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Hepatitis C virus elimination in Swiss opioid agonist therapy programmes – the SAMMSU cohort

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Summary

BACKGROUND: Hepatitis C virus (HCV) infections in Switzerland are mainly related to intravenous drug use. Since 2017, all patients with chronic hepatitis C can be treated with direct-acting antivirals (DAAs) irrespective of fibrosis stage. In March 2019, the Federal Office of Public Health (FOPH) published guidelines for HCV management in people who use drugs. To achieve HCV elimination by 2030, 80% treatment uptake is necessary.

AIM: To evaluate the benefit of interferon-based and interferon-free HCV treatment in patients on opioid agonist therapy (OAT) and monitor HCV elimination, a 2-year study commissioned by the FOPH and conducted within the Swiss Association for the Medical Management in Substance Users (SAMMSU) cohort was performed.

METHODS: Since 2014, the SAMMSU cohort has recruited OAT patients from eight different centres throughout Switzerland. In addition to yearly follow up, cross-sectional data were collected at the time-points 1 May 2017, 1 May 2018 and 1 May 2019. HCV treatment uptake, adherence and success, as well as reinfection rates, the effect of early versus late treatment and the efficacy of the "treatment-as-prevention" approach were analysed.

RESULTS: Between 1 May 2017 and 1 May 2019, the number of patients enrolled into the SAMMSU cohort increased from 623 to 900: 78% were male, the median age was 45 years, 81% had ever used intravenous drugs, 13% were human immunodeficiency virus (HIV) positive and 66% were HCV antibody positive. HCV treatment up to 2012 was exclusively interferon based (maximum 21 patients/year) and since 2016 exclusively interferon free (102 patients in 2017). Treatment success increased from 57% (112/198; interferon based) to 97% (261/268; interferon free) irrespective of cirrhosis or prior non-response to interferon. Simultaneously, treatments became shorter and better tolerated in the interferon-free era, resulting in fewer preterm stops (17% vs 1%) and adherence problems (9% vs 2%). Between 2015 and 2018, the proportion of patients with no/mild fibrosis (F0/F1) at first HCV treatment increased from 0% to 61%. Earlier treatment reduced the duration of infectiousness. Between 1 May 2017 and 1 May 2019, the proportion of chronic hepatitis C patients ever treated increased from 62% (198/321) to 80% (391/490). In parallel, the HCV-RNA prevalence among HCV antibody-positive patients declined from 36% (139/385) to 19% (113/593). The reinfection rate after successful treatment was 2.7/100 person-years. The number of HCV first diagnoses per year decreased from >20 up to 2015 to <10 in 2017 and 2018.

CONCLUSION: With nearly 100% DAA treatment success and a low reinfection rate, treatment uptake directly translates into a reduction of HCV-RNA prevalence. Eighty percent treatment uptake is feasible in OAT patients, and adherence and treatment success are not worse than in other populations. Duration of infectiousness and thus HCV transmission can be reduced by early detection and treatment of chronic hepatitis C.

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Introduction

Hepatitis C is a blood-borne viral infection, which is highly prevalent among persons who inject drugs (PWID) as a result of the common use of injection material (needle, syringe, filter, spoon, water) [1]. Hepatitis C virus (HCV) transmission also occurs if snorting straws for intranasal drug use are shared [2, 3]. Although about 25% of HCV infected people spontaneously clear the virus, the remaining 75% develop chronic infection [4]. Presenting mostly with unspecific symptoms slowly appearing over years, such as fatigue, joint pain and neurocognitive disorders, hepatitis

C may remain undetected for years and become a "silent killer" [5]. About 20% of chronically infected individuals develop liver cirrhosis after 20 years [6], with an annual risk of hepatocellular carcinoma of 1–5% and of hepatic decompensation of 3–6%. After an episode of decompensation, the risk of death in the following year is 15–20% [7]. In addition, hepatitis C is associated with an elevated non-liver-related mortality [8].

Globally, there are 15.6 million PWID, with 52.3% being HCV antibody positive [9]. The HCV antibody prevalence in Switzerland is 0.7% in the general population [10], 26-48% in oral opioid agonist therapy (OAT) programmes and 60–80% in heroin substitution programmes [11]. Of the 22,000–27,000 opioid addicts in Switzerland [12], about 80% are cared for in OAT programmes (oral OAT: 18,000; heroin: 1600) [13]. In about 60%, OAT is prescribed by a general practitioner (GP) [13]. About 27% of Swiss OAT patients have ongoing intravenous drug use (IDU) [14].

In view of the highly effective and well tolerated pangenotypic interferon-free direct-acting antiviral (DAA) treatments available [15–18], access to diagnosis, care and treatment has become the main challenge in chronic hepatitis C management. Early diagnosis and successful treatment of chronic hepatitis C prevents HCV-related complications and extrahepatic manifestations (individual benefit), as well as further transmission ("Treatment as Prevention; TasP)" [19] (social benefit).

Both the World Health Organization (WHO) and the Swiss Hepatitis Strategy aim at HCV elimination by the year 2030 [20, 21]. In order to reach this goal, 80% treatment uptake is necessary [20]. The "National Addiction Strategy 2017–2024" aims to reduce premature deaths due to addiction [22]. This includes prevention and treatment of infectious diseases such as hepatitis C. Since May 2017, PWID and since October 2017, all patients with chronic hepatitis C in Switzerland can be treated with DAAs irrespective of liver fibrosis stage [23, 24]. Before, reimbursement restrictions withheld DAA treatment from two thirds of patients with chronic hepatitis C, i.e., those with no or only mild fibrosis (F0/F1) [25]. Due to the high costs (CHF 30,706.20 for 8 weeks of Maviret® [glecaprevir/pibrentasvir] and CHF 30,952.20 for 12 weeks of Epclusa® [sofosbuvir/velpatasvir] http://www.spezialitätenliste.ch/ShowPreparations.aspx), only infectious disease specialists, gastroenterologists and addiction specialists with experience in HCV treatment (http://www.bag.admin.ch/slref) are allowed to prescribe DAAs in Switzerland. In March 2019, the Federal Office of Public Health (FOPH) published guidelines for HCV management in drug users [26].

Since 2014, the Swiss Association for the Medical Management in Substance Users (SAMMSU)-cohort (http://www.sammsu.ch/cohort-database.html) has recruited OAT patients from eight different centres throughout Switzerland [27].

To evaluate the benefit of interferon-based and interferon-free HCV treatment in OAT patients and monitor HCV elimination, a 2-year study commissioned by the Swiss FOPH and conducted within the SAMMSU cohort was performed between 2017 and 2019. HCV treatment uptake, adherence and success, as well as reinfection rates, the effect of early versus late treatment and the efficacy of the "treatment-as-prevention" approach were analysed.

Materials and methods

Ethical considerations

The SAMMSU cohort was approved by the ethics committees of all participating centres (leading ethical committee: St Gallen, EKSG 13/144). All participants gave written informed consent. Data are stored and analysed in an anonymised way.

Patient recruitment and data collection

SAMMSU cohort database

The SAMMSU cohort is an open cohort, which has, since 2014, recruited current or former drug users >18 years old in all parts of Switzerland. Participants must have been in an OAT programme for at least one day. There are no exclusion criteria. During routine clinical care or on HCV action days, patients of the eight currently participating centres (Aarau, Basel, Bern, Geneva, Lausanne, Lugano, St Gallen and Zurich) are contacted by study nurses/physicians. Both centralised and decentralised OAT settings are represented, i.e., specialised OAT programmes with integrated somatic care (led by a psychiatrist, somatic physician on-site) as well as patients receiving their OAT via the general practitioner (GP).

In contrast to the Swiss Hepatitis C Cohort Study (SCCS) [28], which enrols only HCV-positive patients, and the Swiss HIV Cohort Study (SHCS) [29], which enrols only human immunodeficiency virus (HIV)-positive patients, the SAMMSU cohort also recruits both HCV- and HIV-negative individuals.

At enrolment and thereafter at yearly intervals, study nurses/physicians of each centre enter sociodemographic and medical data into an electronic questionnaire, including information about drug use / risk behaviour, comorbidities, medication, HCV treatment, diagnostic tests (e.g., liver biopsy, Fibroscan®, abdominal sonography), vaccinations and laboratory values. Every study nurse/physician has a personal password-protected account and can only edit data of her/his own centre. At first data entry, every patient gets a unique ID consisting of two letters for the centre and a five-digit consecutive number. Every centre maintains its own code list. The web-based central database was established with SecuTrial® and is maintained by the Clinical Trial Unit of the University Basel. For this study, a database extract from 2 September 2019 was used.

Cross-sectional survey at the patient level

To evaluate the effect of the abrogation of the DAA reimbursement restrictions for PWID on HCV treatment uptake, two cross-sectional surveys at the patient level were conducted one and two years after the 1 May 2017. This also allowed three point-prevalence measurements regarding HCV antibody and HCV-RNA positivity (1 May 2017, 1 May 2018, 1 May 2019).

Cross-sectional survey at the centre level

To evaluate if patients enrolled into the SAMMSU cohort are representative for the Swiss population of OAT patients

and to describe the OAT settings on the 1 May 2017, 1 May 2018 and 1 May 2019, the SAMMSU centres received an additional centre questionnaire in May 2018 and May 2019.

The questionnaires for the cross-sectional surveys at patient and centre level were collectively developed by the study physicians and are presented in appendices 2 and 3, respectively.

Definitions

New HCV infection: first detection of HCV antibodies (first diagnosis), irrespective of the time-point of infection.

HCV reinfection: first detection of HCV-RNA after spontaneous clearance or successful treatment.

Spontaneous clearance/elimination: HCV-RNA becomes persistently undetectable without treatment.

Chronic hepatitis C: HCV-RNA persistence 6 months after new infection or reinfection.

HCV treatment uptake: proportion of patients with chronic hepatitis C ever treated.

Treatment success = sustained virological response (SVR): 12 or 24 weeks after HCV treatment no HCV-RNA detectable.

Preterm treatment stop: treatment stop before the intended treatment duration has been completed.

Adherence: assessment by the treating physician (SAMMSU cohort: adherence problems during treatment: yes/no; cross-sectional survey at the patient level: excellent/moderate/bad).

