



Evolution of Hepatitis C Virus Treatment During the Era of Sofosbuvir-Based Therapies: A Real-World Experience in France

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Abstract

Background Treatment of hepatitis C virus (HCV) has been dramatically improved with the introduction of direct-acting antiviral agents (DAAs). Universal access to pangenotypic DAAs was provided in France from 2017, expanding the type of patients treated. Real-world studies are important to confirm effectiveness and safety in clinical practice, particularly in vulnerable populations.

Aims To assess real-world effectiveness and safety of sofosbuvir-based therapy in adults with chronic HCV infection before and after universal access to DAAs in France.

Methods This multicenter, non-interventional, prospective study assessed the effectiveness, safety, patient-reported outcomes and adherence with sofosbuvir-based regimens from October 2015 to July 2016 (Period 1: sofosbuvir-based therapy excluding sofosbuvir/velpatasvir) and from October 2017 to July 2018 (Period 2: pangenotypic sofosbuvir/velpatasvir-based therapy).

Results Baseline data were documented for 1029 patients. Overall, 797 (77%) had sustained virologic response data available ≥ 9 weeks after treatment completion. Per protocol response was high (97%) irrespective of age, alcohol consumption, recreational drug use, or HIV/HCV coinfection. Adverse events occurred in approximately 25% of patients with the majority experiencing Grade 1 or 2 events. Sofosbuvir-based regimens improved health-related quality of life from baseline to end of treatment in patients with data at all timepoints. Overall, 99% of patients reported total or almost total adherence to therapy.

Conclusions Sofosbuvir-based therapy, including pangenotypic sofosbuvir/velpatasvir, is effective for the treatment of HCV in real-world clinical practice. This is an important step towards HCV elimination.

Keywords Hepatitis C · Sofosbuvir · Treatment outcome · Practice guidelines as topic · France

Abbreviations

ALT	Alanine aminotransferase	CNIL	Commission nationale de l'informatique et des libertés
AP-HP	Assistance Publique-Hôpitaux de Paris	DAA	Direct-acting antiviral agent
BMI	Body mass index	DCV	Daclatasvir
CCTIRS	Comité consultatif sur le traitement de l'information en matière de recherche	EOT	End of treatment
CI	Confidence interval	EQ-5D	EuroQOL five dimensions
		F	Fibrosis stage
		GT	Genotype
		HBV	Hepatitis B virus
		HCC	Hepatocellular carcinoma
		HCV	Hepatitis C virus
		HRQoL	Health-related quality of life
		HELIOS	HEpatitis C real-Life study for patients On Sofosbuvir
		HIV	Human immunodeficiency virus

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IFN	Interferon
LDV	Ledipasvir
LLOQ	Lower limit of quantification
MICE	Multivariate Imputation by Chained Equations
NAFLD	Nonalcoholic fatty liver disease
OST	Opioid substitution therapy
PEG-IFN	Pegylated interferon
PP	Per protocol
PPI	Proton pump inhibitor
PRO	Patient-reported outcome
RBV	Ribavirin
RNA	Ribonucleic acid
SD	Standard deviation
SMV	Simeprevir
SOF	Sofosbuvir
SVR	Sustained virologic response
TEAE	Treatment-emergent adverse event
VAS	Visual analog scale
VEL	Velpatasvir
WHO	World Health Organization
WPAI	Work Productivity and Activity Impairment

Introduction

Hepatitis C virus (HCV) is a major health issue: 71 million individuals are chronically infected with HCV [1] and 700,000 HCV-related deaths occur annually worldwide [2]. HCV is a systemic disease associated with both hepatic and extrahepatic manifestations and represents a substantial burden to both the patient and society [3]. Patients chronically infected with HCV report poor health-related quality of life (HRQoL), fatigue and reduced work productivity [4–6].

Treatment of patients chronically infected with HCV substantially improved with the introduction of direct-acting antiviral agents (DAAs) [7, 8] in 2013. Sofosbuvir (SOF) has become the backbone of multiple interferon (IFN)-free HCV treatment regimens [9]. Data from clinical trials have demonstrated that SOF, either with ribavirin (RBV) alone or as a fixed-dose combination with other DAAs, such as ledipasvir (LDV) [10–12] or velpatasvir (VEL) [13, 14], achieves a sustained virologic response (SVR) and is able to cure HCV in at least 90% of patients, including those historically considered difficult to treat, such as patients with decompensated cirrhosis [15], those coinfecting with human immunodeficiency virus (HIV) [16, 17] and people who inject drugs [18, 19]. With high efficacy and a favorable tolerability profile, DAAs have revolutionized the management of HCV and are recommended by the World Health Organization (WHO) to enable elimination of HCV [20]. Introduction of the WHO targets along with the rapid evolution of DAAs, including availability of pangenotypic regimens such as SOF/VEL, has

allowed the development of simplified HCV management strategies in a diverse range of populations with chronic HCV infection [21–23].

In France, DAA therapy was initially only available to patients with severe liver disease before gradual changes to national policy allowed the treatment of all patients regardless of fibrosis or genotype, meaning that the patient profile receiving HCV treatment has changed considerably since 2013. In 2017, pangenotypic regimens including SOF/VEL, which is the most frequently prescribed therapy in France, became widely available and allowed simplified management and treatment of HCV.

Real-world studies are important for confirming effectiveness and tolerability in patient populations in routine clinical practice, as well as providing information on patient management and the long-term effects of therapy [24]. Results from several real-world studies conducted in the USA and Europe support the effectiveness of SOF-based regimens observed in clinical trials [25–37]. Knowledge of the long-term efficacy and safety profiles of DAAs, and their impact on adherence and patient-reported outcomes (PROs) in daily practice, is still evolving, especially in specific high-risk patients such as those using recreational drugs, receiving opioid substitution therapy (OST) or consuming excessive alcohol (≥ 3 units/day).

The aim of the HEpatitis C real-Life study for patients On Sofosbuvir (HELIOS) was to assess real-world effectiveness, safety, adherence and PROs with SOF-based therapy in France. The objective was to assess changes in patient characteristics during the two assessment periods and investigate the outcomes of evolving therapeutic strategies, including the introduction of pangenotypic regimens, as recommended by guidelines throughout the DAA era.

Methods

Design

HELIOS was a multicenter, non-interventional, prospective study to assess the effectiveness and safety profile of SOF-based regimens in patients (≥ 18 years of age) with chronic HCV managed in routine clinical settings in France. The study was conducted in accordance with good pharmacoepidemiology guidelines, pharmacovigilance practice guidelines, and the 1964 Helsinki Declaration; initially authorized by the Advisory Committee on the Treatment of Research Information (CCTIRS) and the Data Protection Committee (CNIL), the second recruitment period was authorized by a central ethics committee, in accordance with new French Regulations on research Involving Human Beings.

