swiss medical weekly

Original article | Published 24 June 2024 | doi:https://doi.org/10.57187/s.3698
Cite this as: Swiss Med Wkly. 2024;154:3698

Real-life experience of chronic hepatitis C treatment in Switzerland: a retrospective analysis

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Summary

BACKGROUND AND AIM: Direct-acting antivirals (DAAs) have revolutionised the management of chronic hepatitis C. We analysed the use of different generations of DAAs over time in Switzerland and investigated factors predictive of treatment failure.

METHODS: This retrospective study was conducted within the framework of the Swiss Association for the Study of the Liver and the Swiss Hepatitis C Cohort Study; it included all patients with chronic hepatitis C treated with DAAs between January 2015 and December 2019 at eight Swiss referral centres.

RESULTS: A total of 3088 patients were included; 57.3% were male, and the median age was 54 years. Liver cirrhosis was present in 23.9% of the cohort, 87.8% of whom were compensated. The overall sustained virological response (SVR) rate (defined as undetectable HCV RNA at week 12 after the first course of DAA-based treatment) was 96.2%, with an increase over time. The rate of treatment failure dropped from 8.3% in 2015 to 2.5% in 2019. Multivariable analysis revealed that female sex, the use of the latest generation of pangenotypic DAA regimens, Caucasian origin, and genotype (gt) 1 were associated with SVR, whereas the presence of active hepatocellular carcinoma (HCC), gt 3, and increasing liver stiffness were associated with treatment failure. Notably, the presence of active HCC during treatment increased the risk of DAA failure by a factor of almost thirteen.

CONCLUSIONS: SVR rates increased over time, and the highest success rates were identified after the introduction of the latest generation of pangenotypic DAA regimens. Active HCC, gt 3 and increasing liver stiffness were associated with DAA failure.

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Introduction

Chronic hepatitis C virus (HCV) infection is one of the most prevalent causes of advanced liver disease and hepatocellular carcinoma (HCC). Approximately 10–20% of individuals who are chronically infected develop complications over a period of 20–30 years, including cirrhosis, liver decompensation, and HCC [1, 2]. In 2019, HCV infection led to 287,000 deaths; two-thirds of these were related to cirrhosis and end-stage liver disease, and one-third were related to HCC [3]. An estimated 56.8 million individuals are chronically infected worldwide [4]. In Switzerland, an estimated 32,100 individuals were chronically infected at the beginning of 2020 [5].

Sustained virological response (SVR) is associated with a decrease in liver-related and all-cause mortality [6]. According to the European Association for the Study of the Liver (EASL), the American Association for the Study of Liver Diseases (AASLD), and the Infectious Diseases Society of America (ISDA), antiviral treatment should be proposed to all patients with chronic HCV infection except those with a limited life expectancy that cannot be improved by antiviral therapy, liver transplantation (LT), or other liver-directed therapies [7, 8]. The World Health Organization (WHO) has stated that it aims to eliminate (i.e. control) HCV infection by 2030 [9].

The treatment of chronic hepatitis C entered a new era when direct-acting antivirals (DAAs) were introduced in 2011. These drugs show excellent tolerance and a relatively short treatment duration, and the latest pangenotypic regimens are associated with SVR rates of >95% [10–14].

Real-life data on DAA treatment in Switzerland are limited [15–17]. Access to DAA treatment for chronic hepatitis C in Switzerland was restricted to patients with advanced fibrosis or cirrhosis (Metavir stages F3 and F4) until the first

half of 2015 and a Metavir stage of at least F2 until the fall of 2017. These restrictions were primarily due to the high cost of DAAs, prompting healthcare authorities to prioritise treatment for individuals at the highest risk of liver-related complications. Since the fall of 2017, DAA treatment has been reimbursed regardless of the fibrosis stage.

This study's primary aim was to assess the real-life SVR rates (defined as undetectable HCV RNA at week 12 after the end of treatment). The secondary aim was to identify risk factors for DAA treatment failure in a large cohort of patients followed at eight referral centres in Switzerland.

Patients and methods

Study design and patient population

This observational retrospective multicentre study was conducted within the framework of the Swiss Association for the Study of the Liver (SASL Study 44) and the Swiss Hepatitis C Cohort Study. The study included all adult patients with chronic HCV infection who were treated with interferon-free DAA regimens between January 2015 and December 2019 at eight referral centres in Switzerland. Patients with HIV coinfection were excluded.