Adherence-supporting measures: directly observed therapy (DOT) ≥5×/week, weekly dispensing of the HCV medication in a pill box.

Duration of infectiousness: first intravenous drug use (IDU) as potential time-point of infection until first HCV treatment.

Liver fibrosis stage according to Fibroscan®: F0/F1 (no/mild fibrosis): ≤7.0 kPa; F2 (significant fibrosis): >7.0 kPa and ≤9.5 kPa; F3 (severe fibrosis): >9.5 kPa and ≤12.5 kPa; F4 (cirrhosis): >12.5 kPa [30, 31]

Statistical analysis

Categorical variables were compared with the chi-square and the Fisher's exact tests. Continuous variables were analysed with the Wilcoxon rank-sum test (unpaired data). A two-sided p-value <0.05 was considered significant.

Time-to-event analyses: For the primary HCV infection rate, the observation time was from the first IDU to HCV first diagnosis (first positive HCV antibody test) or the last negative HCV antibody test for patients remaining HCV antibody negative. For the HCV re-infection rate after successful treatment, the observation time was from the end of treatment until the patients became HCV RNA positive again or the last negative HCV RNA for patients remaining HCV RNA negative.

Test-frequency analyses: Observation time was one year prior to registration until the last follow up.

All statistical analyses were performed with Stata Version 12.0.

Results

Patient characteristics

On 1 May 2017, 1 May 2018 and 1 May 2019, 623, 757 and 900 patients, respectively, were enrolled in the SAMMSU cohort. This is a yearly increase of 22% (134 patients) and 19% (143 patients). There was no significant change in the baseline characteristics at registration over time. Of the 900 patients registered by 1 May 2019, 87% were male, the median age was 45 years at registration and 20 years at first IDU, 81% reported ever using intravenous drugs and 89% ever using intranasal drugs, 13% were HIV positive (99% ever HIV treatment) and 66% HCV antibody positive. Of the 457 patients with chronic hepatitis C, 59% had already been treated at least once at registration (table 1).

Of the 900 SAMMSU patients, 80.6% (725) were from the German-speaking part of Switzerland (Aarau, Basel, Bern, St Gallen, Zurich), 6.4% (58) from the French-speaking part (Geneva, Lausanne) and 13.0% (117) from the Italian-speaking part (Lugano). At 40.8%, the biggest proportion of patients came from the SAMMSU centre Aarau, followed by Zurich (18.4%), Lugano (13.0%) and Basel (11.9%). Centre-specific differences in the baseline characteristics are described in table 1.

Centre/setting characteristics and representativeness

In Aarau, 58% (367/631) of all OAT patients in the canton and 59% (75/128) of the heroin substitution programme in Brugg were enrolled into SAMMSU. In Basel, 66% (41/62) of the OAT patients of a private practice, 10% (19/199) of the ADS (Ambulanter Dienst Sucht) and 15% (22/150) of the heroin substitution programme Janus were recruited. In Bern, 12% (22/190) of the patients of the heroin substitution programme KODA (Kontrollierte Drogenabgabe) were enrolled. In Lausanne, 6% (24/415) of the POLADD (Policlinique d'Addictologie, Département de Psychiatrie du CHUV) patients and in Lugano, 13% (117/900) of the OAT patients of the canton Ticino (no heroin substitution) were recruited. In St Gallen, 48% (12/25) of the patients of the methadone substitution programme of the Infectious Diseases Outpatient Clinic of the Cantonal Hospital St Gallen, 32% (23/72) of the MSH1 (heroin substitution programme) and 4% (3/102) of the MSH2 (methadone substitution programme) were enrolled. In Zurich, 18% (159/881) of the Arud patients in Zurich take part in SAMMSU, but none of the 98 Arud patients in Horgen.

Heroin substitution programmes offer twice daily substitution 7 days/week, whereas institutions without heroin substitution are normally open only 5 days/week. The number of substitution patients ranges from 10 to 881 and the yearly fluctuation rate is 12–37%. HCV and HIV antibody rapid tests are routinely used in 5/13 institutions. So far, capillary HCV-RNA measurement on dried blood spots is established only in POLADD, Lausanne. Only 4/13 institutions offer sonography on site, whereas Fibroscan® is available in 6 institutions. In four institutions, HCV action days take place several times a year, where HCV/HIV rapid tests, capillary HCV RNA quantification (GeneXpert®), Fibroscan®, sometimes sonography, venous blood draw for hepatitis A and hepatitis B virus (HAV/HBV) serology and HAV/HBV vaccination are offered on site.

On 1 May 2019, on-site prescription of DAA treatments was possible in only 7/13 institutions.

In the SAMMSU cohort, the proportion of patients with unknown HCV serostatus is <1% (table 2). However, in many institutions from which the SAMMSU patients were recruited, it was 20–25% on 1 May 2018 and decreased to 10–15% on 1 May 2019. The proportion of HCV antibody-positive patients with unknown HCV-RNA status was ≤10% in most institutions, but <5% in SAMMSU. The proportion of HCV antibody-positive patients with known HCV-RNA who had ever had chronic hepatitis C was 60–80% in the source institutions, but 80% in SAMMSU. Between 1 May 2017 and 1 May 2019, HCV treatment uptake has increased, but 80% or even 90% had not yet been achieved in all institutions.

Differences between HCV antibody-positive and -negative persons

Patients already HCV antibody positive at registration were about 8 years older (47 vs 39 years), their first IDU was longer ago (25 vs 13 years) and the proportion who had ever used intravenous drugs was almost twice as high (96% vs 52%) (table 3). Besides, the proportions with ongoing IDU (27% vs 17%) and ever using cocaine and benzodiazepines were higher in HCV antibody-positive patients. HIV positivity (18% vs 2%) and ever having a syringe abscess (17% vs 3%) were more frequent. Overall, HCV antibody-positive patients were longer exposed, had more frequent and more risky injections and had ben-

Table 1: Baseline characteristics at registration (Status: 1 May 2019).

	Total (n = 900)	Aarau (n = 367)	Basel (n = 107)	Bern (n = 29)	Geneva (n = 20)	Lausanne (n = 38)	Lugano (n = 117)	St Gallen (n = 56)	Zurich (n = 166)
Male	77.8% (700/900)	77.4% (284/367)	72.9% (78/107)	62.1% (18/29)	80% (10/20)	78.9% (30/38)	79.5% (93/117)	76.8% (43/56)	83.1% (138/166)
Median age (y) at reg. (IQR)	45.0 (37.1–50.3)	38.7 (31.4–45.8)	49.5 (43.6–54.2)	46.3 (41.4–49.7)	47 (39.3–51.1)	47.7 (41.5–50.2)	48 (43.7–51.8)	49 (44.6–53.5)	46.7 (41.5–51.7)
Ever IDU	80.9% (715/884)	75.4% (276/366)	96.9% (94/97)	85.7% (24/28)	80% (16/20)	89.5% (34/38)	87.2% (102/117)	92.3% (48/52)	72.9% (121/166)
Median age (y) at first IDU (IQR)	20 (18–25) (n = 696)	20 (17–25) (n = 264)	21 (18–25) (n = 87)	24 (20–31) (n = 24)	21.5 (19.5–26.5) (n = 16)	22 (18–28) (n = 34)	20 (17–23) (n = 102)	21 (18–30) (n = 48)	20 (18–26) (n = 121)
Median time (y) between first IDU and reg. (IQR)	23.5 (13–30) (n = 696)	17 (8–26) (n = 264)	28 (20–33) (n = 87)	19 (12–27.5) (n = 24)	25.5 (15–33) (n = 16)	23.5 (15–26) (n = 34)	28 (21–34) (n = 102)	24.5 (19–30) (n = 48)	25 (19–29) (n = 121)
Ever intranasal drug use	89.5% (784/876)	89.0% (325/365)	97.8% (89/91)	66.7% (18/27)	85% (17/20)	71.1% (27/38)	94.9% (111/117)	94.2% (49/52)	89.2% (148/166)
HIV positive	12.8% (115/897)	5.5% (20/366)	10.3% (11/107)	17.9% (5/28)	10% (2/20)	36.8% (14/38)	4.3% (5/117)	69.1% (38/55)	12.0% (20/166)
Ever HIV-treatment*	99.1% (113/114)	100% (20/20)	100% (11/11)	100% (5/5)	100% (2/2)	100% (14/14)	75% (3/4)	100% (38/38)	100% (20/20)
HCV antibody positive	66.1% (593/897)	48.4% (177/366)	86.9% (93/107)	89.3% (25/28)	60% (12/20)	86.8% (33/38)	83.8% (98/117)	87.3% (48/55)	64.5% (107/166)
Ever CHC	87.2% (457/524)	78.5% (106/135)	89.2% (83/93)	87.5% (21/24)	91.7% (11/12)	100% (33/33)	85.6% (83/97)	84.4% (38/45)	96.5% (82/85)
Ever HCV treatment if ever CHC	58.9% (269/457)	44.3% (47/106)	71.1% (59/83)	33.3% (7/21)	54.5% (6/11)	45.5% (15/33)	72.3% (60/83)	44.7% (17/38)	70.7% (58/82)

y = years; reg. = registration; IQR = interquartile range; IDU = intravenous drug use; HIV = human immunodeficiency virus; HCV = hepatitis C virus; CHC = chronic hepatitis C; HAART = highly active antiretroviral therapy * For 98 of the 115 HIV patients on 1 May 2019, the year of the first HIV treatment was available. In 13% (13/98) it was before 1996, i.e., in the pre-HAART era, and in 87% it was thereafter. At the registration visit, 96% (110/115) were currently under HIV treatment.

Table 2: HCV cascade on 1 May 2017, 1 May 2018 and 1 May 2019 (cohort data).