Setting and Patients

Recruitment took place over two periods in 46 centers across France October 2015–July 2016 (Period 1) and October 2017–July 2018 (Period 2). Participating physicians enrolled eligible patients in whom they planned to initiate SOF-based therapy for 8–24 weeks according to local recommendations (Period 1: LDV/SOF ± RBV, SOF ± RBV, SOF + DCV ± RBV, or SOF + SMV ± RBV; Period 2: SOF/VEL ± RBV). Treatment was prescribed at the physician's discretion. Study drugs were not provided by the sponsor.

Initially, the number of patients enrolled per center was limited to 10 to prevent any site bias in the study; however, to ensure all patients were recruited within the planned period, the number of patients per site was increased in Period 2. A limited number of sites involved in Period 1 decided not to participate in Period 2.

Participating sites primarily specialized in hepato-gastroenterology, infectious diseases or internal medicine to provide a representative cross section of current practice in France.

Study Assessments and Data Collection

Informed consent was obtained from all individual participants included in the study; permission was given for the collection of anonymized medical data from their medical files. Prospective data were recorded at baseline, end of treatment (EOT) and post-treatment Week 12. To reflect the reality of clinical practice, the HELIOS Scientific Committee agreed to accept SVR values if they were available from ≥ 9 weeks after completion of treatment. Data were collected from medical records using electronic case report forms and questionnaires completed by patients. Patient demographics, medical history, presence of extrahepatic manifestations, liver-related parameters and routine laboratory parameters were collected, as well as treatment-specific variables (genotype, treatment history, prescribed treatment and treatment duration). The cutoff values for fibrosis assessments are described in Supplementary Table 1. PROs were collected using standard instruments: HRQoL was assessed with the EuroQOL five dimensions (EQ-5D) questionnaire, and impairment in functioning was assessed using the work productivity and activity impairment (WPAI) questionnaire. During the post-treatment follow-up period, any patient who initiated a new HCV treatment was no longer followed up within this study (except for safety events occurring within 30 days of study HCV regimen discontinuation).

Endpoints

The primary endpoint of the analysis was to assess effectiveness of SOF-based therapies through the proportion

of subjects achieving SVR, defined as HCV ribonucleic acid (RNA) < 25 IU/mL (lower limit of quantification). Plasma HCV RNA was quantified using locally available assays. HCV RNA values were collected at the closest time point to the anticipated date 12 weeks from the end of treatment for each patient. All patients who received at least one dose of SOF-based therapy and had a post-baseline effectiveness or safety assessment were included in the overall population. The per protocol (PP) population excluded patients lost to follow-up, patients who initiated a new HCV treatment, and patients who completed the study but had missing HCV RNA assessment for SVR at ≥ 9 weeks after completion of treatment.

Secondary endpoints included assessment of tolerability, safety, adherence and impact on HRQoL. Patient adherence to HCV treatment was assessed using a self-reported questionnaire. Adherence was scored from 0 (not followed treatment at all) to 10 (no drug dose missed). HRQoL was assessed using the self-reported EQ-5D questionnaire at baseline, EOT and post-treatment Week 12. Only patients with values at all visits were included in these analyses. Both the EQ-5D descriptive and visual analog scale (VAS) were administered. In the EQ-5D descriptive system, patients indicated their health state in five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Patients were asked to indicate which statements best described their health state on the day of the assessment in each of the five dimensions with scores ranging from 1 to 5 (worst to best health state, respectively). The EQ-5D index was calculated from this score, with a higher index indicating a better health state. The EQ-5D score corresponds to the result of the EQ-5D VAS ranging from 0 to 100 (worst to best health state). Impairment in functioning was assessed using the self-reported WPAI questionnaire at baseline, EOT and post-treatment Week 12; this instrument quantifies impairment in the patient's work productivity and daily activities that the patient considers to be a consequence of a specific health problem (i.e., HCV infection). The WPAI has two dimensions. The work productivity impairment dimension is a sum of impairment in work productivity due to missed work hours (absenteeism) and decreased productivity while working (presenteeism); this dimension is only assessed in employed patients. The second dimension relates to activity impairment (i.e., daily activities other than work) and is assessed regardless of employment. Both dimensions of the WPAI are inversely related to health status with a greater impairment indicating worse health. The safety analysis included all treated patients, and safety endpoints included adverse events leading to permanent discontinuation of treatment.

Statistical Analysis

Mean, 95% confidence intervals (CIs), standard deviation (SD), median, first and third quartile (Q1, Q3) range, minimum and maximum were calculated for continuous variables. For categorical variables, the number and percentage of patients were reported. Comparative analyses were performed using the chi-square test and/or Fisher's exact tests for qualitative variables; *t* tests for analyses of variance were performed for quantitative variables. Non-parametric tests were used in the case of a non-normal distribution. Univariate and multivariate regression analyses were employed to identify predictors of SVR adjusting for covariates (value at inclusion) as appropriate.

Mixed model analysis was used to identify predictors of the EQ-5D index at selected study visits adjusting for covariates as appropriate, and to compare EQ-5D scores between visits. Covariates included patient age, sex, race, body mass index, presence of extrahepatic manifestations, current addiction, prior HCV treatment, treatment regimen, hepatocellular carcinoma (HCC), presence of comorbidities, employment status, previous liver transplant and RBV use (at baseline, EOT and post-treatment Week 12). A step-by-step backward selection of predictors was used to remove non-specific covariates. However, visit, age, sex and ethnicity were forced into the model based on the literature. Sensitivity analyses were performed with missing values imputed using a multivariate imputation by chained equations (MICE) algorithm. Statistical analysis was performed using the SAS v9.2 statistical software package. See the Supplementary Appendix for additional details on the statistical analyses performed.

Results

Baseline Characteristics

Overall, 1041 patients were prospectively screened and enrolled; of these, 1029 patients had a baseline visit documented and were included in analysis of the overall population (Table 1). Patients received SOF-based treatment for 8–24 weeks; most were treated for 12 weeks without RBV. Among the patients included in the overall population analysis, 1000/1029 (97%) completed treatment and 725/1029 completed the study (Fig. 1).

Patients enrolled into the HELIOS study were predominantly male, Caucasian and non-cirrhotic, with a median age (range) of 56 (20–91) years in Period 1 and 53 (24–83) years in Period 2. Over both periods, 28% of patients had at least one comorbidity (Table 1). The mean (range) number of concomitant medications was 2.1 (0–32) in Period 1 and 3.0 (1–32) in Period 2; 7% of patients in both Period 1

and Period 2 used proton pump inhibitor (PPI) medication (Table 1).

