

# Hepatitis C prevalence and cascade of care among patients in the decentralised opioid agonist therapy programme of the canton of St Gallen, Switzerland: a cross-sectional study

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## Summary

**BACKGROUND:** To eliminate chronic hepatitis C virus (HCV) infection by 2030, 90% of those infected must be diagnosed and 80% treated. In Switzerland, >40% of the estimated 32,000 infected people are still undiagnosed. In the canton of St Gallen, HCV prevalence and cascade of care have only been studied in the centralised opioid agonist therapy (OAT) setting (institutions), although about 80% of OAT patients are treated decentrally (general practitioner [GP] or pharmacy).

**AIM:** To describe HCV prevalence and cascade of care among patients in the decentralised OAT programme of the canton of St Gallen, Switzerland, and compare it to contemporaneous data from the centralised setting.

**METHODS:** For each patient receiving his/her OAT from a GP or pharmacy on 1 April 2021, the cantonal medical office sent a questionnaire to the prescribing GP. Patient characteristics, HCV antibody (Ab)/RNA screening uptake, HCV Ab/RNA prevalence and HCV treatment uptake were obtained and compared to those of patients of the Medizinisch-soziale Hilfsstelle 1 in St Gallen (centralised setting).

**RESULTS:** Of the 563 OAT patients under the care of 127 GPs, 107 patients from 41 GPs could be analysed (median age: 48 years [IQR: 40–56]; ongoing intravenous drug use: 25%; OAT provider: 66% GP, 34% pharmacy). HCV Ab screening uptake was 68% (73/107) with an HCV Ab prevalence of 68% (50/73) among those tested. Of the HCV Ab-positive patients, 84% (42/50) were HCV RNA-tested, among whom 57% (24/42) were viraemic. HCV treatment uptake was 83% (20/24), with 95% (19/20) achieving a sustained virological response. Non-uptake of HCV screening and treatment tended to be higher among patients receiving OAT at the pharmacy vs at the GP's office: 37% vs 26% ( $p = 0.245$ ) for screening and 30% vs 7% ( $p = 0.139$ ) for treatment. The proportion never HCV Ab-tested and the proportion of HCV Ab-positives never HCV RNA-tested was significantly higher in the decentralised compared to the centralised setting: 32% vs 3% ( $p < 0.001$ )

never Ab-tested and 16% vs 0% ( $p = 0.002$ ) never RNA-tested. In contrast, HCV treatment uptake (83% vs 78%), sustained virological response rate (95% vs 100%) and residual HCV RNA prevalence among the HCV Ab-positive (12% vs 14%) were comparable for both settings.

**CONCLUSION:** In the decentralised OAT setting of the canton of St Gallen, HCV Ab prevalence is high. Since HCV Ab and RNA screening uptake are markedly lower than in the centralised setting, potentially >40% of patients with chronic HCV are not diagnosed yet. HCV screening in the decentralised setting needs improvement, e.g. by increasing awareness and simplifying testing. High HCV treatment uptake and cure rates are possible in centralised and decentralised settings.

## Introduction

Chronic hepatitis C virus (HCV) infection is still one of the main causes of chronic liver disease with an estimated 57 million chronically infected people worldwide [1]. In a 2020 review, Bechler et al. assume that in Switzerland 30–50% of patients with chronic viral hepatitis are unaware of their infection [2]. Late diagnosis of chronic hepatitis increases mortality and morbidity and is a potential reservoir for new infections. As a result of this global epidemic and due to the availability of well-tolerated pangenotypic direct-acting antivirals (DAA) with cure rates of nearly 100% [3, 4], the World Health Organization (WHO) has set a global target of eliminating HCV by 2030 [5]. Worldwide, most infections were acquired during non-sterile medical procedures [6], whereas in Switzerland the most common source of infection is intravenous drug use, with about 80% of newly acquired HCV infections acquired through needle exchange among people who inject drugs [7, 8]. Switzerland is generally considered a low-prevalence country with an estimated HCV antibody (Ab) prevalence of 0.7% in the general population but up to 46% in the core groups with the highest risks [7]. At the end of 2016, it was estimated that 39,500 chronically HCV-infected people live in Switzerland [7]. This number had de-

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clined to 32,100 at the beginning of 2020 [9]. In contrast, a study from Bertisch et al., which is also based on 2020 data but primarily uses sources with effective HCV management, estimates the number to be significantly lower [10–13]. According to the Federal Office of Public Health (FOPH) reporting system and the Swiss Hepatitis C Cohort Study (SCCS), the proportion of people who inject drugs among the Swiss HCV population is about 60% [14–16].

Since 1993, an HCV Ab screening test has been recommended in Switzerland for individuals with risk factors for chronic HCV (risk-based screening approach) [17]. To date, however, routine screening is only performed consistently for blood donors and people living with human immunodeficiency virus (HIV) in the Swiss HIV Cohort study (SHCS) [18]. HCV rapid tests with capillary blood or saliva are currently not reimbursed. There is no HCV registry in Switzerland, but all new HCV diagnoses must be reported to the Federal Office of Public Health. Since 2014, a Swiss HCV strategy exists [19] and in 2019 the Federal Office of Public Health published HCV guidelines for people who use drugs (PWUD) [20]. Since 2017, DAAs are reimbursed in Switzerland irrespective of the liver fibrosis grade. Until the end of 2021, however, DAA prescribing was restricted to gastroenterologists, infectious disease specialists and addiction specialists with experience in HCV treatment [21].

Of the 22,000–27,000 opioid-dependent people in Switzerland [20], about 80% participate in an opioid agonist therapy (OAT) programme. In 60% of them, OAT is prescribed by a general practitioner (GP). In Switzerland, any practising physician can provide OAT with reimbursement via health insurance to his or her patients. The only requirement is that the patients must be registered with the cantonal authorities. Accordingly, many GPs care for only a few OAT patients [22, 23]. For OAT, the following substances are used: methadone, buprenorphine, slow-release morphine, levomethadone and other opioids [24]. The prescribing of diacetylmorphine is not part of the cantonal programme but is controlled by the Federal Office of Public Health and restricted to 23 institutions in 14 cantons [25]. In Switzerland, the regulations for dispensing drugs vary from canton to canton. In the canton of St Gallen, GPs can dispense the OAT directly to patients in their office, so-called self-dispensing, or can deposit a prescription for their patient at a local pharmacy [26].

