HCV-MICROELIMINATION PROGRAM AND PATIENT TRAJECTORIES AFTER HCV CURE IN AN OUTPATIENT HIV CLINICAL UNIT.

Running title: HCV MICROELIMINATION PROGRAM

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Conflict of Interest

I Poizot-Martin: reports personal fees from Gilead Sciences, MSD, for consultancies, and support from Gilead sciences, ViiVhealthcare for travel/accommodation/meeting expenses, outside the submitted work.

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C Solas: reports personal fees from Viiv, Abbvie, Gilead for consultancies, and support from MSD, Viiv, Gilead for travel/accommodation/meeting expenses, outside the submitted work.

C Lions, O Zaegel-Faucher, E Ressiot, C Tamalet, MA Pieve, AS Ritleng, C Debreux, A Ivanova, Obry-Roguet, P Carrieri, P Geneau De Lamarliere: no conflicts of interest

Source of funding: This study was conducted with a grant of Gilead sciences. The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Abstract

Objective

Treatment recommendations for hepatitis C now make no distinction between HIV/HCV-coinfected and HCV-monoinfected patients. The largest challenge remained lack of effective models to eliminate HCV in people living with HIV.

We report the results of a microelimination program evaluating the possibility of eradicating HCV infection in an HIV-outpatient clinical unit within 12 months.

Methods

This HCV-microelimination program began in February 2016 in an unit following approximately 1000 HIV-infected patients and combined screening and therapeutic components according to the French guideline. A nested cohort study evaluating the impact of HCV cure on different health outcomes was conducted through self-administered questionnaires and using generalized mixed models.

Results

Among 601 patients eligible for HCV serological testing, 445 were evaluated, and two HCV acute infection were diagnosed. Among the 151 patients eligible for HCV RNA quantification, 119 were evaluated, and one reinfection with HCV was diagnosed.

Among the 110 patients eligible for DAA treatment, 51 (46.4%) patients initiated treatment within the 12 months program, and 35 (31.8%) after. Sustained virologic response (SVR) rate was 96.1%, and two treatment failed. At least one self-reported symptom was declared by

72.5% (n=29) of patients. Positive impact of HCV cure was observed on various markers of physical and mental health as well as on health habits.

Conslusion

Our program should be considered as a proof of concept, which confirmed the feasibility of a HCV-microelimination program at the scale of an HIV clinical unit. However, 12 months were not sufficient to achieve our objective despite the specific organization.

Keywords

DAA ; HCV-microelimination program ; HCV cure ; Health outcomes ; Cohort

Introduction

People living with hepatitis C virus (HCV) infection are overrepresented in the healthcare system due to various individual and contextual circumstances, including comorbidities and socioeconomic marginalization [1]. However, direct-acting antivirals (DAA) have revolutionized the treatment of chronic hepatitis C virus (HCV) infection, and the increasing number of patients who are cured of HCV could potentially result in less severe patterns of hospital-related comorbidities over time [2].

The burden of HCV is likely to be higher in HIV-infected patients than in HCV-monoinfected patients. Indeed, although healthcare-related visits by people living with HIV and HCV decreased in recent years, the number of visits remains significantly higher than that of patients only living with HIV, as recently reported [3].

Treatment recommendations for hepatitis C now make no distinction between HIV/HCV-coinfected and HCV-monoinfected patients, as there are no differences in response rates

regardless of liver cirrhosis, shortened treatment duration or age [4,5]. Although HIV/HCV-coinfected patients require careful evaluation of potential interactions between HCV drugs and HIV antiretroviral therapy, medication for substance abuse, substances consumed and other comedications, the largest challenge globally remains the lack of effective models to eliminate HCV in HIV-infected patients receiving care in hospital outpatient clinics [6]. Thus, microelimination could be a big deal for HCV and HIV services [7].

Here we report the results of an HCV-microelimination program conducted in order to evaluate the possibility of eradicating HCV infection in an HIV-outpatient clinical service within a period of 12 months.

Materials and methods

This HCV-microelimination program was conducted in an HIV- outpatient clinical unit following approximately 1000 patients annually and using an electronic medical record (NADIS®) [8]. Patient-related data are recorded during medical encounters in a structured database, allowing clinical, epidemiological or therapeutic studies. Data quality is ensured by automated checks during data capture, regular controls, annual assessments, and ad hoc processes before any scientific analysis is performed. The data collection was approved by the French National Commission on Informatics and Liberty (CNIL 2001/762876), and all patients signed an informed consent form before being included in this database.

HCV microelimination program

The elimination program was initiated in February 2016 and combined screening and therapeutic components, which were both defined according to the French guidelines for HCV-HIV coinfection care [9]. We included a sub-study evaluating the impact of HCV cure on

different health outcomes through self-administered questionnaires in the program. This research program was approved by the Ethical Committee CCP-Sud-mediterranée-1 Marseille, France, number 2015-A01913-46.

Screening phase of the program

In the screening phase, according French guidelines, HCV serology was performed for patients with a previous negative result for more than 12 months or an unavailable test; in cases of positive serology, HCV RNA was quantified. For cured HCV patients after HCV treatment, HCV RNA was systematically controlled if the previous HCV RNA quantification was over 6 months or in case of HCV reinfection risk factors; for patients who spontaneously cleared HCV infection, HCV RNA was performed if the precedent test occurred more than 12 months prior.

