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Management of hepatitis C virus (HCV) infection in drug substitution programs

Comparison of HCV treatment uptake and success rate with Swiss hepatitis C cohort study (SCCS) and Swiss HIV cohort study (SHCS) data

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Summary

BACKGROUND: In Switzerland, intravenous drug use (IDU) accounts for 80% of newly acquired hepatitis C virus (HCV) infections. Early HCV treatment has the potential to interrupt the transmission chain and reduce morbidity/mortality due to decompensated liver cirrhosis and hepatocellular carcinoma. Nevertheless, patients in drug substitution programs are often insufficiently screened and treated.

OBJECTIVE/METHODS: With the aim to improve HCV management in IDUs, we conducted a cross sectional chart review in three opioid substitution programs in St. Gallen (125 methadone and 71 heroin recipients). Results were compared with another heroin substitution program in Bern (202 patients) and SCCS/SHCS data.

RESULTS: Among the methadone/heroin recipients in St. Gallen, diagnostic workup of HCV was better than expected: HCV/HIV-status was unknown in only 1% (2/196), HCV RNA was not performed in 9% (13/146) of anti-HCV-positives and the genotype missing in 15% (12/78) of HCV RNA-positives. In those without spontaneous clearance (two thirds), HCV treatment uptake was 23% (21/91) (HIV-: 29% (20/68), HIV+: 4% (1/23)), which was lower than in methadone/heroin recipients and particularly non-IDUs within the SCCS/SHCS, but higher than in the, mainly psychiatrically focussed, heroin substitution program in Bern (8%). Sustained virological response (SVR) rates were comparable in all settings (overall: 50%, genotype 1: 35–40%, genotype 3: two thirds). In St. Gallen, the median delay from the estimated date of infection (IDU start) to first diagnosis was 10 years and to treatment was another 7.5 years.

CONCLUSIONS: Future efforts need to focus on earlier HCV diagnosis and improvement of treatment uptake among patients in drug substitution programs, particularly if patients are HIV-co-infected. New potent drugs might facilitate the decision to initiate treatment.

Key words: *methadone; heroin; drug substitution program; spontaneous clearance; HCV treatment uptake; HCV treatment success; HIV-HCV-co-infection; genotype distribution; potential treatment barriers; delay of diagnosis and treatment*

Alphabetic list of abbreviations

DOT Directly observed therapy
H22 Methadone substitution program of the Outpatient Clinic of the Department of Infectious Diseases of the Cantonal Hospital St. Gallen
HCC Hepatocellular carcinoma
HCV Hepatitis C virus
HIV Human immunodeficiency virus
i.v. Intravenous
IDU Intravenous drug use
KODA Heroin substitution program Bern
MSH1 Heroin substitution program of the addiction aid trust St. Gallen
MSH2 Methadone substitution program of the addiction aid trust St. Gallen
SCCS Swiss Hepatitis C Cohort Study
SHCS Swiss HIV Cohort Study
SVR Sustained virological response (HCV RNA negative 6 months after the end of treatment)

Introduction

In Switzerland, approximately 80% of newly acquired hepatitis C virus (HCV) infections are due to sharing injection equipment among intravenous drug users (IDUs) [1]. In Western Europe, HCV seroprevalence ranges from 33% to 98% in this population [2]. Due to the slow progression of the disease, the peak of hepatitis C induced liver failure is not expected until 2015, despite a currently decreasing incidence [3].

Thus, successful HCV treatment not only results in an individual benefit by preventing progression to decompensated liver cirrhosis and hepatocellular carcinoma (HCC), but may also help to contain the epidemic by eliminating a potential source of infection. Although treatment adherence, side effects and treatment response do not differ between IDUs and non-IDUs [4–6], several studies have shown that HCV treatment uptake is substantially lower in patients in opioid substitution programs compared to non-IDUs (8.7% versus 44% according to Swiss Hepatitis C Cohort data from 2006/2007) [2, 7, 8].

A total of 8% of the patients in opioid substitution programs are HIV-HCV-co-infected and thus prone to experience faster progression to liver cirrhosis [9, 10]. Meanwhile, in HIV-patients, liver failure has advanced to become the second most frequent cause of death after AIDS [11–14].

At the end of 2005, 16'200 patients (56% of all Swiss opioid dependants) were cared for in drug substitution programs (80% methadone, 8% heroin, 3% buprenorphine) [2]. Long term abstinence is achieved in only 25–33% of all opioid dependants. On the other hand, after 2.5 years 50% are still in the heroin program and 25% remain there for >10 years [3]. Long term care with a once to twice daily appearance provides an ideal setting for directly observed therapy (DOT) of hepatitis C [15, 16] (and other diseases such as HIV). The re-infection rate after successful treatment of chronic hepatitis C is 7% for active IDUs [1].

For several years, the three main drug substitution programs in St. Gallen (H22, MSH1 and MSH2) have had a somatic physician on site, whereas the heroin substitution program in Bern (KODA) has a more psychiatric focus. Differences in the quality of HCV management could accentuate the need for improving somatic care in a mainly psychiatric setting.

The Swiss Hepatitis C Cohort Study (SCCS) enrols both HCV-mono- and HIV-HCV-co-infected patients, whereas the Swiss HIV Cohort Study (SHCS) is restricted to HIV-HCV-co-infected patients because HIV-positivity is an inclusion criterion. The SCCS does not include HCV-negative people and the SHCS does not enrol HIV-negative people at risk of the respective infection. SCCS or SHCS participation requires regular cohort visits once or twice a year and implies a certain standard of care. Only patients expected to be compliant enough will be included. The drop-out rate is as high as 31% in the SCCS, with participants lost to follow-up being more likely to be younger and to have injection drug use as a reported risk factor [7].