A cross-sectional study conducted in 2009 in the three largest institutions for OAT in the canton of St Gallen (Medizinisch-soziale Hilfsstelle 1 [MSH1], Medizinisch-soziale Hilfsstelle 2 [MSH2] and the Division of Infectious Diseases of Cantonal Hospital St Gallen [KSSG]), which offer standardised routine HCV screening, showed a high HCV Ab prevalence of 75%, of whom 59% had detectable HCV RNA [27]. However, 79% of OAT patients in the canton of St Gallen are not registered with one of these large centres but are cared for in a decentralised setting by GPs and/or pharmacies and have therefore not been investigated to date [28].

HCV screening uptake in this major group of OAT patients in the canton of St Gallen has not been studied yet. We hypothesised that the HCV Ab prevalence in the group of decentrally managed OAT patients is as high as in the three major institutions where medical assessment was per-

formed before, but a substantial proportion has not been tested yet. Since it must be assumed that 75% of undiagnosed HCV Ab-positive patients are chronically infected [29], a significant number of OAT patients in the decentralised setting would still require antiviral therapy to reduce disease burden and the spread of the disease in this core group.

The aim of our study was to describe the HCV prevalence and the cascade of care among patients in the decentralised OAT programme of the canton of St Gallen and compare it to contemporaneous data from the centralised setting.

## Methods

The study was conducted by the Division of Infectious Diseases of the Cantonal Hospital St Gallen (KSSG) with support from the the canton of St Gallen Medical Office and the participating GPs in the canton of St Gallen.

### Study population

The study was carried out in the German-speaking canton of St Gallen, which has about 526,000 inhabitants [30] and is situated in the eastern part of Switzerland. It is predominantly rural, with the city St Gallen as its urban centre (81,000 inhabitants) [31].

In Switzerland, patients who receive OAT (methadone, buprenorphine, slow-release morphine, levomethadone or other opioid) on a regular basis outside of an acute illness must be registered with the cantonal substitution programme. All patients who were registered in the programme of the canton of St Gallen on 1 April 2021 and whose OAT was prescribed by a GP formed the study population.

### Data collection and analysis

For data collection, paper-based questionnaires provided by the study team were sent by the cantonal medical office by regular mail to the GPs (questionnaire: see appendix). GPs were asked to complete one questionnaire for each of their OAT patients and to return them to the study team. The questionnaires were divided into a general part for all patients (year of birth, the place of opiate provision, current substance use, whether an HCV Ab screening test had ever been performed, if yes: date of positive or negative result) and a second part for those with incomplete HCV testing information. For patients without an HCV Ab test result, the reason for non-testing was asked. For patients with a reactive result, the result and date of an HCV RNA test were sought. The GPs were encouraged to provide the corresponding laboratory results, if available. For patients with a positive HCV RNA test, additional questions on past or current HCV treatment were asked. A single reminder was sent by email to all GPs who had not responded by June 2021. All questionnaires that were returned by the end of September 2021 were included in the study.

Patient characteristics and the HCV cascade of care (HCV Ab screening uptake, HCV Ab prevalence, HCV RNA testing uptake among HCV Ab-positive patients, HCV treatment uptake, residual HCV RNA prevalence) were compared to data from 72 OAT patients of the Medizinisch-soziale Hilfsstelle 1 (MSH1) in St Gallen (a centralised heroin substitution programme) that had been col-

lected on 1 May 2021 in the framework of an Federal Office of Public Health (FOPH) project in the Swiss Association for the Medical Management in Substance Users (SAMMSU) cohort [32, 33]. The SAMMSU cohort is a nationwide cohort enrolling OAT patient in eight centres throughout Switzerland since 2014, and has been described previously [32].

In the event of a negative test result and ongoing risk for HCV, the HCV Ab/RNA screening should be repeated annually [20]. Accordingly, patients were considered to have a “current HCV screening test” if the data of the screening test provided by the GP on the questionnaire were from the year 2020 or 2021. Patients were considered to have “no current screening test” if they were at ongoing risk for acquiring HCV infection and the screening test data were from 2019 or earlier. It should be noted that the study team did not have access to the patient’s complete medical file, so the assessment is based solely on the information provided in the questionnaire. HCV treatment uptake was defined as the proportion of patients with chronic hepatitis C (ever HCV RNA-positive) ever receiving HCV treatment irrespective of treatment outcome. Patients with undetectable HCV RNA who were never treated were considered to have spontaneously cleared the virus. Residual HCV RNA prevalence among the HCV Ab-positive patients or the total population was based on still HCV RNA-positive patients, including not-yet or not-successfully-treated chronic hepatitis C patients and patients potentially reinfected after successful treatment or spontaneous clearance.

To estimate the potential number of undiagnosed chronic hepatitis C patients in our study population, we assumed that the HCV Ab prevalence and chronification rate are the same in tested and untested patients. First, we multiplied the HCV Ab prevalence among the tested patients with the total number of OAT patients in the study to obtain the potential total number of HCV Ab-positive patients. Then, we multiplied the result with the chronification rate observed among the HCV Ab-positive patients with known HCV RNA to calculate the potential total number of patients with ever chronic HCV. Finally, we subtracted from the result the number of already diagnosed chronic hepatitis C patients to yield the potential number of undiagnosed chronic hepatitis C patients. To calculate the proportion of chronic hepatitis C patients potentially not diagnosed yet, the potential number of undiagnosed chronic hepatitis C patients was divided by the potential total number of patients with ever chronic HCV.

