PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Aas, Christer; Vold, Jørn; Skurtveit, Svetlana; Odsbu, Ingvild; Chalabianloo, Fatemeh; Økland, Jan; Leiva, Rafael; Vickerman, Peter; Johansson, Kjell Arne; Fadnes, Lars

VERSION 1 – REVIEW

REVIEWER	Federico García Hospital Clínico Universitario San Cecilio, Granada, Spain
REVIEW RETURNED	19-Jan-2020

GENERAL COMMENTS	Major comment Lines 403-404. "However, Norway is far from universal coverage of HCV treatment" My belief is that this is true for the study period, which goes up to 2017. Any conclusion from this study cannot be accepted for year 2020, so authors should take care of the wording and try to make this very clear throughout the text. This should also be included as a limitation in the limitations section. Minor comments Line 111; "creates an opportunity to eradicate HCV epidemics". May be the term eradication is not appropriate; better to use elimination Line 116; "public health treat by" should be threat Line 143, "with a curation rate of >90%"; better >95% Lines 158-159, Is objective 2 necessary or timeline? I suggest to delete this objective

REVIEWER	Daniel Schmidt Robert Koch Institute, Berlin, Germany
REVIEW RETURNED	16-Apr-2020

GENERAL COMMENTS	**HCV treatment among PWID in Norway** The study describes DAA treatment among patients receiving OAT in Norway from 2013-2017 as well as the shift to interferon-free treatment regimens. Further, adherence to DAAs among OAT patients across all genotypes in Norway was analyzed using logistic regression. The study uses different data sources combining prescription data from the Norwegian Prescription Database (NorPD) for DAA treatment, data from The Norwegian Centre for Addiction Research for estimating the prevalence of chronic HCV among OAT patients and data from The Norwegian Institute of Public Health and Meijerink et al. (14) for HCV incidence among

	Norwegian PWIDs. Additionally, expert opinion were obtained from clinicians in addiction medicine for HCV incidence. The study shows a marked scale-up in HCV treatment attributed by a shift to interferon-free regimens among Norwegian OAT patients. However, the authors show that Norway is far from universal coverage of HCV treatment and a need to establish a more accurate monitoring system and more precision in prevalence and incidence rates of chronic HCV among PWID. The authors also recommend more efficiency of health system strategies 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. The paper is of interest and is mostly clearly written and well drafted. However, several issues remain to clarify the methods, results and conclusions. Generally, it would be good to further discuss and compare the treatment coverage as well as the adherence with other studies and maybe other countries to put the results in a larger context and allow a better interpretation of the results. ***Abstract (Conclusion)*** However, a further substantial scale-up in HCV treatment is required to reach the universal targets of controlling and eradicating the HCV endemic. Isn´t this a very moderate way to say that the treatment coverage is unacceptable low? It would be helpful to contrast your findings and numbers/proportions with other studies and countries at least in the discussion section of the main text. ***Background*** Number of PWID in Norway is stable at around 9000 (2.6 per 1000 inhabitants aged 15-64 years)… Can you indicate what period you are referring to when you say numbers are stable. Modelling studies suggest that around 7000 former and current PWIDs are living with chronic HCV with an estimated 400 new cases anually. Can you also indicate here for clarity which period or year you are referring to. Because in the methods you say that Meijerink et al. Have demonstrated the incidence in a compartmental model for HCV infections from 1973-2030 in Norway. So it is not clear what you mean by former and current. In table 2 the reader can find the numbers from Meijerink et al. for 2013-2017 but this is sort of inconvenient. Taking these numbers of 7000 former and current PWIDs living with chronic HCV to the number of 9000 PWIDs this would give a HCV prevalence of 78%. How does this fit with your prevalence of 43-51% between 2013-

	2017? It would be good to discuss those estimates with your findings and contrast to your HCV treatment coverage. 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). Why number of sex partners? 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). Are these results available and what is the HCV prevalence and incidence? Can you compare that to your numbers? 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). Globally, the coverage of HCV curative treatment was 13% by 2016 (26). Is this coverage of 13% comparable to your later findings of 8.5% in 2016? Maybe pick up on this in the discussion section if those numbers can be compared with another. 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). How much does DAA treatment cost in Norway? Is treatment paid by health insurances and are PWID covered there? It would be good to include in the discussion section what the reasons are for treatment coverage being so low among PWID despite WHO and Norwegian guidelines supporting DAA treatment among PWID and health insurances covering it (if they do)? ***Methods*** 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. The group J05AP includes HCV treatment combinations as well as single substances such as single simeprevir, sofosbuvir, daclatatsvir etc. that have to be combined in ordert o have a fully active HCV regimen. How did you combine and count these single substances and how did you avoid overcounting?