In the light of existing recommendations from the Swiss Society of Addiction Medicine [2], the purpose of this study was to evaluate the current state of HCV management in the three largest opioid substitution programs in St. Gallen (125 methadone and 71 heroin recipients) and to identify potential targets for future optimisation. In a second step, we compared demographic and treatment data with data from a heroin substitution program with a psychiatric focus in Bern (202 patients), as well as with SCCS and SHCS data as a benchmark. We hypothesised that HCV treatment uptake-rates are lower in patients enrolled in the drug substitution programs (i.e. former or still active IDUs), lower than in SCCS/SHCS-participants in general and non-IDUs in particular. Furthermore, HCV treatment uptake-rates were compared between heroin/methadone recipients and non-IDUs within the SCCS and SHCS, respectively.

Patients and Methods

Three opioid substitution programs in St. Gallen

In December 2009, a cross sectional study was performed in a total of 196 patients evaluating the HCV-management in the three largest opioid substitution programs in St. Gallen. All patients enrolled in these institutions at the time of the study were included (MSH1: 71 heroin recipients; MSH2: 90 methadone recipients, H22 (Outpatient Clinic of the Department of Infectious Diseases of the Cantonal Hospital St. Gallen): 35 methadone recipients). Data were collected by review of paper and electronic medical records.

Heroin substitution program KODA in Bern

Since 1995, KODA Bern has provided heroin substitution (twice daily i.v., switch to or combination with methadone possible), basic somatic, psychiatric and nursing care for ≥18-year-old patients with a history of IDU of 2 years or more and at least 2 failed abstinence oriented treatments. In 2008, a cross-sectional survey was performed in all 202 IDUs treated in KODA at that time (median age: 39 years (range: 21–71), 28% female), to evaluate their somatic health status and the need for improving on-site somatic care.

SCCS (Swiss Hepatitis C Cohort Study)

The SCCS is a prospective multicentre study carried out at 8 major Swiss hospitals and their local affiliated centres which has recruited HCV-positive patients since September 2000 [7]. In April 2010, it had 3'602 participants (median age: 48 years, 37% female, 10% HIV-co-infected, 24% in drug substitution programs, 43% without IDU as a risk factor).

SHCS (Swiss HIV Cohort Study)

The SHCS is a prospective multicentre study carried out at 7 major Swiss hospitals and their local affiliated centres which has enrolled HIV-positive patients since 1988 (www.shcs.ch) [17]. In April 2010, 16'285 participants were included (median age: 48 years, 29% female, 29% HCV-co-infected, 9% in drug substitution programs, 71% without IDU as a risk factor).

Data collection and analysis

In the cross sectional, retrospective, chart review conducted in the three largest opioid substitution programs in St. Gallen, we focussed on the following issues: screening for HCV and HIV, immunisation against hepatitis A and B, proportion of SCCS and SHCS participation, rate of HCV treatment uptake in mono- and HIV-co-infected patients, delay of HCV diagnosis and treatment, HCV treatment response rates, potential barriers to treatment and, with regard to new drugs which will be available soon, genotype distribution of those still in need for treatment.

In a second step, we compared demographic and treatment data with data from a similar cross-sectional survey in a heroin substitution program with a psychiatric focus (KODA Bern), as well as with SCCS and SHCS data as a benchmark. Updated data sets from the SCCS and the SHCS were provided in the framework of a specific cohort project involving both cohorts (SHCS #639, SCCS: no project number available). We hypothesised that HCV treatment uptake-rates would be lower in patients enrolled in the drug substitution programs (i.e. former or still active IDUs), lower than in SCCS/SHCS-participants in general and non-IDUs in particular. Furthermore, HCV treatment uptake-rates were compared between heroin/methadone recipients and non-IDUs within the SCCS and SHCS, respectively.

Definitions

First diagnosis of HCV was defined as the first documented positive HCV antibody test or the time point since the patient first knew (that) he was HCV-positive – whichever came first.

Spontaneous clearance rate was calculated as the ratio between patients HCV RNA-negative without treatment and all anti-HCV-positive patients with available HCV RNA.

Statistical methods

Statistical analyses were performed using Open Source Epidemiologic Statistics for Public Health, Version 2.3 (www.OpenEpi.com). Categorical data were assessed in two-way contingency table analyses by using Chi-square test, or Fisher's exact test when the sample size was small. To demonstrate and quantify factors associated with HCV treatment uptake and sustained virological response (SVR), logistic regression derived odds ratios (OR) with 95% confidence intervals (CI) were calculated by means of Taylor Series. 95% CI not including 1 and p values <0.05 were considered significant.

Results

Patient characteristics (St. Gallen)

Table 1 shows the characteristics of the patients cared for in the three drug substitution programs in St. Gallen (extended version: supplementary table 1).

According to the focus of the programs, MSH2 has no HIV-patients, while two thirds of the H22-patients are HIV-HCV-co-infected. The proportion of patients who have not performed intravenous drug use (never IDU) correlates with the proportion of patients neither HIV- nor HCV-infected. All HIV-positive patients participate in the SHCS, whereas only half of the HCV-positive patients are enrolled in the SCCS.

Fluctuation (i.e. the annual number of admissions and exits) is highest (about 50% per year), and the proportion of patients appearing daily is lowest (about three quarter) in the methadone-substitution program MSH2. In contrast, the heroin substitution program MSH1 has the lowest fluctuation rate (about 10% per year), all patients attend at least once daily and 93% even attend several times a day.

HCV- and HIV-screening, HCV- and HIV-prevalence (St. Gallen and Bern)

In St. Gallen's opioid substitution programs, HIV- and HCV-status was unknown in only 1% (2/196) of all patients. However, in about 50% of negatively screened patients, the last test was older than one year. In HCV-positive patients, HCV RNA was not determined in 9% (13/146), and genotype was missing in 15% (12/78) of HCV RNA-positive patients.

Prevalence rates were 75% for HCV (59% of them HCV RNA-positive), 19% for HIV and 18% for HIV-HCV-co-infection (table 1 and 2).

Comparable numbers were found in KODA Bern, where HCV- and HIV-screening was missing in only 1% and 5%, respectively. Out of the patients with available serology, 80% were HCV-positive (65% of them HCV RNA-positive, genotype available for 8% only) and 13% were HIV-infected (table 2).