Notable numerical differences between patients in Period 2 versus Period 1 were: a higher proportion of genotype 3 patients; a lower proportion of genotype 1 patients; less severe fibrosis stage (F); a higher proportion of treatment-naïve patients; fewer extrahepatic manifestations; fewer patients with HIV/HCV coinfection; and a greater proportion of patients reporting excessive alcohol consumption and/or recreational drug use or receiving OST (Table 1).

Effectiveness Endpoints

Of the 1029 patients enrolled in the study, 797 (77%) had SVR assessment ≥ 9 weeks after completion of treatment and were included in the PP analysis. SVR results were available for 567/624 (91%) in Period 1 and 230/405 (57%) in Period 2. Baseline characteristics such as fibrosis stage, current drug abuse, excessive alcohol consumption, HIV/HCV coinfection, ≥ 3 comedications and treatment with PPIs were not predictive of availability of SVR results in Period 1. However, current drug use ($P < 0.001$) and excessive alcohol consumption ($P = 0.031$) were predictive for no HCV RNA assessment during Period 2.

Overall, 97.0% (773/797) of patients in the PP population achieved an SVR, including 97.8% (490/501) for LDV/SOF \pm RBV; 99.6% (226/227) for SOF/VEL \pm RBV; and 100% (226/226) for SOF/VEL without RBV. SVR rates of 97.3% (330/339) and 97.4% (222/228) were achieved in Period 1 and 99.4% (175/176) and 100% (54/54) in Period 2 in treatment-naïve and treatment-experienced patients, respectively. High response rates were achieved irrespective of treatment regimen, treatment duration and genotype (Table 2).

According to univariate analysis, SVR rates were high irrespective of age, alcohol consumption, recreational drug use or HIV/HCV coinfection during both periods of the study (Supplementary Table 2).

Safety Endpoints

Overall, 27% of patients in Period 1 and 16% of patients in Period 2 experienced treatment-emergent adverse events (TEAEs). The most common TEAEs are listed in Table 3 and were in accordance with expected adverse events described in the summary of product characteristics of SOF-containing regimens. Early treatment discontinuation due to TEAEs in Period 1 was reported in two patients (asthenia and pruritus) and 19 patients changed dose or interrupted treatment due to TEAEs (12 anemia, two asthenia, two irritability, one insomnia, one affective disorder, one sleep disorder, one hepato-renal syndrome, one hemoglobin decreased, one headache, one pain in extremity). Two

Table 1 Baseline demographics (intention-to-treat population)

	Period 1		Period 2
	LDV/SOF-based regimen (<i>n</i> = 554)	Other SOF-based regimen ^a <i>n</i> = 70	SOF/VEL- based regimen (<i>n</i> = 405)
Median age, years (range)	56 (20–91)	55 (34–80)	53 (24–83)
Male, <i>n</i> (%)	337 (61)	43 (61)	237 (59)
Ethnicity, <i>n</i> (%)			
Asian	12 (2)	2 (3)	15 (4)
Black/African Heritage	47 (9 ^b)	15 (21)	54 (14)
Caucasian	481 (87)	52 (74)	321 (81)
Other	14 (3)	1 (1)	5 (1)
BMI (kg/m ²), mean ± SD	24.3 ± 4.3	24.6 ± 3.4	24.7 ± 4.5
HCV genotype, <i>n/N</i> (%)			
GT 1	456/533 (86)	4/67 (6)	189/381 (50)
GT 2	1/533 (< 1)	22/67 (33)	50/381 (13)
GT 3	0	35/67 (52)	92/381 (24)
GT 4	69/533 (13)	6/67 (9)	37/381 (10)
GT 5	4/533 (< 1)	0	7/381 (2)
GT 6	3/533 (< 1)	0	3/381 (1)
HIV/HCV co-infection, <i>n/N</i> (%)	84/534 (16)	11/67 (16)	18/385 (5)
HBV/HCV co-infection, <i>n/N</i> (%)	2/534 (< 1)	1/67 (1)	7/385 (2)
Extrahepatic manifestations, <i>n</i> (%)			
≥ 1 extrahepatic manifestation ^c	115 (21)	12 (17)	55 (14)
Cryoglobulinemia	36 (7)	4 (6)	12 (3)
Lymphoma	3 (< 1)	1 (1)	0 (0)
Arthralgia	32 (6)	4 (6)	8 (2)
Depressive syndrome	70 (13)	7 (10)	40 (10)
Alcohol consumption			
Alcohol consumption within the previous year, <i>n/N</i> (%)			
Abstinent (0 units/day)	300/548 (55)	42/69 (61)	202/390 (52)
Occasional (< 3 units/day)	181/548 (33)	22/69 (32)	118/390 (30)
Excessive (≥ 3 units/day)	67/548 (12)	5/69 (7)	70/390 (18)
Current alcohol consumption, <i>n/N</i> (%)			
Abstinent (0 units/day)	339/547 (62)	47/68 (69)	226/391 (58)
Occasional (< 3 units/day)	177/547 (32)	19/68 (28)	127/391 (33)
Excessive (≥ 3 units/day)	31/547 (6)	2/68 (3)	38/391 (10 ^b)
Experience of alcohol overconsumption, <i>n/N</i> (%)	111/546 (20)	11/69 (16)	94/387 (24)
Tobacco and recreational drug use, <i>n/N</i> (%)			
Current tobacco use	177/541 (33)	29/69 (42)	163/393 (42)
Recreational drug use within the previous year	72/550 (13)	8/69 (12)	77/393 (20)
Current recreational drug use	53/551 (10)	7/68 (10)	44/392 (11)
Addiction ^d	75/547 (14)	8/68 (12)	69/391 (18)
Current OST treatment ^e	44/554 (8)	7/70 (10)	41/405 (10)
Registered long-term health condition, <i>n</i> (%) ^f	476/551 (86)	62/70 (89)	340/402 (85)
Employment status			
Employed, <i>n/N</i> (%)	250/551 (45)	32/69 (46)	168/401 (42)
Employed and currently on sick leave, <i>n/N</i> (%)	15/250 (6)	2/32 (6)	7/166 (4)
Mean duration of sick leave, days ± SD	93 ± 122	30	89 ± 122
Prior treatment history, <i>n</i> (%)			
≥ 1 prior HCV treatment	224 (40)	25 (36)	89/405 (22)
PEG-IFN + RBV	171 (31)	18 (26)	59/405 (15)

Table 1 (continued)