	Further it also includes the first generation DAAs Boceprevir and Telaprevir. How did you handle those? I´d recommend considering to provide a table that shows HCV treatment including substances and duration. 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. If the cumulative frequency is just the addition of successive years how do you handle patients with treatment starting but not finishing in the same year in your calculation of treatment coverage and adherence because accordingly they would not be adherent according to your definition. 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%). Can you explain what assumptions lead you to 0.7 and discuss what implications this has and the potential error if this assumption would be incorrect. 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. How did you decide on these factors, which other factors where considered but not chosen for the analysis? What about origin? Which other factors where potentially available? Line 220 and Table 3: 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. Isn´t this 2 x 28 DDD = ≥56 DDD? Please check Table 3 as well for this. Line 225 – 227 and Table 1 & 3 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). Categories differ, check them and correct please. ***Results*** The majority of the OAT patients were treated with buprenorphine-based OAT medication (55% in 2013, 60% in 2017). I believe it must be 61% for 2017 as Table 1 shows.

	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. Why is your denominator the number all OAT patients if HCV prevalence among OAT patients is ~55% and therefore not all OAT patients are in need for HCV treatment? 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%. How do you explain the difference in adherence? ***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. I believe it must be “too low“ instead of “to low“. 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. See comment in the results section regarding need for treatment among OAT patients. 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. Are the numbers comparable to your treatment coverage or is this actually comparable to your treatment uptake? Would be helpful to discuss and clarify so the reader doesn´t have to look this up the reference. It would be also helpful to compare your findings with other studies and countries if possible to put them in a larger context. 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). So what is the coverage and would´nt it be good to compare and discuss with your numbers even though eligibility criteria

have changed.

It would be good to further discuss the expected reasons for the treatment coverage being so low among PWID.

Who pays for treatment in Norway, and are immigrants ensured and eligible for HCV treatment?

About two-thirds of all patients were considered adherent to DAAs according to recommendations from the prescribing specialist, across all genotypes.

In Table 3 adherence by gender shows in total 828/1111 (75%) being adherent?

Whats the adherence generally, isn´t 2/3 quite low? Could you compare and discuss.

Table 3

For gender you show the proportions for the respective columns. However, for age and OAT medication you show the proportion for the rows.

Why is N=1111 instead of 1235 patients?

Strengths and limitations

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).

This is somewhat confusing, are drugs initiated and administered in outpatient clinics included or not and what does that mean for your treatment coverage and validity of the data?

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.

Could you conclude what that means for the adherence and your results regarding the difference seen between younger and older persons.

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

As said before, it would be good to further discuss the expected reasons for the treatment coverage being so low among PWID on OAT. Especially given the fact that your

	population of people on OAT is already a selection of people who have successfully entered the medical system and who receive medical care which expectedly would bias your results towards better coverage and adherence.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Federico García

Major comment Lines 403-404. "However, Norway is far from universal coverage of HCV treatment" My belief is that this is true for the study period, which goes up to 2017. Any conclusion from this study cannot be accepted for year 2020, so authors should take care of the wording and try to make this very clear throughout the text. This should also be included as a limitation in the limitations section.

We agree with the reviewer, this is only true for the study period. During the study period from 2013 to 2017 treatment with DAAs were limited by stage of liver fibrosis according to Metavir scoring system (>F2-F4). Only from February 1, 2018, treatment with new DAAs were offered universally regardless of liver fibrosis in Norway. This is made clear in the discussion section (line 329-331). We have made additional changes in the manuscript:

- Removed this statement from the Conclusion section completely (line 403-404)
- Included this as limitation under the 'Strengths and limitations – Summary' and in the main section under point 5.