HCV spontaneous clearance, treatment uptake and success rate (St. Gallen and Bern)

In St. Gallen, the rate of spontaneous clearance was about one third, both for HCV-mono- and HIV-HCV-co-infected patients (32/100 and 12/35, respectively). In KODA Bern, the spontaneous clearance rate was very similar at 32% (48/150).

Altogether in St. Gallen, the HCV treatment uptake-rate in those without spontaneous clearance was 23% (21/91) (29% (20/68) in HCV-mono-infected and 4% (1/23) in HIV-HCV-co-infected patients).

A total of 47% patients (8/17, 4x still running therapy) achieved SVR (sustained virological response = HCV RNA not detectable 6 months after the end of treatment) (genotype 1: 38% (3/8), genotype 3: 67% (4/6)). The only HIV-HCV-co-infected patient treated (genotype 1) had undetectable HCV RNA at the end of the treatment, but experienced a relapse (table 2).

In KODA Bern, which had a mainly psychiatric focus until 2008, the HCV treatment uptake rate was somewhat lower at 8% (8/102) (treatment outcome: SVR in 5/8 patients).

Additional work-up with sonography, liver biopsy, fibroscan and endoscopy (St. Gallen)

In St. Gallen, HCV RNA-positive patients without spontaneous clearance were further evaluated with sonography in 63% (57/91) (54% splenomegaly), fibroscan in 66% (60/91) (23% liver stiffness ≥13 kPa) and liver biopsy in 35% (32/91) (68% fibrosis score ≥2 (Metavir score); median

time from HCV diagnosis to liver biopsy: 9 years (range: 0–16)).

A gastroscopy was performed in 50% (9/18) of HCV-positive patients with either sonographically verified liver cir-

Table 1: Characteristics of the three drug substitution programs in St. Gallen.

	MSH1	**MSH2**	**H22**
Founded	1995	1993	1990
Capacity (patients)	Max. 75	Max. 100	35
Yearly fluctuation (patients)	about 8 (10%)	50–60 (about 50%)	about 5 (14%)
Open (days/week)	7	6	5
Number of patients included in the cross sectional study	**71**	**90**	**35**
Gender (female)	23% (16/71)	23% (21/90)	31% (11/35)
Median age (years) (range)	42 (26–63)	39 (20–63)	42 (29-61)
Median time in program since last admission (years) (range)	5.0 (0–14)	2.0 (0–16)	3.7 (0–19)
Frequency of attendance – daily – several times a day	 100% (71/71) 93% (66/71)	 77% (69/90) 1% (1/90)	 87% (30/35) 11% (4/35)
Opioid substitution – heroin – methadone – buprenorphine	 94% (67/71) 6% (4/71) 0% (0/71)	 0% (0/90) 97% (87/90) 3% (3/90)	 0% (0/35) 100% (35/35) 0% (0/33)
Never IDU	5% (3/67)	22% (20/90)	0% (0/35)
HIV- and HCV-negative	17% (12/71)	38% (33/87)	0% (0/35)
HCV-infection (anti-HCV+)	82% (58/71)	61% (54/88)	97% (34/35)
HIV-infection	18% (13/71)	0% (0/88)	69% (24/35)
HIV-HCV-co-infection	17% (12/71)	0% (0/87)	66% (23/35)

MSH1 = heroin substitution program of the addiction aid trust St. Gallen, MSH2 = methadone substitution program of the addiction aid trust St. Gallen, H22 = methadone substitution program of the Outpatient Clinic of the Department of Infectious Diseases of the Cantonal Hospital St. Gallen, max. = maximal, IDU = intravenous drug use, HIV = Human immunodeficiency virus, HCV = Hepatitis C virus, SCCS = Swiss Hepatitis C Cohort Study, SHCS = Swiss HIV Cohort Study
An extended version of this table can be found in the supplementary material (Supplementary table 1).

Table 2: Patient characteristics, HCV treatment uptake and success rates.

	SCCS	**SHCS**	**St. Gallen**	**Bern**
Number of patients	3602	16285	196	202
Median age (years) (range)	48 (19–91)	48 (18–101)	41 (20–63)	39 (21–71)
Gender (female)	37% (1335/3602)	29% (4659/16285)	25% (48/196)	28% (57/202)
Drug substitution program	24% (872/3600)	9% (796/8517)	100%	100%
No IDU	43% (1534/3595)	71% (11326/15960)	12% (23/190)	0%
HCV-infected	100%	29% (3319/11527)	75% (146/194)	80% (161/200)
HCV RNA+, if anti-HCV+ and HCV RNA available	68% (2425/3575)	67% (1446/2153)	59% (78/133)	65% (97/150)
HIV-infected	10% (285/2974)	100%	19% (37/194)	13% (26/195)
HIV-HCV-co-infected	10% (285/2974)	29% (3319/11527)	18% (35/193)	13% (26/195)
Liver biopsy, if no spontaneous clearance	66% (2234/3374)	40% (696/1752)	35% (32/91)	No data
HCV treatment uptake rates	**SCCS**	**SHCS**	**St. Gallen**	**Bern**
– **all chronically HCV infected**	57% (1915/3374)	28% (497/1752)	23% (21/91)	8% (8/102)
– HIV-HCV-co-infected (HIV+)	33% (82/246)	28% (497/1752)	4% (1/23)	10% (2/21)
– HCV-mono-infected (HIV-)	60% (1517/2519)	–	29% (20/68)	7% (6/81)
– **all in drug substitution program**	38% (282/753)	24% (128/545)	23% (21/91)	8% (8/102)
– **all non-IDUs**	65% (963/1493)	36% (159/445)	–	–
Proportion with SVR, if treated	**SCCS**	**SHCS**	**St. Gallen**	**Bern**
– **all** (with known genotype)	53% (564/1066)	50% (116/230)	47% (8/17)	63% (5/8)
– all with genotype 1	37% (176/474)	36% (32/89)	38% (3/8)	0% (0/1)
– all with genotype 3	66% (264/399)	65% (69/106)	67% (4/6)	71% (5/7)
– **all HIV+** (with known genotype)	44% (19/43)	50% (116/230)	0% (0/1)	100% (2/2)
– **all HIV-** (with known genotype)	54% (464/856)	–	50% (8/16)	50% (3/6)
– **all in drug substitution program** (with known genotype)	64% (85/133)	46% (26/57)	47% (8/17)	63% (5/8)
– **all non-IDUs** (with known genotype)	49% (274/557)	54% (41/76)	–	–

SCCS = Swiss Hepatitis C Cohort Study, SHCS = Swiss HIV Cohort Study, IDU = intravenous drug use, HCV = Hepatitis C virus, HIV = Human immunodeficiency virus, SVR = sustained virological response (HCV RNA negative 6 months after the end of treatment)
An extended version of this table can be found in the supplementary material (Supplementary table 2).

rhosis or liver stiffness of 13 kPa or more. Varices were found in 4/9 (44%) of patients.