Each centre was represented by a local principal investigator. Data were retrieved manually from electronic medical records and medical archives, and they were anonymised before being transferred to the investigators at Lausanne University Hospital.

This study was approved by the local ethics committees (CER-VD multicentric protocol number 2020-01232). Informed consent was waived.

Data collection and definition

The following data were captured for each patient: age; sex; ethnicity; Metavir fibrosis stage (F0–F4) when a liver biopsy was available or liver stiffness measurement as assessed by transient elastography (FibroScan, Echosens, Paris, France); Child-Turcotte-Pugh (CTP) score (A5–C15); the absence or presence of hepatitis B virus (HBV) coinfection; viral genotype (gt); the results of resistance-associated substitution (RAS) analyses (when available); history of HCC or active HCC (defined as imaging evidence of localised or metastatic disease at DAA initiation); type of DAA regimen; and SVR (SVR group) or failure to achieve SVR after the first course of interferon-free DAA-based treatment (non-SVR group). SVR was defined as undetectable HCV RNA at week 12 after the end of treatment.

Liver cirrhosis was defined by any of the following: Metavir fibrosis stage 4 on liver histology, a liver stiffness measurement of ≥12 kPa, or clinical evidence of cirrhosis based on an evaluation by the referring hepatologist.

Treating physicians chose the type and duration of DAA regimens according to the regularly updated Expert Opinion Statements by the Swiss Association for the Study of the Liver, the Swiss Society of Gastroenterology, and the Swiss Society for Infectious Diseases (available at https://www.sasl.ch). In general, these are in line with the EASL Recommendations [8] as well as the AASLD-IDSA Guidance [7] and consider the approval and reimbursement of the different regimens in Switzerland.

This study divided DAA regimens into two categories: nonpangenotypic and latest generation pangenotypic DAA regimens.

The nonpangenotypic regimen category comprised sofosbuvir + ribavirin (SOF + RBV), simeprevir/sofosbuvir ± ribavirin (SMV/SOF ± RBV), ledipasvir/sofosbuvir ± ribavirin (LDV/SOF ± RBV), ritonavir-boosted paritaprevir/ombitasvir ± dasabuvir ± ribavirin (PTV/r/OBV ± DSV ± RBV), grazoprevir/elbasvir ± ribavirin (GZR/EBR ± RBV), and the early pangenotypic regimen daclatasvir/sofosbuvir ± ribavirin (DCV/SOF ± RBV).

The latest generation pangenotypic regimen category consisted of velpatasvir/sofosbuvir ± ribavirin (VEL/SOF ± RBV), glecaprevir/pibrentasvir ± ribavirin (GLE/PIB ± RBV), glecaprevir/pibrentasvir + sofosbuvir ± ribavirin (GLE/PIB + SOF ± RBV), and voxilaprevir/velpatasvir/sofosbuvir ± ribavirin (VOX/VEL/SOF ± RBV).

Statistical analyses

Descriptive statistics are presented as the mean and standard deviation (SD) or the median and range for continuous variables and frequencies or percentages for categorical variables. The non-SVR group was compared with the SVR group using a logistic regression model. To account for the multicentre design, a robust standard error was calculated for parameter estimation. Univariable analysis was performed to identify factors associated with DAA failure. The strength of the association was measured using the odds ratio (OR) and the calculated p-value. The factors significantly associated with the outcome (i.e. those with a p-value of <10%) were tested in a stepwise backward selection procedure to fit a multivariable model. Standard goodness-of-fit tests for logistic regression were performed to assess the calibration of the fitted model. Statistical analyses were performed using Stata software (Stata Statistical Software: Release 16, StataCorp 2023, College Station, TX, USA).

Results

Study population

Between January 2015 and December 2019, 3088 patients with chronic HCV infection were treated with interferon-free DAA regimens at the eight participating centres. The patients' characteristics are presented in table 1.

The median age was 54 years (range, 18–88 years); 1287 patients (42.7%) were female, and most (93.0%) were Caucasian.

The median liver stiffness measurement was 7.3 kPa (range, 2.8-75 kPa). Of the 3088 patients, 1562 (50.6%) had a liver biopsy before DAA treatment; 126 (8.1%) had Metavir fibrosis stage F0, F1 in 421 (26.9%) had stage F1, 371 (23.7%) had stage F2, 218 (14.0%) had stage F3, and 426 (27.3%) had stage F4. A total of 729 patients (23.9%) had cirrhosis, and the CTP score could be calculated in 672 patients; 590 (87.8%) had CTP A, 76 (11.3%) had CTP B, and 6 (0.9%) had CTP C. Information on cirrhosis diagnosis and CTP score was missing for 38 and 57 patients, respectively.

