Uptake and predictors of direct-acting antiviral treatment for hepatitis C among people receiving opioid agonist therapy in Sweden and Norway: a drug utilization study from 2014 to 2017

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Abstract

Background Treatment with direct-acting antiviral agents (DAAs) offers an opportunity to eliminate hepatitis C virus (HCV) endemic among people who inject drugs (PWID) and people enrolled in opioid agonist therapy (OAT) programs. The objective of this study was to estimate and to compare HCV treatment uptake after the introduction of DAAs among patients receiving OAT in Sweden and Norway. We also aimed to evaluate predictors of DAAs treatment among OAT patients in both countries.

Methods This observational study was conducted with data from The Swedish Prescribed Drug Register and The Norwegian Prescription Database. We studied dispensed medications to calculate HCV treatment among OAT patients from 2014 to 2017 in Sweden and Norway. HCV prevalence was estimated from primary and secondary sources. Dispensations of medicines from different therapeutic areas, which served as proxy for co-morbidities in 2017, were conditionally adjusted for age, gender, and OAT medications. Logistic regression was used to evaluate these parameters.

Results In total 3,529 individuals were identified with dispensed OAT in the Swedish cohort and 7,739 individuals in the Norwegian cohort. HCV treatment was utilized by 407 persons in Sweden and 920 in Norway during the study period. Annual HCV and DAA treatment uptake increased in both countries. The estimated cumulative HCV treatment uptake at the end of 2017 was 31% in Norway and 28% in Sweden. DAA treatment was associated with increased age (aOR 1.8; 95% CI 1.0-3.2) and dispensation of drugs used for diabetes (aOR 3.2; 95% CI 1.8-5.7) in Sweden. In Norway, lipid modifying agents and antibacterials were associated with decreased odds (aOR 0.4; 95%CI 0.2-0.9, aOR 0.8; 95%CI 0.6-1.0).

Conclusions An increase in DAA treatment and HCV treatment uptake was observed among Swedish and Norwegian OAT patients during the introduction period of new direct-acting treatment regimens. However, more than two thirds of the OAT population in Norway and Sweden were untreated at the beginning of 2018. A further scale-up is crucial to be able to control and eliminate the HCV endemic among OAT patients.

1. Background

Treatment of chronic hepatitis C virus (HCV) infection has been subject to vivid changes in the last few years with the introduction of direct-acting antiviral agents (DAAs) [1]. The ambition of any antiviral treatment of HCV infection is elimination of the virus. In that sense, standard treatment prior to 2011 was a combination of pegylated interferon alpha and ribavirin, which saw a sustained virologic response (SVR) in approximately 50 to 56% of patients [1, 2]. SVR is defined as absence of HCV RNA 12 weeks after end of treatment. However, since 2011 various DAAs have become readily available and should make interferon-based therapies almost obsolete. HCV policies including DAA offer countries an opportunity to eliminate HCV endemics, with less side effects, shorter treatment periods and improved adherence as compared to old interferon treatment. Combining two (or three) DAAs have led to a SVR of far beyond 90% also among patients who have been hard to treat in the past [3, 4].

The scale of the HCV endemic among people who inject drugs (PWID) is tragic and is a result of years with failing health policies for vulnerable populations. The HCV prevalence is around 50%, or more, among PWIDs [5, 6] and it is estimated that HCV complications will continue to increase within the next few years [7]. In 2016, the World Health Organization's member states embraced the aim of eliminating viral hepatitis as a public health treat by 2030, which is defined by a 80% reduction in incidence and 65% reduction in mortality, respectively [8].

The coverage of preventive interventions and harm reduction services varies among PWIDs. Although the distribution of needle and syringe programs is relatively poor [9], opioid treatment programs such as opioid agonist therapy (OAT) has higher coverage in many countries [10]..OAT has shown to reduce the risk of HCV acquisition [11], and despite ongoing illicit drug use, patients on OAT are achieving high SVR rates [12]. Hence, OAT programs may be a critical intervention for achieving large reductions in HCV transmissions. Several modelling studies have shown that significant reductions in HCV prevalence can be achieved with an adequate increase in HCV treatment uptake [13–15]. Nevertheless, HCV treatment uptake has remained low [16, 17]. In Norway, annual HCV treatment uptake among OAT patients ranged from 1.3–2.6% in the period from 2004 to 2013 [17]. HCV treatment uptake, and in particular DAA treatment, among OAT patients in Sweden is unknown. Taking into consideration the potential of HCV disease elimination by publicly funded DAA policies in the Scandinavian countries [10, 18] and the high HCV prevalence among the OAT population, it is essential to calculate the DAA treatment within an OAT delivery platform. Such estimates are important for countries aiming for HCV elimination or endemic control in near future.