Therapeutic phase of the program

The therapeutic component of the program included information and a treatment proposal for all patients with positive HCV-RNA quantification. Considering the shorter duration of HCV treatment with a direct antiviral agent (AAD), we aimed to treat all patients over a period of 12 months. To achieve this objective, a dedicated scheme was implemented including (i) an appointment with the hepatologist, an educational nurse consultation, blood tests including HCV-RNA quantification, liver ultrasonography and liver fibrosis assessment with elastometry (FibroScan®, EchoSens, Paris, France) (ii) a schedule of appointments for clinical visits, nurse education session and laboratory measurements defined with the patient at the time of treatment initiation as follows: monthly during the treatment period, then at week (W) 4, W12, W24 and W48 after the end of the treatment. Treatment modalities (DAA and treatment duration) were defined according to the current French guidelines and validated by multidisciplinary staff, in

order to evaluate drug-drug interactions between anti-HCV therapy, antiretrovirals and/or treatment for comorbidities.

Evaluation of the impact of HCV cure on different health outcomes

This substudy started in February 2016. Self-administered questionnaires were completed at treatment initiation, at the end of the treatment, and at 12, 24 and 48 weeks posttreatment. The questionnaires included an evaluation of current and lifelong substance consumption (tobacco, cannabis, alcohol and other substances), physical and mental quality of life, physical activity, level of energy, pain and frailty state.

Alcohol consumption was evaluated using the AUDIT-C scale. A score higher or equal to four for men and three for women was considered as a risky consumption, a score higher or equal to five for men and four for women as a harmful use for health [10–12].

Mental health was evaluated using the validated French version of the CES-D scale (a score over 17 for men and over 23 for women defining potential depression) [13,14].

Quality of life was evaluated using the SF-12 scale [15] composed of the Physical and the Mental Health Composite Scores (PCS and MCS): higher scores represent better health. PCS and MCS were also dichotomized according to values among the general population (a score higher or equal to the 25th percentile of those found in the general population indicated a good quality of life) [16].

Regular practice of physical activity was evaluated and level of energy and health condition perception for stress, depressed and tired were quantified using a visual analogic scale.

The frailty state was assessed using the Fried score combining the five following criteria: unintentional weight loss, self-reported exhaustion, weakness, slow walking speed and low physical activity. The presence of three or more of these criteria defined the frailty phenotype, the presence of two defined the prefrail phenotype [17].

For patients included in this sub-study, observance and tolerance to DAA were prospectively evaluated through specific questionnaires at W2 and W4 and then monthly during the treatment period. Adherence was considered to be <100% if the patient reported at least one of the following situations: interruption of the treatment before the planned end; missing at least one treatment since the start of the treatment; missing all or part of treatment in the past weekend; not taking at least one pill in the four lasts days. Adherence perception was assessed using a four-point scale assessing how the patient respected the treatment: strictly respected all doses (rhythm and quantity) vs other.

Data sources and outcomes

For every patient starting the DAA treatment, we collected the following data from our database: sociodemographic characteristics (age, gender, HIV transmission risk group), CDC stage, antiretroviral drug regimen, HIV and HCV viral load, CD4 and CD8 T cell count. Previous liver fibrosis score was assessed through transient elastography and defined as a function of liver stiffness: ≤7 kPa: F0-F1; 7-14.5 kPa: F2-F3; and ≥14.5 kPa: F4.

A sustained virological response (SVR) was considered to be achieved if HCV RNA was < 12 UI/mL, 12 weeks after the end of treatment.

Study population

According to the French guidelines for HCV-HIV coinfection care, the screening phase of the program concerned 601 patients eligible for HCV serology testing and 151 for HCV RNA quantification.

Concerning the therapeutic component of the program, in November 2015, among the 898 HIV-infected patients regularly followed in our unit, 276 were HCV-HIV coinfected. Among these patients, 14.1% (n=39) cleared HCV infection spontaneously, and 36.3% (n=101) cleared HCV

infection after treatment. HCV RNA quantification was positive in 49.3% (n=136) of patients of whom 14.8% (n=20) were undergoing HCV treatment, 23.5% (n=32) received at least one HCV treatment, and 61.7% (n=84) had never been treated for HCV infection. Thus, when starting the program, 116 patients were eligible for HCV treatment, to which newly screened patients were added during the study period.

Statistical analysis

Medians and interquartile ranges (IQR) and proportions were used to describe the distributions of continuous and categorical variables, respectively. To assess the impact of DAA treatment on the health indicators, we used generalized mixed models depending on the outcome (logistic distribution in the case of categorical variables and linear for continuous variables) with time from HCV clearance as an explanatory variable. The statistical analyses were performed using SAS software version 9 and Stata software version 12.

Role of the funding source

The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Screening phase of the program (January 2016-January 31, 2017)

Among the 898 HIV-infected patients followed in our unit between 01/01/2015 to 31/12/2015, HCV serology was positive in 287 patients and negative in 611 patients (Figure 1). Among those with HCV positive serology, 117 (40.7%) patients cleared HCV infection after treatment and 34 (29%) spontaneously. Thus, there were 151 patients eligible for

HCV RNA quantification according to the French guidelines. Among those with HCV negative serology, 10 patients (1.6%) were already tested in the past year. Thus, 601 (98.4%) were eligible to HCV screening.

Among the 601 patients eligible for HCV serology testing, 45 patients were lost to follow-up during the period of the program, and 445 (74%) patients were evaluated. Two cases of acute HCV genotype 4 infection were diagnosed in two men who have sex with men (MSM). HCV testing was performed in 49 additional patients beyond the study period without additional diagnosis of acute hepatitis C.

Among the 151 patients eligible for HCV RNA quantification, five patients were lost to follow-up during the period of the program, and 119 (79%) patients were evaluated. One case of reinfection with HCV genotype 4 was diagnosed in a man with SVR for nine years, while liver enzymes were normal (ASAT and ALAT<25 UI/mL). HCV RNA was controlled in three additional patients beyond the study period without a new case of reinfection diagnosis.

