International Journal of Drug Policy 133 (2024) 104616

Contents lists available at ScienceDirect

International Journal of Drug Policy

journal homepage: www.elsevier.com/locate/drugpo

Research Paper

Predictors of treatment outcomes for Hepatitis C infection in a nationwide elimination program in Iceland: The treatment as prevention for Hepatitis C (TraP HepC) study☆

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ARTICLE INFO

Keywords:
Hepatitis C virus elimination
Injection drug use
Direct acting antivirals
Hepatitis C virus infection

ABSTRACT

Background: Limited data exists about treatment outcomes in nationwide hepatitis C virus (HCV) elimination programs where injection drug use (IDU) is the main mode of transmission. In 2016 Iceland initiated the HCV elimination program known as Treatment as Prevention for Hepatitis C (TraP HepC). Factors associated with HCV cure in this population are examined.

Methods: Unrestricted access was offered to direct acting antiviral agents (DAAs). Testing and harm reduction was scaled up and re-treatments were offered for those who did not attain cure. Cure rates for the first 36 months were assessed and factors associated with failure to achieve cure analysed using multivariable logistic regression.

Results: Treatment was initiated for 718; 705 consented for the study. Median age was 44 years (IQR 35–56), history of IDU reported by 593 (84.1 %), recent IDU by 234 (33.2 %); 48 (6.8 %) were homeless. Of 705 patients, 635 achieved cure (90.1 %) during the first treatment. A total of 70 (9.9 %) patients initiated two or more treatments, resulting in 673 participants cured (95.5 %). By multivariable analysis, homelessness was the only statistically significant independent factor associated with not achieving cure (OR 2.67, 95 % CI 1.32–5.41) after first treatment attempt.

Conclusion: By reengagement in care and prompt retreatment when needed, a cure rate of 95.5 % was achieved. Unstable housing, a potentially actionable factor is associated with poor outcome.

☆ Clinical trial number: ClinicalTrials.gov, NCT02647879

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https://doi.org/10.1016/j.drugpo.2024.104616

Available online 24 October 2024
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Introduction

Hepatitis C virus (HCV) infection is currently estimated to affect close to 57 million people globally and is one of the leading causes of cirrhosis and hepatocellular carcinoma (HCC) world-wide (Global change in hepatitis C, 2022). Injection drug use (IDU) is the main mode of transmission of HCV in high-income countries, accounting for majority of new infections (Degenhardt et al., 2017).

As a growing number of direct acting antiviral (DAA) agents have become available treatment for HCV has been revolutionized. Clinical trials of DAAs demonstrated cure rates of >95 % and limited side effects (Falade-Nwulia et al., 2017; Flamm et al., 2019). Similar findings were observed in several real-world cohort studies (Berg et al., 2019; Mangia et al., 2020). In 2016 the World Health Organization (WHO) set the ambitious goal of eliminating hepatitis C as a major health threat by the year 2030, including a 65 % reduction in HCV-related deaths and 90 % reduction in HCV incidence (World health Organization, 2016). To achieve these elimination goals the WHO set treatment service coverage targets of diagnosing 90 % of infections and 80 % of eligible patients treated by the year 2030. The targets have subsequently been updated to include an absolute annual HCV incidence of ≤5 per 100,000 persons and of ≤2 per 100 of people who inject drugs (PWID) (World Health Organization, 2021).

Before the advent of pangenotypic DAA regimens for HCV the main predictors of outcome were host and viral factors such as cirrhosis and viral genotypes (Fried et al., 2002). Currently, social, economic, and behavioral factors have become increasingly important in treatment of patients (Wilton et al., 2020). Prioritizing PWID by using antiviral treatment to reduce the pool of infected people and, consequently, prevent or reduce the rate of onward transmission, is a critical strategy to meet the 2030 elimination goals (Hellard et al., 2014). Similarly, early detection and prompt treatment of reinfections is essential among people actively injecting drugs (Johannesson et al., 2022).

Iceland is a typical western European country where HCV infections are generally transmitted by unsafe injection practices among PWID. Iceland can be considered a good setting to study how improved detection and access to treatment could make an early impact on the epidemiology of the disease (Scott et al., 2018).

