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Course of Care for Hepatitis C in Users of Psycho-active Substances According to the Addictological System of Care and Place of the Test and Treat Strategy

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ABSTRACT

Aim: The treatment of addiction is well structured in France, with different care and prevention services available, such as addiction treatment and prevention centers, the network of medical microstructures centred on general practitioners, and lower risk consumption rooms. The objectives of our study were to compare the courses of care for hepatitis C provided within one addictology center offering all three of these services, as well as to clarify the role and factors associated with the test and treat strategy. **Methods:** 573 users were included prospectively from all three of the above-mentioned services: 168 from the addiction treatment and prevention center, 291 from the network of medical microstructures and 114 from the lower risk consumption room. They were consumers of one or several psycho-active substances (illegal substances, alcohol, tobacco). The different hepatitis C courses of care were compared between the three services. The test and treat strategy was evaluated in comparison with conventional strategy in all the users. **Results:** The users were characterized as being predominantly male (65.4%), with high occurrence of polydrug use (61.2%) and low socioeconomic status (complementary health solidarity 43.8%, precarious housing or homelessness 23.9%, living alone 47.1% and lack of paid employment 72.9%). The course of care for hepatitis C did not differ significantly between the three services: screening performed for 90% with HCV RNA detected in 100% of users, access to treat-

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-ment varied from 61 to 100%; hepatitis C was cured in all users. The test and treat strategy was used in the majority of cases, particularly those treated at lower risk consumption room (93.8%). This strategy was associated with type of consumption and low socioeconomic status ($p < 0.001$). It also correlated with easier and faster access to antiviral treatment (80.6%) compared to the conventional strategy (45.4%, $p < 0.05$).

Conclusions: This study confirms the benefit of using the test and treat strategy for fast treatment of hepatitis C in psycho-active drug users leading to consistent cure and the emergence of a new strategy named “test and cure”.

Lay summary: The course of care for hepatitis C did not significantly differ between the different types of care and addiction services for polyusers of psycho-active substances with vulnerable socioeconomic status.

The test and treat strategy was widely used and made access to antiviral treatment quick and easy, ensuring consistent cure and an evolution towards a new test and cure strategy.

Highlights: A total of 90% of the psycho-active drug users were screened for hepatitis C in three types of French addiction treatment and prevention service.

71% of them were able to receive direct-acting antiviral treatment, resulting in consistent cure.

The test and treat strategy accelerated access to treatment in comparison with the conventional strategy (80.6% *vs.* 45.4%).

Keywords: hepatitis C, use of psycho-active substances, course of care, test and treat strategy

INTRODUCTION

In France, the fight against hepatitis C represents a major prong of the government’s 2018-2022 national health strategy. One of the key actions is to intensify prevention and screening efforts for the most at-risk demographics with the goal of eradicating the hepatitis C virus (HCV) by 2025 (1). Since 2017, direct-acting antiviral (DAA) treatment have become available for all patients infected with HCV, irrespective of the severity of their disease (2). These treatments are simple, safe, and effective in over 95% of cases (3). Drug users are the most numerous among the users of psycho-active substances (UPS) who have hepatitis C. Of all the patients treated in France between 2015 and 2019, 21% were drug users (4). The course of care for this population is often complicated and a test and treat strategy has been in practice for the last few years, inspired by the approach to HIV infection (5). This strategy aims to streamline this course and render treatment more quickly and easily accessible by using non-invasive screening and diagnostic methods which offer near-immediate results, such as rapid diagnostic orientation tests (RDOTs) using capillary blood (6), quantitative PCR (qPCR) tests also using capillary blood (7), or hepatic fibrosis analysis using FibroScan (8). The treatment of addiction is a well-organized

field in France, for all types of substances (particularly illegal drugs, alcohol and tobacco), and involves different prevention and care structures, including addiction treatment and prevention centers (*centres de soins, d'accompagnement et de prévention en addictologie, CSAPA*), the network of medical microstructures (*réseau des microstructures médicales, RMS*) centred on general practitioners (GP), and the more recent, and still experimental, lower risk consumption rooms (*salles de consommation à moindre risque, SCMR*). Our study sought to compare the different courses of care provided within the same addiction center offering all three of the above care services and to clarify the role of the test and treat strategy for all UPS.

