uptake 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 secondary objective is to document whether there has been a shift or not to interferon-free treatment regimens.
3) A third objective is to evaluate adherence to DAAs among OAT patients across all genotypes in Norway as there are limited studies among this marginalized group of patients.

Methods

Study design and data sources

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

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

Study population and definitions

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

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

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

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

where HCV cov is HCV coverage, t_HCV = number of OAT patients with dispensed HCV treatment, p_HCV = number of OAT patients with chronic HCV and i_HCV = number of new cases of chronic HCV among OAT patients. Coverage was calculated annually for Norway and by Health County, and as cumulative frequencies.

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

Finally, OAT continuity was defined according to dispensed DDDs and stratified into three categories, ranging from a high level of OAT continuity in category I (>2 DDD), medium in category II (2-1 DDD), and to a low level of OAT continuity in category III (<12 DDD). One DDD for methadone and buprenorphine is 25mg and 8mg respectively.

Statistical analyzes and strategy

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

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

Data handling and ethical considerations

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

Patient and public involvement

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

Results

Basic characteristics of study population

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

(insert Table 1)

HCV treatment uptake and coverage

HCV and DAA treatment uptake

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

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_{cov} 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.

Some individuals collect the drugs at pharmacies as dispensed prescriptions while others receive the drugs at OAT outpatient clinics. Drugs administered in outpatient clinics are not necessarily captured by the prescription database (NorPD). Secondly, OAT and HCV treatment administered to hospitalized and institutionalized patients are not recorded 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, 51). 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. For example, 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.

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. 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 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 genotype 1 and 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%. However, Norway is far from universal coverage of HCV treatment. 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

Ethical approval and consent to participate

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

Consent for publication

Not applicable.

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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Authors' contributions

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. All authors contributed to the conception, writing, and revising the draft(s) critically. All authors have read and approved the version to be published.

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List of Tables and Figure

Table 1:

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)
Buprenorhine based*		4138 (55)	4499 (58)	4604 (59)	4624 (60)	4604 (61)
Dispensions 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)

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
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, Mejierick et al.	396	388	381	374	366	
Incidence chronic HCV OAT from PWIDs n	Expert opinion	277	272	267	262	256	
Treatment coverage chronic HCV %		*3.5*	*3.9*	*5.6*	*8.5*	*17.0*	
Cumulative frequency chronic HCV		*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 = Norwegi
Health, Meijerink et al. (2017): Modelling the burden of hepatitis C infection among people who inject drugs in Norway, 1973–2

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

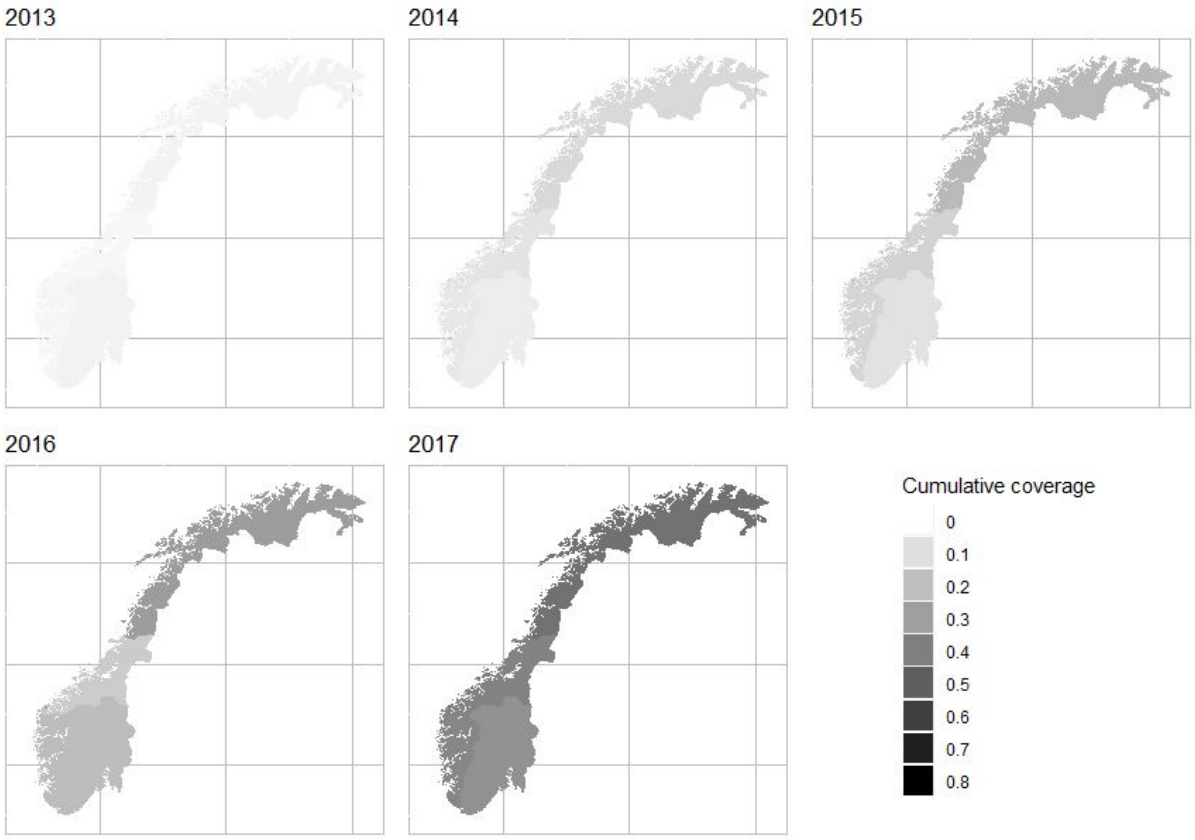
*Logistic regression on factors associated with adherence**