A nationwide public health intervention termed the Treatment as Prevention for Hepatitis C (TraP HepC) program was launched in Iceland in 2016 with a nested prospective study bearing the same name. The main goals were to treat all patients with hepatitis C in the country and thereby reduce the transmission rate of the virus. During the first three years the service coverage targets of diagnosing 90 % and treating 80 % of eligible patients were achieved (Olafsson et al., 2021). In a previous study on the cascade of care the cure rate of infections in the program was reported (Olafsson et al., 2021). Here we analyze the associations of multiple factors with treatment success during the first three years of this nationwide program.

Materials and methods

The population of Iceland at the start of the TraP HepC program in February 2016 was 332,529 (Statistics, Iceland). Iceland's only university hospital (Landspitali - The National University Hospital of Iceland, LUH) located in Reykjavik serves as a tertiary and quaternary referral center for the country and runs its only virology laboratory. The majority of PWID seek addiction treatment at Vogur Hospital in Reykjavik, where patients with a history of injecting drugs have been screened for HCV since 1991 (Hansdottir & Tyrfingsson, 2015). Database on IDU and virological test results is maintained there for all patients. Reporting of HCV to the Chief Epidemiologist in Iceland is mandatory and a registry of all diagnosed cases of HCV has been kept since 1991.

In the 20 years leading up to the TraP HepC program, between 40 and 70 new cases of HCV were diagnosed annually (Chief Epidemiologist Iceland 2019). The estimated total HCV viremic population in 2015 was 800–1000, corresponding to a viremic population prevalence of 0.25–0.31 % (Liakina et al., 2015). A vast majority of people with HCV infection in Iceland have a history of IDU (Olafsson et al., 2021). Based on previous extensive screening among PWID, an estimated 80 % of existing infections had been diagnosed before the start of TraP HepC (Olafsson et al., 2018).

The TraP HepC program

The program has been described in detail elsewhere (Olafsson et al., 2018). Briefly, from February 2016 all patients with chronic HCV infection, 18 years and older, covered by the national health insurance, were offered treatment with DAAs with the aim of treating most cases over the subsequent 36 months. All services were fully reimbursed by Icelandic health authorities and DAAs were provided free of charge by Gilead Sciences. The program is based on a multidisciplinary team approach and close collaboration between infectious disease specialists, hepatologists, and experts in addiction medicine. Harm reduction efforts including needle-syringe programs (NSP) and medication-assisted treatment (MAT) for opioid use disorder were scaled up concomitantly.

Patient recruitment, linkage to care, evaluation and monitoring. Existing cases were identified and linked to care using the HCV registry, Vogur Hospital database, and LUH's virology system. To reach infected but undiagnosed individuals an awareness campaign was launched among health care workers as well as via public web pages, social media, and information leaflets sent to every home in the country. Interview, laboratory work (including virological tests) and liver stiffness measurements (LSM) by shear wave elastography delivered by Fibroscan® were undertaken at baseline. Cirrhosis was defined as value of >12.5 kPa on hepatic elastography. MELD and Child scores were calculated.

Treatment regimens. Treatment selection was based on national clinical guidelines, reflecting changes to the guidelines during the program. Through October 2016 ledipasvir 90 mg/sofosbuvir 400 mg in fixed dose combination (FDC) with or without ribavirin were used and velpatasvir 100 mg/sofosbuvir 400 mg in FDC with or without ribavirin thereafter (Olafsson et al., 2018). Patients with lack of response, relapse or reinfection following initial DAA treatment were promptly offered retreatment. There was no upper limit on the number of retreatments offered.

Virological testing. A single reference virology laboratory confirmed all diagnoses. Serum HCV RNA was measured by the COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test, version 2.0 (Roche Molecular Systems), with a lower limit of quantification of 15 IU per milliliter. All antibody positive blood samples were tested for HCV RNA and genotype using reflex testing. Rapid testing was used in harm reduction facilities and shelters for the homeless (Oraquick®, Orasure Technologies). Patients who did not respond to therapy or relapsed were tested for NS5A RAVs (resistance associated variants). When patients were PCR negative at the end of treatment, but positive with the same genotype 12 weeks post treatment, sequencing was performed to distinguish reinfection from relapse (Viroclinics DDL).

The TraP HepC study

In parallel with the treatment program described above, a monitoring study was initiated to track the epidemiology of the infection and the short-term and long-term outcomes of the patients. The study population includes patients who initiated treatment from February 2016 until February 2019 and provided written informed consent. Those who chose not to participate were offered identical treatment and services. The study was approved by the National Bioethics Committee of Iceland (number 15–087) and registered at clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT02647879).