Patients and methods

This was a prospective study performed from June 2019 to May 2021 at the Association Ithaque, an addiction treatment and care center accommodating all types of addiction. The study was supported by the French association for the fight against liver disease ALMAF (*Association de lutte contre les maladies du foie*) composed of healthcare professionals. Support and expertise were also provided by specialty care center for the fight against viral hepatitis in Alsace (*Service expert de lutte contre les hépatites virales d'Alsace, SELHVA*), in collaboration with the virological laboratory of Strasbourg University Hospitals (*Hôpitaux universitaires de Strasbourg, HUS*), as well as the support of the SOS Hépatites Alsace-Lorraine patient association, which officially represents the users. Furthermore, both SELHVA and ALMAF provided prior training to all the healthcare professionals and social healthcare professionals of Association Ithaque. This training course included not only workshops on clinical cases, prioritizing the test and treat strategy and DAA treatment, but also RDOT, qPCR and FibroScan training, benefiting from a collaboration between healthcare professionals (9).

Patients included

All the users included from each of the three care services (CSAPA, SCMR and RMS) were users of one or several psycho-active substances. The CSAPA is designed to offer multidisciplinary and conceptual care for all types of addiction, irrespective of substance. The SCMR accommodates users of particularly vulnerable socioeconomic status. This service enables users to use psycho-active substances, notably illegal drugs, in a specially-designed safe and sanitary environment. The RMS is a service with local reach working out of a GP with the collaboration of a social worker and psychologist. The various professionals meet regularly for shared briefings to draw up treatment strategies tailored to each user. These microstructures that participated in our study were located across the entire Alsace region. The users were included based on a pre-planned schedule alternating between the three different services based on shared access to the healthcare professionals (two referring nurses employed half-time for the study) and the equipment for RDOTs, qPCR and FibroScan. Each included user gave written consent to participate in the study after being informed in person by the referring doctor of each care service and provided with an information leaflet.

Methods

The different steps of the course of care were as follows, for all three types of care service: a) HCV serology screening combined with HBs antigen and HIV screening following current guidelines (10); b) HCV-RNA PCR test, with a positive result confirming viral replication and a diagnosis of chronic hepatitis C, as well as FibroScan, a non-invasive technique using ultrasound impulse elastometry (Echosens, Paris-France) to assess the severity of liver damage, with an elasticity ≥10kPa defining advanced F3-F4 fibrosis (11); c) pangenotypic DAA treatment for 8 to 12 weeks (2). Sustained virological response was defined as undetectable HCV RNA at 12 weeks post treatment (SVR 12), thus confirming virological cure.

In the test and treat strategy, treatment was ideally commenced immediately after testing. The testing method in our study consisted of an RDOT using capillary blood from a finger prick, producing results within 20 minutes (First response HCV, Biosynex, Illkirch, France). When an RDOT was positive, HCV RNA was tested by RT-PCR GenExpert, also using capillary blood (Xpert HCV Viral Load, Cepheid, Sunnyvale, CA-US), producing results within 58 minutes. The FibroScan produced results immediately. As soon as chronic hepatitis C was diagnosed, DAA treatment could be proposed. In the conventional strategy, the HCV serology screening and HCV RNA PCR were performed using the same venous blood sample. When HCV serology was positive, the viral load was automatically confirmed using the second sample that had systematically been taken. The patient had to be called back in for an appointment after varying waiting times to receive their results and commence antiviral treatment. The choice between the test and treat strategy and the conventional strategy was left up to the discretion of the referring addiction practitioner of each care structure. The majority of blood samples were taken by the referring nurse. HIV blood test and HBs antigen detection was performed via RDOT using capillary blood (Exacto VIH 1 and 2 and First response HBsAg, Biosynex, Illkirch, France). The FibroScan (FibroScan 430 mini mobile) was performed by the referring nurse in the majority of cases, on the same day as the blood sample inside the care service itself, irrespective of which approach was used, in order to keep everything at the same time and in the same place. Antiviral treatment was initiated by the referring addiction practitioner of the service in question. This physician could request a medical opinion if required by calling a liver disease specialist of the SELHVA or ALMAF centers via a 24h hotline.