Statistical analyses were performed with Stata Version 15.0 and OpenEpi ([www.openepi.com](http://www.openepi.com)). Categorical variables were compared using the chi-squared test. Continuous variables were analysed with the Wilcoxon rank-sum test (Mann-Whitney U test). A two-sided p value <0.05 was considered statistically significant. To calculate the 95% confidence intervals, the Wilson score interval was used.

### Screening and treatment offer for study patients not yet tested or not treated

In addition to collecting epidemiological data, we wanted our study to contribute to HCV elimination among OAT users. Hence we offered assistance in the management of

patients with incomplete screening or lack of therapy. Support included selection and implementation of suitable test methods e.g. saliva tests in patients who preferred not to have a blood draw as well as telemedical assistance regarding current therapy options for chronic HCV, which was considered to be a benefit for patients not living close to healthcare centres or refusing referral to an external specialist in infectious diseases or hepatology. At the time of the study, GPs could not prescribe DAAs due to a DAA prescriber restriction in place in Switzerland to the end of 2021 [21].

### Ethical considerations

The elaborate blinding implemented for the study, including delivery of the study questionnaires to the GPs by the cantonal medical office and return of anonymised questionnaires to the study team, as well as minimal demographic data collection (only year of birth, not sex), guaranteed complete anonymisation of the collected data, which could therefore not be traced back to a specific patient by members of the study team. Given that the data for this project were to be collected anonymously and without traceability, the local ethics committee (Ethics Committee of Eastern Switzerland, EKOS) approved the study without the requirement for individual written informed consent (BASEC Nr. Req-2020-00510).

## Results

### Setting and patient recruitment

On 1 April 2021, 563 patients managed by 127 individual GPs were registered in the OAT programme of the canton of St Gallen. Forty-eight GPs responded, corresponding to a response rate of 38%. However, seven of them did not provide any patient data because they no longer had OAT patients under their care or refused participation. Thus, data from 107 OAT patients under the care of 41 different GPs were available for analysis. Of these 41 GPs, 44% (18) provided data for only one OAT patient, 56% (23) for fewer than three and 44% (18) for three or more OAT patients; 12% (5) of the 41 GPs sent data for five or more individuals, with one GP providing data for 10 OAT patients. Original lab data were provided for 15% (16/107) of the included patients.

### Patient characteristics

*OAT patients with OAT prescribed by their GP (n = 107), decentralised setting*

For 105 of the 107 OAT patients, the year of birth was available. Their median age was 48 years (IQR: 40–56) (table 1). 66% (69/104) of the OAT patients in the decentralised OAT programme received their OAT in their GP’s office, while for 34% (35/104), the local pharmacy was the OAT provider (no data for 3 patients.). According to the prescribing GP, 61% (65) of the 107 OAT patients had not engaged in concomitant intravenous drug use for at least one year; for 7% (7), the GP knew that there had been intravenous drug use in the past 12 months, while for another 19% (20) the GP at least suspected intravenous drug use. Thus, a total of 25% (27) of the OAT patients were identified with ongoing or possibly ongoing concomitant intra-

venous drug use. In 14% (15) of cases, the GP was unable to provide any information on current use (table 1). The reasons were either that the patient was not known well enough or that the patient had never engaged in intravenous drug use.

*OAT patients with an institution as OAT prescriber and provider (n = 72), centralised setting*

Of the 72 OAT patients of the MSH1, 79% (57) were male. With a median age of 51 years (IQR: 47–55), the age distribution was not significantly different to that of the decentralised setting ( $p = 0.246$ ) (table 1).

### HCV cascade

In the HCV cascade of care, several diagnosis- and treatment-related gaps were identified.

### HCV screening uptake and prevalence in OAT patients of the decentralised cantonal OAT programme

An HCV Ab test was documented in only 68% (73) of the 107 OAT patients (table 2). Thus, almost one third (32%) were never HCV Ab-screened.

The most frequently reported reasons for not having a screening test were that it was never thought of (14), followed by the wish of the patient not to be tested (8) (table 3). Some GPs have indicated that there was never a risk of chronic HCV and some stated that transaminases were always normal or that the patient was seen only sporadically.

Among OAT patients with an HCV Ab test, the HCV Ab prevalence was 68% (50/73) (table 2). Of the OAT patients with a positive HCV Ab test, only 84% (42/50) were further evaluated with an HCV RNA test. Among the HCV

**Table 1:**

Patient characteristics

	Decentralised setting (general practitioners/pharmacies, April 2021) (n = 107)	Centralised setting (MSH1, May 2021) (n = 72)
Male, in % (n)	No data*	79.2% (57/72)
Median (IQR) age, in years	48 (40–56), Range: 28–69 (n = 105, 2 missing)	51 (47–55), Range: 21–74 (n = 72)
Age category, in % (n)	(n = 105, 2 missing)	(n = 72)
≤29 years	2.9% (3)	4.2% (3)
30–39 years	20.0% (21)	9.7% (7)
40–49 years	29.5% (31)	23.6% (17)
50–59 years	33.3% (35)	56.9% (41)
60–69 years	14.3% (15)	4.2% (3)
≥70 years	0% (0)	1.4% (1)
Place of OAT provision, in % (n)	(n = 104, 3 missing)	(n = 72)
General Practitioner's office	66.3% (69)	0% (0)
Pharmacy	33.7% (35)	0% (0)
Institution	0% (0)	100% (72)
Concomitant intravenous drug use (according to general practitioner's assessment), in % (n)	(n = 107)	
Ongoing concomitant intravenous drug use	6.5% (7)	No data**
Possible ongoing concomitant intravenous drug use	18.7% (20)	
No longer engaging in intravenous drug use (since at least 1 year)	60.8% (65)	
Not evaluable ***	14.0% (15)	

IQR: interquartile range; MSH1: Medizinisch-soziale Hilfsstelle 1.

\* To ensure anonymity without traceability back to a certain patient, only a minimum of demographic data was collected (only year of birth, not sex).

\*\* Data are derived from a questionnaire on centre level, i.e. no individual patient data regarding concomitant intravenous drug use were available.