		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

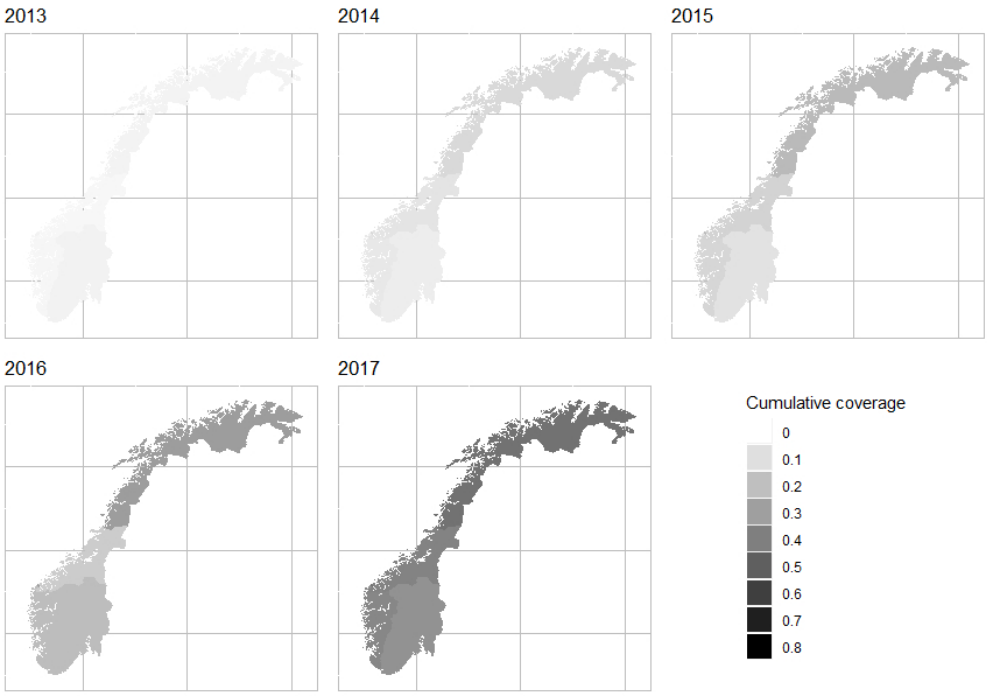
OAT = opioid agonist therapy, DAA = direct-acting antivirals, aOR = adjusted odds ratio, CI = confidence interval
Source: NorPD = Norwegian Prescription Database
*Adherence defined as collected ≥three prescriptions and > 84 DDDs (unless ledipasvir and sofosbuvir which also calculated as ≥two prescriptions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

Figure 1:

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



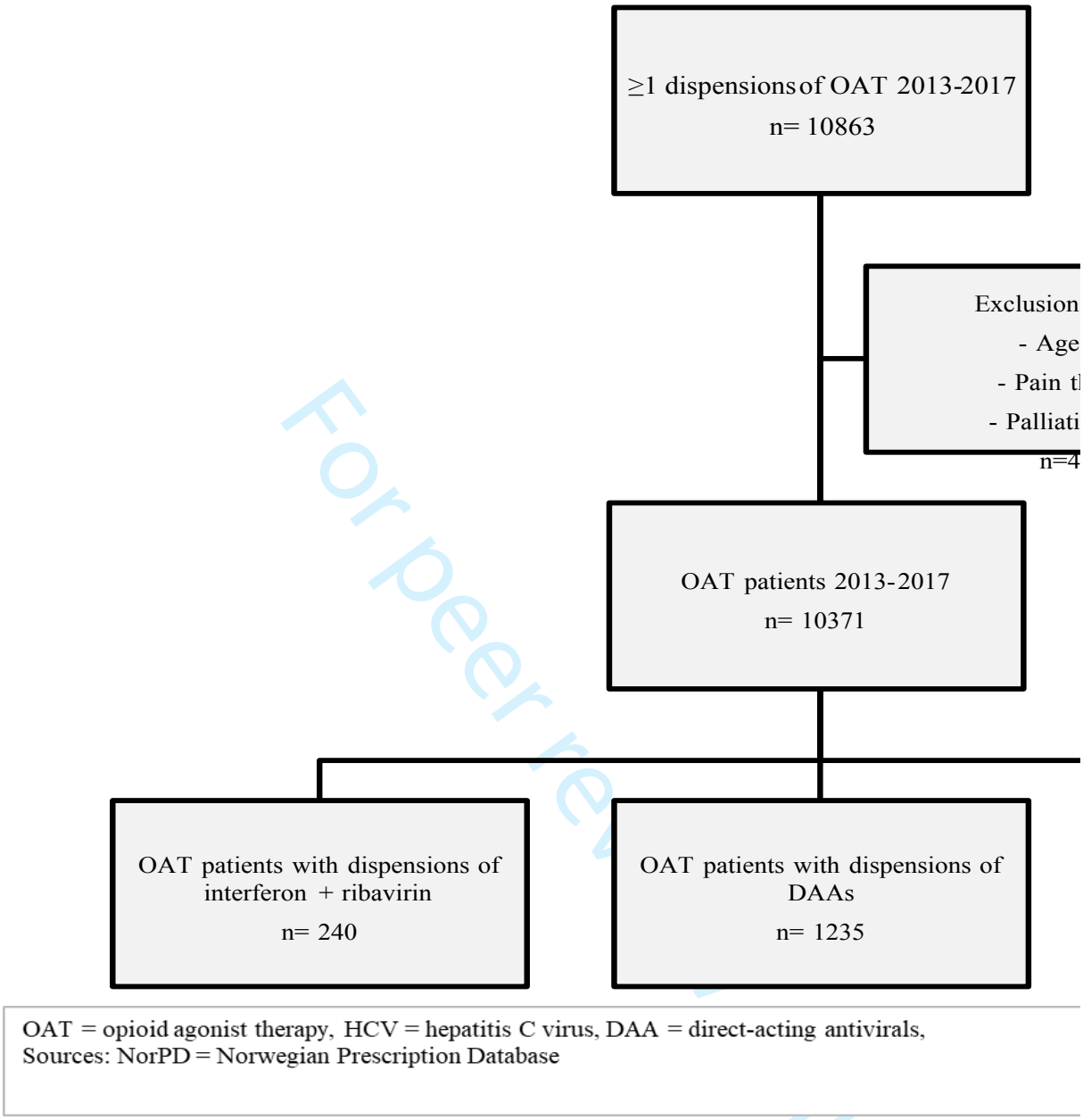
OAT = opioid agonist therapy, HCV = hepatitis C virus
Sources: NorPD = Norwegian Prescription Database, SERAF = The Norwegian Centre for Addiction Research, NIPH = Norwegian Institute for Public Health, Meijerink et al. (2017): Modelling the burden of hepatitis C infection among people who inject drugs 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