The following variables were recorded by the referring nurse from patient health, medical, psychological and social records, shared among the three services. These were: a) demographic characteristics: sex and age; b) type of substance: alcohol, tobacco, cannabis, injected and/or inhaled and/or sniffed (primarily cocaine and heroin) drugs, polydrug use was defined as the combination of at least three different psycho-active substances; c) socioeconomic characteristics, enabling evaluation of level of social vulnerability: complementary health solidarity, precarious living situation or homelessness, living alone and lack of stable paid employment. These records were completed by virological results, FibroScan results, and the choice of strategy - test and treat or conventional.

This study was subject to an agreement with the regional Committee for the Protection of Persons (*CPP Nord-ouest III de Caen*) on March 18, 2019 (Ref. CNRIPH: 18.11.08.62516) and a declaration with the French national agency for the safety of medicines and health products (*Agence nationale de sécurité du médicament et des produits de santé, ANSM*) (research registration number ID RCB: 2018-A03435-50)

For the statistical plan, all variables used were qualitative, except for the users' ages. These variables were compared between the different groups using Chi-squared test. For the ages, the results were expressed as means + /- SD and compared using Student's T test.

RESULTS

Of the 593 users asked to participate in the study, 573 accepted: 168 from the CSAPA, 114 from the SCMR, and 291 from the RMS network. The 20 who refused to participate (3.4%) comprised six from CSAPA, six from the SCMR, and eight from the RMS network.

The users' characteristics have been detailed in *Table 1* according to type of care service. There was a significant difference ($p < 0.001$) between the three services concerning age, sex distribution, different substances used, three of the four socioeconomic vulnerability parameters and advanced fibrosis.

Table 1 - Comparison of the variable studied between the three care services (CSAPA, SCMR and RMS)

(1) proportion calculated on total number of 517 users, 150 in CSAPA, 105 in SCMR and 262 in RMS; (2) proportion calculated on total number of 545 users, 160 in CSAPA, 106 in SCMR and 279 in RMS

Variables	TOTAL (N=573)		CSAPA (N=168)		SCMR (N=114)		RMS (N=291)		p
Age y. (mean ± SD)	46,7 ± 9,1		44,1 ± 12,3		38,6 ± 9		51 ± 7,6		<0.001
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
Gender (male)	375	65.4	130	77.4	96	84.2	149	51.2	<0.001
Consumption									
alcohol (1)	205	39.6	47	31.3	29	27.6	129	49.2	<0.001
tobacco (1)	381	73.7	117	78.0	86	81.9	178	67.9	<0.001
cannabis (1)	165	31.9	41	27.3	48	45.7	76	29.0	<0.001
Illicite drugs	389	67.9	122	72.6	95	83.3	172	59.1	<0.001
polyconsumption (1)	316	61.2	88	52.4	84	80.0	144	55.0	<0.001
Social vulnerability factors									
complementary health solidarity	251	43.8	52	30.9	59	51.7	140	48.1	<0.001
precarious housing or homelessness	137	23.9	33	19.6	72	63.1	32	10.9	<0.001
living alone	270	47.1	88	52.4	79	69.3	103	35.4	<0.001
lack of paid employment	418	72.9	119	70.8	87	76.3	212	72.8	NS
Advanced fibrosis (2)	72	13.2	15	9.4	21	19.8	36	12.9	<0.001
HBV screening	517	90.2	151	89.9	107	93.8	259	89	NS
HIV screening	568	98.8	166	98.8	112	98.2	290	99.6	NS

The results from the different steps of the course of care are presented in *Figure 1*. A total of 90% of patients accepted screening, irrespective of type of service. The rate of HCV seropositivity was higher in the patients at the SCMR, reaching 31% (*Figure 2*). Detection of HCV RNA was carried out in all patients irrespective of care service and technique used (*Figure 1*). HCV RNA positivity was 44%, with no significant difference between the three care services (*Figure 2*). In the 42 HCV-RNA positive users, FibroScan revealed advanced fibrosis in 24% of users, with no significant difference between the three services, although there was only a very small number of individuals at the CSAPA (*Figure 2*). Antiviral treatment was started in 71% of users, with no significant difference between the three services, although only a small number were concerned (*Figure 1*).