	Period 1		Period 2
	LDV/SOF-based regimen (<i>n</i> = 554)	Other SOF-based regimen ^a <i>n</i> = 70)	SOF/VEL- based regimen (<i>n</i> = 405)
PEG-IFN + RBV + BOC	9 (2)	1 (< 1)	3/405 (< 1)
PEG-IFN + RBV + SMV	2 (< 1)	0	1/405 (< 1)
PEG-IFN + RBV + TPV	15 (3)	1 (< 1)	1/405 (< 1)
Other/unknown	61 (11)	9 (13)	34/405 (8)
Treatment outcome, <i>n</i> (%) ^b			
Breakthrough	8 (4)	1 (< 1)	3/83 (4)
Non-responder	101 (46)	6 (9)	26/83 (31)
Relapse	97 (44)	17 (24)	37/83 (45)
Stopped due to intolerance	29 (13)	4 (6)	12/83 (15)
Unknown	19 (9)	1 (< 1)	11/83 (13) ^b
Cirrhosis, <i>n/N</i> (%)	115/507 (23)	17/58 (29)	73/323 (23)
HCC, <i>n/N</i> (%)	9/554 (2)	3/70 (4)	4/405 (1)
Jaundice, <i>n/N</i> (%)	3/554 (< 1)	1/70 (1)	3/405 (< 1)
Liver biopsy performed, <i>n/N</i> (%)	154/554 (28)	10/70 (14)	37/405 (9)
FibroScan [®] fibrosis stage, <i>n/N</i> (%)			
F0	94/461 (20)	5/53 (9)	92/279 (33) ^b
F1	94/461 (20)	10/53 (19)	60/279 (22)
F2	118/461 (26)	19/53 (36)	44/279 (16)
F3	78/461 (17)	7/53 (13)	31/279 (11)
F4	77/461 (17)	12/53 (23)	52/279 (19)
Comorbidities, <i>n/N</i> (%) ^f			
None	405/554 (73)	44/70 (63)	292/405 (72)
1	111/554 (20)	22/70 (31)	83/405 (21)
2	33/554 (6)	3/70 (4)	24/405 (6)
3+	5/554 (1)	1/70 (1)	6/405 (1)
Diabetes	52/540 (9)	10/70 (14)	35/405 (9)
NAFLD	15/554 (3)	3/70 (4)	9/405 (2)
Arterial hypertension	112/554 (20)	18/70 (27)	90/405 (22)
Renal insufficiency	9/554 (2)	0	10/405 (2)
Dialysis	1/554 (< 1)	0	1/405 (< 1)
Renal transplantation	3/55 (< 1)	0	6/405 (2)
Liver transplantation	11/554 (2)	1/70 (1)	1/405 (< 1)
Concomitant medications			
≥ 1 concomitant medication, <i>n/N</i> (%)	376/607 (61)		245/405 (61)
Number of concomitant medications, <i>n</i> ± SD	2.1 ± 2.8		3.0 ± 4.7
Treated with PPI, <i>n/N</i> (%)	45/607 (7)		28/405 (7)

BMI body mass index, *BOC* boceprevir, *DCV* daclatasvir, *F* fibrosis stage, *GT* genotype, *HBV* hepatitis B virus, *HCC* hepatocellular carcinoma, *HCV* hepatitis C virus, *HIV* human immunodeficiency virus, *LDV* ledipasvir, *NAFLD* non-alcoholic fatty liver disease, *OST* opioid substitution therapy, *PEG-IFN* pegylated interferon, *PPI* proton pump inhibitor, *RBV* ribavirin, *SD* standard deviation, *SMV* simeprevir, *SOF* sofosbuvir, *TPV* telaprevir, *VEL* velpatasvir

^aOther SOF-based regimens included SOF + RBV, SOF + DCV ± RBV, or SOF + SMV ± RBV

^bMultiple responses possible; total exceeds 100%

^cDefined as patients with cryoglobulinemia and/or lymphoma and/or arthralgia and/or depressive syndrome

^dDefined as a current excessive alcohol consumption and/or a current recreational drug use

^eTherapies include buprenorphine, buprenorphine/naloxone and methadone

^fLong-term condition for which the treatment qualifies for full reimbursement in the French healthcare system

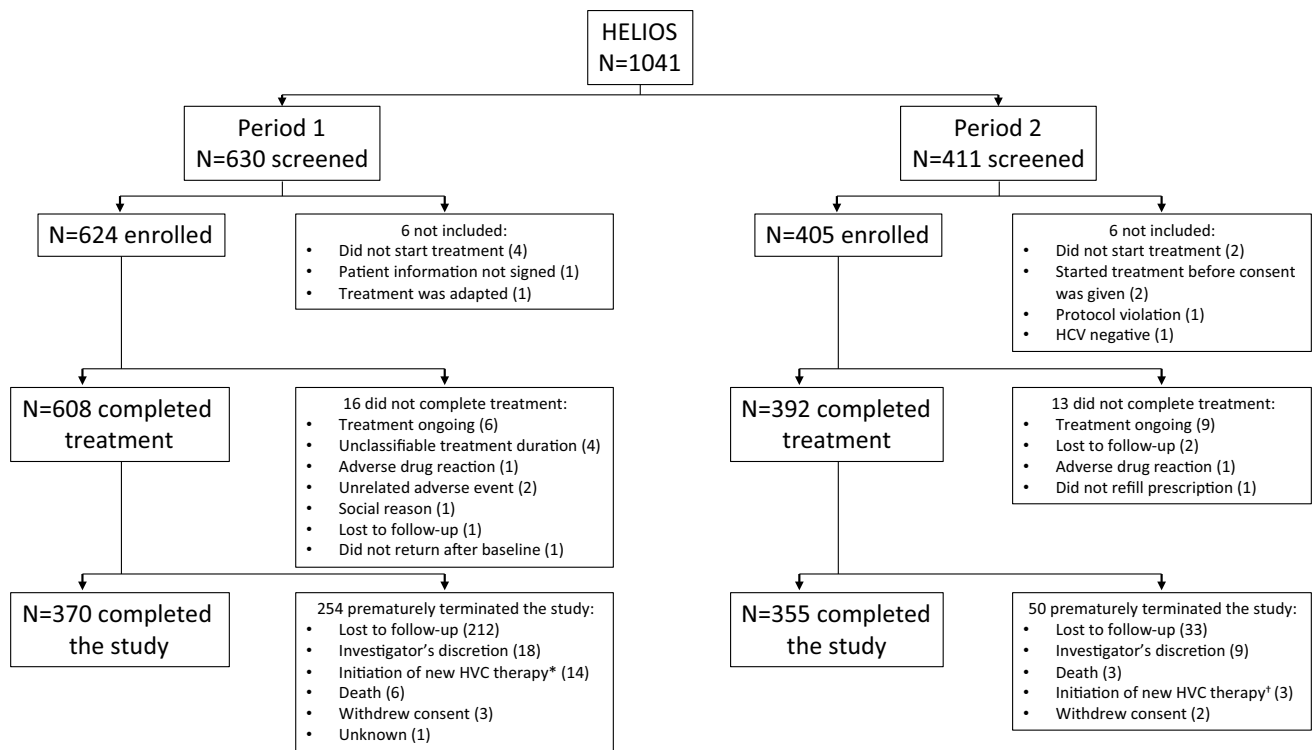


Fig. 1 Patients included in the HELIOS study. Flow diagram describing the number of people with HCV screened, enrolled, completed treatment and completed the full study protocol including follow-up. *Nine cases of lack of effect, five cases of reinfection, one patient

ceased study treatment and initiated an alternative HCV therapy. †Two cases of lack of effect, one case of reinfection. SVR sustained virologic response