Baseline characteristics and follow-up. Detailed information was recorded at baseline, including demographics, drug use, housing, previous HCV treatment, concurrent medications and concomitant diseases

as assessed by the Charlson comorbidity index (Charlson et al., 1987). During follow-up visits patients were asked about ongoing or recent drug use and compliance, with discontinuation of treatment defined as not taking the prescribed DAA for eight or more consecutive days. Living situation was recorded as own property/rental/relatives, halfway house, homeless, penitentiary, or other/unknown.

Outcomes. Cure was defined as a negative PCR test for HCV RNA in plasma 12 weeks or more after the planned end of treatment, corresponding to sustained virological response at week 12 or later (SVR12+). When SVR12+ was not achieved the case was reviewed and classified into the following categories: loss to follow-up (including death before SVR12+ assessment), reinfection (determined by genotype and/or sequencing), virological relapse (PCR negative at end of treatment but positive at SVR12+ with same genotype, excluding reinfection), or PCR+ (corresponding to not attaining SVR12 where neither relapse nor reinfection could be confirmed). Outcomes are reported for the first and final treatments for each participant.

Data management. Patient data were entered at the point of care directly into an electronic patient record (EPR) using a customized interactive module. Data regarding consented study participants were extracted from the EPR for inclusion in a separate deidentified study database used for statistical analysis. During the study, an independent monitor regularly confirmed the completeness of patient records, the accuracy of entries, and adherence to the protocol and Good Clinical Practice.

Statistical analysis. Counts and percentages are reported for baseline characteristics and outcomes. Baseline characteristics were then analyzed for association with failing to achieve SVR12 in the first and final treatments separately using Fisher's exact test and relative risks (RR) calculated. The following variables were dichotomized for analysis: encounter site (university hospital vs other), most common IV drug (stimulants vs opiates or other), non-IV drugs (stimulants vs opiates, cannabis, or other). Age was split into 10-year categories, except for the lowest; ; ; and highest (60+) age groups, and the highest age category used as the reference for each of the others. For multivariable modeling age was included as a continuous variable. Each genotype was tested against all other genotypes pooled. IDU was analyzed as recent (within 6 months) or past (more than six months ago) using those with no history of IDU as the reference group. Living situation was modeled using stable housing (own property, rental property, relatives, halfway house) as the reference group, comparing them to those in an unstable housing situation (homeless, other, unknown), and to those incarcerated.

Baseline variables found to have an association with either outcome at a p level of 0.1 or less on univariable logistic regression analysis were considered for use in a multivariable logistic regression model. Variables with a p-value of <0.05 in the final multivariable model were considered to have a statistically significant association with the outcome. To reduce the risk of over-adjusting and collinearity, an acyclic diagram was constructed and used to identify intermediate variables that should be removed from the model to avoid obscuring the true effects of upstream explanatory variables (Fig. 1). Based on this diagram we excluded the variables for discontinued treatment and encounter site as they are clearly intermediate variables affected by multiple other explanatory variables. Entering them in the model would have risked obscuring the effect of explanatory variables upstream in the causal diagram.

To account for any effects of these model building decisions on our findings we performed a sensitivity analysis where each variable that was excluded based on the causal diagram was included in a model with only age and sex to show the effect of that individual variable. We also constructed a model that included all variables that met the $p < 0.1$ criteria.

All models included age in years and gender as covariates. Data preparation and statistical analysis were performed using JMP v15 and STATA v16.

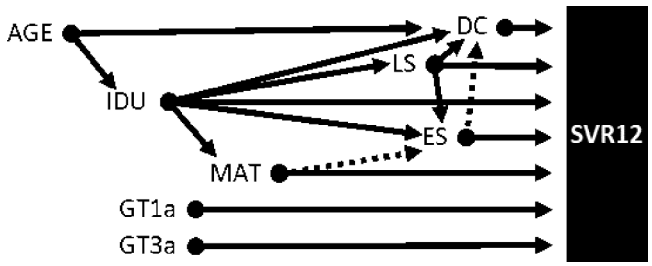

Fig. 1. Causal diagram of the proposed relationship between baseline variables and SVR12 for all variables found to have an association with a $p < 0.1$. Dotted lines indicate a weaker proposed relationship.
IDU=Recent intravenous drug use, MAT=Medication Assisted Treatment, GT=Genotype, LS=Living Situation, ES=Encounter Site, DC=Discontinued Treatment

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report or on the decision to submit the paper for publication.