The HCV genotype distribution was as follows: 1714 patients (55.7%) had gt 1, 246 (8.0%) had gt 2, 699 (22.7%)

had gt 3, 409 (13.3%) had gt 4, 5 (0.2%) had gt 5, and 5 (0.2%) had gt 6. Genotype information was missing for 10 patients (0.3%).

A total of 33 patients (1.2%) had HBV coinfection, 42 (1.4%) had active HCC at the time of DAA treatment, and 52 (1.7%) had a history of HCC.

During the study period, 10 DAA regimens associated or not associated with RBV were used according to the investigators' discretion (see Patients and methods). A total of 1866 patients (60.5%) were treated with nonpangenotypic DAA regimens, and 1221 (39.5%) were treated with latest generation of pangenotypic DAA regimens. Information regarding the DAA regimen was missing for one patient. The treatment duration ranged from 1.5 to 24 weeks, with a median of 12.0 weeks and a mean of 12.5 weeks. One patient with genotype 1a HCV infection who was considered chronically infected stopped treatment with GLE/PIB after 1.5 weeks. However, this patient achieved SVR (confirmed 24 weeks after treatment), suggesting that it was an acute infection.

Treatment outcome

Among the 3088 patients, 2972 (96.2%) achieved SVR after the first course of DAA treatment. SVR rates increased throughout this study, from 91.7% in 2015 to 97.5% in 2019 (figure 1). DAA failure was reported in 116 (3.8%) patients (table 1). Patients in the non-SVR group were mostly male (73.0%) with a median age of 55 years (range, 22–88 years). The median liver stiffness measurements were 7.3 kPa and 9.9 kPa in the SVR and non-SVR groups, respectively. Fifty-one patients in the non-SVR group (44.4%) had cirrhosis, with a CTP score of A in 86.2% and B in 11.8%. The CTP score could not be calculated for one patient in this group.

Table 1:
Baseline characteristics of patients in the SVR and non-SVR groups and univariable and multivariable logistic regression analyses. Variables in bold were significantly associated with DAA failure in the univariable or multivariable analysis. The retained covariables used for the multivariable analysis were sex, liver stiffness, genotype, active hepatocellular carcinoma (HCC), and the latest generation of pangenotypic regimens.

		SVR, n (%)	**Non-SVR, n (%)**	**Univariable analysis, OR (p-value)**	**Multivariable analysis, OR (p-value)**
Total		2972 (96.2%)	116 (3.8%)		
Age (years); mean (SD)		54.4 (12.0)	54.8 (10.5)	1.00 (0.82)	
Sex (female)[1]		1256 (42.3%)	31 (27.0%)	0.50 (0.02)	0.1 (0.004)
Ethnicity[2]	Caucasian	2769 (93.3%)	100 (86.2%)	0.45 ($<10^{-4}$)	0.35 (0.001)
	Asian	72 (2.4%)	4 (3.5%)	1.44 (0.47)	
	African	112 (3.8%)	10 (8.6%)	2.41 (0.001)	
	Latin American	16 (0.5%)	2 (1.7%)	3.24 (0.24)	
Metavir fibrosis score	F0 (reference)	121 (8.1%)	5 (7.5%)		
	F1	410 (27.4%)		0.65 (0.22)	
	F2	356 (23.8%)	15 (22.4%)	1.02 (0.95)	
	F3	215 (14.4%)	3 (4.5%)	0.33 (0.01)	
	F4	393 (26.%3)	33 (49.2%)	2.03 (0.04)	
Liver stiffness (kPa); mean (SD)		10.4 (9.8%)	17.3 (17.9%)	1.03 ($<10^{-4}$)	1.02 (0.003)
Cirrhosis[3 4]		678 (23.1%)	51 (44.4%)	2.65 ($<10^{-4}$)	
Child-Pugh score[4]	A	546 (87.8%)	44 (86.2%)	1.02 (0.94)	
	B	70 (11.2%)	6 (11.8%)	1.07 (0.79)	
	C	6 (1.0%)	0		
Genotype[4 5]	1	1678 (56.6%)	36 (31.6%)	0.35 ($<10^{-4}$)	0.36 (0.01)
	2	241 (8.1%)	5 (4.4%)	0.52 (0.07)	
	3	647 (21.8%)	52 (45.6%)	3.00 ($<10^{-4}$)	2.22 (0.003)
	4	388 (13.1%)	21 (18.4%)	1.49 (0.16)	
	5	5 (0.2%)	0		
	6	5 (0.2%)	0		
HBV coinfection		31 (1.1%)	2 (1.8%)	1.64 (0.54)	
HCC[4]	No HCC	2868 (97.4%)	98 (85.2%)	0.15 ($<10^{-4}$)	
	HCC in remission	47 (1.6%)	5 (4.3%)	2.80 (0.06)	
	Active HCC	30 (1.0%)	12 (10.4%)	11.32 ($<10^{-4}$)	12.99 (0.001)
	Latest generation pangenotypic regimen	1221 (39.5%)	20 (19.4%)	0.35 (0.003)	0.17 ($<10^{-4}$)