Despite the high burden of disease and comorbidity among PWIDs and patients on OAT, knowledge is limited regarding any potential country differences among OAT patients receiving DAAs and those who do not. Furthermore, dispensed medicines from various therapeutic areas, such as psychopharmacological drugs, drugs used in diabetes, and cardiovascular disorders, can serve as a proxy for comorbidities.

Thus, this observational study aims to:

1. calculate HCV treatment annually and cumulatively after the introduction of DAAs among patients receiving OAT in Sweden from 2014 to 2017
2. compare DAA treatment between Norway and Sweden among patients receiving OAT from 2014 to 2017 and estimate HCV treatment uptake
3. evaluate if various dispensed drugs, age, gender and OAT medication can predict DAA treatment among OAT patients in Sweden and Norway in 2017

2. Methods

2.1 Study design and data sources

This is an observational study among patients on OAT in Sweden and Norway from 2014 to 2017. Data were extracted from The Swedish Prescribed Drug Register (SPDR) and The Norwegian Prescription Database (NorPD). The registries cover the entire Norwegian and Swedish populations and record all drugs dispensed from pharmacies. NorPD was established on January 1, 2004 and SPDR on July 1, 2005, administered by The Norwegian Institute of Public Health and The Swedish National Board of Health and Welfare, respectively. All drugs are classified according to The Anatomical Therapeutic Chemical (ATC) classification system. [19]. HCV prevalence data is not readily available for Norway and Sweden. Consequently, we employed primary and secondary sources to model HCV prevalence. Data from the INTRO-HCV study in Norway [20] was used in addition to published data on HCV prevalence among a large cohort of Swedish PWIDs [21]. See additional file 1 for a comprehensive description methodology and data sources.

2.2 Study population and definitions

The study population included all individuals aged 18 to 75 years who received OAT. OAT was defined as being dispensed at least one defined daily dose (DDD) per day per calendar year of buprenorphine, methadone, buprenorphine-naloxone, and levomethadone in Sweden and Norway by summarizing all annually dispensed OAT DDDs divided by 365.25 days.

Moreover, OAT medication per individual was noted as the last dispensation per calendar year. Other opioids are very rarely used for OAT and considered outside national guidelines and were therefore not included in the study [22]. To avoid including other medical indications than OAT, we excluded methadone preparations on the basis of route of administration (injections and tablets), and introduced a dosage criteria in order to make sure that actual patients on OAT were captured. The dosage criteria was set at minimum one DDD daily throughout each calendar year as an inclusion criteria. The study populations were thus chosen annually for both countries and it was possible for an individual to be included in more than one calendar year. See additional file 2 for s flow chart. ATC/DDDs rendering to 2017 [23] were used to quantify the dispensed OAT medications. A more detailed description of OAT and HCV treatment in Sweden and Norway is provided in additional file 3.

2.3 Calculating HCV and DAA treatment and estimating treatment uptake

HCV treatment was defined as being dispensed either one or more pegylated interferon alpha in combination with ribavirin, or one or more of the DAAs per calendar year during the study period. The annual rates were calculated by dividing number of individuals with dispensed HCV treatment by individuals on OAT. The cumulative frequency, which is the addition of successive years of treatment, was then calculated as the proportion of patients with dispensed HCV treatment at some point during the study period. Similarly, DAA treatment was calculated by dividing number of OAT patients with at least one dispensation of DAA by the total number of OAT patients per year and per country, which represents the annual prevalence of DAA use among OAT patients. Based on assumptions, from primary and

secondary sources described in detail in additional file 1, enabled us to derive a formula to estimate the chronic HCV prevalence in Norway and Sweden as follows;

$$\boldsymbol{Expected\ Number\ of\ Chronic\ HCV} = ((\mathbf{1}-\boldsymbol{\delta}) * [\boldsymbol{\phi} * \boldsymbol{\pi_{PWID}} + (\mathbf{1}-\boldsymbol{\phi}) * \boldsymbol{\pi_{NonPWID}}] * \boldsymbol{N}) - \boldsymbol{\tau}$$