Therapeutic component of the program:

During the study period, 14 newly HIV-HCV coinfected patients were included in our database, increasing the number of patients with positive HCV RNA to 130 patients (flow chart Figure **2**). Among them, six patients were lost to follow up, one patient spontaneously cleared HCV infection, and HCV monitoring was performed outside the unit for 13. Thus, 110 patients were eligible to the program.

Patients' characteristics are described in table 1. Most of them were male, infected through intravenous drug use, and followed for HIV infection for more than 20 years in the median. The CD4 cell count was $\geq 500/mm^3$ in more than half of patients, and 97.7% (n=127) were on antiretroviral therapy (ART), with an undetectable HIV viral load in 83.8% (n=109) of cases.

Most patients were infected with HCV genotype 1, but the prevalence of HCV genotype 4 was higher among new patients. The liver fibrosis score was F0-F1 (≤7 kPa) in 56.2% (n=73) of patients, and 5.5% (n=4), 9.7% (n=3) and 7.7% (n=1) of patients were classified as F4 (≥14.5 kPa) in the naive, treatment-experience and new patients, respectively. Moreover, 12 patients required HIV treatment adjustment because of the interaction risk with HCV treatment, and HIV treatment was initiated in two patients, leading to a delay in DAA treatment initiation.

At the end of the program period, 51 (46.4%) patients were able to start HCV treatment and four patients refused for personal reasons. Treatment was denied by physicians for medical reasons in 16 cases and for a lack of compliance in four cases (Figure **2**).

The most common DAA treatment was sofosbuvir/ledipasvir combination in 56.9% (n=29) of patients, combined with ribavirin in four of them, followed by daclatasvir + sofosbuvir in 27.5% (n=14), ombitasvir + paritaprevir/ritonavir + ribavirin in 7.8% (n=4), glecaprevir/pibrentasvir in 5.9% (n=3), and sofosbuvir+ ribavirin in 2.0% (n=1).

The treatment duration was eight weeks in 17.6% (n=9), 12 weeks in 70.6% (n=36) and 24 weeks in 9.8% (n=6) of patients. HCV cure was achieved in 96.1% (n=49). Two treatment failures were observed, both in HCV genotype 3-infected patients. The two patients were treatment-naïve, one with a fibrosis score F1, and the other one with a fibrosis score F4.

Dynamic of HCV treatment initiation

The rate of treatment initiation increased to 2.6 per month versus 1.5 per month before the implementation of the HCV-microelimination program. Furthermore, 459 medical consultations dedicated to HCV treatment were implemented in addition to regular medical follow-up for HIV infection. And finally, 35 (31.8%) patients initiated HCV treatment after the end of the program. No additional treatment failure was observed among them.

Evaluation of patient trajectories during and after HCV treatment

Fifty patients were included in the substudy and responded to the questionnaires. The characteristics of these patients did not differ from those of the eligible patients (Table 1). Adherence data are reported in table 2. At W2, 10% (n=3) of patients reported an adherence of less than 100%, which dropped to 27.3% (n=6) at the end of the treatment (p=0.04). In addition, 95% (n=38) and 89% (n=39) of patients declared having strictly respected all doses after two weeks of treatment and at the end of treatment, respectively (difference not significant). Significantly fewer patients declared having strictly respected all doses at W4 and W12 of treatment (p=0.05 and p=0.04, respectively) compared to W2, with no difference according to treatment duration.

Self-reported symptoms during HCV treatment with DAA

Self-reported symptoms during treatment are described in Table 2. After two weeks of treatment, 72.5% (n=29) of patients declared at least one symptom, which included fatigue in 38% (n=15); breathlessness, dry mouth, and headache in 22% (n=8, 7, 8 respectively); gastrointestinal symptom in 40% (n=16); increase in appetite in 19% (n=7); loss of appetite in 8% (n=3); and articular and muscular pain in 14% (n=5) and 11% (n=4), respectively. No significant differences in the proportion of self-reported symptoms (considered by type) were observed over the follow-up period.

Impact of HCV cure with DAA on substance abuse

The evolution of substance abuse is reported in table 3, and the results of the mixed model for each marker are shown in table 6. The proportion of patients with a harmful use of alcohol significantly decreased during the treatment period, and this evolution was maintained until 48

weeks after the end of treatment. Binge drinking frequency declared in the previous months following the beginning of the treatment was reduced at the end of treatment, with 23% (n=5) and 35% (n=8) of patients reporting binge drinking at the end of treatment and six months later respectively, versus 59% (n=19) at the time of treatment initiation (p=0.02; p=0.04, respectively). However, 12 months after the end of the treatment, 46% (n=11) of patients declared binge drinking behavior. Although still lower than before HCV treatment, the difference was no longer significant. Tobacco consumption was not modified during and after treatment, and cannabis use significantly increased after the end of treatment (at W12 and W24 post treatment).

Drug use at least once in the past three months was reported by a few patients (cocaine (n= 3), crack (n=1), opioids (n=1), poppers (n= 1), and MDMA (n= 1)) at baseline and did not increase during or after the end of treatment (data not shown).

Impact of HCV cure with DAA on mental and physical health (table 4; table 5; table 6)

We observed an improvement in mental and physical quality of life at the end and 3 months after the end of treatment, respectively. Whereas nearly 50% (n=24) of patients obtained a score corresponding to an altered physical quality of life at the time of treatment initiation, there were 32% (n=12) to obtain a similar score three months after the end of treatment (p=0.03). Similarly, 35% (n=15) of patients had an altered mental quality of life at the time of treatment initiation, this proportion was 16% (n=6) at the end of treatment (p=0.03). The proportion of patients with depressive symptoms evaluated by the CES-D scale remained stable during the treatment and until 48 weeks after the end of treatment, as did energy level. Compared to the time of treatment initiation, at the end of treatment, the proportion of patients who declared having a physical activity decreased significantly (p=0.03), which was no longer observed at W12, W24 and W48 after the end of treatment.