[1] Information on sex was missing for one patient.

[2] Information on ethnicity was missing for three patients.

[3] Data regarding the presence or absence of cirrhosis was missing for 38 patients. The Child–Pugh score could be determined for 672 of 729 cirrhotic patients.

[4] Each category was tested against the other categories taken together.

[5] Information on genotype was missing for 10 patients.

DAA, direct-acting antiviral; HBV, hepatitis B virus; OR, odds ratio; SD, standard deviation.

In total, 42 patients (1.4%) had active HCC at the time of DAA treatment, 30 (1.0%) of whom were in the SVR group and 12 (10.4%) of whom were in the non-SVR group. Furthermore, 52 patients (1.7%) had a history of HCC, 47 (1.6%) of whom were in the SVR group and 5 (4.3%) of whom were in the non-SVR group.

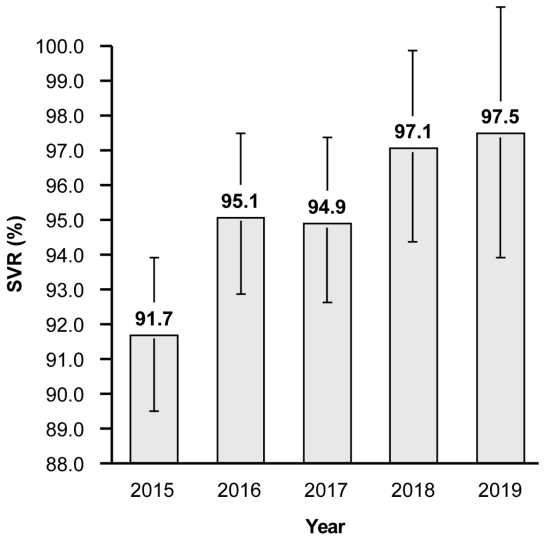
Risk factors for DAA failure

Several parameters were tested for possible association with DAA failure (table 1), including age, sex, ethnicity, Metavir score, liver stiffness measurement, the presence or absence of cirrhosis, CTP score, genotype, HBV coinfection, active HCC or history of HCC, and DAA regimen.

The univariable analysis revealed that the presence of active HCC at the time of antiviral treatment (OR 11.3, 95% confidence interval [CI] 4.8–26.2), gt 3 (OR 3.00, 95% CI 2.14–4.20), cirrhosis (OR 2.65, 95% CI 2.02–3.48), African ethnicity (OR 2.41 95% CI 1.45–3.99), Metavir stage F4 (OR 2.03, 95% CI 1.04–3.94), and liver stiffness measurement (OR 1.03, 95% CI 1.02–1.04) were significantly associated with DAA failure. Conversely, the absence of HCC (OR 0.15, 95% CI 0.07–0.36), Metavir stage F3 (OR 0.33, 95% CI 0.15–0.76), the use of the latest generation of pangenotypic DAA regimens (OR 0.35, 95% CI 0.15–0.76), gt 1 (OR 0.35, 95% CI 0.28–0.43), Caucasian origin (OR 0.45, 95% CI 0.37–0.54), and female sex (OR 0.50, 95% CI 0.28–0.87) were significantly associated with increased chances of achieving SVR.