Minor comments

Line 111; "creates an opportunity to eradicate HCV epidemics". May be the term eradication is not appropriate; better to use elimination Line 116; "public health treat by" should be threat Line 143, "with a curation rate of >90%"; better >95% Lines 158-159, Is objective 2 necessary or timeline? I suggest to delete this objective

We have made the following changes:

- Used elimination instead of eradication throughout the manuscript (four changes made)
- Changed spelling error from 'treat' to 'threat'
- Changed …>90% to '…curation rate of approximately 95%'

After discussing aim and objectives of the study among co-authors we also agree that objective 2 is not strictly necessary and removed it entirely.

Reviewer: 2
Reviewer Name: Daniel Schmidt

Comments and questions in the attached file, pasted in here. There are several issues that need to be addressed in order to clarify the methods, results and conclusions.

BMJ open
HCV treatment among PWID in Norway
The study describes DAA treatment among patients receiving OAT in Norway from 2013-2017 as well as the shift to interferon-free treatment regimens. Further, adherence to DAAs among OAT patients across all genotypes in Norway was analyzed using logistic regression. The study uses different data sources combining prescription data from the Norwegian Prescription Database (NorPD) for DAA treatment, data from The Norwegian Centre for Addiction Research for estimating the prevalence of

chronic HCV among OAT patients and data from The Norwegian Institute of Public Health and Meijerink et al. (14) for HCV incidence among Norwegian PWIDs. Additionally, expert opinion were obtained from clinicians in addiction medicine for HCV incidence. The study shows a marked scale-up in HCV treatment attributed by a shift to interferon-free regimens among Norwegian OAT patients. However, the authors show that Norway is far from universal coverage of HCV treatment and a need to establish a more accurate monitoring system and more precision in prevalence and incidence rates of chronic HCV among PWID. The authors also recommend more efficiency of health system strategies 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.
The paper is of interest and is mostly clearly written and well drafted. However, several issues remain to clarify the methods, results and conclusions.

Generally, it would be good to further discuss and compare the treatment coverage as well as the adherence with other studies and maybe other countries to put the results in a larger context and allow a better interpretation of the results.

One of our key motivations for conducting the study was the revealing that HCV treatment coverage in Norway/Scandinavia/Europe was not well documented after the introduction of DAAs and it was hard to find comparable studies and countries. We therefor fully agree with the reviewer it would be good to further compare our results and try to put them into broader context. We have made the following general changes:

- Included a new paragraph at the beginning of the discussion to put our result in to more comparable context with other European countries (hereunder particular Sweden and Denmark)
- Restructured and included more recent studies under the adherence paragraph in the discussion section to better compare and discuss our findings

Abstract (Conclusion)
However, a further substantial scale-up in HCV treatment is required to reach the universal targets of controlling and eradicating the HCV endemic. Isn´t this a very moderate way to say that the treatment coverage is unacceptable low? It would be helpful to contrast your findings and numbers/proportions with other studies and countries at least in the discussion section of the main text.

The HCV coverage is too low (during the study period) if we are to achieve the WHO goals by 2030 and the even more ambitious goals of the Norwegian Government's hepatitis strategy by 2023. We have showed in the discussion section that our findings put Norway somehow in the middle among European countries (significantly behind countries such as Germany and France, however similar to Sweden and ahead of Denmark which we often compare towards due to similar demographics. After this study we did a similar registry based study, which studied HCV treatment coverage in Sweden from 2014 to 2017, and we saw that Norway had slightly higher HCV cumulative treatment coverage during the period (this study is not yet published). We have added the following sentence in the conclusion section/abstract to better highlight this:

- "Despite a large increase in treatment, overall HCV coverage is inadmissibly too low…"

Background
Number of PWID in Norway is stable at around 9000 (2.6 per 1000 inhabitants aged 15-64 years)… Can you indicate what period you are referring to when you say numbers are stable.

Number of PWIDs in Norway seems to have peaked in 2001, followed by a decline from 2008-2012. Since 2012 number of PWIDs seems stable around 9000 up until the end of study period (though with large uncertainty estimates).