\*\*\* Patient either not known well enough or never engaged in intravenous drug use.

**Table 2:**

Comparison of the HCV cascades in the decentralised and the centralised OAT setting.

	Decentralised setting (general practitioners /pharmacies, April 2021)	Centralised setting (MSH1, May 2021)	P
Number of patients	107	72	
HCV antibody test	68.2% (73/107)	97.2% (70/72)	<0.001
HCV antibody-positive	68.5% (50/73)	81.4% (57/70)	0.075
HCV RNA if HCV antibody-positive	84.0% (42/50)	100% (57/57)	0.002
Ever chronic HCV	48.0% (24/50)	63.2% (36/57)	0.115
Ever chronic HCV if HCV antibody-positive and HCV RNA known	57.1% (24/42)	63.2% (36/57)	0.545
Ever HCV treatment if ever chronic HCV	83.3% (20/24)	77.8% (28/36)	0.598
Cured/sustained virological response if treated	95% (19/20)*	100% (28/28)	0.232
Still HCV RNA-positive (total population)	4.7% (5/107)**	11.1% (8/72)	0.104
Still HCV RNA-positive if HCV antibody-positive and HCV RNA known	11.9% (5/42)**	14.0% (8/57)	0.756

HCV: hepatitis C virus; OAT: OAT; MSH1: Medizinisch-soziale Hilfsstelle 1 (heroin substitution programme).

\* One patient who terminated his HCV treatment prematurely did not achieve a sustained virological response.

\*\* Three patients with chronic HCV were never treated; treatment status is unknown in one still HCV RNA-positive patient; one patient who terminated his HCV treatment prematurely did not achieve a sustained virological response.

Ab-positive OAT patients with known HCV RNA, 57% (24/42) had ever had documented viraemia (table 2).

#### *HCV treatment uptake in case of chronic HCV infection and residual HCV RNA prevalence in OAT patients of the decentralised cantonal OAT programme*

Of the 24 patients who were ever diagnosed with chronic HCV, 20 had received HCV therapy in the past, corresponding to an HCV treatment uptake rate of 83% (table 2). Of those who had received therapy, 95% (19) achieved a sustained virological response; one, who discontinued therapy before completion, remained HCV RNA-positive. Three chronically HCV-infected patients had never received treatment: for one, the GP reported that treatment had been planned but not yet started; another patient refused treatment; no reason was specified for one. For another HCV RNA-positive patient, no information regarding treatment was provided. In total, five patients were still HCV RNA-positive and thus in need of treatment.

#### *Gaps in HCV screening and treatment uptake according to place of OAT provision in the decentralised setting (pharmacy versus GP's office)*

Of the 35 patients receiving their OAT at the pharmacy, 37% (13) had never been HCV Ab-tested compared to 26% (18) of the 69 patients receiving their OAT at the GP's office ( $p = 0.245$ ) (figure 1).

For 30% (3) of the 10 chronically HCV-infected patients receiving their OAT at the pharmacy, no HCV treatment was documented, compared to 7% (1) of the 14 chronically HCV-infected patients receiving their OAT at the GP's office ( $p = 0.139$ ).

#### *Screening and treatment offers for the patients not yet tested and not treated, respectively*

Sixteen (39%) individual GPs had questions about available screening tests and/or current treatment options and, depending on the preferred method of contact, were then contacted, given relevant additional information and offered further support in testing and treatment.

#### **Annual screening in patients with ongoing risk**

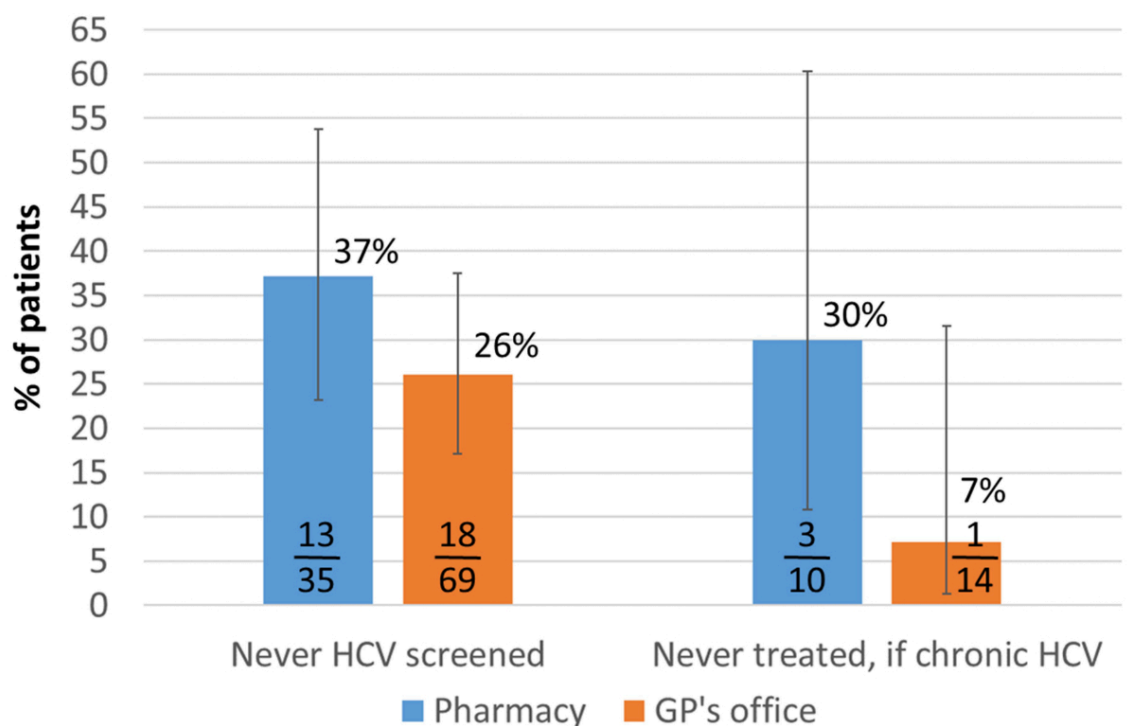
Evaluation of the questionnaires of our study revealed large differences regarding current screening status. Some patients had had a recent screening test (within one year)

**Table 3:**

Reasons for not HCV antibody screening according to the General Practitioner's assessment (n = 34 patients; multiple answers allowed).