Of these parameters, seven were associated with response to treatment in the multivariable analysis. Active HCC during treatment (OR 12.99, 95% CI 2.80–60.13, p = 0.001), gt 3 (OR 2.22, 95% CI 1.30–3.78, p = 0.003), and liver stiffness measurement (OR 1.02, 95% CI 1.00–1.04, p = 0.003) were independent predictors of an increased risk of DAA failure. The presence of active HCC during treatment increased the risk of DAA failure by a factor of almost 13. Liver stiffness measurement (as assessed by transient elastometry) was significantly correlated with the risk of DAA failure; this correlation was nearly linear starting at 40 kPa (figure 2). Conversely, female sex (OR 0.1, 95% CI 0.02–0.48, p = 0.004), the use of the latest generation of pangenotypic DAA regimens (OR 0.17, 95% CI 0.08–0.34 p $<10^{-4}$), Caucasian ethnicity (OR 0.35, 95% CI 0.19–0.64, p = 0.001), and gt 1 (OR 0.36, 95% CI 0.16–0.82, p = 0.01) were significantly associated with SVR.

Figure 1: Sustained virological response (SVR) rates achieved with interferon-free, direct-acting antiviral (DAA)-based treatment of chronic hepatitis C from 2015 to 2019. The vertical bars represent 95% confidence intervals for each year (2015, 89.5–93.9; 2016, 92.8–97.5; 2017, 92.6–97.3; 2018, 94.3–99.9; 2019, 94.0–101.1).



Retreatments

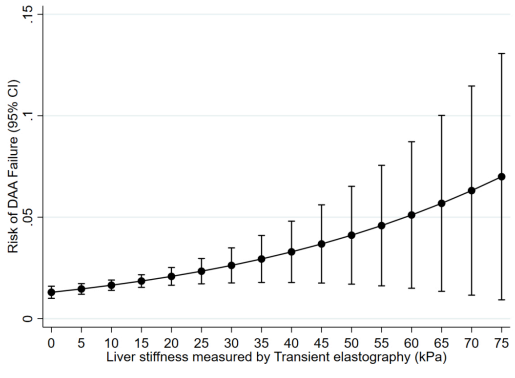
Of the 116 patients in the non-SVR group, 103 (88.8%) were retreated with a second DAA regimen, and 13 were not retreated for various reasons (three declined retreatment, one developed advanced-stage HCC, one died, and eight were lost to follow-up). Retreatment consisted of VOX/VEL/SOF in 43 patients (41.7%), VEL/SOF in 33 patients (32.0%), GLE/PIB in 10 patients (9.7%), GLE/PIB + SOF in 1 patient (1.0%), and nonpangenotypic DAAs in 16 patients (15.5%).

Of the 103 retreated patients, 88 (85.4%) achieved SVR, whereas 13 (12.6%) did not. Information on retreatment outcomes was not available for two patients (1.9%) because of loss to follow-up.

The characteristics of the 13 patients who experienced a second DAA failure are summarised in table S1 in the Appendix. These patients had a median age of 57 years (range, 35–73 years) and were mostly male (69.2%) and Caucasian (84.6%). Six patients (46.2%) had cirrhosis with a median CTP score of 5 (range, A5–B9). Five patients had gt 3 infection (38.5%).

Of the 13 patients who presented a second DAA failure, 11 received a third course of DAA treatment; 10 received VOX/VEL/SOF ± RBV, and 1 had missing information on the treatment used. One patient with decompensated cirrhosis and one patient with advanced HCC were not retreated. Nine of the eleven patients achieved SVR after a third course of DAAs, whereas two experienced a third DAA failure. One of the latter patients was retreated with a fourth course of DAAs (GLE/PIB + SOF + RBV for 24 weeks) and achieved SVR. No decision regarding further treatment was made for the second patient during the study

Figure 2: The adjusted predicted risk of DAA failure as a function of liver stiffness. Liver stiffness (as assessed by transient elastography) was significantly correlated with the risk of DAA failure, with a near-linear correlation starting at 40 kPa. For the multivariable model, see table 1.



period. The results of RAS analyses regarding those patients are presented in table S1 (patients 5 and 10).

The multivariable analysis revealed that the use of VOX/VEL/SOF ± RBV was associated with SVR when used as a second DAA regimen compared with other regimens (p = 0.005). Treatment success was not significantly affected by other baseline features, such as sex (p = 0.73), ethnicity (p = 0.65), liver stiffness measurement (p = 0.57), the presence of cirrhosis (p = 0.76), gt (p = 0.2), or the presence of active HCC (p = 0.63).

Resistance-associated substitution analyses

The results of RAS analyses were available for 86 of the 116 patients with DAA failure (74.1%). The analysis of the nonstructural protein 5A (NS5A) region was most frequently available (table 2). A total of 57 patients (66.2%) presented a significant RAS in the NS5A region, and 24 patients (27.9%) had no detectable RAS.