At the time of treatment initiation, 15.4% (n=6) of patients had a frail phenotype, and 64.1% (n=25) were prefrail (table 5). At the end of treatment, 12.9% (n=4) and 67.7% (n=21) of patients presented a frail and prefrail phenotype, respectively (difference not significant). Considering the different criteria separately, we observed a significant decrease in the proportion of patients with slow walking speed after 24 weeks after the end of treatment (p=0.003).

Discussion

This study demonstrates the feasibility of implementing a microelimination program for HCV eradication at the scale of an HIV clinical unit. Indeed, this dedicated organization allowed us to increase both the rate of HCV screening and treatment initiation with a consistent percentage of sustained virological responses. However, twelve months was not enough to reach our objective despite a specific organization, due to numerous medical and personal conditions that are required to be met before DAA initiation (control of : HIV viral load, comorbidities, drug-drug interactions, and adhesion to closed planned appointments). Our data also confirm the relevance of the guidelines with the early diagnosis of two cases of HCV seroconversion and one case of reinfection before the occurrence of clinical signs or abnormal biological markers.

The scaling-up of regular HCV testing, access to HCV treatment without restrictions, close monitoring for reinfection and retreatment of reinfections are considered the key components to enable HCV elimination among people living with HIV [18]. Although the new infection rate was low in our cohort compared with others [19], HCV treatment of these three patients participated to the reduction of HCV transmission risk, which actually remains a challenge, especially among men who have sex with men (MSM) starting pre-exposure prophylaxis [20,21]. Furthermore, even if only 46.4% of eligible patients were treated during the study

period, a dynamic of treatment initiation was launched as shown by the rate of 1.5 treatments initiated per month before the program compared to 2.6 per month since the initiation of the program.

Other microelimination initiatives have been implemented in other countries to achieve nationwide HCV elimination [22]. Our program should be considered a proof of concept, which confirmed the feasibility of the program at the scale of an HIV clinical unit. However, 12 months were not sufficient to achieve our objective despite a specific scheme that required, for the 50 patients evaluated with specific questionnaires, 832 clinical visits and nurse consultations. Interestingly, few patients refused the treatment, but treatment was contraindicated for medical conditions in 16 patients. Such situations should be taken into account in the design of an HCV microelimination program.

Despite nurse educational consultation for compliance, only 73% of patients declared having strictly respected all doses at the end of the treatment. However, the SVR rate was similar to those reported in other clinical studies in the routine practice setting [23–25].

At least one self-reported symptom was declared by 73.2% of patients in our study, but no treatment was stopped due to adverse events (AE). In a recent study performed on 78 HCV-HIV coinfected patients, AE secondary to DAA were reported by 26.9% of patients [26]. However, in our patients, tolerance was investigated through specific self-administered questionnaires that could allow more exhaustive data collection. The distribution of AE reported in this study was similar to the self-reported symptoms observed in our patients, with fatigue (47.6%), gastrointestinal symptoms (38.1%) and headache (14.3%) being the most common AEs.

The evaluation of patient trajectories after HCV cure showed a positive impact of recovering from HCV on various markers of physical and mental health as well as on health habits. Indeed, we found a reduction in harmful alcohol use after treatment. However, this reduction may be compensated by an increase in cannabis consumption, which we found to significantly increase after HCV cure. A significant decrease in both alcohol use and binge drinking was previously reported after pegylated interferon-based therapy, irrespective of HCV clearance, with no significant effect on tobacco use and regular cannabis use [27]. Few patients declared consuming other substances at the time of initiation of treatment, and no increase of this use was observed until one year after the end of treatment. Reduced physical activity was reported upon treatment and may be related to fatigue. However, an improvement of physical and mental quality of life, as well as walking speed, were observed after HCV cure. Our results are consistent with data reported by Kleefeld et al. in HCV monoinfected patients, showing a positive effect of DAA treatment on mental health and fatigue related to a positive effect on some cognitive domains [28]. Unfortunately, we did not evaluate the cognitive impact of DAA in our study.

Limits

Our study presents some limitations. For some self-reported outcomes, the absence of an impact by DAA treatment could be explained by the sample size and/or a follow-up period that was too short. Furthermore, we could not explore the specific effect according to DAA regimens on self-reported outcomes.

Conclusion

This study confirms the relevance and feasibility of a microelimination program of HCV eradication but requires adaptation to the local human resources and patient profiles. Thus,

setting up such a specific program should allow HCV eradication in clinical units should reduce HCV transmission risk. Furthermore, we confirmed the direct benefit for patients to clear HCV infection through improvement of self-reported health outcomes, such as physical and mental QOL and reduction of alcohol use in their daily lives. Few patients refused treatment, showing that in the HCV interferon-free regimen era, patients are amenable to treatment.

Acknowledgments

The authors are grateful to all participants and nurse assistants.