- We have now updated the time period in the manuscript

Modelling studies suggest that around 7000 former and current PWIDs are living with chronic HCV with an estimated 400 new cases anually. Can you also indicate here for clarity which period or year you are referring to. Because in the methods you say that Meijerink et al. Have demonstrated the incidence in a compartmental model for HCV infections from 1973-2030 in Norway. So it is not clear what you mean by former and current. In table 2 the reader can find the numbers from Meijerink et al. for 2013-2017 but this is sort of inconvenient.

- We have updated the time period in the manuscript

Taking these numbers of 7000 former and current PWIDs living with chronic HCV to the number of 9000 PWIDs this would give a HCV prevalence of 78%. How does this fit with your prevalence of 43-51% between 2013-2017? It would be good to discuss those estimates with your findings and contrast to your HCV treatment coverage.

We see that this needs to be explained more carefully as these groups are not completely overlapping. The 9000 is the estimate over people who actively inject drugs daily (in the study referred to as active-PWIDs, and this group it is estimated a HCV prevalence of 42.7 to 48.8%), whereas the former is people for the most part who have a history of injecting drug use. It would therefore be inaccurate to calculate HCV prevalence based on these groups as they are not the same. We have made the following changes in the manuscript:

- Clarified that the 9000 are people who inject drugs actively

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). Why number of sex partners?

No specific reason, we have thus removed number of sex partners from the manuscript.

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). Are these results available and what is the HCV prevalence and incidence? Can you compare that to your numbers?

The INTRO-HCV study consist of a multicenter randomized controlled trial, where the main aim of the study is to compare the efficacy of integrated and standard treatment of HCV and a longitudinal observation study. Parts of the study is still ongoing and therefore not published and included as discussion here, however, preliminary results show that HCV prevalence is comparable with our findings towards the end of the study period in 2017. Among 752 patients, initial results from blood samples showed a prevalence of anti-HCV of 80.8% and RNA of 44.5%. Anti-HCV, which is antibodies to the hepatitis C virus, indicate current infection, clearance of the infection, or that anti-viral treatment has been successful, while HCV RNA indicates current infection.

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). Globally, the coverage of HCV curative treatment was 13% by 2016 (26). Is this coverage of 13% comparable to your later findings of 8.5% in 2016? Maybe pick up on this in the discussion section if those numbers can be compared with another.

According to WHO curative treatment was 13% by the end of 2006. However, also according to the WHO, HCV treatment was around 1 million and 1,5 million worldwide in 2015 and 2016 respectively. With 71 million in need of treatment (also WHO), this would give a coverage of e.g. 1.4% in 2015. It is thus likely that WHO refer to cumulative treatment and would be best compared with our finding of 21.5% in 2016. Because of the uncertainty and based on WHO operate with global estimates, we found it more accurate to compare Norway with other European countries, and in particular, Sweden

and Denmark as we have included this in the beginning of the discussion after advice from the reviewer (see above).

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). How much does DAA treatment cost in Norway? Is treatment paid by health insurances and are PWID covered there? It would be good to include in the discussion section what the reasons are for treatment coverage being so low among PWID despite WHO and Norwegian guidelines supporting DAA treatment among PWID and health insurances covering it (if they do)?

Norway offers universal health coverage and reimbursement of public expenses, however, during the study period (and up until February 1st, 2018), treatment with DAAs have been restricted according to degree of liver stiffness and genotype according to the Norwegian HCV guidelines (DAA treatment for genotype 1 and 4 was provided independent of stage of liver fibrosis >2017, while genotype 2 and 3 infection only with significant liver fibrosis (F2-F4; liver stiffness measurements > 7.0 kPa). According to Dagens Medisin (https://www.dagensmedisin.no/artikler/2016/02/16/far-50-prosent-rabatt-pa-hepatitt-c-medikament/) a 12 week treatment with Viekirax (ombitasvir/paritaprevir/ritonavir) was NOK 470.000 in 2016 (in euros approximately 47.000). Since then the prices have fallen dramatically (also due to a restructuring through a process of procurement and shifting the responsibility for financing towards the regional health services which could then coordinate purchases).