HCV genotype distribution (St. Gallen)

Genotype distribution among those with detectable HCV RNA and thus still in need of treatment was as follows: 50% (33/66) with genotype 1, 24% (16/66) with genotype 3 and 26% (17/66) with genotype 4.

In contrast, genotype distribution among those who had ever received HCV treatment was 43% (9/21) with genotype 1, 48% (10/21) with genotype 3 and 5% (1/21) with genotype 4.

Delay of HCV diagnosis and treatment (St. Gallen)

The median delay from the estimated date of infection (start of i.v.-drug use) to HCV diagnosis was 10 years (range: –5 to 37 years, n = 136), and the median delay from the diagnosis to the start of HCV treatment was another 7.5 years (range: 0–13 years, n = 20), resulting in a total median delay of 17 years (range: 5–33 years, n = 19) from the estimated date of infection (start of i.v.-drug use) to the therapy start (fig. 1).

Potential barriers to treatment (St. Gallen)

A substantial proportion of the 78 HCV RNA-positive patients had an alcohol consumption >40 g/d (26%), suffered from depression (32%), had already attempted to commit suicide (17%), and/or had a history of epilepsy (21%). In contrast, thyroid disease was rather rare with 1%. Only 40% (31/78) had none of these five potential barriers to treatment.

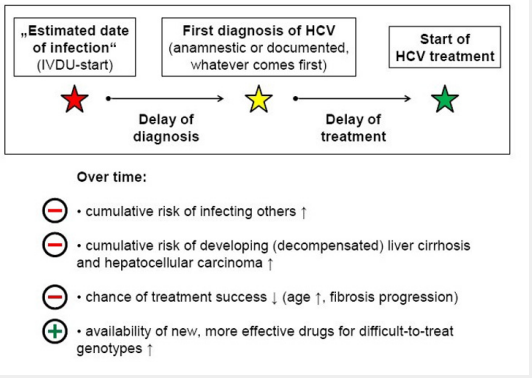

Figure 1

Delay of HCV diagnosis and treatment.

Comparison between patients ever treated and never treated for HCV (St. Gallen)

HCV treatment uptake rates were highest in genotype 3 patients and lowest in genotype 4 patients (genotype 1: 24% (9/37), genotype 3: 43% (10/23), genotype 4: 6% (1/18)). HCV genotype 3 patients were significantly more likely to receive treatment than patients with other genotypes (OR 3.40 (1.15–10.25)). In contrast, HCV treatment uptake was significantly lower in HIV-HCV-co-infected patients compared to HCV-mono-infected patients (OR 0.11 (0.005–0.67) (table 3).

There was a tendency towards a higher frequency of depression and suicide attempts, and a lower prevalence of alcohol-consumption >40 g/d in treated versus untreated patients in St. Gallen (data collection in most cases after the end of HCV treatment). However, differences were not statistically significant (p values >0.2) (supplementary table 3). Besides, a documentation bias favouring the documentation of depression and suicide attempts in treated patients cannot be excluded.

Patients receiving heroin substitution were over-represented among HCV-treated patients (OR for HCV treatment uptake: 2.57 (0.95-6.96) for heroin versus methadone substitution, $p = 0.06$) (table 3 and supplementary table 3).

HIV-co-infection (St. Gallen and Bern)

Almost 80% (29/37) of HIV-positive patients in St. Gallen were on antiretroviral treatment, translating to a proportion of >70% (27/37) with completely suppressed viremia (i.e. HIV RNA <50 cop/ml). About 80% (23/29) had an abacavir and about 20% (5/29) underwent a tenofovir-based HIV-therapy (in combination with lamivudine (3TC) or emtricitabine (FTC)). For the majority (>90%; 27/29), the regimen was protease inhibitor-based (given potential interactions between non-nucleoside reverse transcriptase inhibitors and methadone). Almost half of the patients (46% (17/37)) had a CD4-nadir <200/ul. However, the most recent CD4-count was ≥200/ul in about 90% (23/37) of patients, ≥350/ul in 62% (23/37) and ≥500/ul in 41% (15/37).

In KODA Bern, the proportion of HIV-positive patients on antiretroviral treatment was 65% (17/26). Three of the nine untreated individuals would have qualified for therapy according to current guidelines.

Hepatitis A and B (St. Gallen and Bern)

Hepatitis A and B screening and vaccination in the case of negative titers is a well-accepted standard of care in HCV infected patients [2].

Table 3: Logistic regression derived odds ratios for treatment uptake.