HCV RDOTs were performed in 80.3% of users with a significant difference (p <0.001) between the three services (*Figure 3*). Their use was most common in the SCMR (93.8%). For all users, the test and treat strategy was associated with

alcohol and drug use, as well as polyconsumption use, and two socioeconomic vulnerability parameters (p <0.001) (*Table 2*). The proportion of users accessing antiviral treatment was significantly higher with the test and treat strategy (25/31, i.e, 80.6%) compared to the conventional strategy (5/11, i.e., 45.4%) (p<0.05). For the 25 users following the test and treat strategy, antiviral treatment was commenced immediately in 20 (80%) and within less than 15 days in the other five. For the five users following conventional strategy, the treatment was commenced after 10, 30, 45, 60 and 90 days, respectively. No antiviral treatment was received by 12 users, six from the conventional strategy, of whom five were lost to follow up and one with no valid insurance cover after 3 months, and six from the test and treat strategy, of whom two were lost to follow up and four had no valid insurance after 3 months. Virological cure was confirmed in all treated patients, irrespective of which strategy was followed.

DISCUSSION

All in all, this study found that the course of care did not significantly differ between the three care services. The test and treat strategy was widely used. It was associated with type of substance and socioeconomic vulnerability. Moreover, our study confirmed that this strategy ensured faster and easier access to antiviral treatment for all UPS.

Table 2 - Factors associated with the test and treat strategy (1) proportion calculated on total number of 517 users, 414 in the test and treat strategy and 103 in the conventional strategy; (2) proportion calculated on total number of 517 users, 442 in the test and treat strategy and 103 in the conventional serology group

Variables	Test and treat strategy (N=460)		Conventional strategy (N=113)		p
Age y. (mean ± SD)	44,1 ± 10,8		46,4 ± 8,9		NS
	n	**%**	**n**	**%**	
Gender (male)	300	65.2	75	66,4	NS
Consumption					
alcool (1)	148	35.7	57	55,3	<0.001
tobacco (1)	308	74.4	73	70,9	NS
cannabis (1)	136	32.8	29	28,1	NS
illegal drugs	366	79.5	23	20,3	<0.001
polyconsumption (1)	276	66.7	40	38,8	<0.001
Social vulnerability factors					
complementary health solidarity	223	48.5	28	24.8	<0.001
precarious housing or homelessness	122	26.5	15	13,3	<0.001
living alone	220	47.8	50	44,2	NS
lack of paid employment	359	78.0	90	79,6	NS
Advanced fibrosis (2)	57	12.9	15	14.5	NS