We agree that treatment among PWID are too low, and there were several barriers for DAA treatment in place during the study period. Eligibility criteria was one, which could limit access to treatment for some patients, due to high prices of DAAs, another was lack of adequate HCV surveillance systems during part of the study period, while yet others could be the capacity and infrastructure of Norwegian OAT and health care delivery platforms. This we have briefly discussed in the discussion part. In addition, another reason could be the lack of understanding of this marginalized patient group specific needs and how to engage and provide a system of both testing and linkage to care for both OAT and PWID patients (OAT treatment is not uniform in Norway, in addition HCV testing and treatment are not integrated and patients have to be referred to an outpatient infectious or gastroenterology clinic close to a central hospital, which can be very challenging for many patients). We have made the following changes in the manuscript:

- We have added and restructured the paragraph in the discussion section to better communicate possible reasons and barriers to the low HCV treatment coverage among PWIDs (despite being recommended by HCV guidelines and covered by public expenses)

Methods

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. The group J05AP includes HCV treatment combinations as well as single substances such as single simeprevir, sofosbuvir, daclatatsvir etc. that have to be combined in ordert o have a fully active HCV regimen. How did you combine and count these single substances and how did you avoid overcounting? Further it also includes the first generation DAAs Boceprevir and Telaprevir. How did you handle those? I´d recommend considering to provide a table that shows HCV treatment including substances and duration.

We searched the data file from NorPD for dispensations of DAAs according to ATC-codes in the J05AP-group (except ribavirin (J05AP01)), which were available in Norway during the study period, and constructed variables with DAA “first date, ATC-code and year” registered. Patients were counted from the year of treatment initiation with a DAA, regardless of the length and combination of other DAAs/antivirals (i.e. to prevent double counting patients with treatment regimens that went across a given year during the study period). This includes telaprevir (J05AP02) and boceprevir (J05AP03) in 2013 before being withdrawn from the Norwegian market. We prevented over-counting because patients (by patient ID) were only included when they started DAA treatment that particular year (and also receiving OAT medication the same year).

We have made the following changes:

- To clarify this better in the manuscript, we have added a table in additional files over all DAAs with corresponding ATC-codes, which were available in Norway and listed the most prevalent DAAs (according to first registered DAA by ATC-code)

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. If the cumulative frequency is just the addition of successive years how do you handle patients with treatment starting but not finishing in the same year in your calculation of treatment coverage and adherence because accordingly they would not be adherent according to your definition.

- Treatment coverage: Patients were included in the year they started treatment, i.e. the first date treatment was dispensed according to ATC code. If a patient initiated treatment in one year, but continued into another year, treatment was only registered the calendar year of treatment initiation. We have updated this under the method section in the manuscript.
- Adherence: Patients were counted with the date of first and last dispensed DAA, ATC code, DDD, and number of dispensations, which allowed us to examine adherence based on number of dispensations and DDDs. Thus, patients were included regardless if the treatment continued into another year, except for 2017 when inclusion was ceased 01.10.17. A new categorical variable with 1 (adherent based on definition) and 0 (non-adherent to the definition) was generated and subsequently analyzed.

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%). Can you explain what assumptions lead you to 0.7 and discuss what implications this has and the potential error if this assumption would be incorrect.

We see that there is text missing in the manuscript and this could lead to confusion for the reader. New cases of chronic HCV among OAT patients are unknown, hence the rationale behind the assumption of 0.70 (or 70%) is that OAT patients accounts for only a proportion of the overall estimated 400 new cases annually of chronic HCV among all PWIDs in Norway during the study period. Estimates from SERAF (The Norwegian Centre of Addiction Research) suggest that OAT coverage is between 50 and 60% among people with opioid dependence.

- If there was no adjustment, the HCV treatment rates would be 3.4, 3.8, 5.5, 8.2, and 16.5 (cumulative 37.4) for the study period

If our assumption was incorrect we could risk to either over- or underestimate the HCV incidence among OAT patients, which would affect our overall results. With no adjustment, the cumulative frequency would be 37.4 versus the 38.5 we found with this assumption. We believe, however, that the 0.7 (70%) proportion is not a conservative estimate and the biggest risk is that we overestimate the HCV incidence. We have made the following changes in the manuscript:

- We have updated the methods section to clarify this
- We have added a sentence on this in the limitation section

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. How did you decide on these factors, which other factors where considered but not chosen for the analysis? What about origin? Which other factors where potentially available?