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

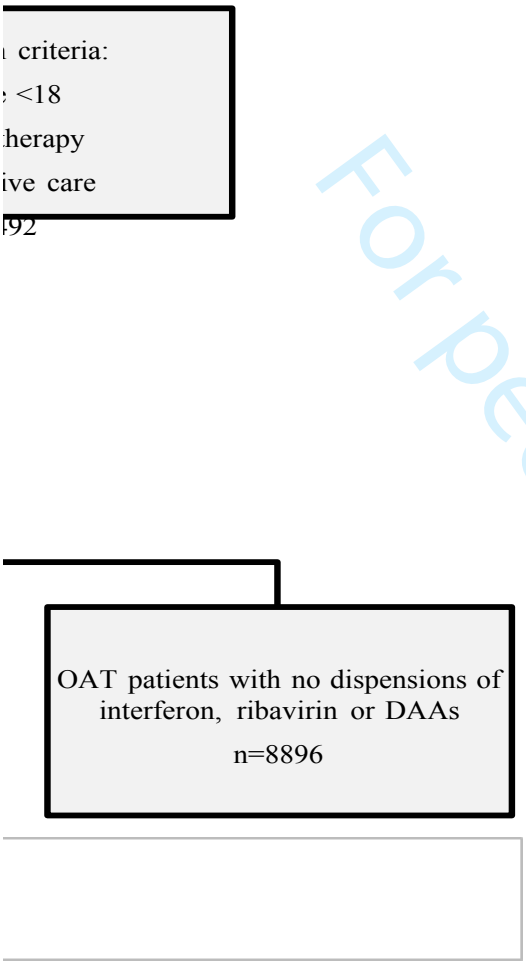


Table S1: Annual and cumulative chronic HCV treatment uptake, crude, among OAT patients

	Source	**2013**	**2014**	**2015**
HCV treatment n (overall)	NorPD	146	167	243
DAAs, n	NorPD	46	95	212
DAAs % 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
DAAs		0.6	1.2	2.7
Cumulative frequency HCV overall		1.9	4.1	7.2
Cumulative frequency DAAs		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 (DAAs)		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

2016	2017	Total
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 treament 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, Mejierick et al.	249
Incidence HCV Helse Vest, PWIDs	NIPH, Mejierick et al.	79
Incidence HCV Helse Midt, PWIDs	NIPH, Mejierick et al.	44
Incidence HCV Helse Nord, PWIDs	NIPH, Mejierick et al.	24
Incidence HCV Helse Sør-Øst, OAT, n	NIPH, Mejierick et al.	175
Incidence HCV Helse Vest, OAT, n	NIPH, Mejierick et al.	55
Incidence HCV Helse Midt, OAT, n	NIPH, Mejierick et al.	30
Incidence HCV Helse Nord, OAT, n	NIPH, Mejierick et al.	17
Treatment coverage HCV Helse Sør-Øst %		*3.5*
Cumulative frequency HCV Helse Sør-Øst		*3.5*
Treatment coverage HCV Helse Vest %		*2.8*
Cumulative frequency HCV Helse Vest		*2.8*
Treatment coverage HCV Helse Midt %		*3.8*
Cumulative frequency HCV Helse Midt		*3.8*
Treatment coverage HCV Helse Nord %		*2.4*
Cumulative frequency HCV Helse Nord		*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
Title and abstract	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
Introduction			
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
Methods			
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	-
Results			
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	

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 (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5/6 - n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	6
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
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
Generalisability	21	Discuss the generalisability (external validity) of the study results	7
Other information			
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

*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.

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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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.

Methods

Study design and data sources

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

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

Study population and definitions

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

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

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

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

where HCV cov is HCV coverage, t_HCV = number of OAT patients with dispensed HCV treatment, p_HCV = number of OAT patients with chronic HCV and i_HCV = number of new cases of chronic HCV among OAT patients. Coverage was calculated annually for Norway and by Health County, and as cumulative frequencies.