In NS5A, Q30R was predominant in patients infected with gt 1a, whereas Y93H was predominant in those with gt 1b and gt 3 infections. Overall, Y93H was the most frequently identified RAS in NS5A, identified in 31 patients (36.0%).

Discussion

This is the largest real-life study evaluating the efficacy of interferon-free, DAA-based treatment for chronic hepatitis C in Switzerland to date; it included 3088 consecutive patients from eight referral centres. The overall SVR rate after the first treatment course across all HCV genotypes and the study period ranging from 2015 to 2019 was 96.2%. SVR rates increased during the first interferon-free, DAA-based treatments (a period of 5 years) until the latest generation of pangenotypic regimens, which are still and will likely remain standard-of-care. The introduction of the latter regimens may have contributed substantially to increasing SVR rates across the study period. However, patients with advanced liver disease, especially in the cirrhosis stage, were initially prioritised for access to DAAs and were at higher risk of treatment failure. In 2019, the SVR rate reached 97.5%, which is comparable to the SVR rate of phase 3 and real-life studies performed in other countries using the latest generation of pangenotypic regimens [10-14, 17, 18].

As expected, gt 1 was the predominant genotype observed in our study (55.7%), followed by gt 3 (22.7%). However, gt 3 was the predominant genotype among patients who failed to achieve SVR after the first course of DAA-based treatment (44.8%), followed by gt 1 (31.0%) [19].

Our secondary aim was to characterise baseline demographic, clinical, and virological parameters associated with DAA failure. In a study published by Arias et al. [20], a total of 363 patients with chronic hepatitis C had completed a course of all-oral DAA treatment outside of clinical trials. Based on their multivariable analysis, only advanced liver fibrosis (Metavir stages F3 and F4) and HIV coinfection were significantly associated with an increased risk of treatment failure. Patients with HIV coinfection were excluded from our study.

In our univariable analysis, the presence of active HCC at the time of antiviral treatment, gt 3, cirrhosis, African ethnicity, Metavir stage F4, and increasing liver stiffness were significantly associated with DAA failure. Conversely, the absence of HCC, Metavir stage F3, the use of the latest generation of pangenotypic DAA regimens, gt 1, Caucasian origin, and female sex were significantly associated with increased chances of achieving SVR.

The multivariable analysis revealed that active HCC at treatment, gt 3, and liver stiffness measurement were independent predictors of an increased risk of DAA failure. Conversely, female sex, the use of the latest generation of pangenotypic DAA regimens, Caucasian ethnicity, and gt 1 were significantly associated with SVR.

The observation that gt 3 infection is independently associated with a reduced probability of achieving SVR compared with other genotypes is in line with previous reports [21, 22].

Another important factor associated with an increased risk of DAA failure on multivariable analysis was an increased liver stiffness measurement as assessed by transient elastography. Importantly, an almost linear progression of DAA failure risk was observed above a liver stiffness measurement of 40 kPa. This observation is consistent with previous reports of an increased risk of DAA failure in the presence of cirrhosis and portal hypertension [23–26].

Notably, the presence of active HCC at the time of DAA treatment was independently associated with DAA failure. Patients with active HCC at the time of DAA initiation had an almost 13-fold increased risk of DAA failure compared with those without HCC. This is in line with previously published data [27-30]. In a study by Prenner et al., DAA failure was observed in 21% of patients with HCC, whereas it was only observed in 12% of patients without HCC (p = 0.009) [27]. The vast majority of nonresponders in this study presented active HCC. Similarly, Beste et al. included 482 patients with HCC and 16,863 patients without HCC with chronic HCV infection who were treated with DAAs; they reported significantly lower SVR rates in patients with HCC across all genotypes [28]. The HCV-TARGET study also compared patients with treated to untreated HCC and reported similar results [29]. SVR was achieved in 87% of the non-HCC group compared with 78% of the treated HCC group and 72% of the untreated HCC group. Finally, a recent meta-analysis by Ji et al., including 3341 patients with HCC and 35,701 without HCC, found a 4.8% SVR reduction in patients with HCC compared with those without HCC. The largest SVR rate reduction (18.8%) occurred in patients with active HCC (SVR 73.1% vs. 92.6%, p = 0.002) [30].

In our multivariable analysis, African ethnicity was not associated with an increased risk of DAA failure. However, this demographic variable was associated with signifi-

Table 2:
Most frequently reported RAS in NS5A region after first DAA treatment.