	St. Gallen OR (95% CI)	SCCS OR (95% CI)	SHCS OR (95% CI)
Heroin vs. methadone substitution	2.57 (0.95–6.96)	–	–
Drug substitution program vs. never IDU	–	0.32 (0.27–0.39)	0.47 (0.35–0.63)
HCV genotype 3 vs. other HCV genotype	3.40 (1.15–10.25)	1.69 (1.44–1.99)	2.29 (1.80–2.92)
HCV genotype 1 vs. HCV genotype 3	0.42 (0.14–1.27)	0.58 (0.49–0.69)	0.50 (0.39–0.64)
HCV genotype 4 vs. HCV genotype 3	0.08 (0.009–0.68)	0.41 (0.31–0.54)	0.27 (0.19–0.40)
HIV-HCV-co-infection vs. HCV-mono-infection	0.11 (0.005–0.67)	0.33 (0.25–0.44)	–

Statistically significant results are highlighted with red colour.
OR = odds ratio, 95% CI = 95% confidence interval, SCCS = Swiss Hepatitis C Cohort Study, SHCS = Swiss HIV Cohort Study, IDU = intravenous drug use, HCV = Hepatitis C virus, HIV = Human immunodeficiency virus

In St. Gallen, hepatitis A/B-serology was lacking in about 10%. In those with available serology, three-quarters were immune against hepatitis A (anti-HAV positive: 134/175) and B (anti-HBc positive or anti-HBs >100 positive: 129/171). A total of 50% of all patients were anti-HBc positive (94/186; i.e. someday naturally infected), and only 1% (1/160) were HBsAg positive (i.e. chronically infected; HBV-DNA not determined). As a general observation, the hepatitis A/B vaccination status was often insufficiently documented.

In KODA Bern, hepatitis A/B-serology was also available in about 90%. Of those, 81% (147/182) were anti-HAV positive and 85% (158/186) were anti-HBs and/or anti-HBc positive. The proportion with anti-HBc-positivity, and thus the presumed previous infection, was 73% (135/186). A positive HBs-Ag was found in 4% (7/186).

HCV treatment uptake and outcome in comparison with SCCS and SHCS data

With 23% (HIV-: 29%, HIV+: 4%; St. Gallen) and 8% (Bern), HCV treatment uptake in the absence of spontaneous clearance was lower in the investigated drug substitution programs than in the SCCS (57%; HIV-: 60%, HIV+: 33%) and the SHCS (28%, all HIV+) in general. It was also lower than in drug substitution program participants within the SCCS (38%; HIV-: 42%, HIV+: 22%) and SHCS (24%, all HIV+), and particularly lower than in non-IDUs within the SCCS (65%; HIV-: 68%, HIV+: 58%) and SHCS (36%, all HIV+) (table 2 and supplementary table 2).

The odds ratios for HCV treatment uptake and SVR in comparison with St. Gallen are given in table 4.

For patients with genotype known, SVR-rates were about 50% (genotype 1: 36-37%, genotype 3: 65-66%) both in the SCCS and SHCS, which is comparable with those in the drug substitution programs of St. Gallen (table 2).

Within the SCCS, SVR-rates were not significantly higher in HIV-negative compared to HIV-positive patients (54% versus 44%, $p = 0.20$; OR 1.49 (0.80–2.80)). Within the SHCS, not significantly higher SVR-rates were achieved in non-IDUs than in patients in drug substitution programs (54% versus 46%, $p = 0.35$; OR 1.39 (0.70–2.80)). However, the opposite was observed in the SCCS (49% in non-IDUs versus 64% in opioid substitution program participants, $p = 0.002$; OR 0.55 (0.37–0.81)) (table 2).

Comparison between patients treated at least once and patients never treated for HCV (SCCS and SHCS)

Similar to the observations in the three drug substitution programs of St. Gallen, SCCS and SHCS patients with HCV genotype 1 and 4 were less likely to receive HCV treatment compared to genotype 3 patients ($p < 0.01$). Likewise, the likelihood of HCV treatment uptake was significantly lower for HIV-HCV-co-infected patients than for HCV-mono-infected patients in the SCCS (OR 0.33 (0.25–0.44), $p < 0.01$). Drug substitution program participants were significantly less likely to get HCV treatment than patients without IDU as a risk factor both in the SCCS and SHCS ($p < 0.01$) (table 3).

Discussion

HCV-screening

Considering the multiple difficulties in the medical management of drug addicts and prior study results, the diagnostic work-up of HCV was better than expected.

In Zurich, the most highly populated canton in Switzerland, the HepCOP1-Study demonstrated, in 2008, that 50% of all patients treated with methadone substitution were insufficiently screened for HCV (in 29% there was no HCV antibody test, in 22% of the anti-HCV-positives there was no HCV RNA and in 53% of the HCV RNA-positives no genotype was available) [3, 18]. In the three drug substitution programs in St. Gallen, we observed incomplete HCV assessment in only 14% (27/196) (in 1% a HCV antibody test was missing, in 9% HCV RNA was lacking and in 15% genotype was lacking). However, in about 50% of the HCV-negative screened patients, the last test was older than one year. Difficulties to obtain blood by venous puncture in former IDUs might complicate retesting, which can be overcome by using capillary diagnostic tools [19]. In June 2010, the first HCV-rapid test (OraQuick® HCV Rapid Antibody test) was FDA-approved (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm217318.htm).

HCV treatment uptake

Insufficient HCV treatment uptake (particularly in HIV-co-infected patients) is still a major problem, although the cost-effectiveness of HCV treatment has been shown in several studies [20, 21]. Achieving SVR means long-term remission of disease, with liver-related mortality comparable to the general population [22]. Drug substitution pro-

Table 4: Comparison of HCV treatment uptake and success between St. Gallen, Bern, SCCS and SHCS.

	OR for HCV treatment uptake (95% CI)	OR for SVR (95% CI)
St. Gallen	1	1
Bern	0.28 (0.12–0.68)	1.88 (0.34–10.46)
SCCS	4.38 (2.67–7.16)	1.26 (0.48–3.30)
SHCS	1.32 (0.83–1.47)	1.15 (0.43–3.07)
Drug substitution program in the SCCS	2.00 (1.20–3.32)	1.99 (0.72–5.50)
Drug substitution program in the SHCS	1.02 (0.60–1.73)	0.94 (0.32–2.79)
Non-IDU in the SCCS	6.06 (3.68–9.98)	1.09 (0.41–2.86)
Non-IDU in the SHCS	1.85 (1.10–3.13)	1.32 (0.46–3.78)

Statistically significant results are highlighted with red colour.
OR = odds ratio, 95% CI = 95% confidence interval, SVR = sustained virological response (HCV RNA negative 6 months after the end of treatment), SCCS = Swiss Hepatitis C Cohort Study, SHCS = Swiss HIV Cohort Study, IDU = intravenous drug use, HIV = Human immunodeficiency virus

grams have improved survival of IDUs [3]. However, the extended life expectancy increases the relevance of HCV-induced liver morbidity and mortality [23]. The costs of HCV treatment with pegylated interferon and ribavirin (approximately 20'000 CHF for genotype 1 and 15'000 CHF for genotype 2/3 [24]) must be weighed against the costs for liver transplantation (120'000 CHF) [25], post-transplantation care as well as management of decompensated liver cirrhosis and HCC [23].