The NorPD had a limited list of background variables available, which subsequently restricted our choices. The factors in the model were decided based on the assumed relevant variables that could

affect the outcome, such as age, gender and level of OAT continuity, which were available. Geography is an example of a variable we considered to include. However, due to data minimization information was not available at county level. Nor did we have access to origin/ethnicity of the patients or other sociodemographic variables such as income or living conditions.

Line 220 and Table 3: The exception is the drug combination ledipasvir/sofosbuvir, which may be prescribed for eight weeks (two collections and □□□ DDD) for cases of previously untreated genotype 1 infections. Isn´t this 2 x 28 DDD = □□□ DDD? Please check Table 3 as well for this.

Yes, 2x28DDD=56. We have updated the manuscript and Table 3 accordingly.

Line 225 – 227 and Table 1 & 3 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). Categories differ, check them and correct please.

Yes, this was inconsistent. We have updated the manuscript, Table 1 and 3 accordingly.

Results

The majority of the OAT patients were treated with buprenorphine-based OAT medication (55% in 2013, 60% in 2017). I believe it must be 61% for 2017 as Table 1 shows.

Yes, the number should be 61% in the manuscript. We have updated the manuscript.

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. Why is your denominator the number all OAT patients if HCV prevalence among OAT patients is ~55% and therefore not all OAT patients are in need for HCV treatment?

We agree with the reviewer, this is confusing and there is a need to clarify this. HCV treatment uptake, which refers to the crude treatment rate without adjusting for people actually in need of treatment, can be misinterpreted. Other papers also use treatment uptake to refer to treatment coverage. We have made the following changes throughout the manuscript and relevant tables:

- Changed HCV treatment uptake to simply HCV treatment as reflection of crude treatment rates
- HCV treatment coverage remains unchanged

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%. How do you explain the difference in adherence?

We really do not have a good explanation for this. A speculation would be that unlike genotype 3 infections (which had restrictions during the entire study period), genotype 1 infections with indication for elbasvir/grazoprevir was accessible earlier, and perhaps many of these patients who had been awaiting treatment were highly motivated to commence.

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. I believe it must be “too low“ instead of “to low“.

Correct, should be ‘too low’. We have updated the manuscript

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. See comment in the results section regarding need for treatment among OAT patients.

View our comments above in result section.

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. Are the numbers comparable to your treatment coverage or is this actually comparable to your treatment uptake? Would be helpful to discuss and clarify so the reader doesn´t have to look this up the reference.

We agree with the reviewer, this need clarification. See comments above in result section. The results from Midgard et al. study is comparable to our study as it includes OAT patients treated (nominator) adjusted for HCV prevalence (denominator) both annually and cumulatively in Norway. By using the same terminology; HCV treatment coverage and cumulative treatment coverage, readers can understand that the studies are comparable.

It would be also helpful to compare your findings with other studies and countries if possible to put them in a larger context.

We agree. View our comments above under general advices from the reviewer and changes in the manuscript in the discussion section.

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). So what is the coverage and would´nt it be good to compare and discuss with your numbers even though eligibility criteria have changed. It would be good to further discuss the expected reasons for the treatment coverage being so low among PWID.

See our comment under Background section. We agree with the reviewer. However, the report from The Norwegian Institute of Public Health only refers to number of people treated in the period from 2014 to 2018 in Norway without adjusting for prevalence, and highlights which patient groups have been mostly included so far (former PWIDs and immigrants, largely excluding current PWIDs from treatment). We have made the following changes in the manuscript:

- We have added this in the paragraph in the discussion section, while also discussing potential barriers to the low HCV treatment coverage among current PWIDs

Who pays for treatment in Norway, and are immigrants ensured and eligible for HCV treatment?

HCV treatment is publicly funded in Norway (see comments above), and immigrants are also eligible for treatment.