	1 May 2017 (n = 623)	1 May 2018 (n = 757)	1 May 2019 (n = 900)
HCV antibody status known	99.7% (621/623)	99.6% (754/757)	99.7% (897/900)
HCV antibody positive	66.5% (413/621)	69.1% (521/754)	68.6% (615/897)
HCV-RNA known if HCV antibody positive	93.2% (385/413)	95.6% (498/521)	96.4% (593/615)
Currently HCV-RNA positive if HCV antibody positive and HCV-RNA known	36.1% (139/385)	24.3% (121/498)	19.1% (113/593)
Ever CHC	77.7% (321/413)	80.4% (419/521)	79.7% (490/615)
Ever HCV treatment if ever CHC	61.7% (198/321)	74.5% (312/419)	79.8% (391/490)
Ever SVR if ever HCV treatment	91.9% (182/198)	92.6% (289/312)	89.8% (351/391)
Ever SVR or last HCV-RNA neg. if ever HCV treatment*	93.9% (186/198)	95.8% (299/312)	95.7% (374/391)

HCV = hepatitis C virus; CHC = chronic hepatitis C; SVR = sustained virological response * For some patients receiving HCV treatment, no check for SVR has taken place (lost to follow-up between end of treatment and SVR check) and for many of the only recently treated patients, the time for SVR check has not been reached yet. In these cases, the last available HCV-RNA measurement was used as a surrogate for HCV treatment success, even if it was the first HCV-RNA measurement under treatment or the check at the end of treatment.

efitted less from harm reduction (OAT, needle syringe programmes).

HCV treatment uptake and success

By 2 September 2019, 505 HCV treatments were documented in the SAMMSU cohort (405 first, 78 second, 17 third, 4 fourth and 1 fifth HCV treatments). Thirty-nine percent (198) were interferon-based and 61% (307) interferon-free (16 still ongoing). Up to 2012, HCV was treated exclusively with interferon-based treatments (maximum 21 patients/year) and since 2016 with exclusively interferon-free treatment (102 patients in 2017; fig. 1).

Treatment success increased 1.7-fold (95% CI 1.5–2.0) from 56.6% (112/198; 95% CI 49.6–63.3%; interferon-based) to 97.4% (261/268; 95% CI 94.7–98.7%; interferon-free; p <0.001; fig. 2). Prior non-response to interferon (onetime or repeated) reduced the SVR rate for another interferon-based, but not for interferon-free, treatment (fig. 2).

For 60% (242) of the 405 first HCV treatments, a Fibroscan® result was available before treatment (20 [8.3%] interferon-based and 222 [91.7%] interferon-free treatments). Median time between Fibroscan® and start of the first HCV treatment was 90 days (IQR 42–231). With interferon-free treatment, the SVR rate was ≥97% irrespective of fibrosis stage: F0/F1 97.6% (81/83), F2 100% (33/33), F3 97.1% (33/34), F4 97.5% (39/40).

By 2 September 2019, there were 373 HCV treatments with documented SVR in 362 patients. In 2017, when DAA reimbursement restrictions were abrogated in Switzerland, 87 SVRs were achieved, as many as in the entire interferon era (86 SVRs between 1987 and 2012). The proportion with "SVR after first treatment" among all SVRs per year increased from 68.8% (33/48) in 2015 to 88.9% (48/54) in 2018 (p = 0.012).

Adherence

Compared with the interferon era, the proportion with preterm treatment stop decreased in the interferon-free era, from 17.2% (34/198, 95% CI 12.6–23.0%) to 0.7% (2/307, 95% CI 0.2–2.3%; p <0.001) and the proportion with adherence problems from 8.6% (17/198, 95% CI 5.4–13.3%) to 2.3% (7/307, 95% CI 1.1–4.6%; p = 0.001; fig. 3).

From 2016 onwards (interferon-free era), there were 201 HCV treatments in the cross-sectional data from seven centres. In 97.9% (183/187) adherence was classified as "excellent", in 1.6% (3) as "moderate" and in 0.5% (1) as "bad". Overall, the SVR rate was 97.7% (171/175).

Table 3: Baseline characteristics of HCV antibody-positive and -negative patients (cohort data).

	HCV antibody positive at reg. (n = 613)	HCV antibody negative at reg. (n = 326)	p-value	OR (95% CI)
Male	77.2% (473/613)	79.4% (259/326)	0.421	0.87 (0.63–1.21)
Median age (y) at registration (IQR)	46.9 (41.4–51.5)	38.5 (31–47.2)	<0.001	
Ever IDU	95.7% (575/601)	51.9% (167/322)	<0.001	20.53 (13.09–32.18)
Ongoing IDU if ever IDU	27.5% (158/575)	16.8% (28/167)	0.005	1.88 (1.21–2.94)
Median age (y) at first IDU (IQR)	20 (17–25) (n = 559)	22 (19–27) (n = 160)	<0.001	
Median time (y) between first IDU and registration (IQR)	25 (17–30) (n = 559)	13 (4.5–23) (n = 160)	<0.001	
Ever intranasal drug use	91.2% (541/593)	87.0% (280/322)	0.042	1.56 (1.01–2.40)
Ongoing intranasal drug use if ever intranasal drug use	29.9% (162/541)	28.2% (79/280)	0.606	1.09 (0.79–1.50)
HIV positive	18.1% (111/613)	1.8% (6/326)	<0.001	11.79 (5.13–27.13)
Ever heroin	99.0% (596/602)	96.3% (312/324)	0.004	3.82 (1.42–10.28)
Ever cocaine	95.0% (569/599)	89.1% (287/322)	0.001	2.31 (1.39–3.84)
Ever benzodiazepine	72.5% (430/593)	61.7% (195/316)	0.001	1.64 (1.23–2.19)
Ever cannabis	92.8% (555/598)	89.4% (286/320)	0.074	1.52 (0.96–2.46)
Ever syringe abscess	18.6% (95/510)	3.4% (7/204)	<0.001	6.44 (2.94–14.1)
Year of first IDU:	(n = 559)	(n = 160)		
1970–1979	7.3% (41)	0.6% (1)	0.129	4.28 (0.55–33.17)
1980–1989	36.0% (201)	13.1% (21)		1.0 (ref.)
1990–1999	32.6% (182)	26.3% (42)	0.005	0.45 (0.26–0.80)
2000–2009	18.1% (101)	28.8% (46)	<0.001	0.23 (0.13–0.42)
2010–2019	6.1% (34)	31.3% (50)	<0.001	0.07 (0.03–0.15)

HCV = hepatitis C virus, reg. = registration, OR = odds ratio, CI = confidence interval, y = years, IQR = interquartile range, IDU = intravenous drug use, HIV = human immunodeficiency virus, ref. = reference

All three patients with only moderate adherence achieved SVR. In less than half of the treatments (45.1%, 78/173), DOT was used to support adherence. One centre (Lugano) used virtually no adherence-supporting measures (DOT and weekly pill box in only 2.7%, 1/37) without a negative effect on adherence (excellent in 100%, 35/35) and treatment success (97.1%, 34/35 SVR).

Time-point of treatment and treatment success

Although cirrhotic patients can be treated with success rates similar to those of patients with earlier stages of fibrosis with interferon-free treatments (see above), the time-point of treatment matters.

In the past, diagnosis and treatment of hepatitis C were delayed (fig. 4). The median time between the first IDU (surrogate for the time of infection) and the first diagnosis of HCV was 9 years (IQR 4–18; n = 539), and the median time between the first IDU and the first HCV treatment 22 years (IQR 13–29; n = 378) – the time in which the patients were infectious and could develop cirrhosis.

For 226 patients, the year of first IDU was known and a Fibroscan® result available prior to the first HCV treatment (HCV therapy start years 2007–2019). The median duration of infectiousness in patients already cirrhotic at the start of their first HCV treatment was 30 years (IQR 23–33; n = 51). In patients treated at earlier liver fibrosis stages (F0–F3), the median duration of infectiousness was 25 years (IQR 16–31; n = 175; p = 0.020; fig. 5).

Between 2015 and 2018, the proportion of patients already cirrhotic at first HCV treatment declined from 50% (15/30)

Figure 1: Number of interferon-based and interferon-free hepatitis C virus treatments per calendar year. IFN = interferon (status as of 2 September 2019, overall 942 SAMMSU patients).

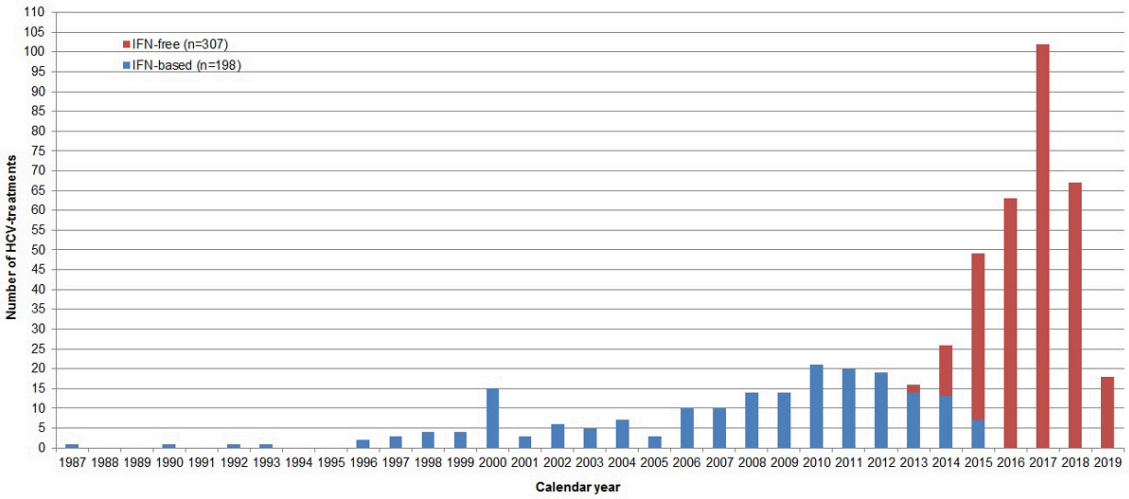


Figure 2: Sustained virological response (SVR) rate after interferon-based and interferon-free HCV treatment, if outcome known (overall and according to the number of prior HCV treatments). HCV = hepatitis C virus; IFN = interferon. * Once in combination with telaprevir and once in combination with sofosbuvir (status as of 2 September 2019, overall 942 SAMMSU patients).