Table 2 Virologic response by treatment regimen and duration (per-protocol population, N= 789)

Genotype	Period 1						Period 2		
	LDV/SOF (± RBV)			SOF+ RBV	SOF+ DCV (± RBV)		SOF+ SMV (± RBV)		SOF/VEL (± RBV)
	8 weeks (n=94)	12 weeks (n=391)	24 weeks (n=16)	12 weeks (n=20)	12 weeks (n=28)	24 weeks (n=10)	12 weeks (n=2)	24 weeks (n=1)	12 weeks (n=227)
Total	90/94 (96)	385/391 (99)	15/16 (94)	19/20 (95)	26/28 (93)	9/10 (90)	2/2 (100)	1/1 (100)	226/227 (99.6)
GT 1	85/88 (97)	309/314 (98)	9/10 (90)	–	3/3 (100)	–	–	1/1 (100)	106/106 (100)
GT 1a	38/40 (95)	198/200 (99)	3/3 (100)	–	2/2 (100)	–	–	1/1 (100)	74/74 (100)
GT 1b	41/42 (98)	99/102 (97)	6/6 (100)	–	1/1 (100)	–	–	–	28/28 (100)
GT 2	–	1/1 (100)	–	19/20 (95)	1/1 (100)	–	–	–	23/24 (96)
GT 3	–	–	–	–	19/21 (90)	8/9 (89)	–	–	53/53 (100)
GT 4	2/3 (67)	57/58 (98)	4/4 (100)	–	3/3 (100)	–	2/2 (100)	–	18/18 (100)
GT 5/6	–	7/7 (100)	–	–	–	–	–	–	7/7 (100)

The number of patients and data reported in this table are included from those with exact treatment duration available
 DCV daclatasvir, GT genotype, LDV ledipasvir, RBV ribavirin, SMV simeprevir, SOF sofosbuvir, VEL velpatasvir

patients developed serious TEAEs (one black stool and one hepato-renal syndrome). There were seven deaths in Period 1: one treatment-emergent case of hepato-renal syndrome in the LDV/SOF group and six (HCC, heart failure, cardiac

arrest, traffic accident, infectious bilateral pneumonitis and septic shock) not related to antiviral treatment.

In Period 2, early treatment discontinuation due to TEAEs was reported in one patient (experiencing drug interaction,

Table 3 Summary of safety in the intention-to-treat population ($N=1029$)

	Period 1 ($N=624$) N (%)	Period 2 ($N=405$) n (%)
At least one TEAE	171 (27)	63 (16)
At least one TEAE (Grade 1)	99 (16)	41 (10)
At least one TEAE (Grade 2)	42 (7)	18 (4)
At least one TEAE (Grade 3)	3 (<1)	1 (<1)
At least one TEAE (Grade 4)	0	0
At least one serious TEAE	2 (<1)	0
At least one TEAE leading to permanent treatment discontinuation	2 (<1)	1 (<1)
TEAEs occurring in >2% of patients		
Asthenia	74 (12)	28 (7)
Headache	54 (9)	20 (5)
Nausea	18 (3)	7 (2)
Anemia	20 (3)	–

In Period 1, patients were treated with LDV/SOF ± RBV, SOF + RBV, SOF + DCV ± RBV or SOF + SMV ± RBV ($n=624$). In Period 2, patients were treated with SOF/VEL ± RBV ($n=405$)

TEAE treatment-emergent adverse event

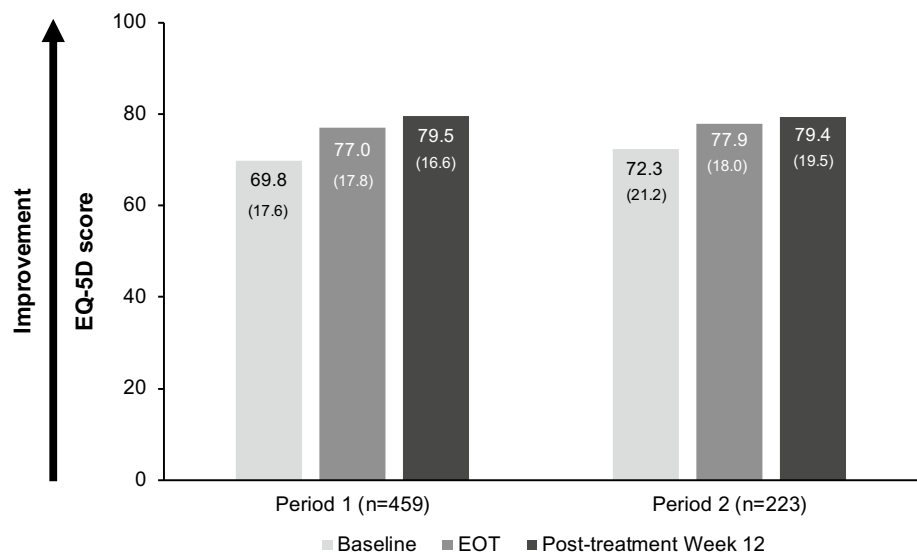
buprenorphine overexposure and alteration of the general condition). No patients changed dose or interrupted treatment due to TEAEs or developed serious TEAEs; there were three deaths (pulmonary adenocarcinoma, alteration of the state of health and acute liver failure) not related to antiviral treatment.