Figure 1– Comparison of the cascade of care between the three care services

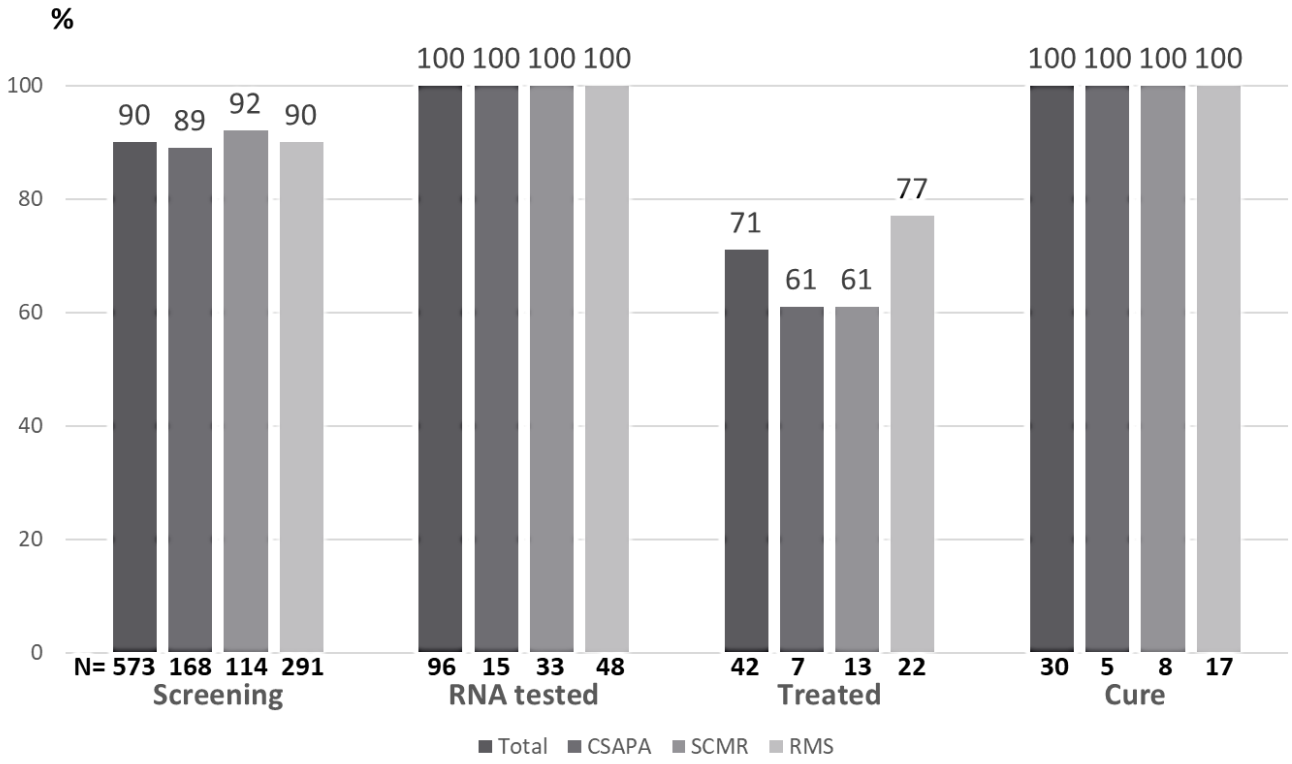


Figure 2 – Comparison of the proportion of patients seropositive for HCV, RNA-HCV positive and with advanced fibrosis between the three care services