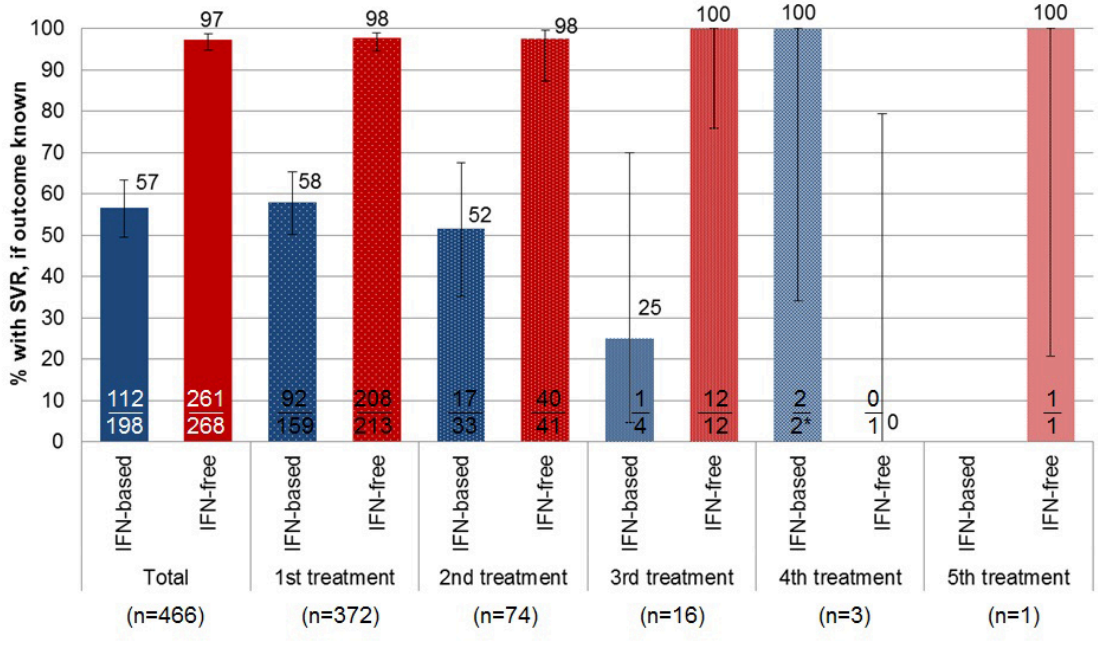


Figure 3: Proportion of interferon-based and interferon-free HCV treatments with pre-term stop and adherence problems, respectively. HCV = hepatitis C virus; IFN = interferon (status as of 2 September 2019, overall 942 SAMMSU patients).

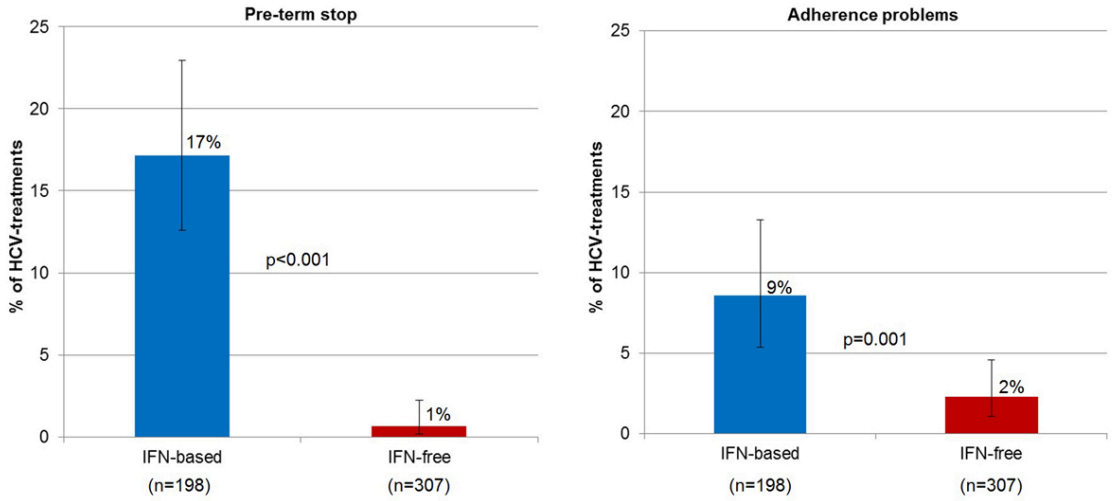


Figure 4: Number of patients with first IDU, first diagnosis of HCV, first time positive for HCV-RNA and first HCV treatment per calendar year. IDU = intravenous drug use; HCV = hepatitis C virus. Data at registration and follow-up (status as of 2 September 2019, overall 942 SAMMSU patients).

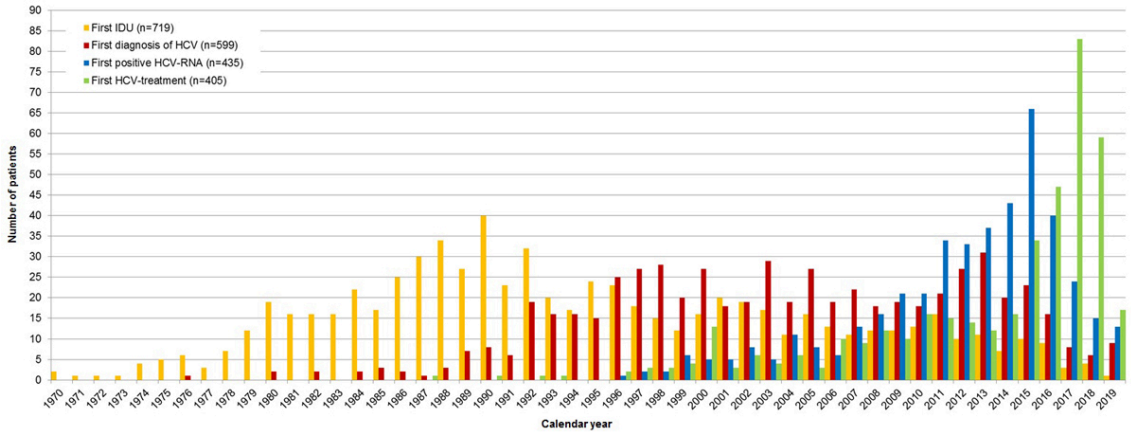
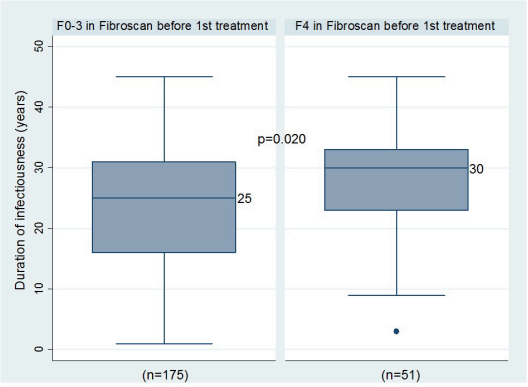


Figure 5: Duration of infectiousness according to fibrosis stage at first HCV treatment. Patients with Fibroscan® measurement before the first HCV treatment and year of first intravenous drug use known (n = 226, start year of first HCV treatment 2007–2019) (status as of 2 September 2019, overall 942 SAMMSU patients). HCV = hepatitis C virus. Liver fibrosis stage according to Fibroscan®: F0/F1 (no/mild fibrosis) ≤7.0 kPa; F2 (significant fibrosis) >7.0 kPa and ≤9.5 kPa; F3 (severe fibrosis) >9.5 kPa and ≤12.5 kPa; F4 (cirrhosis) >12.5 kPa.



to 13% (7/54; p <0.001) and the proportion of patients with no or mild fibrosis at first HCV treatment increased from 0% (0/30) to 61% (33/54; p <0.001; fig. 6).

Treatment as prevention

At enrolment into the SAMMSU cohort, 95.7% (112/117) of the HIV patients were under HIV treatment, with 94.0% (109/116) having undetectable HIV-RNA (<50 cop/ml, i.e., untransmittable). At the reference dates 1 May 2017, 1 May 2018 and 1 May 2019, the HIV-RNA prevalence (≥50 cop/ml) among the HIV positives was 6.7% (6/90), 5.7% (6/105) and 6.1% (7/114, 95% CI 3.0–12.1%), respectively. Among all SAMMSU cohort patients (i.e., all HIV positives and negatives), the HIV-RNA prevalence was 1.0% (6/623), 0.8% (6/757) and 0.8% (7/900, 95% CI 0.4–1.6%) on the respective reference dates. Until 2002/2003, up to eight patients yearly were newly diagnosed with HIV, whereas in the eight years after 2011, there was only one HIV first diagnosis, in 2015 (fig. 7).

Between 1 May 2017 and 1 May 2019, HCV treatment uptake increased from 61.7% (198/321) to 79.8% (391/490; table 2). In parallel, the HCV-RNA prevalence de-

creased from 36.1% (139/385) to 19.1% (113/593; 95% CI 16.1–22.4%) among the HCV antibody-positive patients and from 22.3% (139/623) to 12.6% (113/900, 95% CI 10.6–14.9%) among all SAMMSU cohort patients (i.e., all HCV positives and negatives).

This development can also be seen in the cross-sectional data of seven SAMMSU centres (fig. 8): the higher the increase in treatment uptake the higher the decrease in HCV-RNA prevalence among the HCV antibody-positive patients. On the 1 May 2019, some centres had already achieved >90% treatment uptake, which was associated with a reduction of HCV-RNA prevalence to <10%. On the 1 May 2019, the SAMMSU centre Aarau, with a high proportion of patients cared for in a decentralised setting, had a markedly lower rate (79.4%, 104/131; 95% CI 71.7–85.4%) than the other five centres taken together (93.1%, 241/259; 95% CI 89.3–95.6%; p <0.001; supplementary table S1 in appendix 1.

Reinfection risk

To calculate the rate of HCV first diagnosis, the year of first IDU was available for 663 patients (total observation time 8801.8 years, median observation time 11.8 years, IQR 5.5–20.1, range 0.4–45.9). Between 1970 and 2019, there were 518 HCV first diagnoses, resulting in an HCV first diagnosis rate of 5.89 per 100 person-years (95% CI 5.40–6.41) and a cumulative HCV infection rate of 78.1% (95% CI 74.8–81.1%).