According to historical SCCS data from 2006/2007, 44% (485/1092) of non-IDUs, but only 8.7% (77/882) of patients in opioid substitution programs were treated for their chronic hepatitis C [2, 7]. The current data show an improvement to 65% for non-IDUs and 38% for heroin/methadone recipients (table 2). Thus, the treatment gap tends to decrease but has not disappeared, although adherence, side effects and treatment outcome do not differ (no matter whether IDU is entirely stopped or still ongoing) [6]. This trend might be a result of the new international consensus guidelines of 2002, not advising against HCV treatment in IDUs and heroin/methadone recipients anymore [26–28].

Treatment uptake-rates in HIV-co-infected patients were consistently lower both in the SCCS (overall: 33%, in drug substitution program: 22%) and the SHCS (overall: 28%, in drug substitution program: 24%) compared to 60% in HCV-mono-infected SCCS-participants (table 2).

Comparing treated with untreated patients (supplementary table 3), non-IDUs and HCV-genotype 3-infected patients (possibly faster fibrosis progression than other genotypes [29]) were more likely to receive therapy, and methadone/heroine recipients, HCV-genotype 4-infected and HIV-co-infected patients were less likely to receive therapy (table 3). Lower treatment response rates in HCV-genotype 4 as well as HIV-co-infected patients (generally 10–15% lower than in HCV-mono-infected) [30], and a longer duration of therapy might be an obstacle. Among treated patients, methadone recipients were under-represented and heroin recipients were over-represented, suggesting that the heroin setting with a low yearly fluctuation and twice daily contacts allowing DOT is advantageous for HCV treatment.

The low treatment rate in KODA Bern may be explained by the lack of somatic physicians in a program mainly focussed on psychiatric care. Several potential barriers to treatment (mainly alcohol abuse, depression, former suicide attempts, epilepsy) must be managed prior to and during HCV therapy, demanding a multidisciplinary approach including psychiatrists, neurologists and hepatologists and/or infectious diseases specialists. Absolute abstention from alcohol and IDU is not mandatory during HCV treatment, as long as adherence is not jeopardised [6, 31].

Delay of HCV diagnosis and treatment

In contrast to HIV, HCV is a potentially curable disease with the best responses to treatment in its acute phase (80–90% SVR irrespective of genotype), i.e. if treated within 12 weeks in patients whose acute HCV-infection does not spontaneously resolve by week 8 [32, 33]. Once liver fibrosis has developed, HCV treatment becomes less effective [34] and in the case of decompensated liver cirrhosis, liver transplantation remains the last option. However, even the new AASLD practice guidelines from 2009 continue to recommend HCV treatment still mainly, when liver fibrosis is already established [35].

Due to its often asymptomatic course, hepatitis C is usually not diagnosed in its acute phase. Taking into account that new IDUs are at high risk of acquiring HCV infection shortly after initiating injecting [36, 37], the day of the first intravenous drug use might serve as a proxy for the date of HCV-infection in IDUs. Accordingly, in the drug substitution programs of St. Gallen, the median delay between the "estimated date of infection" (IDU start) and the first diagnosis of HCV was 10 years and the median delay between diagnosis and treatment initiation was another 7.5 years. Thus, the median lag time from infection to treatment was approximately 17 years, a time frame in which cirrhosis can already develop (up to 20% over a 20–25-year period [38]). Advanced age results in a reduced treatment response [35] and the period of infectiousness is extended (fig. 1).

In IDUs, faster liver disease progression must be postulated because of multiple additional hepatotoxic factors such as alcohol [39], cannabis [40, 41], HBV- [42] and HIV-co-infection [9, 10], as well as co-medication. Accordingly, a general indication for HCV treatment in IDUs irrespective of the fibrosis grade might be worth discussion.

One argument in favour of postponing treatment would be to wait for the availability of new, more effective drugs for difficult-to-treat genotypes. In 2012, the protease-inhibitors telaprevir and boceprevir will come onto the market for HCV-genotype 1, increasing treatment response rates to >70%, in some cases after only 24–28 weeks (comparable to genotype 2/3) [43]. In combination with ribavirin and pegylated interferon, twice daily telaprevir seems not to be inferior to three times a day [44], permitting DOT. This is of special relevance for the patients in the three drug substitution programs in St. Gallen, because among those still in need of treatment (currently HCV RNA positive) 50% (33/66) have genotype 1. Certainly, additional side effects (more anaemia and rashes) must be managed, at least with the first generation protease inhibitors.

However, the best medicine is useless, if it is not applied. Thus, not only an improvement of drugs, but also a further increase of treatment uptake is necessary in order to prevent more liver-related deaths by HCV treatment [22]. In a US-survey, the primary reason for lack of treatment was lack of diagnosis (about 50% of respondents), another 24% were recommended by their doctor not to be treated and only 12% finally received treatment [22]. A total of 72% of primary care physicians would not refer a patient with normal liver enzymes for treatment [45], despite evidence that such patients can develop progressive disease [46].

HCV treatment outcomes

Irrespective of HIV- and IDU-status, SVR rates were quite similar in the investigated drug substitution programs in St. Gallen and Bern as well as in the SCCS and SHCS, which were about 50% overall (table 2 and supplementary table 2).