This study was conducted with a grant of Gilead sciences. The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

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Figure legends

Figure 1: Flow chart of the screening phase

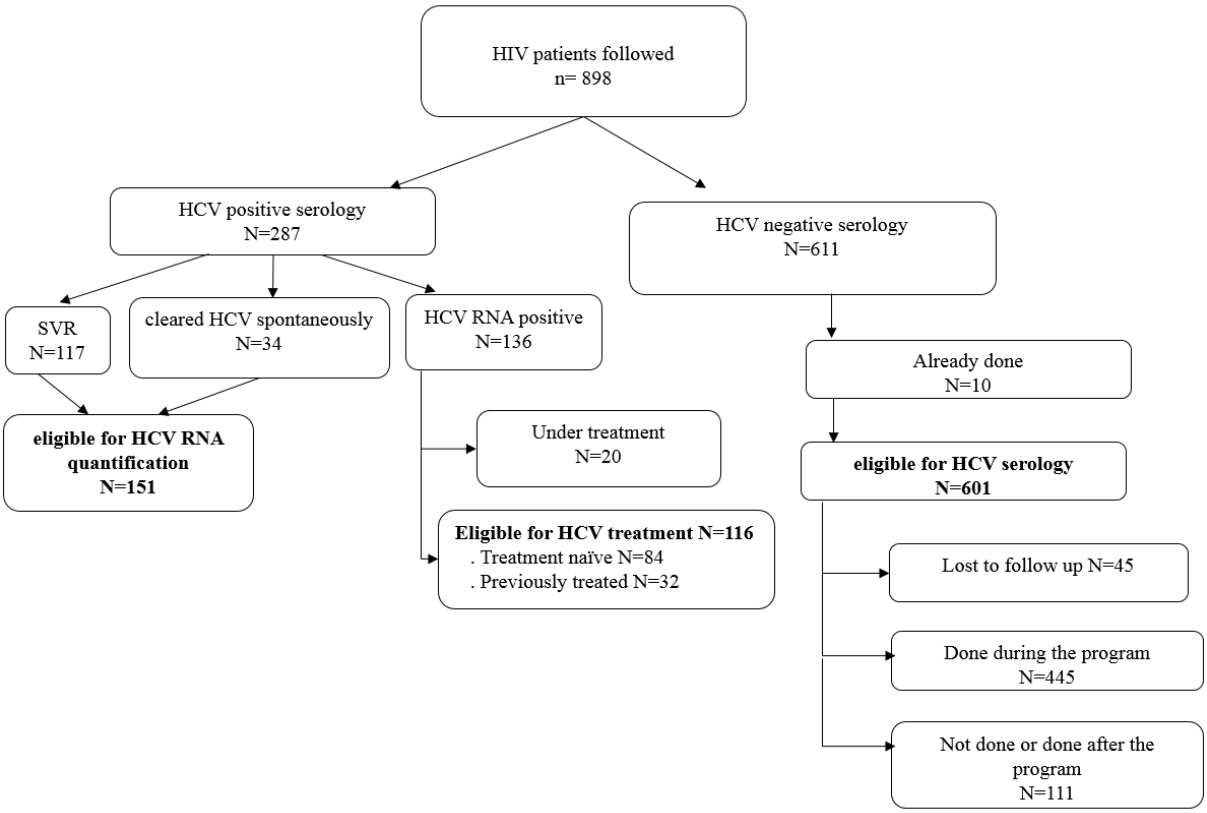
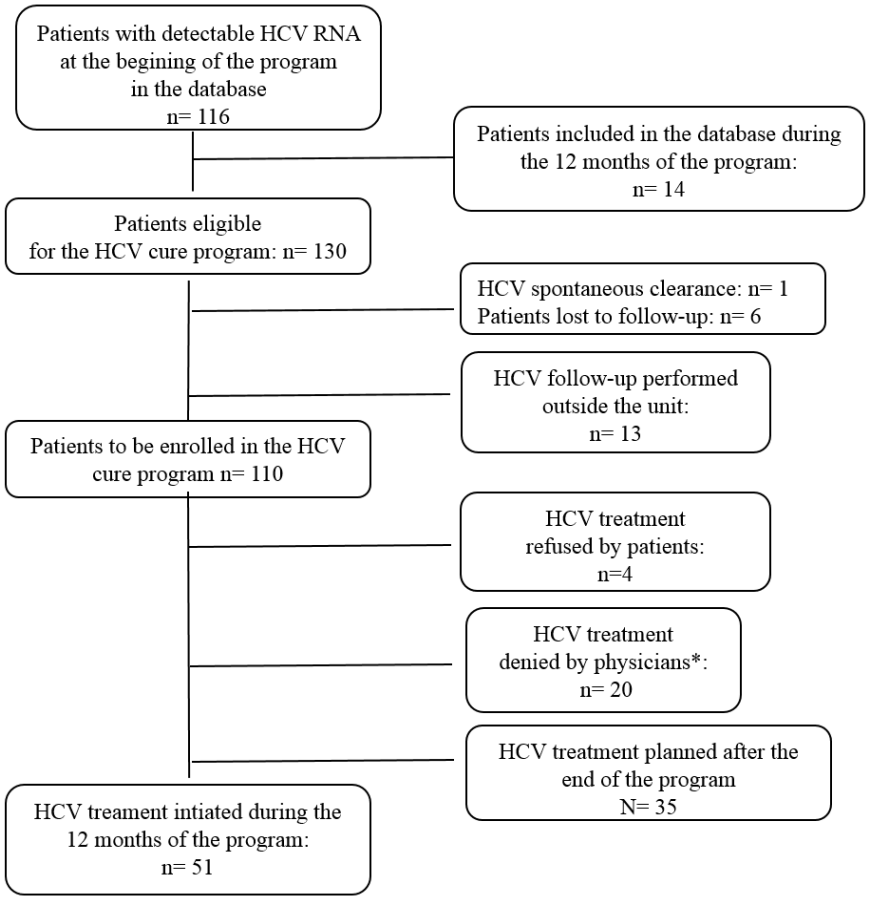


Figure **2**: Flow chart **of the Therapeutic phase**



* For compliance: 4; uncontrolled HIV infection: 9; comorbidities: 1; cancer: 2; requiring investigation: 3, unstable psychiatric disorder: 1.