To calculate the reinfection rate after successful treatment, information on 280 patients with a total observation time of 739.4 years was available (median observation time 1.1 years, IQR 0.4–3.2, range 0.003–29.1). From 1988 to

Figure 6: Distribution of fibrosis stage at first HCV treatment according to calendar year. Two hundred and forty-two first HCV treatments with Fibroscan® measurement before treatment (start year of first HCV treatment 2007–2019) (status as of 2 September 2019, overall 942 SAMMSU patients). Liver fibrosis stage according to Fibroscan®: F0/F1 (no/mild fibrosis) ≤7.0 kPa; F2 (significant fibrosis) >7.0 kPa and ≤9.5 kPa; F3 (severe fibrosis) >9.5 kPa and ≤12.5 kPa; F4 (cirrhosis) >12.5 kPa

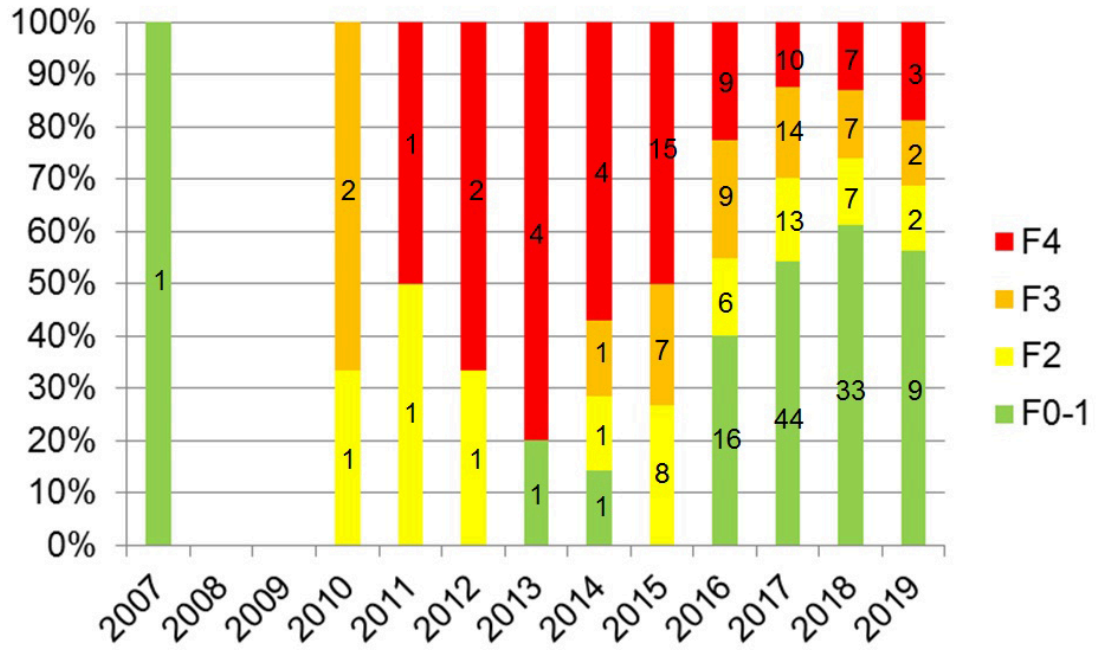
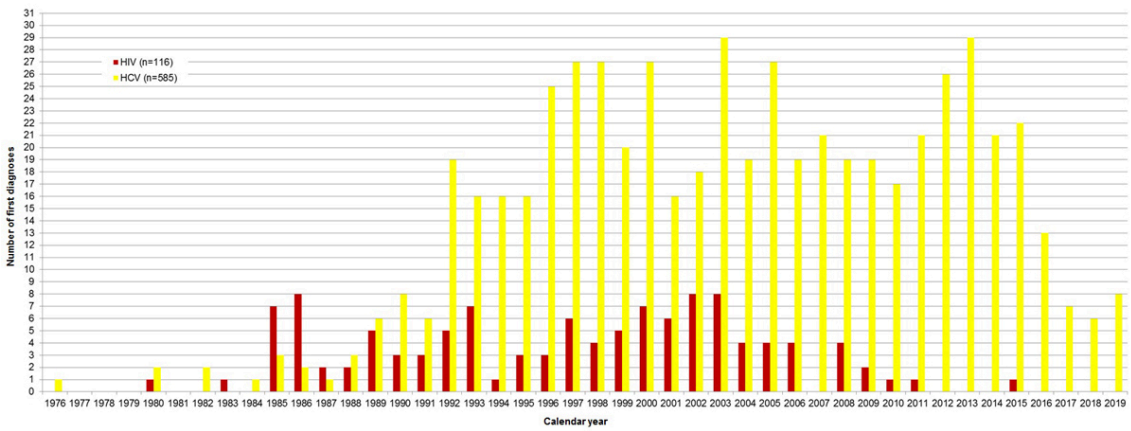


Figure 7: Number of first diagnoses of HIV and HCV per calendar year. Data at registration (status as of 2 September 2019, overall 942 SAMMSU patients). HIV = human immunodeficiency virus; HCV = hepatitis C virus



2019, there were 20 diagnoses of HCV reinfection after successful treatment, resulting in a reinfection rate of 2.70 per 100 person-years (95% CI 1.75–4.19) and a cumulative HCV reinfection rate of 7.1 per 100 treated patients (95% CI 4.1–10.8).

Seventeen reinfections were observed in 88 patients receiving interferon-based treatment during a total observation time of 545.3 years, and 3 reinfections were observed in 192 patients on interferon-free treatment during a total observation time of 194.2 years. Thus, the reinfection rate after successful interferon-based and interferon-free HCV treatment was comparable, at 3.12 (95% CI 1.94–5.01) versus 1.55 (95% CI 0.50–4.79) per 100 person-years (p = 0.253), but the cumulative reinfection rate was higher after interferon-based treatment at 19.3 (95% CI 12.4–28.8) versus 1.6 (95% CI 0.5–4.5) per 100 treated patients. The large difference between these cumulative reinfection rates is explained by the time of observation, since the median observation time was 5.06 years (IQR 2.63–8.07, range 0.025–29.07) after interferon-based treatment, but only 0.57 years (IQR 0.26–1.56, range 0.003–4.33) after interferon-free treatment.

In the cross-sectional data, 35 reinfections were documented in 33 patients. One third (12) were after spontaneous clearance and two thirds (23) after successful treatment (17 after interferon-based, 6 after interferon-free treatment; fig. 9). In 46% (16/35), the reason for reinfection was unknown. If known, it was unsafe IDU in 95% (18/19) and in one case an HCV positive partner.

In the 11 patients with a first reinfection after spontaneous clearance, the median time since HCV first diagnosis was 11.3 years (IQR 3.3–13.9). Four patients cleared the virus spontaneously, whereas seven developed chronic hepatitis C, of whom four have already been treated successfully.

In the 22 patients with a first reinfection after successful treatment, the median time since the end of treatment was 3.3 years (IQR 1.1–5.1), i.e., 4.2 years (IQR 2.3–5.3) for interferon-based treatment (n = 17) and 0.9 years (IQR 0.9–1.1) for interferon-free treatment (n = 5). Outcome after reinfection was not available for two patients. Among

Figure 8: hepatitis C virus (HCV) treatment uptake and HCV-RNA prevalence in seven of eight SAMMSU centres (cross-sectional data). HCV treatment uptake = proportion of chronically HCV infected patients ever treated; HCV RNA prevalence = proportion of HCV antibody positive patients who were HCV RNA positive.

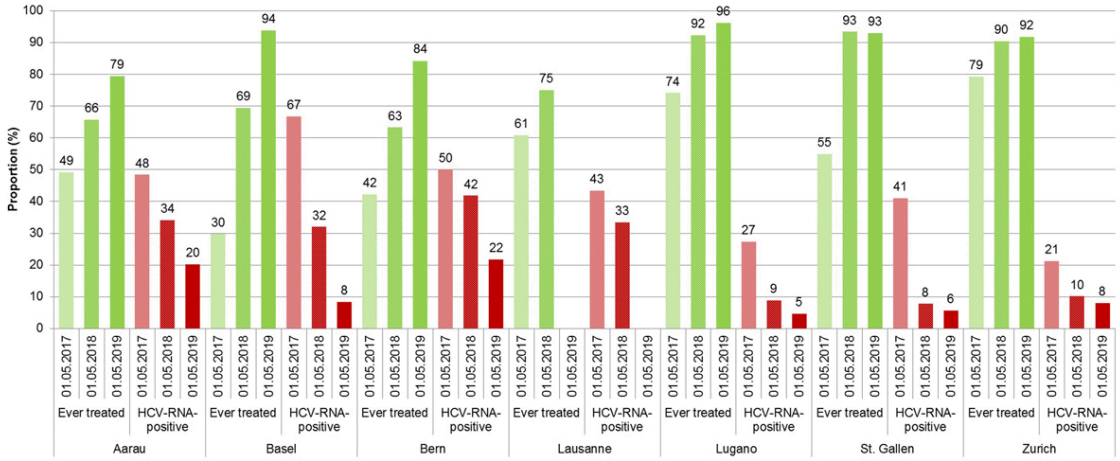
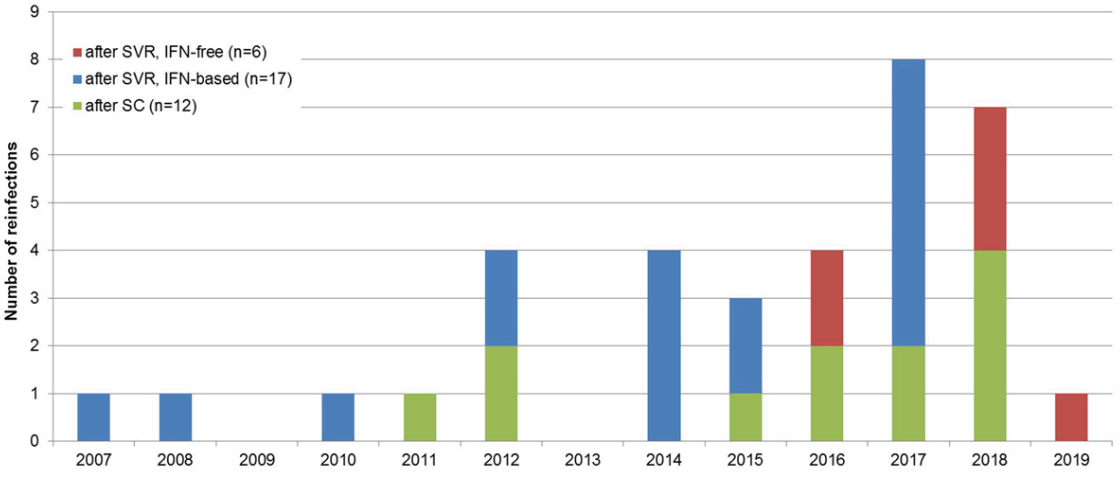


Figure 9: Number of reinfections after spontaneous clearance and successful treatment (interferon-based and interferon-free) per calendar year (cross-sectional data): 35 reinfections in 33 patients. IFN = interferon; SC = spontaneous clearance; SVR = sustained virological response



the remaining patients, 95% (19/20) developed chronic hepatitis C, of whom 15 have already been retreated successfully.