where N is the size of the study population, δ is the rate of spontaneous HCV clearance, ϕ is the proportion of OAT patients who are PWID, π_{PWID} and $\pi_{NonPWID}$ are the anti-HCV prevalence estimates among PWID and non-PWID, respectively, and τ is the number of HCV treatments given. Using the above formula, we calculate the expected number of chronic HCV infections in 2014-2017 for Norway and Sweden, with uncertainty in this quantity arising only from the uncertainty in spontaneous clearance. The chronic HCV prevalence was then calculated by dividing the expected number of chronic HCV infections by the total population size in that particular year and setting (i.e. Norway or Sweden). HCV treatment uptake was then estimated by dividing the HCV treatments in each year by the estimated number of chronic HCV infections in that same year, yielding a percentage of chronic HCV infections that were treated per year. The cumulative HCV treatment uptake was then calculated as the sum of HCV treatment uptake across years.

Potential predictors of DAA treatment uptake were determined a priori and included OAT medication (methadone/levomethadone vs. buprenorphine-based), age, gender and various dispensed drugs (yes vs. no) from different therapeutic areas that were used as proxies for co-morbidities. All dispensations were recorded at the second ATC level (therapeutic subgroup), except for drugs affecting the nervous system, which was recorded at the third, fourth, and fifth ATC level (pharmacological subgroup to chemical substance, see additional file 4).

2.4 Statistical analyzes

All data processing and consecutive analyzes were performed in STATA SE 16.0 (StataCorp, TX, USA). Descriptive data were presented as frequencies, percentages, and means, with corresponding 95% confidence intervals where appropriate. Logistic regression analyses were used to estimate whether DAA treatment uptake were associated with gender, age, OAT medication, and dispensations of other drugs in 2017. Statistical significance was set at the $p < 0.05$ level.

2.5 Data handling and ethical considerations

All data were received anonymous from registry administrators and subsequently analyzed, therefore, no written consent was obtained from any of the individuals in the study. The study was approved by the Regional Ethical Review Committee in Stockholm, Sweden, (no 2018/2080-31/1) on November 14, 2018 and the Regional Committee for Ethics in Medical Research (no. 2018/939) in Norway on June 19, 2018. Furthermore, the study was conducted in accordance with the Helsinki Declaration and as an observational study in accordance with international accepted STROBE guidelines [24].

3. Results

3.1 Basic characteristics

In Sweden, 3,529 individuals receiving OAT were identified. Around 70% were male, with a mean age of approximately 44 years and 45 years in 2014 and 2017, respectively. See additional file 5 for all study years. The majority of the OAT patients were treated with buprenorphine-based OAT medication (52% in 2014 and 56% in 2017). Altogether 407 individuals in the Swedish cohort received HCV treatment during the study period. In Norway, 7,739 individuals were identified during the study period from 2014 to 2017. 70% were male and mean age was 44 in 2014 and almost 46 years in 2017. 55% received treatment with a buprenorphine-based OAT medication in 2017. Altogether 920 individuals in the Norwegian cohort received HCV treatment during the study period.

3.2 Estimated HCV prevalence and treatment uptake

For Sweden, chronic HCV prevalence was estimated to range from 55.6% (uncertainty interval (UI) 53.3 to 58.8) in 2014, to 53.1 (UI: 50.8–56.3) in 2017. In Norway, prevalence was estimated from 54.4 (UI: 52.1–57.5) in 2014 to 50.0 (UI: 47.7–53.1) in 2017. The cumulative HCV treatment uptake was thus projected to be 31% in Norway and 28% in Sweden for the study period (Table 2). Unadjusted treatment rates for both countries are shown in additional file 6.

3.3 Dispensations and predictors of DAA treatment in 2017

OAT patients in Norway and Sweden were stratified according to whether they received DAA treatment or not, and compared in 2017. In the Norwegian cohort 366 individuals (6.6%) received DAA treatment. In Sweden, 123 (4.5%) individuals received treatment. Variations in dispensations within countries were few, except for drugs used for diabetes (Table 3). However, among individuals receiving DAA treatment in Norway, half were also dispensed benzodiazepines compared to only 15% in Sweden. In contrast, 24% and 31% of the Swedish patients treated with DAA also received dispensations of z-hypnotics and antidepressants compared to 15% and 20% in the Norwegian cohort, respectively.