Results

Patient demographics and outcome variables

Of 718 patients who initiated treatment in the TraP HepC Program, 705 (98.2 %) gave informed consent and were included in the TraP HepC Study. Baseline characteristics and crude outcomes are summarized in Table 1. Median age was 44 years (IQR 35-56), males 474 (67.2 %). The most common self-reported route of infection was IDU among 593 (84.1 %), 234 (33.2 %) reported recent (within 6 months) IDU, 48 (6.9 %) were homeless, and 38 (5.4 %) incarcerated at treatment initiation. Stimulants were preferred by 85.2 % (505/593) of PWID. The most common viral genotype was 3a (407; 57.7 %). A total of 41 (5.8 %) were coinfected with HIV and 5 (0.7 %) were HBsAg positive. The mean Charlson comorbidity score was 2.6 (95 % CI 1–3). The mean score on hepatic elastography was 7.2 kPa and 48 (6.8 %) had cirrhosis by elastography. The majority ($n = 377$) of treatments were SOF/VEL. Five patients received treatments with SOF/VEL/VOX. Treatment regimens for all 782 treatment initiations are summarized in supplementary table A.

Treatment outcomes

Of the 705 who initiated treatment, 635 (90.1 %) achieved SVR12+ after the first treatment (Table 1). Table 2 shows the proportion reaching SVR12+ after the first and final treatments, broken down by baseline characteristics with RR estimates and corresponding p-values. Seventy patients (9.9 %) initiated a second, six a third, and one patient a fourth treatment, for a total of 782 treatments. Of the 705 participants who initiated one or more treatments with DAAs, 673 (95.5 %) achieved SVR12+ within the timeframe of the study (Table 2). Of 705 patients, 51 (7.2 %) discontinued their first treatment course.

Of the 70 who did not achieve SVR after the first treatment, 18 (2.6 % of all 705) were lost to follow-up (including four deaths), 11 (1.6 %) were reinfected, 14 (2.0 %) had virological relapse and 27 (3.8 %) remained PCR positive for other reasons. Of those who remained PCR positive for other reasons, 20 had discontinued treatment and in seven it was not possible to differentiate between relapse, reinfection or non-response with virological testing. Of 18 patients lost to follow-up after first treatment, six had a PCR test at end of treatment or thereafter but before 12 weeks had passed, of whom all were negative. The remaining 12 had either no PCR test after initiating treatment or only a test prior to end of treatment.

Table 1
Baseline Characteristics.

Demographics	
Mean age (median, quartiles)	45.1 (44, 35–56)
Female	231 (32.8 %)
Born in Iceland	616 (87.4 %)
Self-reported race	
Asian	12 (1.7 %)
Black	2 (0.3 %)
Caucasian	691 (98.0 %)
Encounter site	
Addiction Treatment Center	185 (26.2 %)
Other	3 (0.4 %)
Penitentiary	34 (4.8 %)
University Hospital	483 (68.5 %)
Living situation	
Halfway house	60 (8.5 %)
Homeless/streets	48 (6.8 %)
Other or unknown	15 (2.1 %)
Own property/rental/relatives	544 (77.2 %)
Penitentiary	38 (5.4 %)
Drug use	
Ever used IV drugs	593 (84.1 %)
Type of IV drug most commonly used	
Methylphenidate	180 (25.5 %)
Other stimulants	325 (46.1 %)
Opiates	76 (10.8 %)
Other	11 (1.6 %)
Recent IV drug use (within 6 months)	234 (33.2 %)
Current medication assisted treatment (MAT)	65 (9.2 %)
Used non-iv substances in the past 7 days	
Opiates	37 (5.3 %)
Cannabis	115 (16.3 %)
Stimulants	71 (10.1 %)
Liver status	
Cirrhosis (Metavir=4 or Fibroscan 12.5 Pa)	48 (6.8 %)
Mean (median, quartiles) hepatic elastography score (kPa)	7.2 (5.4, 4.4–7.0)
Mean (median, quartiles) years from infection	9.7 (8, 2–16)
Virology	
Genotype	
Missing	1 (0.1 %)
1a	247 (35.0 %)
1b	38 (5.4 %)
2	6 (0.9 %)
3a	407 (57.7 %)
4	5 (0.7 %)
6	1 (0.1 %)
Self-reported mode of transmission	
Blood transfusion/blood products	14 (2.0 %)
IV drug use	598 (84.8 %)
Nasal drug use	2 (0.3 %)
Other	9 (1.3 %)
Suspected sexual transmission	21 (3.0 %)
Tattoo/piercing	9 (1.3 %)
Unknown	50 (7.1 %)
Vertical transmission from mother	2 (0.3 %)
HIV coinfection	41 (5.8 %)
HBV coinfection (HbsAg)	5 (0.7 %)
Pre-DAA era treatment for HCV	87 (12.3 %)
Outcomes	
Cured, First treatment only	635 (90.1 %)
Cured, Including all retreatments	673 (95.5 %)