Patient did not want to be tested	8
Cost	1
Never thought of it	14
Uncertainties regarding selection of the correct test	0
Technical problems, e.g. difficult blood sampling	0
No risk of hepatitis C	4
Other / No answer	8

**Figure 1:** Gaps in HCV antibody screening and treatment uptake according to place of OAT provision in the decentralised setting (pharmacy versus General Practitioner's office). The error bars show the lower and upper limits of the 95% confidence interval (Score [Wilson]). GP: general practitioner; HCV: hepatitis C virus.



while for other patients with ongoing risk of acquiring HCV infection, a screening test from  $\geq 10$  years ago was provided (data not shown).

### Comparison of the HCV cascades in the decentralised and the centralised OAT setting

Data at 1 April 2021 from the decentralised setting (GP as OAT prescriber and either the GP or a pharmacy as OAT provider) were compared with data at 1 May 2021 from a centralised setting (MSH1, heroin substitution programme, institution as OAT prescriber and OAT provider) (table 2, figure 2). The proportion of OAT patients never tested for HCV Ab was significantly higher in the decentralised setting (32% vs 3%,  $p < 0.001$ ). The proportion of HCV Ab-positive OAT patients not receiving further evaluation with an HCV RNA test was also significantly higher in the decentralised setting (16% vs 0%,  $p = 0.002$ ).

HCV Ab prevalence was slightly lower in the decentralised setting (68% vs 81%,  $p = 0.075$ ). In contrast, there were no significant differences regarding HCV treatment uptake among chronically HCV-infected patients (83% vs 78%,  $p = 0.598$ ), sustained virological response rate (95% vs 100%,  $p = 0.232$ ) and residual HCV RNA prevalence among HCV Ab-positive patients with known HCV RNA status (12% vs 14%,  $p = 0.756$ ).

### Potential number/proportion of undiagnosed chronic hepatitis C patients in the decentralised OAT setting

We assumed that the HCV Ab prevalence and chronification rate are the same in tested and untested patients (figure 3).

If we apply the HCV Ab prevalence of 68% (50/73) we found among the HCV Ab-screened OAT patients in the decentralised setting to all 107 OAT patients, we would expect 73 HCV Ab-positive patients overall. If we multiply this number by the chronification rate of 57% (24/42) we

found among the HCV Ab-positive patients with known HCV RNA in this setting, we obtain a total of 42 patients with chronic HCV, of whom 24 are already diagnosed and 18 not yet diagnosed (13 among the 34 never HCV Ab-screened patients and 5 among the 8 HCV Ab-positive patients never HCV RNA-tested).

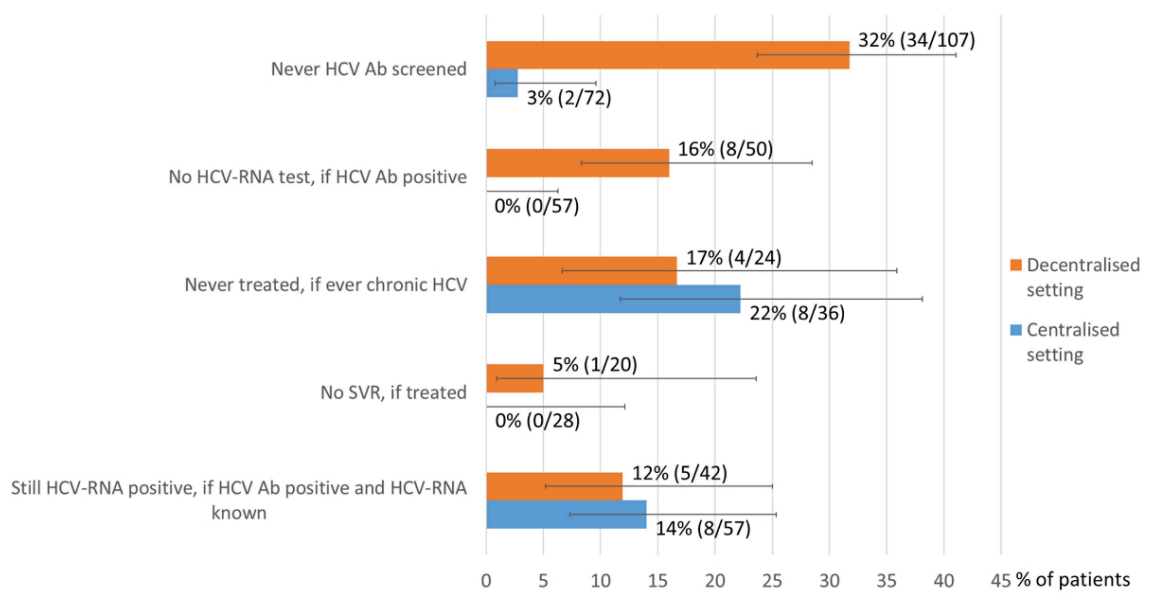
Thus, there are potentially still 18 undiagnosed chronic HCV patients among the 107 OAT patients in the decentralised setting, which would mean that 43% (18/[18+24]) of the patients with chronic HCV are not yet diagnosed in this population. Since all undiagnosed chronic HCV patients are also untreated and thus still HCV RNA-positive, the proportion of OAT patients with chronic HCV not yet treated would increase from 17% (4/24) to 52% (22/42) and the proportion of OAT patients still HCV RNA-positive from 5% (5/107) to 21% (23/107).