Patient-Reported Outcomes

A total of 459 patients in Period 1 and 223 patients in Period 2 had data available at baseline, EOT and post-treatment Week 12. Overall, PROs improved from baseline to EOT and further to post-treatment Week 12, including

EQ-5D score (Fig. 2) calculated from the EQ-5D VAS. Overall, fewer patients reported moderate or severe problems in each of the EQ-5D dimensions at post-treatment Week 12 compared with baseline (Fig. 3). Results were largely comparable in those patients with data available at all three visits compared with those with at least one missing visit (Supplementary Tables 3 and 4). Findings from multivariate regression analyses of predictive factors for HRQoL are reported in Tables 4 and 5. In Period 1, lack of employment at baseline and extrahepatic manifestations at baseline were adversely associated with HRQoL across all five dimensions of the EQ-5D ($P < 0.01$ for all dimensions). Addiction at baseline also negatively affected

Fig. 2 EQ-5D score in patients with values at baseline, end of treatment and post-treatment Week 12. The EQ-5D score corresponds to the result of the EQ-5D questionnaire VAS ranging from 0 (worst health state) to 100 (best health state). SD is shown in brackets. EOT end of treatment, EQ-5D EuroQOL five dimensions, VAS visual analog scale



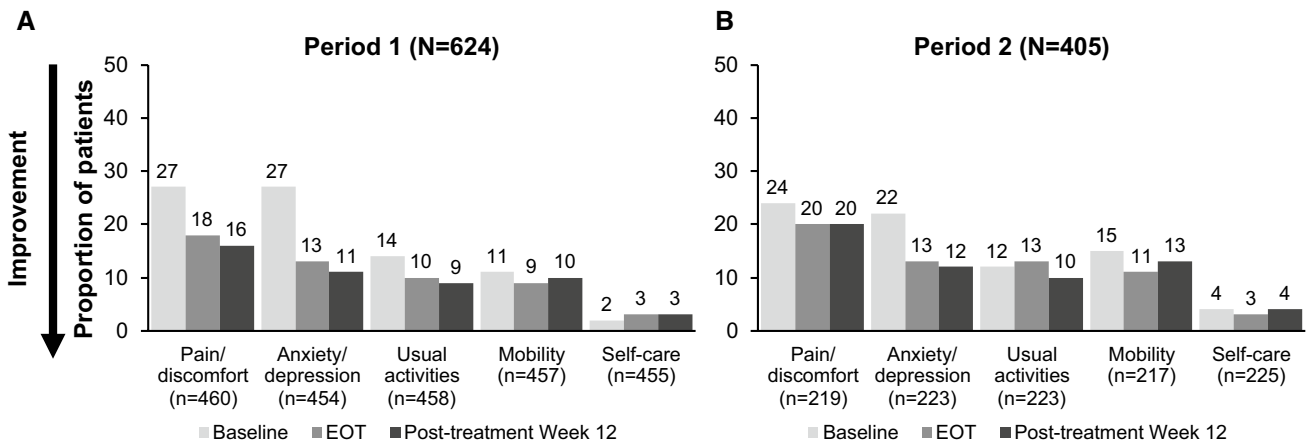


Fig. 3 Proportion of patients with values at baseline, end of treatment and post-treatment Week 12 reporting moderate or severe problems in each of the EQ-5D dimensions (pain/discomfort, anxiety/depression, usual activities, mobility, self-care) at baseline, end of treatment and post-treatment Week 12 in (a) Period 1 (N=624) and in (b) Period

2 (N=405). Fewer patients reporting problems in the EQ-5D dimensions from baseline to post-treatment Week 12 indicate improvement in health-related quality of life. EOT end of treatment, EQ-5D Euro-QOL five dimensions

HRQoL across all dimensions of the EQ-5D except “self-care.” Ethnicity negatively affected HRQoL across all dimensions of the EQ-5D except “anxiety/depression” ($P=0.5027$). BMI, therapeutic strategy and RBV use had no effect in any dimension of EQ-5D. In Period 2, lack of employment at baseline adversely associated with HRQoL across all dimensions of the EQ-5D. Extrahepatic manifestations at baseline negatively affected HRQoL across all dimensions of the EQ-5D except “self-care.” Addiction, prior HCV treatment, HCC, comorbidity, previous liver transplant and RBV use had no effect in any dimension of EQ-5D. Overall, work productivity and regular daily activity improved over both periods with more patients reporting lower impairment scores (i.e., better health status) at EOT and post-treatment Week 12 compared with baseline (Fig. 4).

Adherence

Overall, 99% (816/825) of patients reported that they totally or almost totally followed the prescription. At EOT, 96% (784/820) were $\geq 80\%$ adherent. In the univariate analysis of Period 1, male sex ($P=0.0069$), Black race ($P=0.0065$), addiction ($P<0.001$), RBV use ($P=0.0255$), current unemployment ($P=0.0064$) and cirrhosis ($P=0.0170$) were predictive of treatment adherence $< 80\%$. In the subsequent multivariate analysis, male sex ($P=0.0099$), addiction ($P=0.0014$), Black race ($P=0.0081$) and current unemployment ($P=0.0017$) remained predictive. No baseline characteristics were predictive of adherence $< 80\%$ in the univariate or multivariate analysis of Period 2.

Discussion

HELIOS demonstrated an SVR rate of 97% using SOF-based regimens in a diverse real-world cohort including patients with multiple comorbidities, excessive alcohol consumption and/or recreational drug use. Treatment was generally well tolerated with few discontinuations due to adverse events. The findings were consistent with the virologic cure rates and safety profiles of SOF-based regimens observed in Phase 3 studies and other real-world cohorts [11, 18, 28–30, 32–38]. Genotype, treatment regimen, treatment duration, treatment history, PPI use and OST use had no effect on SVR. Furthermore, response rates were high irrespective of age, alcohol consumption, recreational drug use or HIV/HCV coinfection. The results highlight that vulnerable patient populations can achieve high cure rates despite factors historically associated with poor response to IFN-based treatment. This is in agreement with published studies reporting no differences in SVR in populations such as HIV/HCV or HBV/HCV coinfection, chronic kidney disease or people who inject drugs [39–42] and supports current recommendations to prescribe pangenotypic regimens to all patients infected with chronic HCV, regardless of liver disease severity or lifestyle [22].