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

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

Statistical analyzes and strategy

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

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

Data handling and ethical considerations

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

Patient and public involvement

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

Results

Basic characteristics of study population

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

(insert Table 1)

HCV treatment and coverage

HCV and DAA treatment

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

HCV treatment in 2017. Overall 1475 patients on OAT received HCV treatment during the study period, with an annual HCV treatment 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 S2). 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 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_{cov} and data from Table S3 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 considered to have finished their DAA treatment course (Table 3). There were 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 OAT continuity was associated with adherence to DAAs (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 too low if the ambitious targets of ending the endemic are to be met. Annual treatment rate 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 coverage 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. 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.

It can be useful to compare our results at country levels. 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 (23, 27, 44), partly explained by varying and restricted treatment access policies that prevented a widespread scale-up of DAA treatment during the study period (45). For instance England, saw one of the most restricted access policies to DAA treatment compared to e.g. France and Germany, which had the least restrictions (46). Consequently HCV treatment rates varied dramatically across European countries ranging from 0.6% to 10.2% in 2015 (47). In the same year we found HCV treatment rate of 5.6% in Norway, which is similar to Sweden, however higher than Denmark that saw treatment rate more in

line with the overall 3.7% that year among European countries (47). 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 (48), 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.

The Norwegian Hepatitis C policy identifies improved access to treatment, prevention, and surveillance of the endemic as crucial to succeed with HCV elimination strategies (42). Treatment with DAAs in Norway was until February 1, 2018, limited by 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. From 2014 to June 2018, around 5000 patients were treated for chronic HCV in Norway, however, these patients are mostly former PWIDs and immigrants being infected prior to the arrival in Norway (13). It is unclear how many of these patients were on OAT and overlapped with our results. Nonetheless, despite continued falling prices of DAAs, which have made unrestricted treatment possible for all, HCV treatment and coverage remains low among active PWIDs (13), which is in line with our results demonstrating the need for a significant scale-up to improve HCV coverage and being able to plan elimination strategies. It may therefore be crucial to identify other barriers to treatment for this vulnerable patient group. 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. A substantial scale-up in DAA treatment requires Norway's capacity and health system infrastructure at large, in addition to take place among this group of patients, which have the highest transmission risk in order for treatment-as-prevention strategies to succeed. 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 the DAA regimens. At first this may seem low, however, this may be related to patients being categorized as adherent (100%) and non-adherent (<100%) according to recommendations from the prescribing specialist. For instance, the SIMPLIFY study, while demonstrating that 97% of PWIDs completed DAA treatment, overall 32% were considered non-adherent (<90% adherence) with median adherence at 94% (49). Similar results were reported from another study among PWIDs and OAT patients were 97% completed DAA treatment with a non-adherence of 40% (<90%) and median adherence at 92% (50). Other studies have shown that high adherence to DAAs is achievable with appropriate supportive strategies (51, 52). As such, adherence can be a key predictor for response to DAAs (51). Perhaps the most compelling evidence among PWIDs and OAT patients is a recent systematic review that showed DAA completion rate of above 97% among almost 4500 participants (53). 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 (54). 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, 55) 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, 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 OAT individuals being treated for chronic HCV, and as such can serve as baseline data for further research, especially decision-modelling for eliminating chronic HCV in Norway or similar countries.

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, 56). 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 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

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)
Buprenorhine based*		4138 (55)	4499 (58)	4604 (59)	4624 (60)	4604 (61)
Dispensions 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)

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	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, Mejierick et al.	396	388	381	374	366	
Incidence chronic HCV OAT from PWIDs n	Expert opinion	277	272	267	262	256	
Treatment coverage chronic HCV %		*3.5*	*3.9*	*5.6*	*8.5*	*17.0*	
Cumulative frequency chronic HCV		*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

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

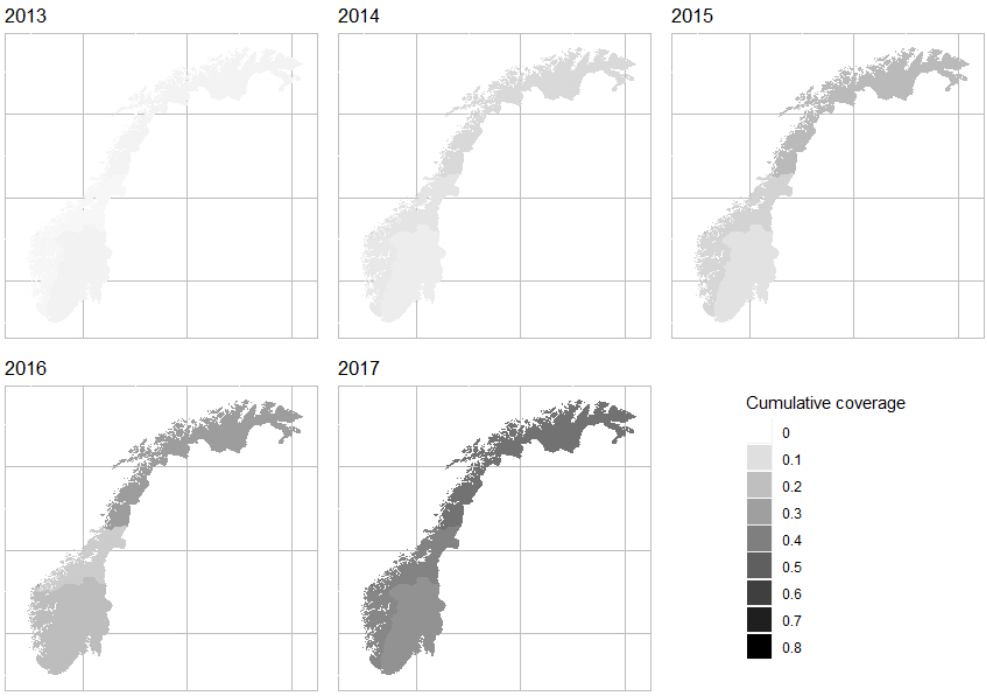
*Logistic regression on factors associated with adherence**			
		aOR (CI 95%)	p-value
Age		0.98 (0.97-1.00)	0.17
Gender			
Male		1.00	
Female		0.92 (0.69-1.23)	0.57
OAT continuity			
Category I: ≥2 DDD		1.00	
Category II: 1-2 DDD		1.36 (1.02-1.82)	0.035
Category III: <1 DDD		1.36 (0.93-1.99)	0.11