Baseline characteristics and crude outcomes.

Predictors of non-SVR

Of the 51 patients who discontinued treatment, 26 (51 %) achieved SVR12+ regardless, rising to 88 % after reengagement in care and retreatments. An additional analysis testing whether discontinuation within four weeks vs later was a predictor of failing treatment found no statistically significant effect for neither the first ($p = 0.25$) nor the final ($p = 0.16$) treatments. Univariable analysis showed an association at a p-level of <0.1 between failure to reach SVR12+ after first treatment and age as a continuous variable (OR 0.98 per added year, $p = 0.016$), encounter site, living situation, recent IDU, preference for opiates over stimulants for IV use, current MAT, genotype 1a (negative association), genotype 3a, and discontinuation of treatment as shown in Table 2. In accordance with our methods, we considered all these for inclusion in a multivariable model. Preference for opiates was not included in the final model due to its high correlation to MAT with a Pearson's correlation coefficient of 0.60 (0.51–0.67), introducing collinearity destabilizing the model. We chose to include living situation in our model, even though it is shown on the acyclic diagram in the methods section as an intermediate variable between IDU and SVR12. This was because recent IDU overlaps unstable housing by less than 50 % and it had the second strongest association with failure to reach SVR12 on univariable analysis, suggesting living situation has the potential to add explanatory value to the model beyond that of IDU alone.

This resulted in a logistic regression model with seven independent variables. Table 3 summarizes the findings of the final multivariable model, which showed that unstable housing was the only statistically significant predictor of non-SVR with an OR of 2.67 (1.32–5.41) for the first treatment. However this was not significant for the final treatment. Initiation of first treatment in a penitentiary was a significant predictor of non-SVR in the final treatment with an OR of 3.54 (1.14–11.02). The effect of discontinuing the first treatment was not a statistically significant independent predictor of non-SVR in the final treatment. The results of the sensitivity analyses described in the methods section supported the links shown in the causal diagram. The data are shown in supplementary tables B and C.

Discussion

The results of the TraP HepC study demonstrate that a nationwide, public health intervention to eliminate HCV which offers close follow-up and good access to reengagement yields a cure rate of 95 % within 36 months, even in a patient population with high rate of recent IDU. Unstable housing showed the strongest association with unfavorable outcome, potentially making it the biggest hurdle to treatment success. However, with reengagement in care and retreatment this could be overcome.

In multivariable analysis, unstable housing was the only independent factor associated with not achieving SVR during first treatment attempt. This is consistent with other studies that reported association of unstable housing with poor outcomes (Bajis et al., 2019; Del Rosario et al., 2021; Harney et al., 2019; Ziff et al., 2021). TraP Hep C is the first to identify this association in a nationwide treatment program however, which makes the results more robust. Recent work has underlined the association between increased risk of HIV and HCV acquisition and homelessness and unstable housing among PWID (Arum et al., 2021). Randomized studies indicate that interventions to improve housing among homeless HIV patients can improve their responses to treatment and are associated with improved survival (Buchanan et al., 2009). Such interventions are therefore important to improve their health and well-being, as well as public health in their communities.

Real-world studies have evaluated the effectiveness and safety of DAAs with results similar to those of clinical trials, demonstrating >95 % SVR (Berg et al., 2019; Mangia et al., 2020). However, other real-world studies report much lower SVR, particularly among PWID who reported current injecting (Hajarizadeh et al., 2018). A cure rate of 90.1 % in the current study for all first treatment initiations reflects real-world effectiveness in a population-based nationwide setting where an unselected HCV-infected population within a country is treated.