Two patients experienced repeated reinfections (Patient 1: chronic hepatitis C → treatment → 1st reinfection → spontaneous clearance → 2nd reinfection → chronic hepatitis C → successful treatment; Patient 2: chronic hepatitis C → treatment → 1st reinfection → chronic hepatitis C → treatment → 2nd reinfection → chronic hepatitis C → successful treatment).

Test frequency

The median HCV antibody test frequency in HCV antibody-negative patients (n = 89) with a median follow-up time of 3.4 years (IQR 2.9–4.3) was every 1.9 years (IQR 1.4–2.9). In patients after spontaneous clearance (n = 30) with a median follow-up time of 3.2 years (IQR 2.3–4.3), the median HCV-RNA test frequency was every 1.8 years (IQR 1.1–3.3), and in patients after successful treatment (n = 7 3) with median follow-uptime of 3.4 years (IQR 2.3–4), every 1.4 years (IQR 0.8–2.2), i.e., slightly higher than after spontaneous clearance (p = 0.062).

Discussion

Principal findings

With interferon-free DAA treatment, HCV treatment success in OAT patients increased to almost 100%, irrespective of cirrhosis or prior non-response to interferon. With shorter and better tolerated treatments, adherence was excellent (even in the absence of adherence-supporting measures) and preterm stops became rare. Between 1 May 2017 and 1 May 2019, HCV treatment uptake could be increased to 80%, resulting in a reduction of HCV RNA prevalence to <20% among the HCV antibody positive patients, who represent two thirds of the SAMMSU cohort. Since DAA reimbursement restrictions were abrogated in Switzerland in 2017, patients are treated at earlier fibrosis stages, which results in a shorter duration of infectiousness. At 2.7/100 person-years, the reinfection rate after successful treatment was low. The number of HCV first diagnoses per year decreased from >20 up to 2015 to <10 in 2017 and 2018. However, HCV transmission is still ongoing, whereas HIV transmission has been virtually stopped with universal ART.

Adherence and treatment-success

Prejudices that PWID are less adherent, have more side effects and less treatment success in the case of HCV treatment persist stubbornly [32], although they were already refuted in the era of interferon-based treatment [33–36]. In our study, with interferon-free DAA treatment, adherence problems and preterm stops declined to 2% and 1%, respectively, irrespective of DOT [37]. In the C-EDGE CO-STAR study (elbasvir/grazoprevir in OAT patients with and without ongoing drug use), similarly high adherence was observed [38]: 96% completed treatment and >97% had an adherence >95%. Drug use at baseline and during HCV treatment did not negatively influence adherence and treatment success. In contrast, in the SIMPLIFY study (sofosbuvir/velpatasvir in patients with IDU in the past 6 months) [39], low adherence (<90%) was observed in one third of the participants. It was associated with recent or ongoing injection of stimulants (cocaine and/or other amphetamines), but did not negatively affect treatment outcome [40]. Remarkably, SVR rates were not worse, even when at least seven consecutive doses were missed [41]. Thus, 100% adherence is not necessary to prevent resistance and consequent treatment failure.

In our study with interferon-free DAA treatment, the SVR rate in those with known outcome was 97%, irrespective of cirrhosis or prior non-response to interferon. In the German Hepatitis C Registry, OAT patients achieved a comparably high per protocol SVR rate, which was not different from that in non-OAT patients (96% vs 95%, p = 0.464) [42]. However, OAT patients had a higher rate of loss to follow-up between the end of treatment and SVR (10% vs 4%, p <0.001), which might be explained by a change of the healthcare setting, difficult venous access and presumed cure given the high treatment efficacy [43]. Since 78% of relapses post-treatment occur within 4 weeks, SVR4 can predict SVR12 with a positive predictive value of 98% and a negative predictive value of 100% [44]. In settings with a high yearly fluctuation rate (up to 37% in our study), SVR4 determination might reduce the proportion of completed HCV treatments with unknown outcome (8%, 23/291, of interferon-free treatments in our study).

Reinfection

The risk of reinfection and the high costs of retreatment are often mentioned as a reason to withhold HCV therapy from people with ongoing IDU. In our study (OAT patients, one quarter to one third with ongoing IDU), the overall HCV reinfection rate was low (2.7/100 person-years), with no difference between interferon-based and interferon-free treatment (3.1 vs 1.6/100 person-years, p = 0.253). A recent meta-analysis (17 studies with interferon-based, 19 studies with DAA treatment) showed a comparable HCV reinfection rate of 3.8/100 person-years (95% CI 2.5–5.8) among OAT patients. It was markedly lower in OAT patients with no recent drug use than in people recently injecting drugs (1.4 vs 6.2/100 person-years) [45]. As in our study, reinfection rates were comparable following interferon-based and DAA treatment (5.4 vs 3.9/100 person-years). Interestingly, the German hepatitis C cohort (GECCO) reported an overall reinfection rate of 1.9/100 person-years (95% CI 1.4–2.5) since 2014 [46]. Reinfection was less frequent in PWID than in men who have sex with men (1.1 vs 9.0/100 person-years).

Mathematical models suggest an increased HCV reinfection incidence in the initial phase of treatment scale-up [14]. However, with decreasing HCV-RNA prevalence, reinfection incidence will decrease again. Actually, more HCV reinfections were diagnosed in recent years in the SAMMSU cohort, but >80% were after spontaneous clearance or interferon-based treatment. Thus, this might partly be explained by increased HCV-RNA testing as a result of better treatment options (detection bias). Reinfection incidence and probability of spontaneous clearance can be underestimated if HCV-RNA testing frequency is too low [47]. Spontaneous clearance of primary HCV infection occurs in about 25%, but spontaneous clearance is more frequent in reinfections after spontaneous clearance (83%) [48]. In our study, 95% of the first reinfections after successful treatment became chronic, compared with only

64% after spontaneous clearance. Anyway, reinfections can be treated as successfully as primary infections. To shorten the duration of infectiousness, chronic hepatitis C can be diagnosed early, i.e., if HCV-RNA decreases <2 log U/ml 4 weeks after diagnosis (85% negative predictive value for spontaneous clearance) [49–51].

Since 95% of reinfections with a known cause were due to unsafe IDU, patient information, sufficient OAT dosing [52] and needle-syringe distribution coverage are important [53].

"Treatment-as-prevention"

Mathematical models have shown that a substantial reduction of HCV-RNA prevalence cannot be achieved with OAT and needle-syringe programmes alone, but treatment uptake must be increased [54]. According to the WHO, 80% treatment uptake is necessary to succeed in HCV elimination by 2030 [20]. In our study, 80% treatment uptake has been achieved with interferon-free DAA treatment and was associated with a reduction of HCV-RNA prevalence to 19% among HCV antibody-positive patients and to 13% in the total SAMMSU cohort. Although the number of HCV first diagnoses per year has declined both in our study and according to FOPH data [55], HCV transmission is still ongoing, whereas HIV transmission has virtually been stopped with universal antiretroviral therapy [56].

For HIV, the UNAIDS 90-90-90-target (90% diagnosed, 90% treated, 90% virologically suppressed) [57] has been achieved in the SAMMSU cohort: 99.7% were tested, 96% of the HIV-positive patients were under antiretroviral therapy, of whom 97% were virologically suppressed. This resulted in an HIV-RNA prevalence of 6% among the HIV positives and <1.0% in the total SAMMSU cohort.

A reduction in HCV-RNA prevalence to 1% in the SAMMSU cohort would require 98% HCV treatment uptake (100% treatment success, 50% ever had chronic hepatitis C). Besides, HCV is ~10 times more infectious than HIV through blood-to-blood contact [58] and SAMMSU cohort patients may be part of injection networks [59] with higher HCV-RNA prevalence. Contact tracing may help to identify individuals not yet engaged in health care and harm reduction [60]. In a model study, a "treat your friends" strategy was more effective than random treatment [59].

Generalisability and future strategies

Treating chronic hepatitis C in OAT patients needs an extra effort. Since they frequently have other priorities and OAT programmes are often exclusively led by psychiatrists, first of all, they must be made aware of the better HCV treatment options available. Referral to gastroenterologists / infectious disease specialists for DAA prescription is often unrewarding because these patients often have difficulty keeping appointments. Additionally, difficult venous access after long-term intravenous drug use complicates diagnosis. Thus, DAA reimbursement irrespective of liver fibrosis stage does not automatically result in increased HCV treatment uptake. Awareness campaigns, HCV treatment on-site and capillary blood HCV antibody [25] and RNA testing [61–64] helped to remove barriers to diagnosis and treatment.