Phase 3 studies have reported improvements in PROs with SOF-based therapies [43–47]; however, real-world data to support clinical findings are scarce. The data from HELIOS indicate that the use of SOF-based regimens leads to significant improvement in HRQoL from baseline to EOT and beyond as measured by the EQ-5D and WPAI, both validated instruments for assessing PROs. Presence of extrahepatic manifestations and employment status, addiction and ethnicity were independent predictors of HRQoL

Table 4 Predictive factors for health-related quality of life (multivariate analysis): Period 1

Parameter	Mobility		Self-care		Usual activities		Pain/discomfort		Anxiety/depression	
	LS _{means} (SD)	P value	LS _{means} (SD)	P value	LS _{means} (SD)	P value	LS _{means} (SD)	P value	LS _{means} (SD)	P value
Visit										
Baseline	1.7 (0.1)	0.0588	1.2 (0.0)	0.0521	2.0 (0.1)	0.0040	2.1 (0.1)	<0.0001	2.1 (0.1)	<0.0001
EOT	1.7 (0.1)		1.2 (0.0)		1.9 (0.1)		1.8 (0.1)		1.9 (0.1)	
Week 12	1.7 (0.1)		1.2 (0.0)		1.9 (0.1)		1.8 (0.1)		1.8 (0.1)	
Age (years)		0.0022		0.4744		0.2584		0.0080		0.8208
Sex										
Female	1.7 (0.1)	0.3852	1.2 (0.0)	0.9859	1.9 (0.1)	0.6284	1.9 (0.1)	0.0204	2.0 (0.1)	0.0092
Male	1.7 (0.1)		1.2 (0.0)		1.9 (0.1)		1.8 (0.1)		1.9 (0.1)	
Ethnicity										
Black	1.9 (0.1)	<0.0001	1.3 (0.0)	0.0055	2.0 (0.1)	0.0116	2.1 (0.1)	<0.0001	1.9 (0.1)	0.5027
Non-Black	1.5 (0.0)		1.2 (0.0)		1.8 (0.1)		1.7 (0.1)		2.0 (0.0)	
Extrahepatic manifestation										
No	1.6 (0.0)	<0.0001	1.2 (0.0)	0.0026	1.8 (0.1)	<0.0001	1.7 (0.1)	<0.0001	1.8 (0.1)	<0.0001
Yes	1.8 (0.1)		1.3 (0.0)		2.1 (0.1)		2.1 (0.1)		2.2 (0.1)	
Addiction										
No	1.6 (0.0)	<0.0001		NS	1.8 (0.1)	0.0012	1.8 (0.1)	0.0007	1.8 (0.0)	<0.0001
Yes	1.9 (0.1)				2.0 (0.1)		2.0 (0.1)		2.1 (0.1)	
Prior HCV treatment										
No		NS		NS		NS	1.8 (0.1)	0.0302		NS
Yes							1.9 (0.1)			
HCC										
No		NS		NS		NS	2.1 (0.1)	0.0309		NS
Yes							1.7 (0.2)			
Comorbidity										
No		NS		NS		NS	1.9 (0.1)	0.0434		NS
Yes							1.8 (0.1)			
Currently employed										
No	1.8 (0.1)	<0.0001	1.3 (0.0)	<0.0001	2.0 (0.1)	0.0001	2.0 (0.1)	0.0003	2.0 (0.1)	0.0020
Yes	1.6 (0.1)		1.2 (0.0)		1.9 (0.1)		1.8 (0.1)		1.9 (0.1)	
Previous liver transplant										
No		NS		NS		0.0010	1.7 (0.0)	NS		NS
Yes							2.2 (0.2)			

Sensitivity analyses were performed with missing values imputed using a multivariate imputation by chained equations (MICE) algorithm. A step-by-step backward selection of predictors was used (visit, age, gender and ethnicity were forced into the model)

In Period 1, patients were treated with LDV/SOF±RBV, SOF+RBV, SOF+DCV±RBV or SOF+SMV±RBV ($n=624$)
 DCV daclatasvir, EOT end of treatment, HCC hepatocellular carcinoma, HCV hepatitis C virus, LDV ledipasvir, LS_{mean} least squares mean, NS not significant, SD standard deviation, SMV simeprevir, SOF sofosbuvir

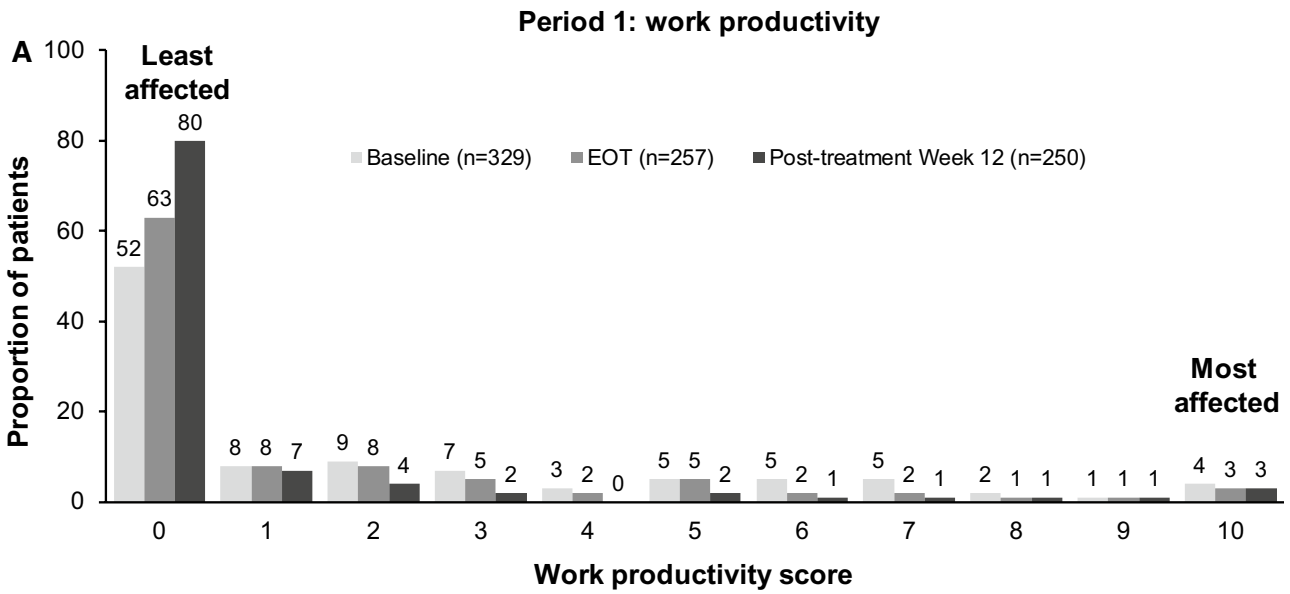
Table 5 Predictive factors for health-related quality of life (multivariate analysis): Period 2