In a logistic regression model (see additional file 7), DAA treatment was associated with increased age (aOR 1.8; 95% CI 1.0-3.2) and dispensation of drugs used in diabetes (aOR 3.2; 95% CI 1.8–5.7) in Sweden. Dispensations of lipid modifying agents and antibacterials were associated with decreased odds (aOR 0.4; 95% CI 0.2–0.9, aOR 0.8; 95% CI 0.6-1.0) of receiving DAA treatment in Norway. Moreover, being female was associated with decreased odds in both countries (S: aOR 0.6; 95% CI 0.3–0.9, N: aOR 0.8; 95% CI 0.6-1.0).

4. Discussion

Amid the hepatitis C endemic among PWIDs and individuals enrolled in OAT programs in Sweden and Norway, the study has revealed a large increase in DAA treatment uptake among OAT patients in both countries from 2014 to 2017. As such, our findings reflect the immense progress, which has been achieved in HCV treatment during the recent years with almost a complete shift from interferon-based

treatment to solely treatment with DAAs among OAT patients. The cumulative frequency of HCV treatment in the OAT population was estimated to be 28% and 31%% in Sweden and Norway, respectively. DAA treatment was associated with increased age and dispensation of drugs used in diabetes in Sweden. Dispensations of lipid modifying agents and antibacterials were associated with lower odds in Norway. Being female was associated with decreased odds for treatment in both countries.

Even if considerable advances have been made in recent year with the introduction of interferon-free treatment regimens for HCV, few have actually engaged in treatment [25]. Several studies have demonstrated continued low treatment uptake among PWIDs and OAT patients [17, 26]. However, concerns about DAA treatment to people who use drugs seems unwarranted as both adherence and high SVR rates in this group have been validated in randomized controlled trials [27, 28]. Our study suggests an increase in HCV treatment in Sweden and Norway, attributed by a complete shift to interferon-free treatment regimens among OAT patients. Treatment with DAAs in Sweden and Norway were previously limited by strict eligibility criteria based on stage of liver fibrosis. However, since 2017 and 2018 in Sweden and Norway, respectively, DAA treatment has been offered as universal health coverage to all HCV patients regardless of genotype and level of liver fibrosis [18, 29]. Treatment demand has naturally soared, especially among former PWIDs [30], while people who are still using drugs have seemingly not been fully able to benefit from the increased accessibility [30]. Arguably, this opts for considering all models of onsite HCV care to people who use drugs in OAT programs, which despite ongoing drug use, may still result in high SVR [12, 16].

Even if the cumulative HCV treatment uptake seems to be similar in Sweden and Norway, there may still be discrepancy not fully captured in our results. Estimated HCV treatment uptake is at best imprecise as accurate prevalence and incidence data among OAT individuals do not exist to our knowledge, and was subsequently modelled for the purpose of this study. The model is likely to overestimate prevalence since the basis of the model employ data from high endemic areas of Stockholm, Bergen and Stavanger. In Norway it is estimated that mean prevalence among OAT patients was 52% and 43% in 2014 and 2017, respectively, with annual incidence of chronic HCV among PWIDs around 400 per year [7, 31]. However, if we consider the prevalence of anti-HCV among PWIDs it seems consistently higher in Sweden compared to Norway [32, 33]. Secondly, the coverage of OAT seems dissimilar. Sweden, with similar demography and roughly twice the general population compared to Norway has significantly less patients enrolled in OAT programs. Waal et al. estimate an overall OAT coverage around 60% among people with opioid dependence in Norway [34] compared to 10–50% OAT coverage in Sweden [35]. Part of the answer may lay in the current guidelines. Norway altered its OAT guidelines in 2010, making opioid addiction the absolute criteria for inclusion and being retained in treatment, however in Sweden, current OAT guidelines allow lower thresholds for OAT cessation in the case of repeated illicit drug use [31, 36]. Hence, it is not unlikely that the Swedish OAT population represents a remarkably smaller and more selected group of patients with less ongoing drug use and may for this reason be viewed more eligible for HCV treatment.