The emphasis on reengagement in care and assessment in overall outcome over several years has been the defining characteristic and a major strength of the TraP HepC program. To date published data from other real-world studies has primarily focused on outcomes after one treatment attempt with limited information on approach and the success of reengagement in care of those who initially did not achieve SVR with DAAs with few exceptions (Byrne et al., 2022). The most common reasons for not achieving cure in the current study (besides lost to follow-up

Table 2
Results of Univariable Analysis.

		First treatment only				Final treatment			
Demographics	n	SVR12+ (n)		RR (95 % CI)	*p*	SVR12+ (n)		RR (95 % CI)	*p*
Age group									
18–29	82	88 %	(72)	2.36 (0.89–6.23)	0.11	94 %	(77)	2.36 (0.58–9.59)	0.28
30–39	191	87 %	(166)	2.45 (1.02–5.77)	<0.05	94 %	(180)	2.23 (0.63–7.82)	0.26
40–49	181	89 %	(161)	2.14 (0.88–5.16)	0.09	96 %	(174)	1.50 (0.39–5.67)	0.75
50–59	135	93 %	(126)	1.43 (0.54–3.82)	0.61	96 %	(130)	1.72 (0.44–6.72)	0.51
60+ (r)	116	95 %	(110)	1		97 %	(113)	1	
Male sex	474	90 %	(427)	1.00 (0.62–1.60)	1.00	96 %	(455)	0.93 (0.46–1.90)	0.85
Female (r)	231	90 %	(208)	1		95 %	(219)	1	
Encounter at addiction treatment center, penitentiary, or other	222	84 %	(186)	2.74 (1.76–4.27)	<0.0001	92 %	(204)	2.47 (1.25–4.85)	0.01
University Hospital (r)	483	94 %	(454)	1		97 %	(469)	1	
Living situation: Unstable (Homeless, other, unknown)	63	75 %	(47)	3.20 (1.93–5.28)	<0.0001	92 %	(58)	2.18 (0.85–5.55)	0.17
Living situation: Penitentiary	38	84 %	(32)	1.99 (0.91–4.35)	0.12	87 %	(33)	2.61 (1.45–9.01)	0.02
Stable (Own property, rental property, relatives, halfway house) (r)	604	92 %	(556)	1		96 %	(615)	1	
Drug use*									
Recent IV drug use (within 6 months)	234	84 %	(197)	2.95 (1.28–6.79)	<0.01	93 %	(218)	2.55 (0.76–8.58)	0.13
Past IV drug use but not in past 6 months	359	93 %	(332)	1.40 (0.59–3.31)	0.53	96 %	(346)	1.35 (0.39–4.66)	0.77
Never IV drug use (r)	112	95 %	(106)	1	.	97 %	(109)	1	
Most commonly used type of IV drug: Opiates or other	33	67 %	(22)	2.56 (1.41–4.68)	<0.01	85 %	(28)	2.75 (1.02–7.42)	0.06
Methylphenidate or other stimulants (r)	200	87 %	(174)	1		95 %	(190)	1	
Current medication assisted treatment (MAT)	65	83 %	(54)	1.84 (1.02–3.31)	0.07	92 %	(60)	1.82 (0.72–4.57)	0.21
No (r)	640	91 %	(582)	1		96 %	(614)	1	
Used non-iv Opaties, cannabis, or other (excluding stimulants) in past week?	71	85 %	(59)	0.90 (0.44–1.82)	0.83	95 %	(67)	0.55 (0.18–1.66)	0.37
Stimulants (alone or with other substances) (r)	92	83 %	(78)	1		90 %	(83)	1	
Genotype (at first treatment)									
1a	247	93 %	(230)	0.59 (0.35–1.00)	<0.05	96 %	(237)	0.84 (0.41–1.75)	0.71
1b	38	89 %	(34)	1.06 (0.41–2.76)	0.78	95 %	(36)	1.17 (0.29–4.71)	0.69
2	6	100 %	(6)	–	1.00	100 %	(6)	–	1.00
3a	407	88 %	(358)	1.71 (1.05–2.79)	0.03	95 %	(387)	1.22 (0.61–2.46)	0.71
4	5	100 %	(5)	–	1.00	100 %	(5)	–	1.00
6	1	100 %	(1)	–	1.00	100 %	(1)	–	1.00
Missing	1	100 %	(1)	–	1.00	100 %	(1)	–	1.00
Other									
Discontinued first treatment	51	51 %	(26)	7.12 (4.79–10.60)	<0.0001	88 %	(45)	2.96 (1.28–6.86)	0.02
No (r)	654	93 %	(608)	1		96 %	(628)	1	
Cirrhosis (Metavir=4 or Fibroscan 12.5 Pa)	48	94 %	(45)	0.61 (0.20–1.87)	0.61	98 %	(47)	0.44 (0.06–3.15)	0.71
No (r)	655	90 %	(590)	1		95 %	(622)	1	