Genotype (n)	NS5A
1a (22)	Q30R > L31M > Y93H > H58D
1b (13)	Y93H > Q30R, L31M/V > H58S
2 (5)	
3 (52)	Y93H > A30K
4 (21)	L31M/V/S > Q30R > L28F/S > T58P > Y93H

RAS, resistance-associated substitution; DAA, direct-acting antiviral

cantly increased failure rates in the univariable analysis. A high prevalence of unusual subtypes, namely gt 1 non-1a, non-1b, 3b/3g, and 4r, has been reported in African patients, contributing to increased failure rates [31–33]. Information on these rare subtypes was not available in our real-life study. A previous subanalysis of patients from Lausanne University Hospital showed that African patients with HCV subtype 4r were overrepresented among patients who relapsed [34].

Finally, the favourable effect of female sex on SVR rates in our study also aligns with previous reports [24].

Prior studies have attempted to identify factors predictive of treatment failure. Most of them initially included patients treated with interferon-based regimens that are no longer prescribed [35]. Few studies have specifically assessed risk factors for DAA failure [20, 21, 30–33]. Based on our analysis of a large cohort of patients, active HCC, gt 3 and increasing liver stiffness measurement as a correlate of cirrhosis and portal hypertension appear as the strongest risk factors while subtype analyses were not available in our real-life study.

Although DAA-based treatment has become simple and highly successful, with SVR rates approaching 100%, some patients remain difficult to treat. Therefore, the risk factors associated with treatment failure identified in this study may allow clinicians to select patients who could benefit from first-line antiviral therapy with a triple DAA regimen, such as VOX/VEL/SOF or GLE/PIB + SOF [36]. Further randomised controlled studies employing this approach should explore this.

In our study, 116 of 3088 (3.7%) patients failed to achieve SVR. Most (103 patients) were retreated with a second course of DAA, and 84.5% of them achieved SVR. The overall SVR rate after DAA retreatment was high in this real-life study. Hence, very few patients failed more than two treatment courses. Notably, gt 3 was predominant among patients who failed a second course of DAA treatment, confirming that attention must still paid to this genotype. VOX/VEL/SOF as the second DAA regimen was the only variable significantly associated with SVR.

Results from RAS analyses were available in roughly three-quarters of patients who experienced failure of the first course of DAA-based treatment in this real-life study. The NS5A region was sequenced in almost all cases; the sequencing of the NS3 protease domain and NS5B was available only in some patients. As expected, and in line with overall good treatment adherence, significant NS5A RASs were detected in many patients who were tested.

Overall, our RAS analysis results are concordant with those of previous reports. A recent publication by SHARED, an international consortium studying HCV drug resistance, highlighted the clinical relevance of RAS [37]. Among 730 virologic failures, 94% had resistance against at least one DAA class. In a European multicentre study involving 938 patients with DAA failure, similar to our study, Q30R in the NS5A region was predominant in patients with gt 1a, whereas L31M and Y93H were the most frequent in patients with gt 1b and Y93H was the most frequent in those with gt 3a [38].

Our study presents some limitations, principally due to its real-life and retrospective nature as well as the exclusion of patients with HIV coinfection. All patients diagnosed with chronic hepatitis C within each centre during the study period were included in the analysis. However, some patients may not have been accounted for, although their absence is not anticipated to substantially affect the overall results. RAS analyses were not performed at baseline or in all non-SVR patients. However, our study has several strengths, including the large number and wide spectrum of patients as well as the representation of referral university and non-university hospitals in different regions across the country. In addition, only a few data points were missing, highlighting the high quality of medical documentation and close follow-up offered in the eight Swiss referral centres.

In conclusion, our study, which included over 3000 patients, confirms the high rates of HCV cure with current DAA regimens outside of clinical trials. Our study did not include patients coinfected with HIV. Nevertheless, our findings align with results previously reported by the Swiss HIV Cohort Study [39]. Our study also revealed factors associated with treatment failure, providing unique large-scale real-life data for Switzerland.

Although these high cure rates offer substantial benefits, they can only be achieved in patients who are diagnosed. Hence, our study underscores the importance of HCV testing in key populations and aligns with ongoing efforts towards the elimination of viral hepatitis and HIV infection in Switzerland.

Acknowledgments

The authors gratefully acknowledge endorsement by and support from the Swiss Association for the Study of the Liver and the Swiss Hepatitis C Cohort Study.