With the provision of DAA treatment available for all Norwegian and Swedish patients, it may be tempting to argue that this is the beginning of the end for the HCV endemic in Sweden and Norway. In addition to

OAT, by maintaining a high coverage of needle and syringe availability in these countries, together with continued scale-up of DAA treatment, it may be possible to reduce incidence by 90% by 2030 as shown in a modeling study from the UK [37]. However, on the other hand it may still seem embryonic as there may be shortcomings in the HCV surveillance systems. HCV has been notified to The Norwegian Surveillance System for Communicable Diseases since 1990, yet, there has been no distinction between anti-HCV, HCV RNA or HCV core antigen reporting before 2016, it is therefore difficult to assess whether cases were acute or chronic, or whether patients achieved SVR on their own, or how many cases were actually notified [17]. The result is that accurate HCV prevalence and incidence data prior to 2016 are not readily available. Furthermore, in order to eliminate HCV as a public health treat by 2030, which both countries have embraced, a coherent and structured national plan seems essential. The Norwegian Health Ministry introduced a national hepatitis C strategy in 2016, and was later revised in 2018, which focuses on DAA treatment, HCV surveillance, and prevention, and aims to reduce HCV incidence by 90% within 2023 [38]. On the contrary, there is not yet established an ambitious national Swedish hepatitis C plan [39]. Coupled with lower OAT coverage and a higher anti-HCV prevalence, HCV elimination may seem more challenging and distant in Sweden compared to Norway.

Our findings suggest few intercountry differences in dispensed drugs among those treated with DAAs and not, except for drugs used for diabetes in the Swedish cohort, which was significantly higher and a predictor for DAA treatment. Chronic HCV might be a risk factor for developing immune system disorders, heart disease and diabetes, especially diabetes type II as the viral infection may increase insulin resistance [40, 41]. This finding was not mirrored in the Norwegian cohort. Even if dispensed drugs can serve as a proxy for co-morbidity it is well established that both somatic and especially mental illness are underdiagnosed and undertreated among individuals with substance use disorders [42], and does not explain the vast differences we observed among dispensations of benzodiazepines, z-hypnotics, and antidepressants comparing Sweden and Norway. Older patients are more likely to have cirrhosis and longer HCV treatment courses compared to younger patients, which may explain the reported association between DAA treatment among patients aged 46–55 in Sweden. Although, a reason for the observed age difference with regard to being treated for HCV may be that the younger patients are usually harder to reach due to an unstable life situation and drug abuse related behavior. Similarly, the analyzes point toward that women are less likely to be treated for HCV, however, this could just as much be that women are underrepresented in services

5. Strengths And Limitations

The national prescription registries capture large populations, and as such, provide researchers with precise and near complete databases. The main strength of this study is that it offers a large sample of OAT patients being treated for HCV.

However, this observational study have several limitations. As the patients were included each calendar year with a dosage criteria, a patient who commenced treatment late or quit early during the year may not obtain sufficient exposure to be included that particular year. We may also have included patients on

methadone mixture that are not true OAT patients. However, to amend for this we did not only exclude methadone preparations on the basis of route of administration, such as tablets and injections, but also introduced a dosage criteria of minimum one DDD per day per calendar year, for all medications used for OAT. Furthermore, OAT treatment in Norway and Sweden is not uniform. Most individuals are dispensed OAT medications at pharmacies while others receive the drugs at OAT outpatient clinics, which means that those latter patients are not identified in this study. In addition, DDD does not necessarily reflect the prescribed daily dose. Also, OAT and HCV treatment administered to hospitalized and institutionalized patients are not recorded in the registries.

Furthermore, HCV treatment uptake data was not linked on an individual level to diagnosis codes of HCV according to International Statistical Classification of Diseases and Related Health Problems version 10 (ICD-10) or the International Classification of Primary Care (ICPC), rather, it was estimated from published reports and modelled where adequate data sources were missing. Thus, there is some uncertainty in the denominator of people with HCV in need of treatment. The predictors for DAA treatment were limited to mainly dispensed drugs and sociodemographic variables and not fully acknowledging there could be other vital reasons why access to DAAs would be limited in this group of patients.

Finally, PWID are a heterogenic group of individuals, and one should be careful not to generalize OAT patients to include all PWIDs.

6. Conclusion

This observational study has demonstrated a large scale-up in DAA treatment among Swedish and Norwegian OAT patients. Both countries have an increased cumulative HCV treatment uptake of around one-third from 2014 to 2017, recognized by a complete shift to DAA treatment regimens. Midst a HCV endemic among PWIDs, it seems clear that two-thirds of people in need of treatment were untreated in the beginning of 2018. Coupled with the prospect of HCV elimination, there is a need for further scale-up of the most effective HCV treatment strategies, by identifying possible predictors of treatment and establishing more accurate surveillance systems to provide a better care to this group of marginalized people.