How to bring HCV treatment to OAT patients differs between centralised and decentralised settings. In decentralised settings with a low case-load, capillary HCV-RNA quantification with the dried blood spot method [65] might be an alternative to Xpert® HCV Viral Load Fingerstick point-of-care testing [61–64]. Similarly in such settings, the aspartate aminotransferase (AST)-to-platelet ratio index (APRI) score [APRI = (AST/upper limit of normal of AST)/platelet count (G/l) × 100] can replace Fibroscan® for non-invasive exclusion of liver cirrhosis. Both an APRI score <1.0 [66] and Fibroscan® ≤12.5 kPa [30] have a negative predictive value of ~95% at a liver cirrhosis prevalence of 15% and 25%, respectively. In our study, chronic hepatitis C patients starting their first HCV treatment in 2018 had a cirrhosis prevalence of 13%.

FOPH guidelines [26] recommend yearly HCV screening of patients at risk (OAT, ongoing drug use [injecting and non-injecting]), which has not been achieved yet in the SAMMSU cohort. In Switzerland, new HCV diagnoses must be reported to the cantonal physician, who also has to review all OAT prescriptions every 1–2 years. Documentation of HCV status for each OAT patient and yearly HCV screening reminders sent to the OAT prescriber/provider (GP/pharmacy) within the already existing platform www.substitution-online.ch could facilitate implementation of the FOPH guidelines and monitoring of HCV elimination.

Unlike in Australia [67] and France [68], in Switzerland GPs cannot prescribe DAA. The HepCare-project, initiated by the Swiss Hepatitis Strategy in spring 2019, allows HCV treatment on the site of OAT provision (GP/psychiatrist). In a randomised controlled trial in Australia, treatment uptake was higher in the GP than the hospital setting (75% vs 35%), whereas treatment success was comparable [43]. Increased retention in care halved the average cost of treatment initiation [69].

Strengths and limitations

With almost 1000 patients in different OAT settings throughout Switzerland, the SAMMSU cohort is a useful tool for monitoring HCV elimination. Patients from German- and Italian-speaking regions of Switzerland are overrepresented (81% vs 63% and 13% vs 8%, respectively), whereas patients from French-speaking Switzerland are underrepresented (6% vs 23%) [70]. Rhaeto-Romanic-speaking Switzerland (0.5%) is not represented. Besides, patients cared for in decentralised OAT settings (OAT via GP or psychiatrist and pharmacy) are underrepresented, not least because their recruitment and follow up is more difficult. Since HCV management is better in centralised than decentralised settings [25], and better inside than outside the cohort [71], HCV screening and treatment uptake in the SAMMSU cohort is probably higher than in the general Swiss OAT population.

Owing to a lack of manpower, in most centres only 5–20% of the patients are enrolled into the SAMMSU cohort. Patients willing to be tested and treated are more likely to be enrolled (enrolment bias), leading to an overrepresentation of HCV antibody-positive patients, patients with chronic hepatitis C and treated patients. HCV antibody-positive patients are older, the proportion with ever and ongoing IDU is higher, their first IDU is longer ago and a higher proportion are HIV positive. In contrast, unstable patients who

are only a short time at one institution are less likely to be enrolled. Thus, adherence might be overestimated.

So far, there are only a few reinfections after DAA treatment and the follow-up time is still quite short. A longer observation period is necessary to estimate the reinfection rate after DAA treatment more reliably.

To counteract the delay of data entry resulting from only yearly follow-up in the SAMMSU cohort, two cross-sectional surveys 1 May 2018 and 1 May 2019 (1 and 2 years after the abrogation of DAA reimbursement restrictions for PWID) were performed. Since the study physician and/or the institution changed, the SAMMSU centre Geneva could not contribute any cross-sectional data, and Lausanne could only provide data in the first survey.

In the SAMMSU-cohort, 91% (445) of the 490 patients who had ever had chronic hepatitis C had a Fibroscan®, but only 27% (131) a liver biopsy (often many years ago).

Conclusion

With nearly 100% DAA treatment success and a low reinfection rate, treatment uptake directly translates into a reduction of HCV-RNA prevalence. Eighty percent treatment uptake is feasible in OAT patients, and adherence and treatment success are not worse than in other populations. Duration of infectiousness and thus HCV transmission can be reduced by early detection and treatment of chronic hepatitis C.

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Potential competing interests

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Appendix 1: Supplementary table

Table S1: HCV treatment uptake and HCV-RNA prevalence in seven of eight SAMMSU centres

	1 May 2017	1 May 2018	1 May 2019
Aarau (n = 367)			
Treatment uptake*	49.1% (57/116)	65.6% (80/121)	79.4% (104/131)
HCV-RNA prevalence†	48.3% (73/151)	34.0% (54/159)	20.2% (35/173)
Basel (n = 82)			
Treatment uptake*	29.7% (19/64)	69.4% (43/62)	93.7% (59/63)
HCV-RNA prevalence†	66.7% (48/72)	31.9% (23/72)	8.3% (6/72)
Bern (n = 27)			
Treatment uptake*	42.1% (8/19)	63.2% (12/19)	84.2% (16/19)
HCV-RNA prevalence†	50% (12/24)	41.7% (10/24)	21.7% (5/23)
Lausanne (n = 33)‡			
Treatment uptake*	60.7% (17/28)	75% (21/28)	
HCV-RNA prevalence†	43.3% (13/30)	33.3% (10/30)	
Lugano (n = 111)			
Treatment uptake*	74.0% (57/77)	92.2% (71/77)	96.1% (73/76)
HCV-RNA prevalence†	27.2% (25/92)	8.8% (8/91)	4.6% (4/87)
St Gallen (n = 46)			
Treatment uptake*	54.8% (17/31)	93.3% (28/30)	92.9% (26/28)
HCV-RNA prevalence†	41.0% (16/39)	7.7% (3/39)	5.6% (2/36)
Zurich (n = 159)			
Treatment uptake*	79.2% (42/53)	90.4% (66/73)	91.8% (67/73)
HCV-RNA prevalence†	21.1% (15/71)	10.1% (10/99)	8.0% (8/100)
Total (n = 825)			
Treatment uptake*	55.9% (217/388)	78.3% (321/410)	88.5% (345/390)
HCV-RNA prevalence†	42.2% (202/479)	23.0% (118/514)	12.2% (60/491)
Total without Aarau (n = 458)			
Treatment uptake*	58.8% (160/272)	83.4% (241/289)	93.1% (241/259)
HCV-RNA prevalence†	39.3% (129/328)	18.0% (64/355)	7.9% (25/318)

HCV = hepatitis C virus * In the case of chronic hepatitis C (currently HCV RNA positive or currently HCV RNA negative and ever treated); † among the HCV antibody positive patients; ‡ no data for 1 May 2019 due to site interruption

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Hepatitis C virus elimination in Swiss opioid agonist therapy programmes – the SAMMSU cohort

Appendices 2 and 3

SAMMSU-ID: _____ *(please insert on all pages)*

Questionnaire – Cross sectional study within SAMMSU May 2018 and May 2019

How to enter not precisely known dates:
If the day is unknown, enter "15/MM/YYYY". If day and month are unknown, enter "15/07/YYYY".

1) On the reference date, what was the patient's HCV-antibody- and HCV-RNA-status?
(0 = negative, 1 = positive, 9 = never tested)

	HCV-antibody	HCV-RNA
1.5.2017		
1.5.2018		
1.5.2019		

1a)-1d) The same values might appear more than once (i.e. "first …" and "last …" may be on the same date or tests may not have been repeated between the reference dates, respectively).

a) if HCV-antibody-neg.(0), last neg. HCV-antibody-test before the respective date:

1.5.2017: ____/____/_____ (DD/MM/YYYY)
1.5.2018: ____/____/_____ (DD/MM/YYYY)
1.5.2019: ____/____/_____ (DD/MM/YYYY)

b) if HCV-antibody-pos.(1), first pos. HCV-antibody-test: ____/____/_____ (DD/MM/YYYY)
if applicable **first pos. HCV-RNA-test after diagnosis:** ____/____/_____ (DD/MM/YYYY)
if applicable **first neg. HCV-RNA-test after diagnosis:** ____/____/_____ (DD/MM/YYYY)
(To determine the duration of infectiousness, please also give the first neg. HCV-RNA-test after a first pos. HCV-RNA-test, i.e. after spontaneous clearance or under successful treatment.)

c) if HCV-antibody-pos.(1)/HCV-RNA-neg.(0), last neg. HCV-RNA before the respective date:

1.5.2017: ____/____/_____ (DD/MM/YYYY)
1.5.2018: ____/____/_____ (DD/MM/YYYY)
1.5.2019: ____/____/_____ (DD/MM/YYYY)

d) if HCV-antibody-pos.(1)/HCV-RNA-pos.(1), last pos. HCV-RNA before the respective date:

1.5.2017: ____/____/_____ (DD/MM/YYYY)
1.5.2018: ____/____/_____ (DD/MM/YYYY)
1.5.2019: ____/____/_____ (DD/MM/YYYY)

2) On the reference date, was the patient ever treated for hepatitis C?
(0 = no, 1 = yes, 9 = unknown)

	Ever HCV-treatment
1.5.2017	
1.5.2018	
1.5.2019	

SAMMSU-ID: _____ *(please insert on all pages)*

a) On the reference date, main reason for no HCV-treatment despite pos. HCV-RNA:
(1 = reimbursement restrictions, 2 = non-compliance with appointments, 3 = patient not motivated enough, 4 = uncontrolled substance use, 5 = uncontrolled alcohol use, 6 = uncontrolled psychiatric disorder, 7 = uncontrolled somatic disease, 8 = unstable life situation, 9 = other)

	Main reason for no HCV-treatment	if other(9), specify
1.5.2017		
1.5.2018		
1.5.2019		