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 ≥three prescriptions and > 84 DDDs (unless ledipasvir and sofosbuvir which also calculated as ≥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.

Figure 1:

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

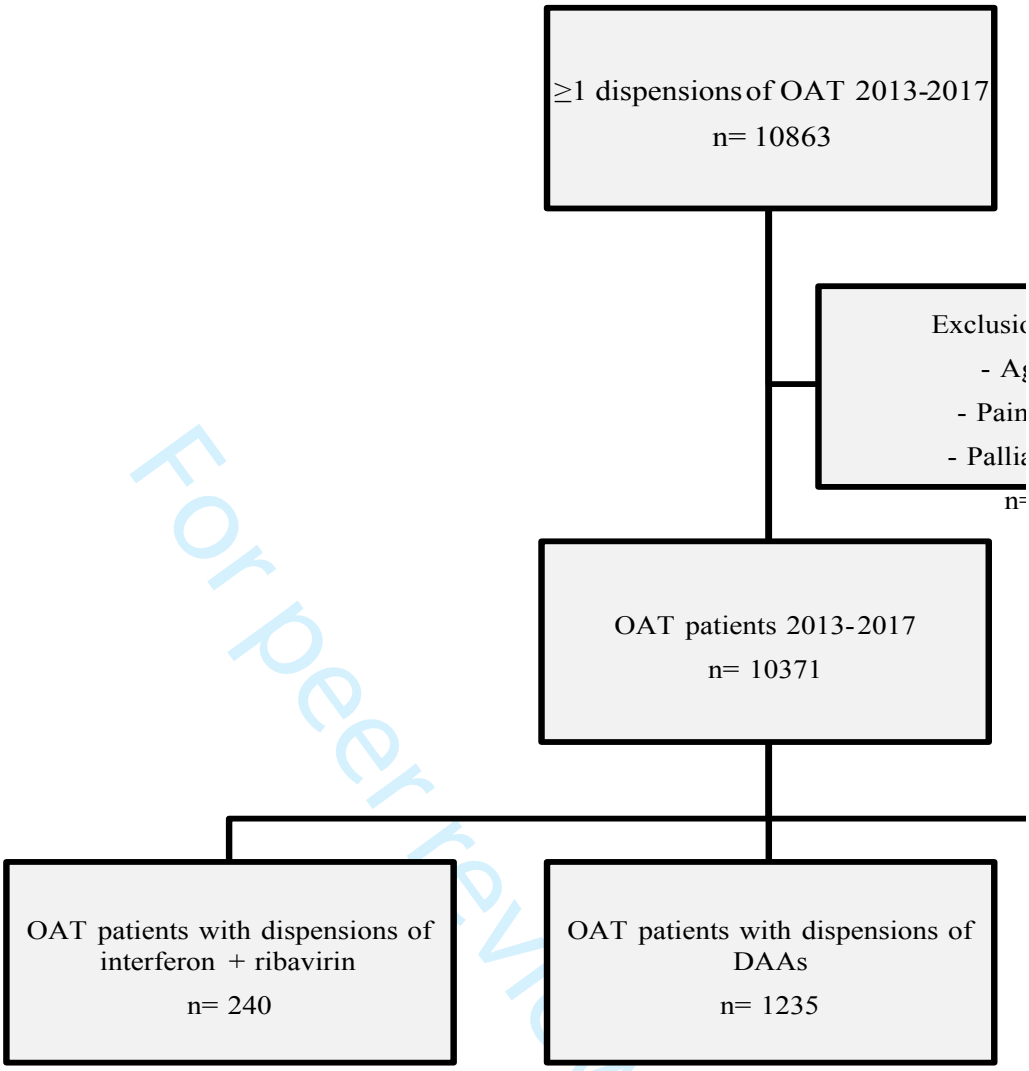
OAT = opioid agonist therapy, HCV = hepatitis C virus
Sources: NorPD = Norwegian Prescription Database, SERAF = The Norwegian Centre for Addiction Research, NIPH = Norwegian Institute for Public Health, Meijerink et al. (2017): Modelling the burden of hepatitis C infection among people who inject drugs 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