Table 1: Characteristics of patients eligible for HCV treatment: n (%) or median [IQR].

	Naive patients (n=84)	**Treatment-experience patients (n=32)**	**News patients (n=14)**	**Responded to questionnaire (n=50)**
Age (yrs)	51 [48 ; 54]	52 [51 ; 56]	50 [37-54]	51 [45-55]
Gender (Male)	52 (61.9)	21 (65.6)	10 (71.4)	33 (66.0)
HIV transmission risk group				24 (48.0)
IVDU	51 (60.7)	21 (65.6)	8 (57.1)	18 (36.0)
Heterosexual	24 (28.6)	7 (21.8)	1 (7.1)	4 (8.0)
Homo-/bisexual	6 (7.1)	2 (6.3)	3 (21.4)	5 (10)
Other[†]	3 (3.6)	2 (6.3)	2 (14.3)	
Duration of HIV follow-up (yrs)	25.8 [20.5 ; 28.2]	26.2 [20.3 ; 28.0]	23 [7 ; 27]	26 [20 ; 28]
CDC stage:				13 (26.0)
A	23 (27.4)	5 (15.6)	4 (28.6)	24 (48.0)
B	43 (51.2)	18 (56.3)	5 (35.7)	13 (26.0)
C	18 (21.4)	9 (28.1)	5 (35.7)	
cART exposure (yrs)	18.3 [13.0 ; 21.1]	19.5 [16.2 ; 20.4]	10 [1 ; 20]	18.5 [8.3 ; 21.5]
class of current cART				
2N+1IP(b)	29 (34.5)	5 (15.6)	5 (45.4)	10 (21.7)
2N+1II	21 (25.0)	10 (31.3)	2 (18.2)	15 (32.6)
2N+1NN	19 (22.6)	10 (31.3)	4 (36.4)	14 (30.4)
3N	0	1 (3.1)	0	0
Others	15 (17.9)	6 (18.8)	0	7 (15.2)
HIV viral load < 40cp/ml	67 (79.8)	31 (96.9)	11 (78.6)	41 (89.1)
CD4 (/mm^3)	568 [350 ; 924]	676 [460 ; 1108]	700 [303-799]	657 [429 ; 1083]
CD4>500/mm^3	50 (59.52)	31 (67.39)	8 (57.14)	34 (68.0)
HCV viral load (log UI/ml)	5.95 [5.30 ; 6.48]	5.84 [5.32 ; 6.32]	6.20 [5.45-6.66]	6.05 [5.50 ; 6.32]

	Naive patients (n=84)	Treatment-experience patients (n=32)	News patients (n=14)	Responded to questionnaire (n=50)
HCV genotype				30 (60.0)
1	53 (63.8)	23 (71.9)	4 (28.6)	1 (2.0)
2	0	1 (3.1)	3 (14.3)	11 (22.0)
3	15 (18.1)	6 (18.8)	3 (14.3)	8 (16.0)
4	14 (16.9)	2 (6.3)	6 (42.8)	
6	1 (1.2)	0	0	
Liver fibrosis score				
F0-F1 (≤7 kPa)	52 (71.2)	14 (45.2)	7 (53.8)	34 (72.3)
F2-F3 (7-14.5 kPa)	17 (23.3)	14 (45.2)	5 (38.5)	9 (19.1)
F4 (≥14.5 kPa)	4 (5.5)	3 (9.7)	1 (7.7)	3 (6.4)
Number of previous HCV TRT				
1		25 (78.1)	1 (7.1)	15 (83.3)
2		5 (15.6)	2 (14.3)	3 (16.7)
3		1 (3.1)	0	0
4		0	0	0
5		1 (3.1)	0	0
Failure to previous HCV TRT	_	16 (51.6)	0	10 (55.6)
Relapse to previous HCV TRT		8 (25.8)	3 (21.4)	4 (22.2)
Premature stop		7 (22.6)	0	4 (22.2)

†: blood exposure accident N=1 among patients with prior treatment, hemophilic/blood transfusion N=1 among patients with prior treatment, maternofetal transmission: N=1 in naive and news patients; Unknown N=2 in naive and N=1 in news patients.

Table 2: Adherence and self-reported symptoms during DAA treatment.

	W2	W4	W8	W12	W16	W20	End of treatment	P[†]
Adherence	N= 30	N= 32	N= 25	N= 2	N= 2	N= 4	N= 22	0.40
100%	27 (90.00)	29 (90.63)	20 (80.00)	2 (100.00)	1 (50.00)	3 (75.00)	16 (72.73)	
<100%	3 (10.00)	3 (9.38)	5 (20.00)	0 (0)	1 (50.00)	1 (25.00)	6 (27.27)[a]	
Adherence perception	N= 40	N=45	N=31	N=4	N=3	N=4	N=44	0.47
All doses strictly respected [‡]	38 (95.00)	38 (84.44)	28 (90.32)	3 (75.00)	3 (100)	4 (100)	39 (88.64)	
Others§	2 (5.00)	7 (15.56)[*]	3 (9.68)	1 (25.00)[**]			5 (11.36)	
	W2	W4	W8	W12	W16	W20	W24	p
Self-reported symptoms								
General	24 (60.00)	23 (51.11)	21 (51.22)	17 (50.00)				0.98
Fatigue	15 (38.46)	12 (27.91)	13 (32.50)	11 (39.29)				0.93
Loss of appetite	3 (8.11)	3 (7.14)	4 (10.26)	5 (15.63)				0.92
Increased appetite	7 (18.92)	8 (18.60)	9 (24.32)	3 (12.00)				0.94
Sweats	6 (15.79)	6 (13.95)	8 (20.00)	4 (14.81)				0.98
Respiratory	13 (32.50)	12 (26.67)	12 (29.27)	12 (35.29)				0.99
Cough	8 (21.62)	5 (12.20)	3 (7.69)	3 (10.00)				0.75
Breathlessness	8 (21.62)	11 (26.19)	10 (25.64)	11 (35.48)				0.95
Gastrointestinal	16 (40.00)	17 (37.78)	17 (41.46)	11 (32.35)				0.87
Nausea	6 (15.38)	7 (16.67)	5 (13.16)	3 (9.68)				0.97
Abdominal pain	6 (15.38)	3 (6.98)	4 (10.26)	1 (4.00)				0.77
Skin	15 (37.50)	15 (33.33)	16 (39.02)	12 (35.29)				0.99
Dry skin	5 (13.51)	8 (19.51)	8 (20.51)	7 (24.14)				0.95