A univariate analysis of the proportion of participants who achieved SVR12+ (a negative PCR test 12 weeks or more following treatment) after the first treatment only and after all the treatments received, by various baseline characteristics.
Relative risk (RR) is calculated to show the risk of failing to reach SVR12+. Fisher's exact test is used to calculate p-values. For age groups, the 60+ group was used as a reference group for each of the other age groups. For genotypes, each genotype was compared to all the others. Encounter site, living situation, IV drug, and non-IV drug variables were dichotomized as described in the methods. (r) = reference group for calculation of relative risk * = self-reported.

for SVR testing) were reinfections, virological relapses and premature discontinuations of treatment. As there was no limit to the number of retreatments in the TraP HepC program, patients who did not complete therapy or who became re-infected after achieving cure were promptly offered retreatment. With this approach the low cure rate associated with unstable housing could be overcome. The organization of the program was designed to seamlessly facilitate such reengagement through a program coordinator and a common electronic medical record. As an example, patients who initiated treatment in an infectious disease clinic and then discontinued treatment were commonly

Table 3
Results of multivariable model.

	N	First treatment only OR (95 % CI)	Final treatment OR (95 % CI)
Age (continuous, years)	705	0.99 (0.97–1.01)	0.99 (0.96–1.03)
Male sex	474	0.97 (0.56–1.69)	0.78 (0.36–1.72)
Recent injection drug use (IDU)	234	1.61 (0.89–2.92)	1.50 (0.64–3.51)
Current medication assisted treatment (MAT)	65	1.59 (0.75–3.34)	1.64 (0.58–4.59)
Living situation: Homeless, other, unknown	**63**	**2.67 (1.32–5.41)**	1.70 (0.56–5.11)
Living situation: Penitentiary	**38**	1.72 (0.65–4.57)	**3.54 (1.14–11.02)**
Genotype 1a	247	0.60 (0.19–1.92)	0.73 (0.15–3.62)
Genotype 3a	407	0.90 (0.30–2.76)	0.80 (0.17–3.83)

Multivariable models showing association with failure to reach SVR12 after first and final treatment.
OR=odds ratio, CI=confidence interval.

retreated within the program in an addiction treatment clinic or within the penitentiary system. People who initiate treatment within the penitentiary system may have to confront unstable housing in addition to other persistent challenges upon release into society, which may explain why this parameter was the only significant predictor of not achieving SVR12 after final treatment.

The results of the Trap HePC study strongly confirm that social and behavioral factors currently determine the treatment outcome for HCV infection. A large proportion of our HCV patients have traditionally faced multiple challenges accessing and maintaining care. Furthermore, the preferred drugs by PWID in Iceland are stimulants, some of which commonly require more frequent injections which may interfere with treatment engagement and adherence (Wu et al., 2004). Nevertheless, when compared to stimulants the use of injected opiates as a preferred drug was associated with lower rates of response after first treatment and this association seemed to persist during subsequent treatment attempts.

The current study examined a few social and behavioural factors impacting on treatment success. The vast majority of those treated had a history of ever injecting drugs (84 %). Whilst recent IDU was significant in the unadjusted analysis it was not significant in adjusted analysis. By multivariable modelling, the only outcome that remained significant for the first treatment was homelessness. -.

Overall, 51 patients (7.2 %) discontinued during the first treatment. Although higher than in clinical trials and many observational studies (Hajarizadeh et al., 2018), this discontinuation rate was low considering the high proportion of patients who traditionally face challenges in treatment access and care. Importantly, 50 % of those who did not complete treatment were cured nevertheless. This is consistent with other studies that have reported that patients may achieve cure despite not completing a full course of treatment (Cunningham et al., 2021).