## Discussion

### Main results

For one third of the OAT patients in the decentralised setting of the canton of St Gallen (GP as OAT prescriber, GP or pharmacy as OAT provider) no HCV Ab test result was available, and 16% of the HCV Ab-positive OAT patients had never been HCV RNA-tested. These diagnostic gaps in the HCV cascade were significantly greater than in the centralised setting (institution as OAT prescriber and provider). Lack of awareness among GPs and patients seems to play a crucial role. In contrast, HCV treatment uptake (about 80%), sustained virological response rate ( $\geq 95\%$ ) and residual HCV RNA prevalence among the HCV Ab-positive patients (about 12%) were not significantly different between the decentralised and centralised setting.

**Figure 2:** Gaps in the HCV cascades: decentralised versus centralised OAT setting. The error bars show the lower and upper limits of the 95% confidence interval (Score [Wilson]). Ab: antibody; Centralised setting (Institution, MSH1: Medizinisch-soziale Hilfsstelle 1); Decentralised setting (general practitioner / pharmacy); HCV: hepatitis C virus; SVR: sustained virological response (HCV RNA undetectable  $\geq 12$  weeks after treatment).



One in four OAT patients in the decentralised setting had ongoing intravenous drug use, which justifies yearly HCV antibody and RNA screening, respectively.

At 68%, HCV Ab prevalence in the decentralised setting was high, but slightly lower than in the centralised setting, where high-risk patients on heroin substitution were cared for.

### Representativeness, ongoing intravenous drug use and HCV Ab prevalence

According to cantonal OAT statistics of 2021, 50% of patients received their OAT in their GP's office and 41% in the pharmacy [28]. Among the 107 OAT patients investigated in our study, only one third received their OAT in the pharmacy. We assume a response bias, because GPs dispensing in their office may know their patients better and were therefore more willing to participate in the study. According to national data, about 50% of OAT patients obtain their opiates from pharmacies and only about a quarter from doctors' offices [34].

In our study, 25% of the OAT patients had ongoing intravenous drug use, which is in good agreement with the 27.4% proportion published by Bruggmann et al. for Switzerland [35].

In 2009, the overall HCV Ab prevalence in the three large opioid-dispensing institutions in the canton of St Gallen was 75%, with 82% in MSH1 (heroin substitution programme) and 61% in MSH2 (methadone substitution programme), respectively [27]. In our study, conducted in April 2021 in the decentralised OAT setting of the canton of St Gallen (GP as OAT prescriber, GP or pharmacy as OAT provider), we found a similar HCV Ab prevalence of 68%. A contemporaneous cross-sectional study in MSH1 in May 2021 showed a slightly higher HCV Ab prevalence of 81%, which was stable compared to 2009 [32]. For comparison: according to national data, HCV Ab prevalence is only 0.7% in the general Swiss population [7], but marked-

ly higher in oral OAT programmes (26–48%) and even higher in heroin substitution programmes (60–80%) [36].

WHO data indicate an HCV Ab prevalence of 53% among people who inject drugs in Western Europe [37], which is lower than what we observed in the decentralised and centralised OAT setting of the canton of St Gallen.

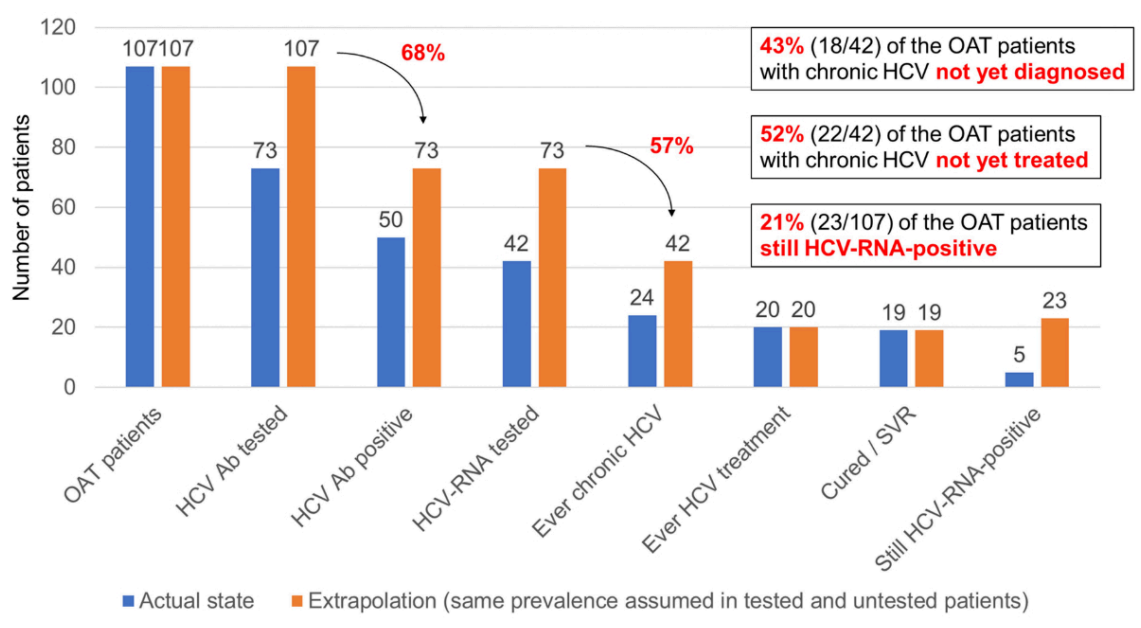
Considering data available at the end of 2020, a recent analysis by Bertisch et al. estimates that the prevalence of chronic hepatitis C in the general Swiss population is  $\leq 0.1\%$ , corresponding to 5900–9200 viraemic people [10] which is definitely lower than former estimations [7, 9]. In their paper, the number of viraemic people who inject drugs in Switzerland was estimated to be 2750–4750. Since data from decentralised OAT settings are scarce, they mainly relied on published data from centralised OAT settings, where the diagnostic work-up has been proven to be systematically better [22, 38]. This might have led to an underestimation, because among undiagnosed chronic hepatitis C patients, HCV treatment uptake is 0%, and with a spontaneous clearance rate of about 25% [29], 75% of the HCV Ab-positive patients undiagnosed so far must be assumed to be still viraemic.