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

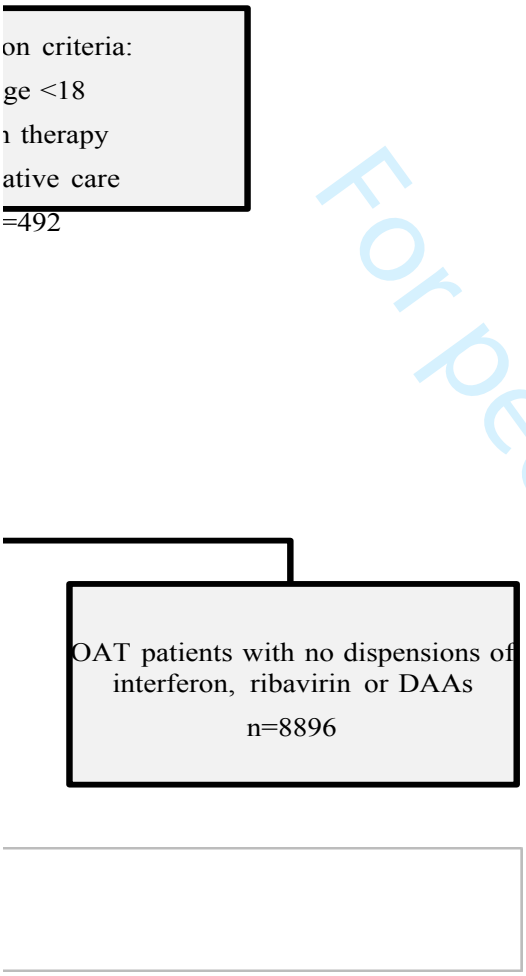


Table S1: ATC classification and dispensed DAAs among OAT patients in Norway from 2013 to 201

Description	**ATC code**
Anti-infective for systemic use	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
Most prevalent DAAs dispensed in Norway among OAT patients**	**Frequency (%)**
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 registred dispension by ATC. For sofosbuvir, daclatasvir, dasabuvir and simeprevir additonal dispensions of other DAA/antivirals may occour.

7

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
DAAs, n	NorPD	46	95	212
DAAs % 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 reatment crude %:				
HCV overall		1.9	2.2	3.1
DAAs		0.6	1.2	2.7
Cumulative frequency HCV overall		1.9	4.1	7.2
Cumulative frequency DAAs		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 (DAAs)		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

way between 2013 and 2017

2016	2017	Total
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 treament 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, Mejierick et al.	249
Incidence HCV Helse Vest, PWIDs	NIPH, Mejierick et al.	79
Incidence HCV Helse Midt, PWIDs	NIPH, Mejierick et al.	44
Incidence HCV Helse Nord, PWIDs	NIPH, Mejierick et al.	24
Incidence HCV Helse Sør-Øst, OAT, n	NIPH, Mejierick et al.	175
Incidence HCV Helse Vest, OAT, n	NIPH, Mejierick et al.	55
Incidence HCV Helse Midt, OAT, n	NIPH, Mejierick et al.	30
Incidence HCV Helse Nord, OAT, n	NIPH, Mejierick et al.	17
Treatment coverage HCV Helse Sør-Øst %		*3.5*
Cumulative frequency HCV Helse Sør-Øst		*3.5*
Treatment coverage HCV Helse Vest %		*2.8*
Cumulative frequency HCV Helse Vest		*2.8*
Treatment coverage HCV Helse Midt %		*3.8*
Cumulative frequency HCV Helse Midt		*3.8*
Treatment coverage HCV Helse Nord %		*2.4*
Cumulative frequency HCV Helse Nord		*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
Title and abstract	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
Introduction			
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
Methods			
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	-
Results			
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	

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 (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5/6 - n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	6
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
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
Generalisability	21	Discuss the generalisability (external validity) of the study results	7
Other information			
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

*Give information separately for exposed and unexposed groups.

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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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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.

Methods

Study design and data sources

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

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

Study population and definitions

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

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

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

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

where HCV cov is HCV coverage, t_HCV = number of OAT patients with dispensed HCV treatment, p_HCV = number of OAT patients with chronic HCV and i_HCV = number of new cases of chronic HCV among OAT patients. Coverage was calculated annually for Norway and by Health County, and as cumulative frequencies.

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

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

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

Statistical analyzes and strategy

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

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

Data handling and ethical considerations

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

Patient and public involvement

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

Results

Basic characteristics of study population

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

(insert Table 1)

HCV treatment and coverage

HCV and DAA treatment

All individuals were stratified according to the year in which they received OAT and HCV treatment. Excluding deaths, this gave a fairly stable OAT population just in excess of 7500 annually. In 2013, 146 OAT patients received HCV treatment. Treatment increased over time with 597 patients receiving HCV treatment in 2017. Overall 1475 patients on OAT received HCV treatment during the study period, with an annual HCV treatment increasing from 1.9% (95% CI: 1.6-2.3%) in 2013 to 7.9% (95% CI: 7.3-8.5%) in 2017 (Table S2). 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 DAAs. The annual DAA treatment 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_{cov} and data from Table S3 were used for these calculations). There were 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 considered to have finished their DAA treatment course (Table 3). There were 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 OAT continuity was associated with adherence to DAAs (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 too low if the ambitious targets of ending the endemic are to be met. Annual treatment rate 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 coverage 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. 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.

It can be useful to compare our results at country levels. 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 (23, 27, 43), partly explained by varying and restricted treatment access policies that prevented a widespread scale-up of DAA treatment during the study period (44). For instance England, saw one of the most restricted access policies to DAA treatment compared to e.g. France and Germany, which had the least restrictions (45). Consequently HCV treatment rates varied dramatically across European countries ranging from 0.6% to 10.2% in 2015 (46). In the same year we found HCV treatment rate of 5.6% in Norway, which is similar to Sweden, however higher than Denmark that saw treatment rate more in line with the overall 3.7% that year among European countries (46). 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 (47), 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.