There are limited data on outcomes from comprehensive national HCV elimination programs. Direct comparison may be difficult because of differences in the underlying nature of HCV epidemics, differences in health systems, and different challenges in reaching and following patients. As an example, Egypt has a large generalized epidemic, while Iceland has a concentrated epidemic among PWID. Furthermore, it is likely that even in national elimination programs, members of patient populations that suffer structural and/or social disadvantage, such as PWID and the homeless may be disproportionally left out and thus underrepresented in data. In Georgia (Averhoff et al., 2020) and Egypt (Waked et al., 2020), two countries with successful HCV elimination programs where large numbers of people underwent treatment, of those treated, 25 % and 17 % respectively, have not been evaluated for SVR. If a disproportionate number of these people suffer social and structural disadvantages then SVR in these two countries may be lower than the reported >98 %. By excluding all with missing data as was done in the reports from Georgia and Egypt, a final cure rate of 98 % could be calculated for Iceland.

Although the population and the number of patients is small compared to larger nations, it can be considered representative for many similar size communities where micro-elimination efforts have been undertaken. Regardless of population size achievement of elimination in any patient population where over 30 % of all patients are actively injecting drugs is challenging.

The study has some limitations. The relatively diverse subgroup of patients dealing with unstable housing is small. The study demonstrates association of homelessness with poor outcome but does not prove causality. Nevertheless it has been demonstrated previously that outcomes can be reversed by targeted intervention, among people living with HIV/AIDS (Aidala et al., 2016) suggesting that increased efforts to improve housing might improve outcomes for our patient group as well.

In conclusion, by concerted efforts using multidisciplinary and public health approaches, including reengagement of those who did not achieve SVR with a first treatment attempt, a cure rate of 95 % was achieved in the TraP Hep C program. In the era of unrestricted access to DAA's, socioeconomic factors, most notably homelessness are the main hurdles to cure. Treatment programs aiming for elimination of HCV as a major health threat need to take this into account.

Data sharing

Our data are accessible to researchers upon reasonable request for data sharing to the corresponding author.

Ethics approval

The authors declare that they have obtained ethics approval from an appropriately constituted ethics committee/institutional review board where the research entailed animal or human participation.

The study was approved by the National Bioethics Committee of Iceland (number 15-087)

Funding sources

This research received funding from the following sources

The Icelandic government provided special funding for the overall organization of the project, diagnostic tests and other services related to the nationwide elimination campaign. Gilead Sciences provided DAAs free of charge in an epidemiological study setting. Gilead Sciences also provided financial support for a contract with PPD (Wilmington, NC, USA), a global contract research organization that provided services on clinical data management and trial monitoring for the TraPHepC study.

The funders of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report or on the decision to submit the paper for publication.

CRediT authorship contribution statement

Sigurdur Olafsson: Writing – original draft, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Thorvardur Jon Love:** Writing – original draft, Investigation, Formal analysis, Conceptualization. **Ragnheidur Hulda Fridriksdottir:** Writing – original draft, Project administration, Investigation, Formal analysis, Data curation, Conceptualization. **Thorarinn Tyrfingsson:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Valgerdur Runarsdottir:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Ingunn Hansdottir:** Writing – review & editing, Investigation, Data curation. **Ottar Mar Bergmann:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Einar Stefan Björnsson:** Writing – review & editing, Investigation, Data curation. **Birgir Johannsson:** Writing – review & editing, Investigation, Data curation. **Bryndis Sigurdardottir:** Writing –

review & editing, Investigation, Data curation. **Arthur Löve:** Writing – review & editing, Data curation. **Guðrún Erna Baldvinsdottir:** Writing – review & editing, Investigation, Data curation. **Marianna Thordardottir:** Writing – review & editing, Data curation. **Ubaldo Benitez Hernandez:** Formal analysis. **Maria Heimisdottir:** Writing – review & editing, Conceptualization. **Margaret Hellard:** Writing – review & editing, Methodology, Conceptualization. **Magnus Gottfredsson:** Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

SO, MG, RHF, and VR report consultancy and speaker's fees from Gilead Sciences. MHel's institute receives funding from Gilead Sciences and AbbVie for investigator-initiated research on which MHel is a chief investigator. All other authors declare no competing interests.

Acknowledgments

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.drugpo.2024.104616.

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