### Diagnostic gaps in the HCV cascade of the decentralised OAT setting

Our data demonstrate that there is still a substantial screening gap and need for improved HCV management in this key population, which might jeopardise the WHO goal of HCV elimination by 2030 [39].

While only 3% of the OAT patients in the centralised setting of the heroin substitution programme of the canton of St Gallen have never been HCV Ab-screened, the proportion is almost one third in the decentralised OAT setting in the same canton. These data strongly support the estimation of Swiss Hepatitis that one third of all people infected with HCV have not yet been tested [40]. In the centralised OAT setting, all HCV Ab-positive patients were further

**Figure 3:** Potential number/proportion of undiagnosed chronic hepatitis C patients in the decentralised OAT setting and their effect on the treatment uptake rate and HCV RNA prevalence. Ab: antibody; HCV: hepatitis C virus; OAT: opioid agonist therapy; SVR: sustained virological response (HCV RNA undetectable  $\geq 12$  weeks after treatment)



evaluated with an HCV RNA test, which was not the case for 16% of the HCV Ab-positive patients in the decentralised OAT setting. In total, 44% (47) of the 107 OAT patients in the decentralised setting are currently not adequately diagnosed or treated (34 without an HCV Ab test, 8 HCV Ab-positive but without HCV RNA, 5 with chronic HCV without therapy). A similar observation of suboptimal HCV management in the decentralised OAT setting was described in a study in the canton of Aargau between 2013 and 2015 [22].

If we extrapolate the HCV Ab prevalence of 68% we found among the OAT patients in the decentralised setting to the 34 untested patients, it can be expected that another 23 HCV Ab-positive patients would be found among them. If we also apply the 57% chronification rate we found in this setting, this would correspond to 13 patients with chronic HCV. Among the 8 HCV Ab-positive patients without HCV RNA testing, another 5 patients with chronic HCV could be expected. Thus, there are probably still 18 cases of undiagnosed chronic HCV among the 107 OAT patients in the decentralised setting (i.e. 17 per 100). This would mean that 43% (18/[18+24]) of the patients with chronic HCV are not yet diagnosed in this population. This figure is close to the estimate of Bihl et al. by 2020 (42%) [9]. Since all undiagnosed chronic HCV patients are also untreated and thus still HCV RNA-positive, the proportion of OAT patients with chronic HCV not yet treated would increase from 17% (4/24) to 52% (22/42) and the proportion of OAT patients still HCV RNA-positive from 5% (5/107) to 21% (23/107). Thus, undiagnosed chronic HCV patients lead to an overestimation of treatment uptake and an underestimation of HCV RNA prevalence. With only 57% of chronic HCV patients diagnosed and 48% treated, the WHO goal of 90% diagnosed and 80% treated [39] is not met.

#### Annual screening in patients with ongoing risk

For patients with ongoing risk, the Federal Office of Public Health guidelines recommend an annual HCV Ab test in HCV Ab-negative patients and an annual HCV RNA test in HCV Ab-positive RNA-negative patients after spontaneous clearance or successful treatment [20]. Evaluation of the questionnaires of our study revealed large differences regarding current screening status. Some patients had had a recent screening test (within the last year) while for other patients with ongoing risk of acquiring HCV infection a screening test from  $\geq 10$  years ago was provided, suggesting suboptimal adherence to the annual screening recommendation. In this context, it should be noted that the medical history regarding ongoing intravenous drug use is often not very reliable. Even patients who were abstinent can experience recurrent drug use, a common observation for addictive disorders. Feelings of guilt or shame often prevent patients from admitting relapse and lead to socially desirable answers instead [41]. Therefore, it can be discussed whether annual screening of all OAT patients, which avoids stigmatisation, would be more appropriate for diagnosing primary HCV infections and reinfections early.

#### HCV treatment uptake

With regard to treatment uptake among patients with known chronic HCV, we did not find any significant difference between the decentralised and centralised OAT setting. In both settings, the 80% treatment uptake goal of the WHO is met [5]. Nevertheless, about 20% of the patients with known chronic HCV remain untreated. Since the introduction of oral DAAs, treatment nowadays takes only 8–12 weeks, is well tolerated and leads to a cure in  $\geq 95\%$  of cases [42, 43]. Due to a prescriber restriction in place to the end of 2021, it was necessary to refer patients to specialised centres for HCV treatment. Some of the patients refused referral either because of the distance but also because of a lack of trust in the centre specialists. Since 2022, GPs are allowed to prescribe HCV therapy themselves. In case of uncertainty regarding the correct choice of therapy, the centres can provide support, as offered for example by HepCare in Switzerland [44]. In a global systematic review and meta-analysis, Oru et al. were able to show that treatment uptake was higher in settings where HCV screening and treatment were provided at the same site as opioid substitution or in prisons compared to settings where patients diagnosed with chronic HCV needed to be referred from their primary care providers to specialised centres [45]. Pharmacist-led HCV treatment in OAT patients cared for in Scottish community pharmacies is a good example of how on-site treatment improves treatment uptake [46].

#### Strengths and limitations

The study has several limitations. First, the response rate of the GPs was only 38%. This could be due to the fact that the study was carried out during the SARS-CoV-2 pandemic. However, studies conducted with questionnaires generally have a low response rate and postal questionnaires rarely achieve a response rate above 20% [47].

Some GPs reported that some of their patients received opiates for pain management and never used drugs. Thus, the number of OAT patients provided by the canton of St Gallen might be an overestimation. Unfortunately, it was not possible to differentiate in the cantonal data between patients receiving opiates due to chronic pain and those receiving opiates due to former or ongoing intravenous drug use. It might be the case that some of the missing responses are from this patient group never considered to be at risk for HCV by the GPs. In addition, 7 of the 127 GPs reported that they no longer had any OAT patients under their care, reflecting the problem of a high fluctuation rate (i.e. many new admissions to and discharges from the OAT programme throughout the year).