In this context, a Swiss study was only recently published reporting equal SVR rates for HCV-mono- and HIV-HCV-co-infected patients with favourable HCV genotypes 2 and 3 after only 6 months of Peginterferon alpha 2a plus rib-

avirin [47]. As already mentioned above, several studies have shown comparable HCV treatment response rates for IDUs and non-IDUs [4–6, 48]. Within the SCCS, SVR-rates were even significantly higher in methadone/heroin-recipients compared to non-IDUs (64% versus 49%, p <0.01). This might be partly explained by the fact that: 1) current or former IDUs have only been treated for a short time and thus were not exposed to less effective treatment regimens of the past, 2) HCV RNA 6 months after the end of treatment is more likely to be available in compliant patients who are also more likely to have treatment success and 3) substituted patients often experience a more intensive care during their HCV-therapy than non-IDUs. However, a selection bias due to stricter patient selection cannot be excluded.

Limitations

Some of the patients in the three largest drug substitution programs in St. Gallen were also participants in the SCCS and SHCS.

Conclusions/Future Strategies

In order to increase the number of liver-related deaths prevented by HCV treatment, not only better drugs which are needed, but also treatment uptake must also be increased (Volk, 2009), particularly in participants of drug substitution programs and HIV-co-infected patients who are currently significantly undertreated despite a comparable treatment response.

HCV-negative patients at risk should be screened in regular intervals [2] to diagnose HCV earlier and treatment should be offered as soon as possible after diagnosis to prevent a delay of treatment. The latter accounts for an increasing risk of developing liver cirrhosis and HCC, and a reducing chance of treatment response over time (already established fibrosis, age >40 years) as well as for an uninterrupted transmission chain (fig. 1), which constitutes a socio-economic problem.

A total of 50% of the patients still in need of treatment (i.e. currently HCV RNA positive) have HCV genotype 1, for which the new protease-inhibitors telaprevir and boceprevir will be available in 2012, increasing SVR rates to >70%, for some patients after only 24 weeks, which is comparable to genotype 2/3. Twice daily dosing of telaprevir and ribavirin in combination with peginterfon-injections once a week permits DOT, particularly in heroin substitution programs. The treatment outcome in HCV genotype 4 might improve with the availability of the new polymerase-inhibitors effective irrespective of genotype.

Due to the numerous co-morbidities and social problems linked to drug addiction, HCV treatment in drug substitution program participants demands an interdisciplinary approach involving social workers, drug addiction specialists, psychiatrists, neurologists and hepatologists/infectious diseases specialists. Insidiously, chronic hepatitis C is usually clinically silent until advanced stages of liver disease have occurred. Thus, insight into the illness and treatment readiness cannot be taken for granted, but must be inspired.

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Supplementary Material

Supplementary table 1: Characteristics of the three drug substitution programs in St. Gallen (extended version).

	MSH1	**MSH2**	**H22**
Founded	1995	1993	1990
Substituted drug	Heroin i.v. 2x/d	Methadone p.o. 1x/d	Methadone p.o. 1x/d
Capacity (patients)	Max. 75	Max. 100	35
Yearly fluctuation (patients)	about 8 (10%)	50–60 (about 50%)	about 5 (14%)
Open (days/week)	7	6	5
Medical care	2x 50% somatic physician on-site + infection case discussions at least every 6 weeks	2x 50% somatic physician on-site + infection case discussions at least every 6 weeks	Outpatient Clinic of the Department of Infectious Diseases
Number of patients included in the cross sectional study	**71**	**90**	**35**
Gender (female)	23% (16/71)	23% (21/90)	31% (11/35)
Median age (years) (range)	42 (26–63)	39 (20–63)	42 (29–61)
Median time in program since last admission (years) (range)	5.0 (0–14)	2.0 (0–16)	3.7 (0–19)
Frequency of attendance – daily – several times a day	 100% (71/71) 93% (66/71)	 77% (69/90) 1% (1/90)	 87% (30/35) 11% (4/35)
Opioid substitution – heroin – methadone – buprenorphine	 94% (67/71) 6% (4/71) 0% (0/71)	 0% (0/90) 97% (87/90) 3% (3/90)	 0% (0/35) 100% (35/35) 0% (0/33)
Never IDU	5% (3/67)	22% (20/90)	0% (0/35)
HIV- and HCV-negative	17% (12/71)	38% (33/87)	0% (0/35)
HCV-infection (anti-HCV+)	82% (58/71)	61% (54/88)	97% (34/35)
HCV RNA+, if anti-HCV+ and HCV RNA available	48% (27/56)	63% (27/43)	71% (24/34)
HIV-infection	18% (13/71)	0% (0/88)	69% (24/35)
HIV-HCV-co-infection	17% (12/71)	0% (0/87)	66% (23/35)
SCCS-participation, if HCV+	50% (29/58)	33% (18/54)	88% (30/34)
SHCS-participation, if HIV+	100% (13/13)	NA*	100% (24/24)

MSH1 = heroin substitution program of the addiction aid trust St. Gallen, MSH2 = methadone substitution program of the addiction aid trust St. Gallen, H22 = methadone substitution program of the Outpatient Clinic of the Department of Infectious Diseases of the Cantonal Hospital St. Gallen, i.v. = intravenous, p.o. = per os, max. = maximal, IDU = intravenous drug use, HIV = Human immunodeficiency virus, HCV = Hepatitis C virus, SCCS = Swiss Hepatitis C Cohort Study, SHCS = Swiss HIV Cohort Study, NA = not applicable, * no HIV+ patients

Supplementary table 2: Patient characteristics, HCV treatment uptake and success rates (extended version).