Itching	9 (24.32)	7 (17.07)	5 (12.82)	4 (14.81)		0.91
Dry mouth	7 (18.92)	12 (28.57)	9 (23.08)	4 (16.00)		0.74
Musculoskeletal	8 (20.00)	11 (24.44)	13 (31.71)	7 (20.59)		0.90
Muscular pain	4 (10.53)	8 (18.60)	8 (20.51)	2 (8.00)		0.80
Articular pain	5 (13.51)	7 (16.67)	8 (20.51)	4 (13.33)		0.98
Neuro-psychiatric	18 (45.00)	23 (51.11)	19 (46.34)	19 (55.88)	1 (33.33)	0.96
Headache	8 (21.05)	10 (23.26)	5 (12.82)	4 (12.90)		0.86
Insomnia	7 (18.92)	7 (17.50)	6 (15.38)	4 (14.81)		0.99
Hypersomnia	8 (21.05)	7 (16.67)	10 (25.00)	8 (29.63)		0.93
Irritability	4 (11.11)	2 (4.88)	5 (13.16)	2 (6.90)		0.45
At least one	29 (72.50)	34 (75.56)	29 (70.73)	26 (76.47)	1 (33.33)	0.98

† mixed model

***** : significant difference (p=0.04)

******: significant difference (p=0.05)

‡ with respect to rhythm and quantity; § others= generally respected all doses; often changed intake; rarely respected intake.

Table 3: Impact of HCV cure with DAA on substance consumption.

	D0	End of treatment	W12 postTRT	W24 postTRT	W48 postTRT	p
Alcohol consumption						0.006
Not at risk	8 (26.67)	13 (61.9)	12 (48)	11 (52.38)	12 (57.14)	
Risky	3 (10)	4 (19.05)	6 (24)	0 (0)	1 (4.76)	
Harmful use for health	19 (63.33)	4 (19.05)	7 (28)	10 (47.62)	8 (38.1)	
Binge drinking once a month or less						0.04
No	13 (40.63)	17 (77.27)	15 (57.69)	15 (65.22)	13 (54.17)	
Yes	19 (59.38)	5 (22.73)	11 (42.31)	8 (34.78)	11 (45.83)	
Current tobacco consumption						0.22
Yes	33 (70.21)	31 (75.61)	31 (73.81)	29 (74.36)	27 (69.23)	
No	14 (29.79)	10 (24.39	11 (26.19)	10 (25.64)	12 (30.77)	
Current cannabis consumption						$<10^{-3}$
No	26 (65)	24 (64.86)	23 (56.1)	23 (58.97)	22 (56.41)	
Yes	14 (35)	13 (35.14)	18 (43.9)	16 (41.03)	17 (43.59)	
Current consumption of at least one psychoactive substance	3 (6.00)	2 (4.35)	3 (7.14)	2 (5.00)	2 (4.88)	

Table 4: Impact of HCV cure with DAA on patient-reported outcomes.

	D0	End of treatment	W12 postTRT	W24 postTRT	W48 postTRT	p
Weight - kg	65 (56-71)	66 (58-75)	66 (55-73)	63 (53-75)	64 (57-73)	0.90
BMI- kg/m^2						0.96
Underweight	5 (10.00)	2 (4.55)	5 (13.51)	5 (16.13)	3 (9.09)	
Normal weight	34 (68.00)	30 (68.18)	22 (59.46)	19 (61.29)	24 (72.73)	
Overweight	9 (18.00)	10 (22.73)	8 (21.62)	5 (16.13)	5 (15.15)	
Obese	2 (4.00)	2 (4.55)	2 (5.41)	2 (6.45)	1 (3.03)	
Depressivity (Ces-d scale)						0.63
No	32 (71.11)	37 (80.43)		28 (73.68)	28 (75.68)	
Yes	13 (28.89)	9 (19.57)		10 (26.32)	9 (24.32)	
Depression scale†						0.45
≤5	38 (88.37)	42 (91.30)		28 (80.00)	34 (100.00)	
>5	5 (11.63)	4 (8.70)		7 (20.00)	0 (0.00)	
Tired scale†						0.68
≤5	33 (76.74)	37 (84.09)		26 (74.29)	27 (81.82)	
>5	10 (23.26)	7 (15.91)		9 (25.71)	6 (18.18)	
Stress scale†						0.12
≤5	35 (81.40)	42 (91.30)		28 (80.00)	31 (91.18)	
>5	8 (18.60)	4 (8.70)		7 (20.00)	3 (8.82)	
Physical activity						0.05
Yes	29 (61.70)	18 (40.91)	24 (58.54)	21 (52.50)	18 (46.15)	
No	18 (38.30)	26 (59.09)	17 (41.46)	19 (47.50)	21 (53.85)	
Physical health QOL						0.27

<25% of the general population	24 (55.81)	15 (40.54)	12 (31.58)	16 (43.24)	14 (40)	
Good	19 (44.19)	22 (59.46)	26 (68.42)	21 (56.76)	21 (60)	
Mental health QOL						0.24
<25% of the general population	15 (34.88)	6 (16.22)	8 (21.05)	9 (24.32)	9 (25.71)	
Good	28 (65.12)	31 (83.78)	30 (78.95)	28 (75.68)	26 (74.29)	

† visual analogic scale.