Our study was insufficiently powered to detect a significant difference in HCV screening and treatment uptake between patients receiving their OAT at the pharmacy compared to those receiving it at the GP's office. Thus, studies with a larger sample size are needed to confirm our observed trend of worse HCV management in case of OAT provision in the pharmacy.

Response bias might also have influenced results. It can be assumed that the more engaged GPs responded to the survey. Accordingly, HCV screening uptake might be even worse among those GPs who did not participate in the study.



Another limitation was that the laboratory results reported by the GPs were not verifiable, since only a minority sent the requested laboratory values.

### Clinical implication of the study

The WHO aims to eliminate viral hepatitis as a public health threat by 2030 [39]. Switzerland actively participates in the global elimination strategy for chronic hepatitis [40] but currently the recommended risk-based screening for HCV in the strongly affected population groups, mainly PWUD, men who have sex with men (MSM), people using HIV pre-exposure prophylaxis (PrEP), sex workers, transgender people, migrant populations from high-prevalence countries, refugees, is not fully implemented, particularly in the decentralised OAT setting, while universal screening of the general population might not be justified in a low-prevalence setting [48, 49]. The elimination targets were included in 2019 in the “Roadmap for eliminating HIV/AIDS and Hepatitis in Switzerland” of the Federal Commission for Issues relating to Sexually Transmitted Infections [50, 51].

So far, there is no national HCV elimination programme, but in the summer session of 2020, Parliament passed a motion calling for the inclusion of viral hepatitis elimination targets in the next national HIV programme as a long overdue move [52].

Our study demonstrates the difficulty in reaching and identifying the widely distributed group of individuals with past or current intravenous drug use, as a majority is not attached to large institutions or even to any institution at all. HCV Ab testing is recommended for any PWUD and can be done during a routine check-up and, if a patient refuses blood sampling, could also be done with alternative methods such as a saliva test [53].

The main health threat of undiagnosed chronic HCV infection remains chronic liver disease with progression to liver cirrhosis and hepatocellular carcinoma. Thus, patients generally benefit from early diagnosis and treatment [54]. In Switzerland, a high-income country with a high coverage of OAT and a needle and syringe programme since the early 1990s [55, 56], the health burden of chronic HCV is mainly driven by its sequelae rather than by transmission rates [57]. The cost-effectiveness of HCV treatment has already been demonstrated, and a sustained virological response after treatment lowers liver-related mortality [58, 59]. As the median age of our study population was 48 years, there is a high potential for reducing the health and economic burden of chronic liver disease. In high-income countries like Switzerland, undiagnosed chronic HCV infections are the main barrier to controlling existing infection and allowing access to current therapy [60–62]. No or rather unspecific symptoms like fatigue, neurocognitive symptoms, joint pain, abdominal pain and others complicate a fast and targeted diagnosis and achieving the elimination goal.

On the part of the GP, the most common reason, mentioned by 14 GPs, for not performing HCV Ab screening was “never thought of it”, while the second most common reason was “patient did not want to be tested”. Thus, lack of awareness both among care providers and patients seems to be a crucial barrier [63]. Although not explicitly men-

tioned in our study, difficult venous access after long-term intravenous drug use is a well-known reason why patients refuse testing [64].

In a systematic review and meta-analysis, Cunningham et al. showed that simplified HCV screening methods like point-of-care Ab screening, dried blood spot testing, opt-out screening and reflex RNA testing, reminders in the patients’ medical charts and provider as well as patient education can effectively enhance HCV screening and treatment uptake [65].

Our study itself has contributed to HCV awareness among GPs. On several questionnaires, the GPs stated that they will perform HCV screening in patients not tested so far. Given that in Switzerland more than half of OAT patients obtain their opiates from a pharmacy [34], our data show a slightly higher HCV screening gap among patients for whom the pharmacy and not the GP is the OAT provider. Moreover offering HCV care in pharmacies has been shown to increase screening and treatment uptake [46, 66], so pharmacies should be involved in the implementation of a national screening campaign. A recent publication has shown that HCV Ab screening using rapid tests with saliva is feasible in Swiss community pharmacies [67].

The canton of St Gallen, a mainly rural area with an urban centre, is about the Swiss average in terms of population density (266.1 inhabitants/km<sup>2</sup> vs 216.8 for Switzerland) [68]. Of the 8.7 million inhabitants of Switzerland, 15,996 (0.18%) are registered in an OAT programme. In the canton of St Gallen, the proportion is similar (0.15%) [69].

However, in the canton of St Gallen, one of around half of cantons where self-dispensation is allowed, OAT is more often dispensed in the GP’s practice (50% vs 26% for the whole of Switzerland). Since our study pointed towards better screening and treatment uptake among patients receiving their OAT in the GP’s office, HCV management might be worse outside the canton of St Gallen.

### Conclusion

In the decentralised OAT setting of the canton of St Gallen (GP as OAT prescriber, GP or pharmacy as OAT provider), potentially >40% of patients with chronic HCV are not diagnosed yet. Thus, HCV care and the measures taken so far by healthcare providers and health authorities to eliminate HCV in this population are insufficient. There is a need to improve HCV screening in the decentralised setting, e.g. by increasing awareness both among patients and care providers and simplifying testing (e.g. with point-of-care tests with saliva/capillary blood, dried blood spot testing, reflex RNA testing, opt-out screening and screening in pharmacies). One in four OAT patients in the decentralised setting had ongoing intravenous drug use, which justifies annual HCV Ab and RNA screening, as recommended by national and international guidelines.

High HCV treatment uptake (80%) and cure rates (≥95% sustained virological response) with consecutive HCV RNA prevalence reduction are possible both in centralised and decentralised OAT settings.

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#### Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. The authors stated that Abbvie had no influence on the study design, the analysis and the writing of the manuscript and no other potential conflict of interest related to the content of this manuscript was disclosed.

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## Appendix

The appendix is available for download as a separate file at <https://doi.org/10.57187/s.3352>.