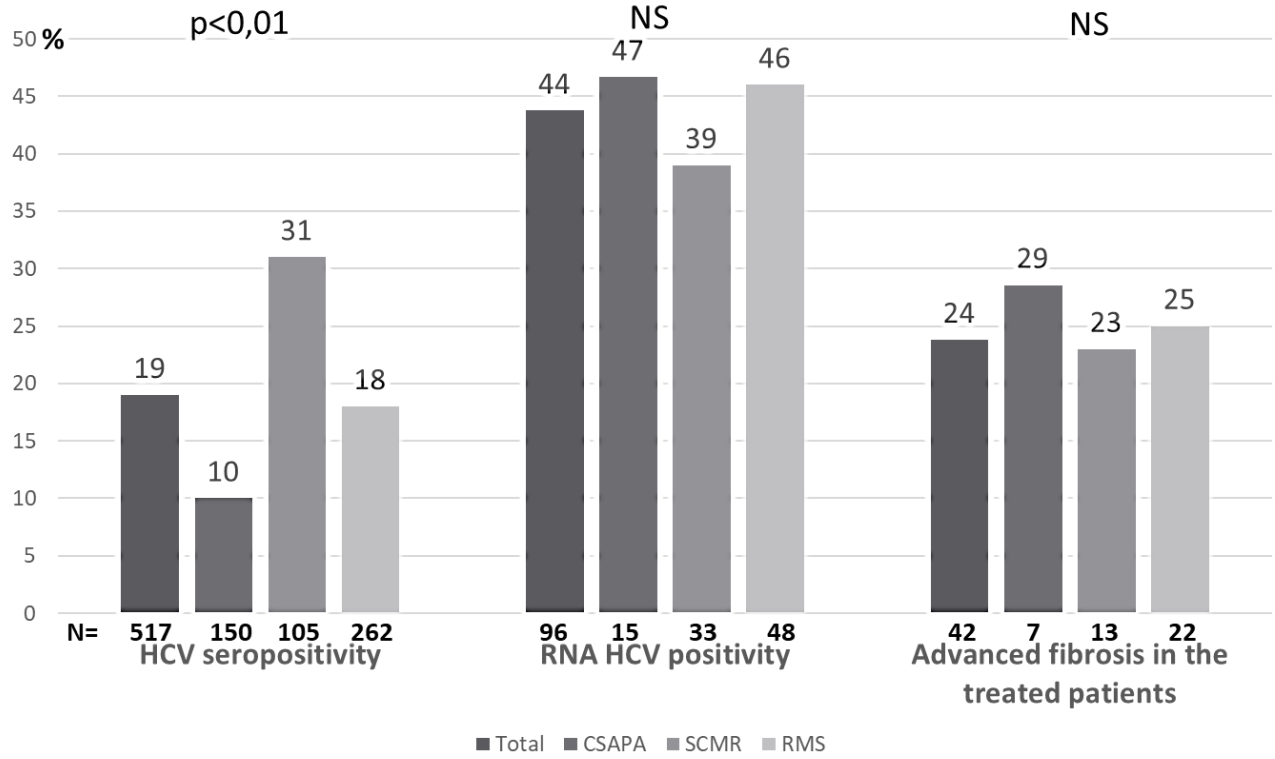
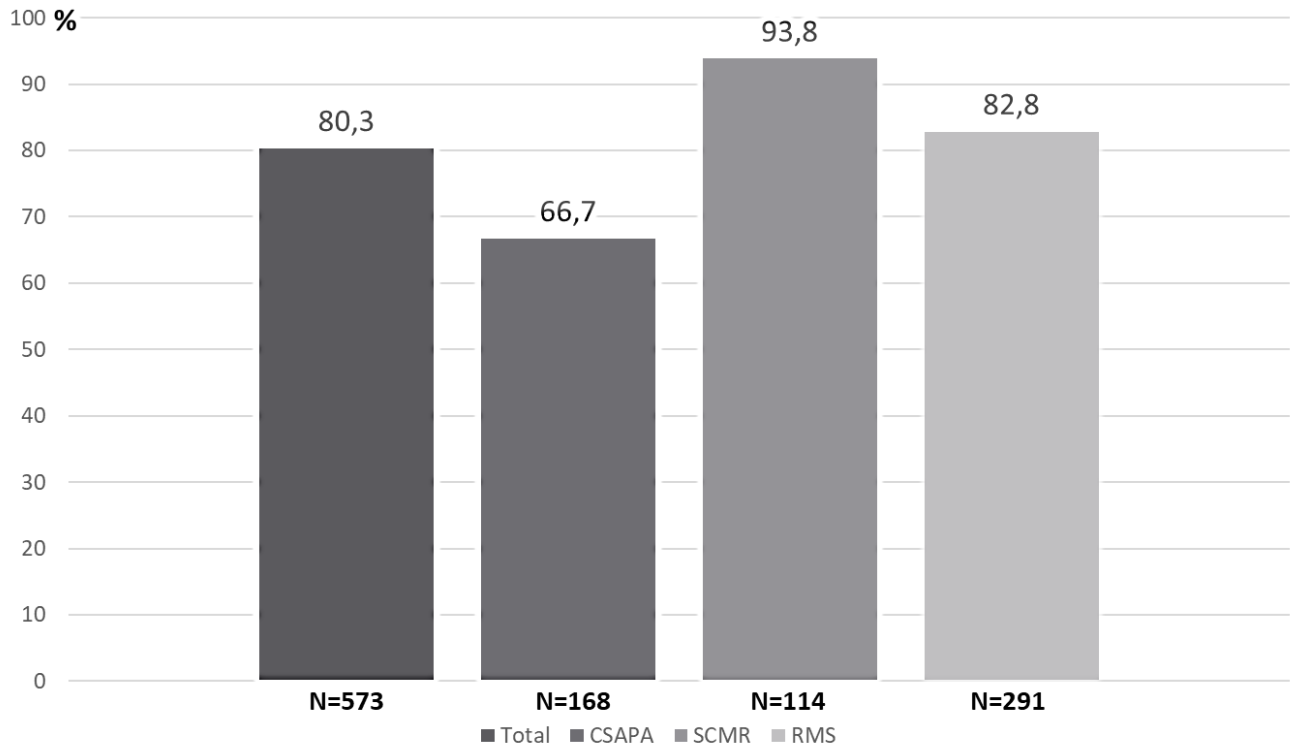