QOL: Quality of life

BMI: Body mass index

Table 5: Evolution of frailty state.

	D0 N=39	End of treatment N=31	W12 postTRT N=30	W24 postTRT N=25	W48 postTRT n=28	p
Frailty						
No	8 (20.51)	6 (19.35)	11 (36.67)	7 (28.00)	10 (35.71)	0.17
Prefrail phenotype	25 (64.10)	21 (67.74)	17 (56.67)	16 (64.00)	16 (57.14)	
Frail phenotype	6 (15.38)	4 (12.90)	2 (6.67)	2 (8.00)	2 (7.14)	
Weight loss	8 (20.51)					
Weakness/grip strength	3 (7.69)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	-
Exhaustion	6 (15.38)	2 (6.45)	4 (13.33)	2 (8.00)	5 17.86)	0.93
Slowness/walk time	18 (46.15)	12 (38.71)	8 (26.67)	7 (28.00)*	9 (32.14)	0.22
Low physical activity	19 (48.72)	19 (61.29)	12 (40.00)	13 (52.00)	16 (57.14)	0.26

Table 6: Mixed model for each indicator.

	End of treatment vs D0		W12 postTRT vs D0		W24 postTRT vs D0		W48 postTRT vs D0		P global
AUDIT-C	OR [IC]	p	OR [IC]	p	OR [IC]	p	OR [IC]	p	0.006
Not at risk	1		1		1		1		
Risky	0.82 [0.14-4.66]	0.82	1.33 [0.26-6.94]	0.73	--	--	0.22 [0.02-2.53]	0.23	
Harmful use for health	0.13 [0.03-0.52]	0.04	0.25 [0.07-0.85]	0.03	0.38 [0.12-1.26]	0.11	0.28 [0.08- 0.95]	0.04	
Binge drinking once a month or less									0.04
Yes vs No	0.05 [0.01-0.34]	0.002	0.40 [0.09-1.69]	0.22	0.14 [0.03- 0.73]	0.02	0.40 [0.09-1.73]	0.22	
Current tobacco consumption									0.22
Yes vs No	1.99 [0.13-30.16]	0.62	6.59 [0.41-105.78]	0.18	2.12 [0.06-70.28]	0.67	0.23 [0.02-2.73]	0.24	
Current cannabis consumption									$<10^{-3}$
Yes vs No	12.85 [0.43-382.89]	0.14	159.60 [5.00-5095.87]	0.004	1466.32 [71.28- 30164.07]	$<10^{-3}$	729.02 [24.74- 21479.75]	$<10^{-3}$	
Current consumption of at least one psychoactive substance									
Yes vs No	0.67 [0.07-6.93]	0.74	1.29 [0.15-11.20]	0.82	0.56 [0.05-5.82]	0.63	0.64 [0.06-6.71]	0.71	0.96
Weight									0.96
Underweight	0.45 [0.08-2.510]	0.37	1.55 [0.40-5.97]	0.53	1.79 [0.46-6.98]	0.40	0.85 [0.19-3.90]	0.83	

Normal weight	1								
Overweight	1.26 [0.45-3.51]	0.66	1.37 [0.46-4.10]	0.57	0.99 [0.29-3.40]	0.99	0.79 [0.23-2.64]	0.70	
Obese	1.13 [0.15-8.55]	0.90	1.55 [0.20-11.79]	0.68	1.79 [0.23-13.75]	0.58	0.71 [0.06-8.26]	0.78	
Depression scale									0.68
>5 vs ≤5	0.47 [.011-2.08]	0.32			1.15 [0.26-5.03]	0.85	0.71 [0.15-3.30]	0.66	
Tiredness scale							--		0.45
>5 vs ≤5	0.63 [0.12-3.23]	0.58			2.47 [0.51-11.84]	0.26			
Stress scale									0.12
>5 vs ≤5	0.03 [0.00-0.71]	0.03			0.55 [0.06-5.21]	0.61	0.04 [0.00-1.09]	0.06	
CES-D: depressivity									0.63
Yes vs No	0.32 [0.06-1.76]	0.19			0.63 [0.12-3.46]	0.60	0.55 [0.09-3.15]	0.50	
Physical QOL									0.27
Good vs No good	2.31 [0.76-7.06]	0.14	3.48 [1.10-11.05]	0.03	2.33 [0.75-7.20]	0.14	2.50 [0.78-8.02]	0.12	
Mental QOL									0.24
Good vs No good	5.18 [1.19-22.46]	0.03	2.98 [0.75-11.88]	0.12	2.86 [0.73-11.19]	0.13	2.30 [0.58-9.14]	0.24	
Physical activity									0.05
Yes vs No	0.10 [0.88-17.94]	0.03	0.58 [0.15-2.31]	0.44	0.52 [0.13-2.07]	0.35	0.33 [0.08-1.37]	0.13	

Frailty									0.17
Prefrail/Frail vs Normal	1.51 [0.24-9.63]	0.66	0.22 [0.04-1.31]	0.10	0.21 [0.03-1.52]	0.12	0.18 [0.03-1.24]	0.08	

QOL: Quality of life