Abbreviations

OAT	Opioid agonist therapy
DAA	Direct-acting antiviral agents
HCV	Hepatitis C virus
PWID	People who inject drugs
NorPD	The Norwegian Prescription Database

SPDR	Swedish Prescribed Drug Register
ATC	Anatomical Therapeutic Chemical classification system
DDD	Defined daily dose
Anti-HCV	Antibodies to the Hepatitis C virus
SVR	Sustained virologic response
INTRO-HCV	Integrated treatment of hepatitis C study

Declarations

Ethical approval and consent to participate

The study was approved by the Regional Ethical Committee (no. 2018/939), Norway, on June 19, 2018 and by the Regional Ethical Review Committee in Stockholm (no 2018/2080-31/1), Sweden, on November 14, 2018. No informed consent from the participants was required.

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.

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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Authors’ contributions

This observational study was led by CFA in terms of study design, analyzes, drafting and writing the article. 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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Tables

Table 1: Basic characteristics of patients receiving OAT in 2014 and 2017 in Sweden and Norway

	2014		2017	
Country	Sweden	Norway	Sweden	Norway
OAT studypopulation, n	2663	6057	2739	5545
Gender, n (%)				
Male	1911 (72)	4266 (70)	1961 (72)	3870 (70)
Female	752 (28)	1791 (30)	778 (28)	1675 (30)
Age, n (%)				
18-35	671 (25)	1219 (20)	647 (24)	878 (16)
36-45	817 (31)	2181 (36)	819 (30)	1747 (32)
46-55	744 (28)	2044 (34)	713 (26)	1998 (36)
56-75	431 (16)	613 (10)	560 (20)	922 (17)
Mean age (SD)				
Male	44 (10)	44.1 (9)	45.1 (11)	46.1 (9)
Female	43.5 (11)	43.1 (9)	44.3 (12)	45.2 (10)
OAT medication, n (%)*				
Methadone/levomethadone	1267 (48)	2810 (46)	1198 (44)	2504 (45)
Buprenorphine	875 (33)	2049 (34)	1075 (39)	2190 (40)
Buprenorphine/naloxone	521 (20)	1198 (20)	466 (17)	851 (15)

OAT = opioid agonist therapy; SD = standard deviation;
Sources: The Swedish Prescribed Drug Register (SPDR), The Norwegian Prescription Database (NorPD)
*Last registered OAT medication each calendar year

Table 2: Annual and cumulative estimated HCV treatment uptake in Norway and Sweden among OAT patients 2014-2017

	2014		2015		2016		2017	
Country	**Norway**	**Sweden**	**Norway**	**Sweden**	**Norway**	**Sweden**	**Norway**	**Sweden**
HCV treatment n (overall)	148	54	178	105	216	124	378	124
Study population n,	6057	2663	6005	2640	5537	2683	5545	2739
HCV treatment % (95% CI)	*2.4 (2.1-2.8)*	*2.0 (1.5-2.6)*	*3.0 (2.5-3.4)*	*4.0 (3.2-4.7)*	*3.9 (3.4-4.4)*	*4.6 (3.8-5.4)*	*6.8 (6.2-7.5)*	*4.5 (3.8-5.3)*
Expected proportion of OAT patients who are not PWID, n*	303	133	300	132	276	134	277	137
Expected Anti-HCV, weighted by PWID status, n**	4651	2075	4612	2057	4252	2091	4258	2135
Expected chronic HCV after spontaneous clearance, n (UI)***	3442 (3303-3628)	1536 (1474-1619)	3413 (3274-3597)	1523 (1461-1605)	3147 (3019-3317)	1547 (1485-1631)	3151 (3023-3321)	1580 (1516-1665)
Expected chronic HCV after treatment, n (UI)	3294 (3155-3480)	1482 (1420-1565)	3235 (3096-3419)	1418 (1356-1500)	2931 (2803-3101)	1423 (1361-1507)	2773 (2645-2943)	1456 (1392-1541)
Expected chronic HCV after spontaneous clerance and treatment, % (UI)	54.4 (52.1-57.5)	55.6 (53.3-58.8)	53.9 (51.6-56.9)	53.7 (51.4-56.8)	52.9 (50.6-56.0)	53.1 (50.7-56.2)	50.0 (47.7-53.1)	53.1 (50.8-56.3)
Estimated HCV treatment uptake % (UI)	***4.5 (4.3-4.7)***	***3.6 (3.5-3.8)***	***5.5 (5.2-5.7)***	***7.4 (7.0-7.7)***	***7.4 (7.0-7.7)***	***8.7 (8.2-9.1)***	***13.6 (12.8-14.3)***	***8.5 (8.0-8.9)***
Estimated HCV cumulative treatment uptake % (UI)	***4.5 (4.3-4.7)***	***3.6 (3.5-3.8)***	***10.0 (9.5-10.4)***	***11.1 (10.5-11.5)***	***17.4 (16.4-18.1)***	***19.8 (18.7-20.7)***	***31.0 (29.3-32.4)***	***28.3 (26.7-29.6)***