The Norwegian Hepatitis C policy identifies improved access to treatment, prevention, and surveillance of the endemic as crucial to succeed with HCV elimination strategies (48). Treatment with DAAs in Norway was until February 1, 2018, limited by 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. From 2014 to June 2018, around 5000 patients were treated for chronic HCV in Norway, however, these patients are mostly former PWIDs and immigrants being infected prior to the arrival in Norway (13). It is unclear how many of these patients were on OAT and overlapped with our results. Nonetheless, despite continued falling prices of DAAs, which have made unrestricted treatment possible for all, HCV treatment and coverage remains low among active PWIDs (13), which is in line with our results demonstrating the need for a significant scale-up to improve HCV coverage and being able to plan elimination strategies. It may therefore be crucial to identify other barriers to treatment for this vulnerable patient group. 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. A substantial scale-up in DAA treatment requires Norway's capacity and health system infrastructure at large, in addition to take place among this group of patients, which have the highest transmission risk in order for treatment-as-prevention strategies to succeed. 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 the DAA regimens. At first this may seem low, however, this may be related to patients being categorized as adherent (100%) and non-adherent (<100%) according to recommendations from the prescribing specialist. For instance, the SIMPLIFY study, while demonstrating that 97% of PWIDs completed DAA treatment, overall 32% were considered non-adherent (<90% adherence) with median adherence at 94% (49). Similar results were reported from another study among PWIDs and OAT patients were 97% completed DAA treatment with a non-adherence of 40% (<90%) and median adherence at 92% (50). Other studies have shown that high adherence to DAAs is achievable with appropriate supportive strategies (51, 52). As such, adherence can be a key predictor for response to DAAs (51). Perhaps the most compelling evidence among PWIDs and OAT patients is a recent systematic review that showed DAA completion rate of above 97% among almost 4500 participants (53). 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, which was only moderate after introduction of DAAs, although it increased markedly after 2015 (54). In addition, since included patients were only counted once upon DAA initiation, there is some uncertainty whether patients in the non-adherent group had lengthier treatment courses due to for instance awaiting liver transplantation or becoming reinfected with HCV. Rate of reinfection is controversial and less understood, however it seems to be low between 1 to 5% in the interferon era (55). After the introduction of DAAs, a study found six cases of reinfection among 301 patients (4.6 reinfections per 100 person-years), with three of those experiencing spontaneous clearance of their reinfection (56).

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 (48, 57) 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, 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

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

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)
Buprenorhine based*		4138 (55)	4499 (58)	4604 (59)	4624 (60)	4604 (61)
Dispensions 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)

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
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, Mejierick et al.	396	388	381	374	366	
Incidence chronic HCV OAT from PWIDs n	Expert opinion	277	272	267	262	256	
Treatment coverage chronic HCV %		*3.5*	*3.9*	*5.6*	*8.5*	*17.0*	
Cumulative frequency chronic HCV		*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

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

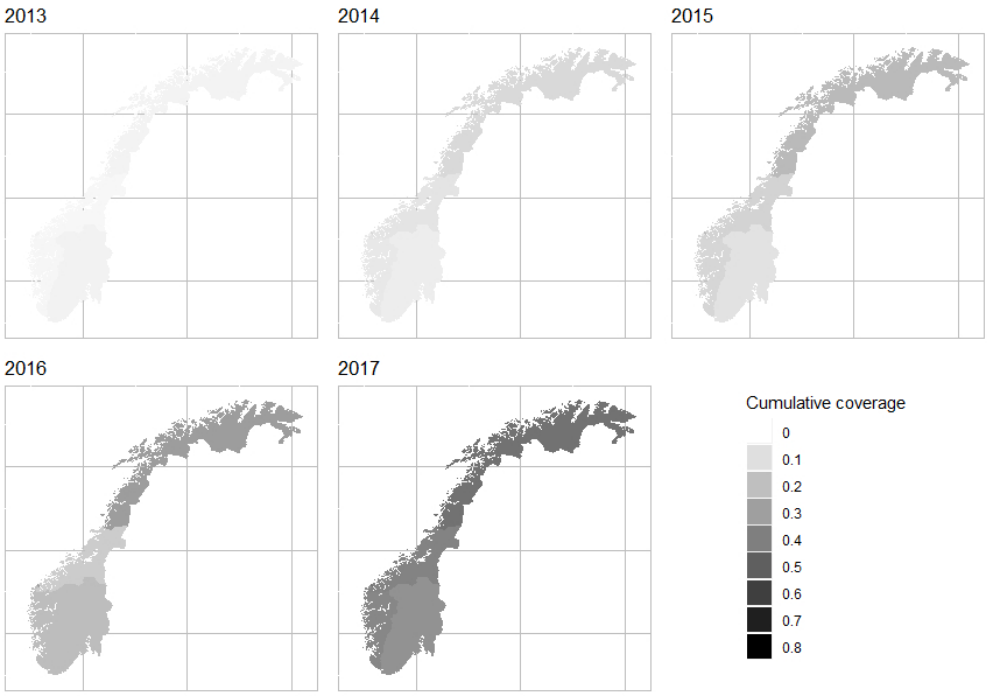
*Logistic regression on factors associated with adherence**			
		aOR (CI 95%)	p-value
Age		0.98 (0.97-1.00)	0.17
Gender			
Male		1.00	
Female		0.92 (0.69-1.23)	0.57
OAT continuity			
Category I: ≥2 DDD		1.00	
Category II: 1-2 DDD		1.36 (1.02-1.82)	0.035
Category III: <1 DDD		1.36 (0.93-1.99)	0.11

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 ≥three prescriptions and > 84 DDDs (unless ledipasvir and sofosbuvir which also calculated as ≥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.