The authors confirm contribution to the paper as follows: study conception and design: Eleni Moschouri, Darius Moradpour, Montserrat Fraga; data collection: Eleni Moschouri, Gloria Salemme, Adriana Baserga, Ansgar Deibel, Marie-Anne Meier, Marie Ongaro, Marielle Grosjean, Patrizia Künzler-Heule, Gabriel Hobi, Adeline Mathieu, Elise Mdawar-Bailly; analysis and interpretation of results: Eleni Moschouri, Andreas Cerny, Beat Müllhaupt, Christine Bernsmeier, Francesco Negro, Olivier Clerc, David Semela, Mohamed Faouzi, Darius Moradpour, Montserrat Fraga; draft manuscript preparation: Eleni Moschouri, Darius Moradpour, Montserrat Fraga. All authors reviewed the results and approved the final version of the manuscript.

Financial disclosure

This study was supported in part by the Swiss Association for the Study of the Liver and the Swiss Hepatitis C Cohort Study.

Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest related to the content of this manuscript was disclosed.

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Appendix

Table S1:
Characteristics of patients who experienced a second DAA failure.

Patient	Geno-type	Cirrhosis	Active HCC	Previous IFN-based treatment	1 st DAA treatment	2 nd DAA treatment	3 rd DAA treat-ment	SVR after 3 rd DAA treatment	RAS analysis after 1 st DAA treatment	RAS analysis after 2 nd DAA treatment
1	3	Yes	No	PegIFN + RBV	DCV/SOF + RBV	VEL/SOF + RBV	None[1]	NA	NS5A: Y93H	NS5A: Y93H
2	1a	Yes	Yes	PegIFN + RBV	VEL/SOF + RBV	VEL/SOF	None[2]	NA	NS5A: Q30R/L31M	NA
3	4	Yes	No	PegIFN + RBV	PTV/r/OBV + RBV	SOF + RBV	VOX/VEL/SOF	Yes	NA	NS5A: M28V
4	4	Yes	No	IFN	LDV/SOF	SOF + RBV up to LT	VOX/VEL/SOF + RBV after LT	Yes	NS5A:L28F/Q30R/ Y93H	NA
5	3	F3	No	No	DCV + SOF	VEL/SOF + RBV	VOX/VEL/SOF[3]	No	NS5A: Y93H	NA
6	3	Yes	No	PegIFN + RBV	SOF + RBV	VEL/SOF + RBV	VOX/VEL/SOF	Yes	NA	NA
7	1a	No	No	PegIFN + RBV	LDV/SOF	SMV + SOF + RBV	VOX/VEL/SOF	Yes	NA	NA
8	2	No	No	No	SOF + RBV	VEL/SOF	VOX/VEL/SOF	Yes	NA	NA
9	2	No	No	No	SOF + RBV	VEL/SOF + RBV	VOX/VEL/SOF	Yes	No RAS	NA
10	1b	F3	No	PegIFN + RBV	LDV/SOF	VEL/SOF + RBV	VOX/VEL/SOF + RBV[4]	No	NS5A: Y93H	NS5A: Y93H/L31M
11	1a	No	No	PegIFN + RBV	GZR/EBR	VOX/VEL/ SOF	NA	Third-line treatment during study period	NS5A: no RAS	NS5A: no RAS
12	3a	Yes	No	Peg-IFN + RBV	SOF+RBV	DCV/SOF + RBV	VOX/VEL/SOF	Yes	NA	NS5A: A30K
13	3h	Yes	No	PegIFN + RBV	SOF/ DCV+RBV	VEL/SOF + RBV	VOX/VEL/SOF	Third-line treatment during study period	NS5A: no RAS	NA

[1] Patient with decompensated cirrhosis and portal hypertension.

[2] Patient died.

[3] Virological failure. Fourth-line DAA treatment with GLE/PIB + SOF + RBV resulted in SVR.

[4] Virological failure. Missing data on any further DAA treatment.

DAA, directly acting antiviral; DCV, daclatasvir; GZR/EBR, grazoprevir/elbasvir; IFN, interferon-α; LDV/SOF, ledipasvir/sofosbuvir; LT, liver transplantation; NA, not available; PegIFN, pegylated interferon-α; PTV/r/OBV, ritonavir-boosted paritaprevir/ombitasvir; RAS, resistance-associated substitution; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; VEL/SOF, velpatasvir/sofosbuvir; VOX/VEL/SOF, voxilaprevir/velpatasvir/sofosbuvir.