	SCCS	**SHCS**	**St. Gallen**	**Bern**
Number of patients	3602	16285	196	202
Median age (years) (range)	48 (19–91)	48 (18–101)	41 (20–63)	39 (21–71)
Gender (female)	37% (1335/3602)	29% (4659/16285)	25% (48/196)	28% (57/202)
Drug substitution program	24% (872/3600)	9% (796/8517)	100%	100%
No IDU	43% (1534/3595)	71% (11326/15960)	12% (23/190)	0%
HCV-infected	100%	29% (3319/11527)	75% (146/194)	80% (161/200)
HCV RNA+, if anti-HCV+ and HCV RNA available	68% (2425/3575)	67% (1446/2153)	59% (78/133)	65% (97/150)
HIV-infected	10% (285/2974)	100%	19% (37/194)	13% (26/195)
HIV-HCV-co-infected	10% (285/2974)	29% (3319/11527)	18% (35/193)	13% (26/195)
Liver biopsy, if no spontaneous clearance	66% (2234/3374)	40% (696/1752)	35% (32/91)	No data
HCV treatment uptake rates	**SCCS**	**SHCS**	**St. Gallen**	**Bern**
– **all chronically HCV infected**	57% (1915/3374)	28% (497/1752)	23% (21/91)	8% (8/102)
– HIV-HCV-co-infected (HIV+)	33% (82/246)	28% (497/1752)	4% (1/23)	10% (2/21)
– HCV-mono-infected (HIV-)	60% (1517/2519)	–	29% (20/68)	7% (6/81)
– **all in drug substitution program**	38% (282/753)	24% (128/545)	23% (21/91)	8% (8/102)
– drug substitution and HIV+	22% (27/123)	24% (128/545)	4% (1/23)	10% (2/21)
– drug substitution and HIV-	42% (234/564)	–	29% (20/68)	7% (6/81)
– **all non-IDUs**	65% (963/1493)	36% (159/445)	–	–
– non-IDU and HIV+	58% (18/31)	36% (159/445)	–	–
– non-IDU and HIV-	68% (737/1084)	–	–	–
Proportion with SVR, if treated	**SCCS**	**SHCS**	**St. Gallen**	**Bern**
– **all** (with known genotype)	53% (564/1066)	50% (116/230)	47% (8/17)	63% (5/8)
– all with genotype 1	37% (176/474)	36% (32/89)	38% (3/8)	0% (0/1)
– all with genotype 3	66% (264/399)	65% (69/106)	67% (4/6)	71% (5/7)
– **all HIV+** (with known genotype)	44% (19/43)	50% (116/230)	0% (0/1)	100% (2/2)
– HIV+ with genotype 1	38% (8/21)	36% (32/89)	0% (0/1)	–
– HIV+ with genotype 3	50% (10/20)	65% (69/106)	–	100% (2/2)
– **all HIV-** (with known genotype)	54% (464/856)	–	50% (8/16)	50% (3/6)
– HIV- with genotype 1	38% (140/369)	–	43% (3/7)	0% (0/1)
– HIV- with genotype 3	68% (226/334)	–	67% (4/6)	60% (3/5)
– **all in drug substitution program** (with known genotype)	64% (85/133)	46% (26/57)	47% (8/17)	63% (5/8)
– drug substitution and genotype 1	57% (24/42)	45% (14/31)	38% (3/8)	0% (0/1)
– drug substitution and genotype 3	67% (53/79)	46% (10/22)	67% (4/6)	71% (5/7)
– **all non-IDUs** (with known genotype)	49% (274/557)	54% (41/76)	–	–
– non-IDU with genotype 1	33% (98/294)	44% (12/27)	–	–
– non-IDU with genotype 3	63% (74/118)	74% (23/31)	–	–

SCCS = Swiss Hepatitis C Cohort Study, SHCS = Swiss HIV Cohort Study, IDU = intravenous drug use, HCV = Hepatitis C virus, HIV = Human immunodeficiency virus, SVR = sustained virological response (HCV RNA negative 6 months after the end of treatment)

Supplementary table 3: Characteristics of patients treated versus not treated for hepatitis C (St. Gallen, SCCS, SHCS).

	Treated (St. Gallen)	Not treated (St. Gallen)	*p* values*	Treated (SCCS)	Not treated (SCCS)	*p* values*	Treated (SHCS)	Not treated (SHCS)	*p* values*
Median age at first diagnosis (years) (range)	33 (18–50)	31 (19–54)		38 (10–78)	35 (8–81)		35 (18–58)	34 (16–68)	
Median age at treatment start (years) (range)	38 (21–57)	–		43 (16–80)	–		42 (23–61)	–	
Median time since first diagnosis at treatment start (years) (range)	7.5 (0–13)	–		3 (0–38)	–		7 (0–20)	–	
Methadone substitution	48% (10/21)	70% (49/70)	$p = 0.06$	–	–		–	–	
Heroin substitution	52% (11/21)	30% (21/70)	$p = 0.06$	–	–		–	–	
Drug substitution program	–	–		14% (263/1828)	32% (460/1435)	$p < 0.001$	28% (128/453)	45% (418/930)	$p < 0.001$
Never IDU	–	–		51% (927/1824)	37% (524/1433)	$p < 0.001$	26% (129/488)	16% (198/1272)	$p < 0.001$
Genotype 1	45% (9/20)	48% (28/58)	$p = 0.80$	46% (677/1460)	55% (769/1404)	$p < 0.001$	45% (179/397)	52% (574/1109)	$p = 0.02$
Genotype 3	50% (10/20)	22% (13/58)	$p = 0.02$	36% (518/1460)	25% (344/1404)	$p < 0.001$	42% (167/397)	24% (267/1109)	$p < 0.001$
Genotype 4	5% (1/20)	29% (17/58)	$p = 0.03$	8% (114/1460)	13% (184/1404)	$p < 0.001$	10% (39/397)	20% (228/1109)	$p < 0.001$
HIV-co-infection	5% (1/21)	31% (22/70)	$p = 0.01$	5% (79/1534)	14% (161/1149)	$p < 0.001$	–	–	
Depression	43% (9/21)	30% (21/70)	$p = 0.27$						
Suicide attempt	29% (6/21)	16% (11/70)	$p = 0.31$						
Alcohol-consumption >40 g/d	14% (3/21)	27% (19/70)	$p = 0.22$						
Epilepsy	24% (5/21)	19% (13/70)	$p = 0.80$						
Thyroid disease	10% (2/21)	0% (0/70)	$p = 0.10$						

* *p* values were calculated with Chi-square or Fisher's exact test, when sample sizes was small. Statistically significant results are highlighted with red colour.
SCCS = Swiss Hepatitis C Cohort Study, SHCS = Swiss HIV Cohort Study, IDU = intravenous drug use, HIV = Human immunodeficiency virus