Comments: _____

b) All HCV-treatments in chronological order: from when until when, with what,
*(**IFN (interferon):** 0 = no, 1 = interferon-alpha, 2 = pegylated interferon;*
***RBV (ribavirin):** 0 = no, 1 = yes, 9 = unknown;*
***DAA (direct-acting antivirals)/other:** 0 = no, 1 = Incivo (telaprevir), 2 = Victrelis (boceprevir), 3 = Sovaldi (sofosbuvir), 4 = Harvoni (ledipasvir/sofosbuvir), 5 = Viekirax/Exviera (ombitasvir/paritaprevir/ritonavir/dasabuvir), 6 = Viekirax (ombitasvir/paritaprevir/ritonavir), 7 = Daklinza/Sovaldi (daclatasvir/sofosbuvir), 8 =Zepatier (grazoprevir/elbasvir), 9 = Epclusa (velpatasvir/sofosbuvir), 10 = Maviret (glecaprevir/pibrentasvir), 11 = Vosevi (sofosbuvir/velpatasvir/voxilaprevir), 12 = other (specify under comments), 99 = unknown)*
HCV-genotype (gt),
*(**Num. (number):** 1-7, 9 = unknown; **Let. (letter):** 1 = a, 2 = b, 3 = c, 4 = d, 5 = multiple subtypes, 9 = subtype not defined)*
and outcome
(0 = ongoing treatment, 1 = SVR (sustained virological response), 2 = EOT (end of treatment response; if HCV-treatment is completed, but SVR not yet determined), 3 = relapse, 4 = viral breakthrough, 5 = non-response, 6 = PTS (pre-term stop)), 9 = unknown;
***Why PTS:** 1 = toxicity/complication related to HCV-treatment, 2 = medical complication not related to hepatitis C treatment, 3 = patient's wish, 4 = loss to follow-up, 5 = death, 6 = other (specify under comments), 9 = unknown*)**:**

	Start (DD/MM/YYYY)	End (DD/MM/YYYY)	Medication			HCV-gt		Out-come	Why PTS
			IFN	RBV	DAA/other	Num.	Let.		
1st									
2nd									
3rd									
4th									
5th									

Comments: _____

c) What about adherence during HCV-treatments (in chronological order)?
DOT = Directly observed therapy
(0 = no, 1 = yes, 9 = unknown), #(Adherence:** 1 = excellent, 2 = moderate, 3 = bad, 9 = unknown)*

	DOT (≥5x/week)*	Weekly dispensing in pill box*	Adherence#
1st			
2nd			
3rd			
4th			
5th			

Comments: _____

SAMMSU-ID: _____ *(please insert on all pages)*

d) Current liver fibrosis stage *(last available result: 1.5.2017 (I), 1.5.2018 (II) and 1.5.2019 (III))*; **if HCV-treatment, additionally results before (B) and after (A) 1st, 2nd, 3rd, … treatment**
(The same examination might appear more than once.)

	Fibroscan					Liver biopsy	
	Date (DD/MM/YYYY)	**Median stiffness (kPa)**	**IQR (kPa)**	**Valid measure-ments**	**Success Rate (%)**	**Date** (DD/MM/YYYY)	**Fibrosis-Score (F0-4)**
(I)							
(II)							
(III)							
B 1st							
A 1st							
B 2nd							
A 2nd							
B 3rd							
A 3rd							
B 4th							
A 4th							
B 5th							
A 5th							

3) On the reference date, has the patient ever experienced HCV-reinfection?
**(0 = no, 1 = yes)*
*#(**After:** 1 = spontaneous clearance, 2 = successful treatment)*
§(1 = unsafe intravenous drug use, 2 = unsafe intranasal drug use, 3 = unsafe anal intercourse, 4 = other (specify under comments), 9 = unknown)
*$(**Outcome:** 1 = spontaneous clearance, 2 = chronic infection, 9 = unknown)*

	Ever HCV-Reinfection*
1.5.2017	
1.5.2018	
1.5.2019	

	Diagnosis of HCV-reinfection (DD/MM/YYYY)	**After#**	**Most likely reason for HCV-reinfection§**	**Outcome$**
1st				
2nd				
3rd				

Comments: _____

4) Drug use on the reference date
(Ever:** 0 = no, 1 = yes, 9 = unknown)*
*#(**Cont. (continued):** 0 = no (last use >12 months ago), 1 = yes (last use ≤12 months ago), 9 = unknown)*

	intravenous		**intranasal**	
	Ever*	**Cont.#**	**Ever***	**Cont.#**
1.5.2017				
1.5.2018				
1.5.2019				

a) first year of intravenous drug use: _____ (YYYY)

b) first year of intranasal drug use: _____ (YYYY)

SAMMSU-ID: _____ *(please insert on all pages)*

5) Please enter <u>all</u> available HCV-RNA-values into the SAMMSU-database!

Thank you very much!

	Cross sectional study 01.05.2018	**Cross sectional study 01.05.2019**
Last contact with the patient (DD/MM/YYYY)		
Completed by:		
Date:		

Please note:
For patients recruited after the 01/05/2018, please complete the whole questionnaire, i.e. both cross sectional studies (01/05/2018 and 01/05/2019) in 2019.

SAMMSU-Centre: _____ *(please insert on all pages)*

Centre-Questionnaire – Cross sectional study within SAMMSU May 2018 and May 2019
Main form

1) On the reference date, how was your centre organised?
(1 = specialised opioid substitution centre with integrated somatic care, 2 = specialised opioid substitution centre without integrated somatic care, 3 = private practice, 4 = decentralised setting, 5 = other (specify under comments)

	Centre characteristic*	Number of institutions	Number of sites
1.5.2017			
1.5.2018			
1.5.2019			

Comments: _____

2) Please list the names of the institutions/sites, you are going to further characterise one by one:

A) _____
B) _____
C) _____
D) _____
E) _____

Comments: _____

3) Please fill in and attach a separate form (page 2-4) for each of the institutions/sites!

Thank you very much!

	Cross sectional study 01.05.2018	Cross sectional study 01.05.2019
Completed by:		
Date:		

Please note:
For centres/institutions/sites recruited after the 01/05/2018, please complete the whole questionnaire, i.e. both cross sectional studies (01/05/2018 and 01/05/2019) in 2019.

SAMMSU-Centre: _____ *(please insert on all pages)*

Centre-Questionnaire – Cross sectional study within SAMMSU May 2018 and May 2019
Institution/Site: _____

1) Does this institution/site provide substitution treatment?
(0 = no, 1 = yes)

1.5.2017	**1.5.2018**	**1.5.2019**

a) if yes, number of patients receiving their substitution directly in the institution/site: ____
number of patients receiving their substitution in a pharmacy: ____

b) if yes, which substitution treatments are provided?
(0= no, 1 = yes, 9 = unknown)

	Heroin	**Methadone (incl. levo-methadone)**	**Buprenorphine**	**Sevre-Long**	**Diazepam**	**Other***
1.5.2017						
1.5.2018						
1.5.2019						

***if other, specify:** _____

c) if yes, give further details:

	Opening days/week *(1-7)*	**Max. frequency of appearance/day** *(1-3)*	**Number of patients at the end of the past year** *(e.g. 1.5.2017 → end of 2016)*	**Number of newly admitted patients during the past year** *(readmissions included)*	**Number of patients leaving during the past year**
1.5.2017					
1.5.2018					
1.5.2019					

2) Please provide the HCV treatment cascade of this institution/site:

	1.5.2017	**1.5.2018**	**1.5.2019**
Total number of substitution patients			
- HCV-antibody-tested			
HCV-antibody-positives			
- HCV-RNA-tested			
Ever chronically HCV-infected			
- HCV-genotype known			
- liver biopsy performed			
- fibroscan performed			
- ever treated for HCV			
- cured *(SVR, Sustained virological response)*			
Number of patients enrolled into SAMMSU			

SAMMSU-Centre: _____ *(please insert on all pages)*

Institution/Site: _____

Comments: _____

3) How is the institution/site regularly equipped?
(0 = no, 1 = yes)

	1.5.2017	1.5.2018	1.5.2019
Capillary blood examination (hematology/chemistry)			
Venous blood draw on site			
Centrifuge			
HCV rapid tests			
HIV rapid tests			
Capillary HCV-RNA (Dried blood spot)			
Capillary HCV-RNA (GeneXpert)			
Sonography			
Fibroscan			
Liver biopsy			
Prescription of HCV therapy on site			
Somatic physician on site			

Comments: _____

4) How is the institution/site regularly staffed?
(n = number of individuals, FTE = full-time equivalents [1 FTE = 100% position])

	1.5.2017		1.5.2018		1.5.2019	
	n	FTE	n	FTE	n	FTE
Social workers						
Addiction specialists						
Psychiatrists						
Somatic physicians						
Infectious disease specialists						
Hepatologists						
Study nurses						
Technical and clinical assistants (e.g. MPA, clinical nurse)						
Physicians						

Comments: _____

5) To whom does the institution/site regularly refer patients for the following:
(multiple answers allowed, please start with highest priority and separate by comma)
(0 = no referral, done within the institution/site, 1 = infectious disease specialist in hospital, 2 = hepatologist in hospital, 3 = infectious disease specialist in private practice, 4 = hepatologist in private practice, 5 = general practitioner, 6 = other (specify under comments)

	1.5.2017	1.5.2018	1.5.2019
Sonography			
Fibroscan			
Liver biopsy			
HCV treatment			
Somatic problems			

Comments: _____

SAMMSU-Centre: _____ *(please insert on all pages)*

Institution/Site: _____

6) Does this institution/site perform hepatitis C action days?
(0 = no, 1 = yes)

1.5.2017	1.5.2018	1.5.2019

a) if yes, how many hepatitis C action days did the institution/site perform in the past year?
(e.g. 1.5.17 → 2016)

1.5.2017	1.5.2018	1.5.2019

Comments: _____

b) if yes, what was offered?
(0 = no, 1 = yes)

	1.5.2017	1.5.2018	1.5.2019
HCV rapid test (capillary blood)			
HCV rapid test (saliva)			
HIV rapid test			
Capillary HCV-RNA (Dried blood spot)			
Capillary HCV-RNA (GeneXpert)			
Venous blood draw			
Hepatitis B serology			
Hepatitis A serology			
Hepatitis B vaccination			
Hepatitis A vaccination			
Sonography			
Fibroscan			
Prescription of HCV therapy (Test and treat)			
Referral to HCV therapy prescriber			
Other (1), specify:			
Other (2), specify:			
Other (3), specify:			
Other (4), specify:			
Other (5), specify:			

Comments: _____

c) if yes, how were the events staffed?
(n= number of individuals) (DAAs = Direct-acting antivirals)

	1.5.2017	1.5.2018	1.5.2019
	n	n	n
Nurses			
Physicians			
Addiction specialists authorised to prescribe HCV therapy (DAAs)			
Infectious disease specialists			
Hepatologists			