OAT = opioid agonist therapy, HCV = hepatitis C virus infection, CI = confidence interval, UI = uncertainty interval,
Anti-HCV = antibodies to hepatitis C virus, PWID = people who inject drugs
Sources: The Swedish Prescribed Drug Register (SPDR), The Norwegian Prescription Database (NorPD), Intro-HCV = Integrated treatment of hepatitis C study, Kåberg et al. (2017): Prevalence of hepatitis C and pre-testing awareness of hepatitis C status in 1500 consecutive PWID participants at the Stockholm needle exchange program,
Micallef et al. (2006): Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies
*Expected non-PWIDs among OAT patients set to 5%
**Expected Anti-HCV among PWID in Norway 80.8%, expected Anti-HCV among PWID in Sweden 82%, expected Anti-HCV among non-PWID in both Norway and Sweden is 0.7%
***Expected spontaneous clearance 26% (22-29%)
For more comprehensive details on sources and model calculation, see supplement S6.

Table 3: Dispensed drugs to patients receiving OAT and OAT/DAAs in Norway and Sweden in 2017

Year	*2017*		*2017*	
Country	**Norway**		**Sweden**	
OAT study population, n	5543		2739	
	Only OAT 5177	DAA + OAT 366	Only OAT 2616	DAA + OAT 123
Drugs	No. (%)	No. (%)	No. (%)	No. (%)
Drugs used in Diabetes	197 (4)	14 (4)	161 (6)	18 (15)
Antithrombotic agents	529 (10)	35 (10)	217 (8)	8 (7)
Cardiovascular system drugs *	842 (16)	67 (18)	622 (24)	37 (30)
Lipid modifying agents	271 (5)	10 (3)	121 (5)	4 (3)
Sex hormones and modulators of genital system	654 (13)	51 (14)	430 (16)	14 (11)
Antibacterials for systemic use	1901 (36)	112 (31)	915 (35)	33 (27)
Anti-inflammatory and ant-rheumatic products	1155 (22)	69 (19)	570 (22)	25 (20)
Drugs for obstructive airway diseases	1048 (20)	68 (19)	410 (16)	14 (11)
Benzodiazepines**	2368 (46)	181 (50)	402 (15)	19 (15)
Hypnotics and sedatives***	797 (15)	54 (15)	691 (26)	30 (24)
Antiepileptics****	823 (16)	57 (16)	629 (24)	25 (20)
Antidepressants*****	960 (19)	73 (20)	1008 (39)	38 (31)
Antipsychotics******	1401 (27)	85 (23)	602 (23)	28 (23)

OAT = opioid agonist therapy, DAA = direct-acting antiviral agents
Source: The Swedish Prescribed Drug Register (SPDR), The Norwegian Prescription Database (NorPD)
All drugs on ATC Level 2, except under Nervous system. See Supplement Table S2
*C01, C02, C03, C07, C08, C09
**N05BA01, N05BA04, N05BA06, N05BA12, N05CD02, N05CD03, N05CD08, N03AE01
***N05CF01 and N05CF02
****N03AA, N03AB, N03AF, N03AG, N03AX
*****N06AA, N06AB, N06AF, N06AG, N06AX
******N05AA, N05AB, N05AC, N05AD, N05AE, N05AF, N05AG, N05AH, N05AL, N05AN, N05AX