About two-thirds of all patients were considered adherent to DAAs according to recommendations from the prescribing specialist, across all genotypes. In Table 3 adherence by gender shows in total 828/1111 (75%) being adherent? Whats the adherence generally, isn´t 2/3 quite low? Could you compare and discuss.

We don’t consider the adherence particularly low. However, we agree with the reviewer that we should better explain that we made categorical variables with adherence (100%) and non-adherent (<100%) according to DAA drug recommendations, and compare this with other studies which report both adherence and completion of DAAs to put this in better perspective. We have made the following changes:

- Restructured and included more recent studies under the adherence paragraph in the discussion section to better compare and discuss our findings

Table 3
For gender you show the proportions for the respective columns. However, for age and OAT medication you show the proportion for the rows. Why is N=1111 instead of 1235 patients?

This is an error. We have now updated gender with proportions for the row. N = 1111 in the adherence analysis because inclusion was ceased 01.10.17 to avoid patients being evaluated non-adherent with initiation dates after this. We have updated this under Table 3.

Strengths and limitations
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). This is somewhat confusing, are drugs initiated and administered in outpatient clinics included or not and what does that mean for your treatment coverage and validity of the data?

We agree that this can be confusing. Treatment in OAT outpatient clinics may not be captured in NorPD, while HCV treatment in outpatient clinics are. We have updated this section to clarify this including possible implications.

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. Could you conclude what that means for the adherence and your results regarding the difference seen between younger and older persons.

We have included a sentence for the implications this can have.

Finally, PWIDs are a heterogenic group of individuals, and one should be careful not to generalize OAT patients to include all PWIDs. As said before, it would be good to further discuss the expected reasons for the treatment coverage being so low among PWID on OAT. Especially given the fact that your population of people on OAT is already a selection of people who have successfully entered the medical system and who receive medical care which expectedly would bias your results towards better coverage and adherence.

We agree. Treatment coverage among PWIDs on OAT should be higher for reasons mentioned above, in addition we believe there is a need for integrating HCV testing and linkage to care where patients actually are. From a clinical perspective, having seen too many patients not being able to follow standard HCV treatment with referral to infectious- or gastroenterological outpatient clinics and our hypothesis is that integrating HCV testing and treatment in OAT outpatient clinics would result in higher SVR and higher adherence to DAAs.

VERSION 2 – REVIEW

REVIEWER	Daniel Schmidt Robert Koch Institute Berlin Germany
REVIEW RETURNED	15-Jun-2020

GENERAL COMMENTS	Thank you for your detailed answers and changes you made in the manuscript in order to clarify. Most of my questions were answered. However, questions remain regarding counting patients and length of treatment. You said: Patients were counted from the year of treatment initiation with a DAA, regardless of the length and combination of other DAAs/antivirals (i.e. to prevent double counting patients with

	treatment regimens that went across a given year during the study period). What do you do in case of re-infections and re-treatment because of failure or re-infection?

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
Reviewer Name: Daniel Schmidt
Institution and Country: Robert Koch Institute Berlin Germany Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
Dear Authors,
Thank you for your detailed answers and changes you made in the manuscript in order to clarify. Most of my questions were answered. However, questions remain regarding counting patients and length of treatment.
You said: Patients were counted from the year of treatment initiation with a DAA, regardless of the length and combination of other DAAs/antivirals (i.e. to prevent double counting patients with treatment regimens that went across a given year during the study period).
What do you do in case of re-infections and re-treatment because of failure or re-infection?

We were not able to study cases of re-infection or cases of therapeutic failure, or any other causes for increased length of DAA treatment courses, such as patients awaiting liver transplantation. In some cases, patients may also have longer treatment simply because they lose their medication or being stolen by peers. Since included patients were only counted once upon initiation of DAA treatment (by first registered ATC code), this methodology allowed us to evaluate their adherence to DAAs, which was one of our objectives. In theory, a patient could therefore be re-infected and if found eligible for treatment, having a new course of DAA treatment and only been counted once.

(It should be mentioned that rate of reinfection is controversial and less understood, however it seems to be low at between 1 to 5% in the interferon era (Grady et al 2013), and 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)

We have included this as a limitation and discussed this in the discussion section.