Figure 3 – Comparison of the proportion of HCV screening by rapid diagnostic orientation test between the three care services (p<0.001)



The UPS included in this study were characterized as mostly male, with higher frequency of polydrug use and low socioeconomic status. The SCMR differed from the two other care services in that those patients were younger, more predominantly male, and with higher frequency of psycho-active drug use, polydrug use, and lower socioeconomic status.

The course of care in hepatitis C has been mainly studied among drug users (12). Progression through the cascade of care was demonstrated to vary wildly, whilst often limited by multiple barriers linked to human factors, such as lack of information, ignorance of illness and treatment, absence of insurance coverage, in addition to structural factors like the lack of means and of coordination, along with geographical isolation (13,14). With the advent of DAAs, the HCV cascade of care could be markedly transformed, whereas several barriers should likely remain (15). The methodology used in our study made it possible to limit the majority of these barriers. Thus, training course was provided for all healthcare professionals, the partnership with a patient association has made it possible to adapt the information to all UPS, a specific coordination common to the three care services was set up for the study and an additional referent nurse was recruited. Moreover, our cascade was complete by means of an integrated care practice, thereby encompassing the successive steps of screening, diagnostic assessment, treatment and healing. The extension of the study to all UPS is justified for several reasons: i) polydrug use is frequent, as our study shows; ii) in France, all addictions are taken care of regardless of the structure, as our study also shows; iii) the risk of hepatitis C and progression of fibrosis is increased with polydrug use (16). Regarding the initial step of the course of care, the proportion of UPS screened for HCV was approximately 90% across all care services. In two previous studies we conducted involving drug users, the rates of testing were 77% in eight CSAPAs in Alsace and 80% in the RMS network using

conventional blood testing (17,18). The improved testing rate we found in this study is probably linked to the use of HCV RDOTs in 8/10 cases. An even higher testing rate was observed for HIV and HBV with the use of RDOTs. HCV seropositivity was higher (31%) in the UPS from the SCMR. This finding is not surprising considering that this population is subject to many risk factors, such as being clearly predominantly male and with much higher frequency of drug use as well as low socioeconomic status (19). In contrast, HCV seropositivity was low (10%) in the UPS from the CSAPA, probably due to how long harm-reduction policies have been in place in this type of care service (20,21). As demonstrated in the Amsterdam study combining opiate substitution treatment with integrated harm reduction interventions like needle and syringe exchange programs, thereby enabling safer injection practices, likely exerts beneficial effects on reducing HCV transmission (22). As regards the diagnosis stage of the course of care, HCV RNA detection was consistent, with positive C virus serology in all three services. This is to be expected given that the test and treat strategy means that the GenExpert device was readily available inside every structure, and that when the conventional strategy was followed, a PCR test was immediately performed on the second sample, which was systematically taken alongside the sampling for the blood test. The Xpert fingerstick HCV viral load assay is particularly suitable for the test and treat strategy with an almost immediate result and a very good sensitivity and specificity (23). A FibroScan was performed and interpreted in 95% of users, confirming that this examination is well-accepted and offers high performance (24), even in the most vulnerable users (25), with immediate result. In the spirit of inter-healthcare professional cooperation, all FibroScan were able to be performed on site inside each structure on the same day the blood samples were taken, no matter which strategy was being followed. Keeping these examinations in the same time and place is essential in treating UPS (20). The results of the treatment stage of the course of care are to be interpreted with care, even if all users were considered cured, confirming the excellent efficacy of DAA treatment (3), since the number of users receiving treatment was too small, particularly in the CSAPA (n=7), to be able to confirm the absence of a significant difference between the three services.