Figures

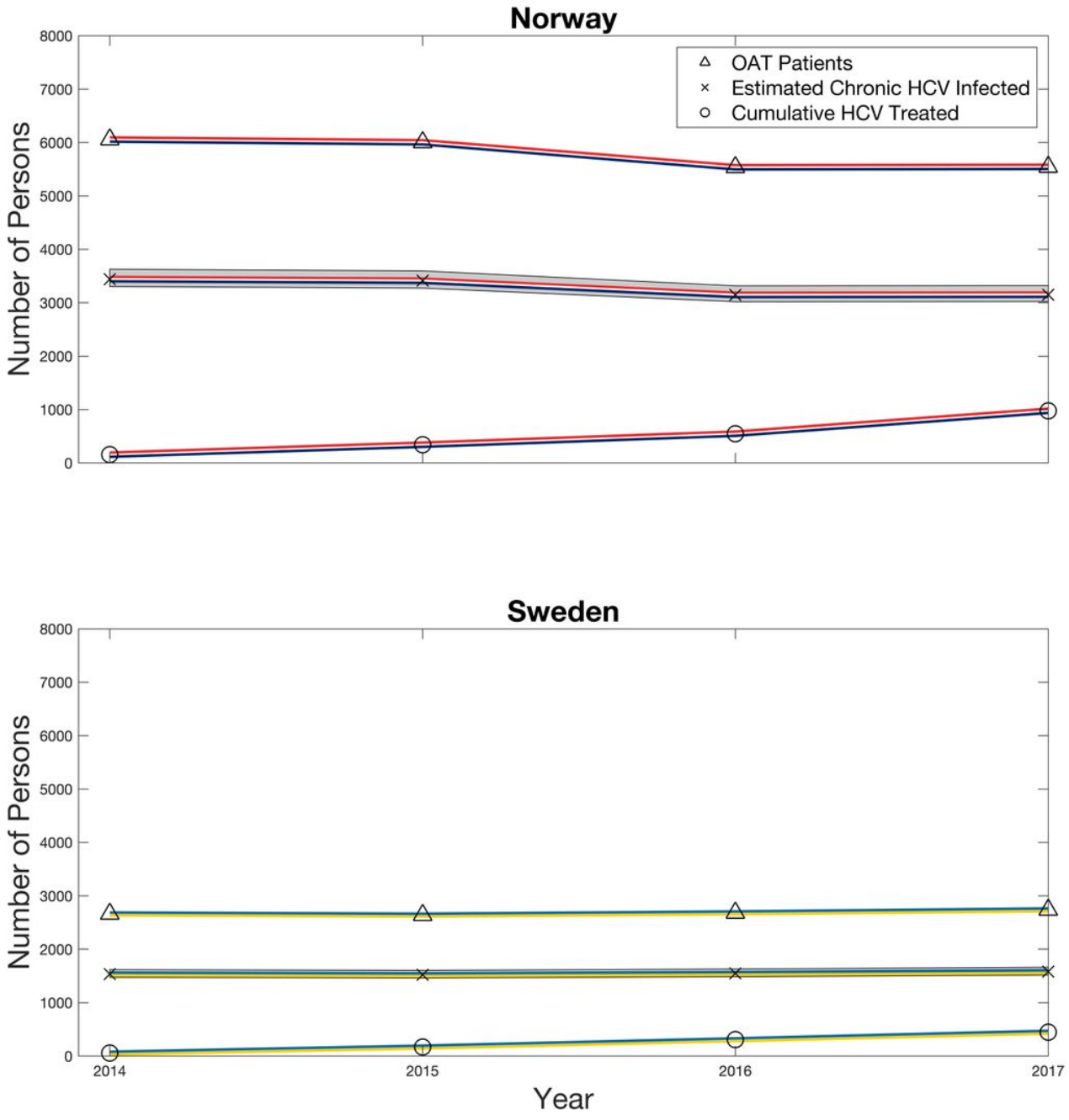

Figure 1

Estimated HCV treatment uptake in Norway and Sweden among OAT patients from 2014 to 2017. HCV = hepatitis C virus infection, OAT = opioid agonist therapy Sources OAT and HCV treatment: The Swedish Prescribed Drug Register (SPDR), The Norwegian Prescription Database (NorPD). Prevalence: Intro-HCV = Integrated treatment of hepatitis C study, Kåberg et al. (2017): Prevalence of hepatitis C and pre-testing awareness of hepatitis C status in 1500 consecutive PWID participants at the Stockholm needle exchange program, Micallef et al. (2006): Spontaneous viral clearance following acute hepatitis C

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