Figure 1:

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

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



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

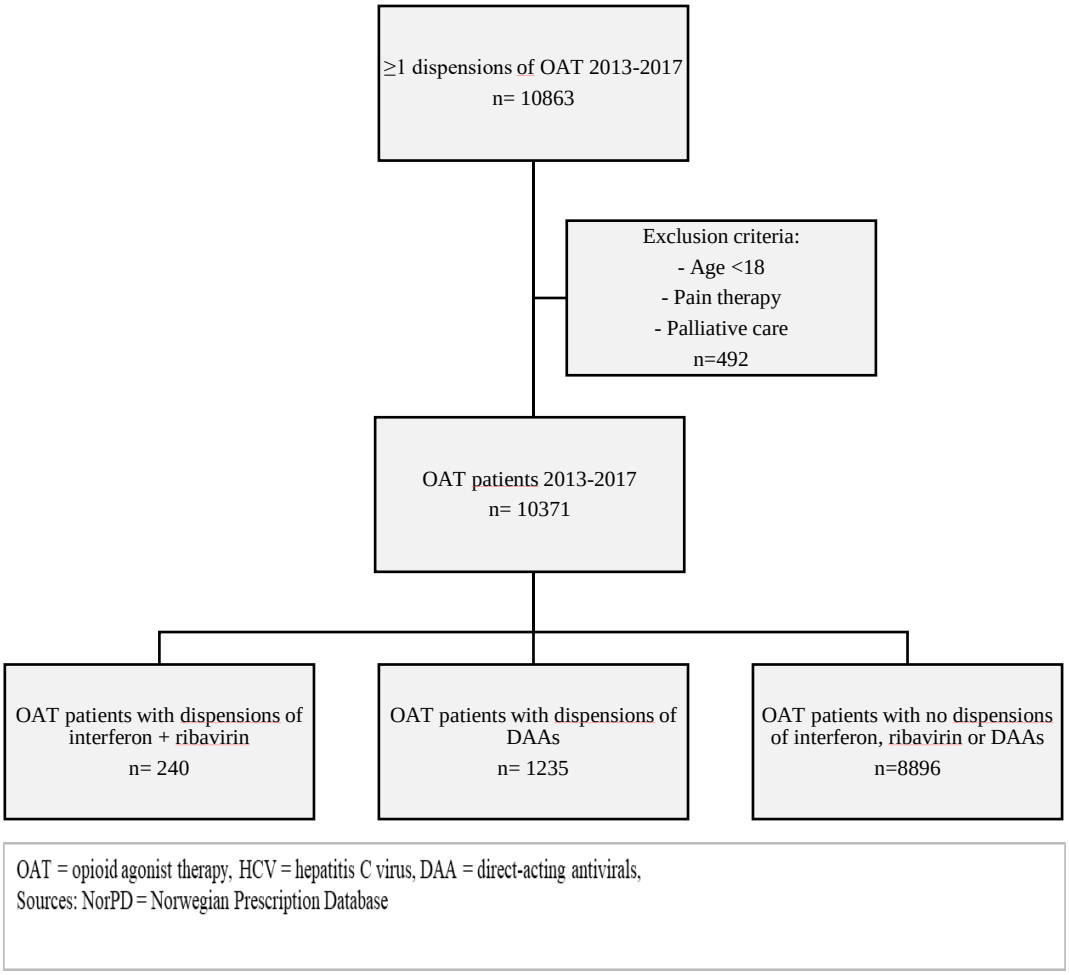

Table S1: ATC classification and dispensed DAAs among OAT patients in Norway from 2013 to 2017

Description	**ATC code**
Anti-infective for systemic use	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
Most prevalent DAAs dispensed in Norway among OAT patients**	**Frequency (%)**
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 dispension by ATC. For sofosbuvir, daclatasvir, dasabuvir and simeprevir additional dispensions 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
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
HCV reatment crude %:							
HCV overall		1.9	2.2	3.1	4.2	7.9	
DAAs		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 DAAs		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 (DAAs)		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 treament 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, Mejierick et al.	24	23	16	11	15
Incidence HCV Helse Sør-Øst, OAT, n	NIPH, Mejierick et al.	175	163	167	165	167
Incidence HCV Helse Vest, OAT, n	NIPH, Mejierick et al.	55	65	64	60	56
Incidence HCV Helse Midt, OAT, n	NIPH, Mejierick et al.	30	27	25	29	23
Incidence HCV Helse Nord, OAT, n	NIPH, Mejierick et al.	17	16	11	8	10
Treatment coverage HCV Helse Sør-Øst %		*3.5*	*3.5*	*5.7*	*7.8*	*16.7*
Cumulative frequency HCV Helse Sør-Øst		*3.5*	*7.1*	*12.8*	*20.7*	*37.4*
Treatment coverage HCV Helse Vest %		*2.8*	*2.6*	*3.4*	*7.0*	*18.1*
Cumulative frequency HCV Helse Vest		*2.8*	*5.4*	*8.8*	*15.9*	*34.0*
Treatment coverage HCV Helse Midt %		*3.8*	*4.4*	*5.5*	*6.9*	*18.1*
Cumulative frequency HCV Helse Midt		*3.8*	*8.2*	*13.7*	*20.6*	*38.7*
Treatment coverage HCV Helse Nord %		*2.4*	*9.3*	*9.9*	*9.0*	*13.6*
Cumulative frequency HCV Helse Nord		*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, Meijerink 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
Title and abstract	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
Introduction			
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
Methods			
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	-
Results			
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	

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 (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	5/6 - n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	6
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
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
Generalisability	21	Discuss the generalisability (external validity) of the study results	7
Other information			
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

*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.