The test and treat strategy was prioritized in this study, particularly in the SCMR which accommodates the most difficult UPS cases. The high efficacy and low toxicity of the pangenotypic DAAs provide an exceptional opportunity to greatly simplify HCV diagnostic and care. Pangenotypic DAA regimens no longer depend on quantitative HCV RNA or genotype data to stratify the duration of treatment (26-28) and many international clinical trials and demonstration studies are underway to generate evidence of the efficacy of a simplified approach to diagnostic and treatment monitoring (29). Moreover, excellent safety profiles and limited potential drug-drug interactions also negate the need for intensive on-treatment monitoring (30). Several test and treatment models have been proposed depending on the primary or tertiary of health care settings (31). In our study the test and treat strategy was identical in the three care services with point-of-care HCV diagnostic and rapid liver staging and the analysis of the results was global. The test and treat strategy enabled easier access to antiviral treatment (31), as our study shows with 80.6% of users commencing treatment *vs.* 45.4% who did so following the conventional strategy. The latter percentage is to be interpreted with care, however, since it only applied to 11 UPS. The lack of access to treatment is primarily due to a lack of valid insurance with the test and treat strategy, and due to patients lost to follow up with the conventional strategy. With test and treat strategy, which enables immediate treatment, it is essential to anticipate all paperwork required to obtain adequate coverage (32). With the conventional strategy,

the causes behind patients lost to follow up despite their initial adherence to the study protocol could be attributed to the study's limitations.

For this study did have several limitations, primarily relating to the health crisis of the Covid-19 pandemic. Initially, the number of inclusions planned for the study was 1000, but structure capacities were reduced in all three care services. A more pertinent analysis would therefore have been possible for the data concerning antiviral treatment and the comparison between courses of care in the three services according to the strategy followed. The pre-established schedule alternating between the three services was disrupted, especially in the medical microstructures, and had to be modified according to the available manpower and equipment. The delay between each UPS' admittance to the services and their inclusion in the study thus varied widely, instead of being as short as possible depending on insurance cover, as intended. Finally, the number of UPS attending the services was lower, with more or less prolonged breaks in care.

Nevertheless, our study confirms the value of the test and treat strategy as a fast approach to treating chronic hepatitis C in an addiction center with the participation of GPs. Considering that the virus was consistently cured, a new "test and cure" strategy can be proposed.

ABBREVIATIONS:

ALMAF: association for the fight against liver disease (*Association de lutte contre les maladies du foie*)

ANSM: national agency for the safety of medicines and health products (*Agence nationale pour la sécurité du médicament et des produits de santé*)

CPP: Committee for Personal Protection (*Comité de protection des personnes*)

CSAPA: addiction treatment and prevention centers (*Centre de soins, d'accompagnement et de prévention en addictologie*)

DAA: direct-acting antiviral

GP: general practitioners

HBV: hepatitis B virus

HCV: hepatitis C virus

HIV: human immunodeficiency virus

SCMR: lower risk comsuption rooms (*salle de consommation à moindre risque*)

RDOTs: rapid diagnostic orientation tests

RMS: network of medical microstructures (*Réseau des microstructures médicales*)

SELHVA: speciality care center for the fight against viral hepatitis in Alsace (*Service expert de lutte contre les hépatites virales d'Alsace*)

SVR 12: sustained virological response at week 12 post-treatment

UPS: users of psycho-active substances

CONFLICTS OF INTEREST:

none.

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This study was conducted with the institutional support of Abbvie.

AUTHOR CONTRIBUTIONS:

Coraline BIEHLER: collected and analyzed the data.

Frederic CHAFFRAIX: contributed to the study, conception and design, drafted and reviewed the manuscript.

Fiorant DI NINO: contributed to the inclusion of the users of psycho-active substances and interpretation of findings.

Camille BRAND: contributed to the inclusion of the users of psycho-active substances.

Flavie OSTER: contributed to the inclusion of the users of psycho-active substances.

Samira FAFI KREMER: contributed to the study and reviewed the manuscript.

Gauthier WAECKERLE: contributed to the study and reviewed the manuscript.

Michel HASSELMANN: reviewed the manuscript.

Michel DOFFOEL: created the original study conception and design and drafted the manuscript.

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