Parameter	Mobility		Self-care		Usual activities		Pain/discomfort		Anxiety/depression	
	LS _{means} (SD)	P value	LS _{means} (SD)	P value	LS _{means} (SD)	P value	LS _{means} (SD)	P value	LS _{means} (SD)	P value
Visit										
Baseline	1.6 (0.1)	0.0010	1.2 (0.0)	0.4029	1.5 (0.1)	0.2553	2.0 (0.1)	0.1522	1.9 (0.1)	<0.0001
EOT	1.6 (0.1)		1.2 (0.0)		1.5 (0.1)		1.9 (0.1)		1.6 (0.1)	
Week 12	1.5 (0.1)		1.2 (0.0)		1.4 (0.1)		1.9 (0.1)		1.6 (0.1)	
Age (years)		0.0043		0.8013		0.4904		0.0167		0.8953
Sex										
Female	1.6 (0.1)	0.1096	1.1 (0.0)	0.0602	1.4 (0.1)	0.0496	2.0 (0.1)	0.5619	1.8 (0.1)	0.2266
Male	1.7 (0.1)		1.2 (0.0)		1.5 (0.1)		1.9 (0.1)		1.7 (0.1)	
Ethnicity										
Black	1.7 (0.1)	0.1223	1.2 (0.1)	0.6411	1.4 (0.1)	0.0915	2.1 (0.1)	0.0084	1.6 (0.1)	0.0004
Non-Black	1.6 (0.1)		1.2 (0.0)		1.5 (0.0)		1.8 (0.1)		1.9 (0.1)	
BMI (kg/m ²)		0.0105		NS		0.0002		NS		NS
Extrahepatic manifestation										
No	1.5 (0.1)	0.0006	1.1 (0.0)	NS	1.3 (0.0)	<0.0001	1.8 (0.1)	0.0006	1.5 (0.1)	<0.0001
Yes	1.8 (0.1)		1.2 (0.1)		1.7 (0.1)		2.1 (0.1)		2.0 (0.1)	
Currently employed										
No	1.8 (0.1)	<0.0001	1.3 (0.0)	<0.0001	1.6 (0.1)	<0.0001	2.1 (0.1)	0.0013	1.9 (0.1)	0.0009
Yes	1.5 (0.1)		1.1 (0.0)		1.3 (0.1)		1.9 (0.1)		1.7 (0.1)	

Sensitivity analyses were performed with missing values imputed using a multivariate imputation by chained equations (MICE) algorithm. A step-by-step backward selection of predictors was used (visit, age, gender and ethnicity were forced into the model)

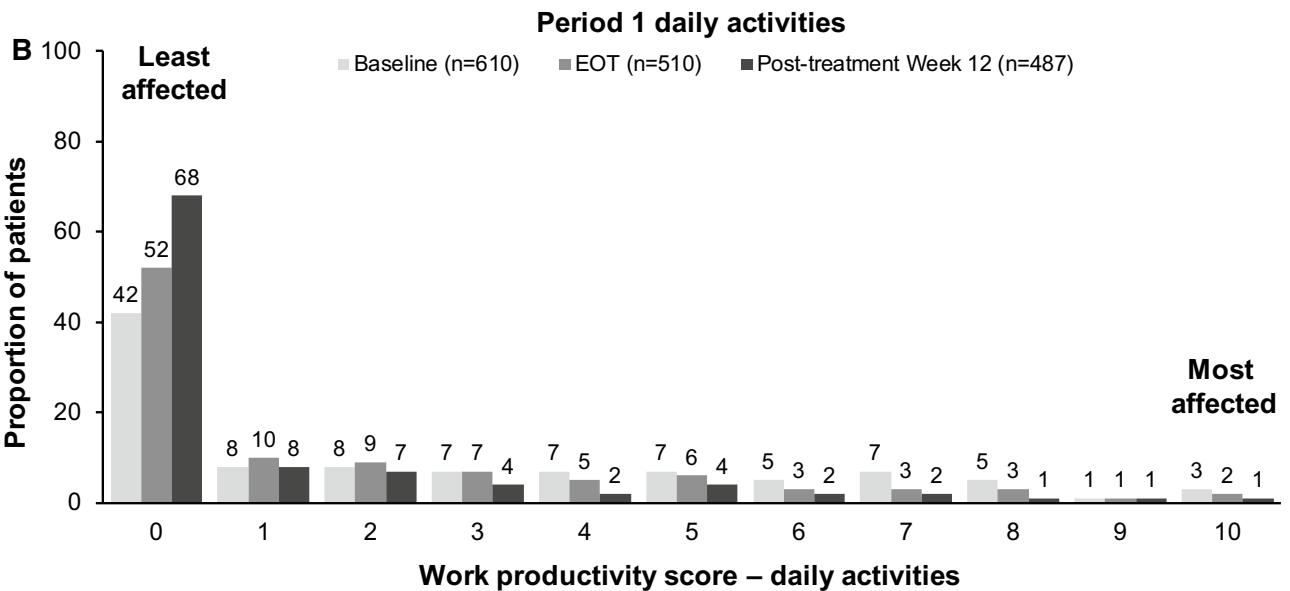
In Period 2, patients were treated with SOF/VEL±RBV (n = 405)

BMI body mass index, EOT end of treatment, HCC hepatocellular carcinoma, HCV hepatitis C virus, LS_{mean} least squares mean, NS not significant, RBV ribavirin, SD standard deviation



Number at:

Baseline	170	25	29	24	11	15	16	16	6	3	14
EOT	163	21	21	14	5	12	5	4	3	2	7
Week 12	200	17	11	4	0	4	1	3	2	2	6



Number at:

Baseline	258	47	49	42	40	45	29	43	31	7	19
EOT	266	52	44	34	24	28	16	14	14	6	12
Week 12	333	41	34	17	9	17	9	9	5	6	7

◀ **Fig. 4** Work productivity and activity impairment (WPAI) score for **a** work productivity at baseline ($n=329$), end-of-treatment ($n=257$) and post-treatment Week 12 ($n=250$) in Period 1, **b** regular daily activity at baseline ($n=610$), end of treatment ($n=510$) and post-treatment Week 12 ($n=487$), in Period 1, **c** work productivity at baseline ($n=168$), end-of-treatment ($n=140$) and post-treatment Week 12 ($n=133$) in Period 2, and **d** regular daily activity at baseline ($n=389$), end of treatment ($n=283$) and post-treatment Week 12 ($n=256$) in Period 2. The WPAI score corresponds to the result of the WPAI questionnaire ranging from 0 (the least affected by HCV is the productivity at work in the last 7 days) to 10 (the most affected by HCV is the productivity at work in the last 7 days). *Note* Results are presented for patients that stated in the WPAI questionnaire that they were employed at each visit (282 patients at baseline, 247 patients at EOT and 221 patients at post-treatment Week 12 in Period 1; 168 patients at baseline, 148 patients at EOT and 140 patients at post-treatment Week 12 in Period 2). Patients with missing data were excluded from the analysis. The WPAI regular activity score corresponds to the result of the WPAI questionnaire ranging from 0 (the least affected by HCV are the regular daily activities in the last 7 days) to 10 (the most affected by HCV are the regular daily activities in the last 7 days). *EOT* end of treatment, *HCV* hepatitis C virus

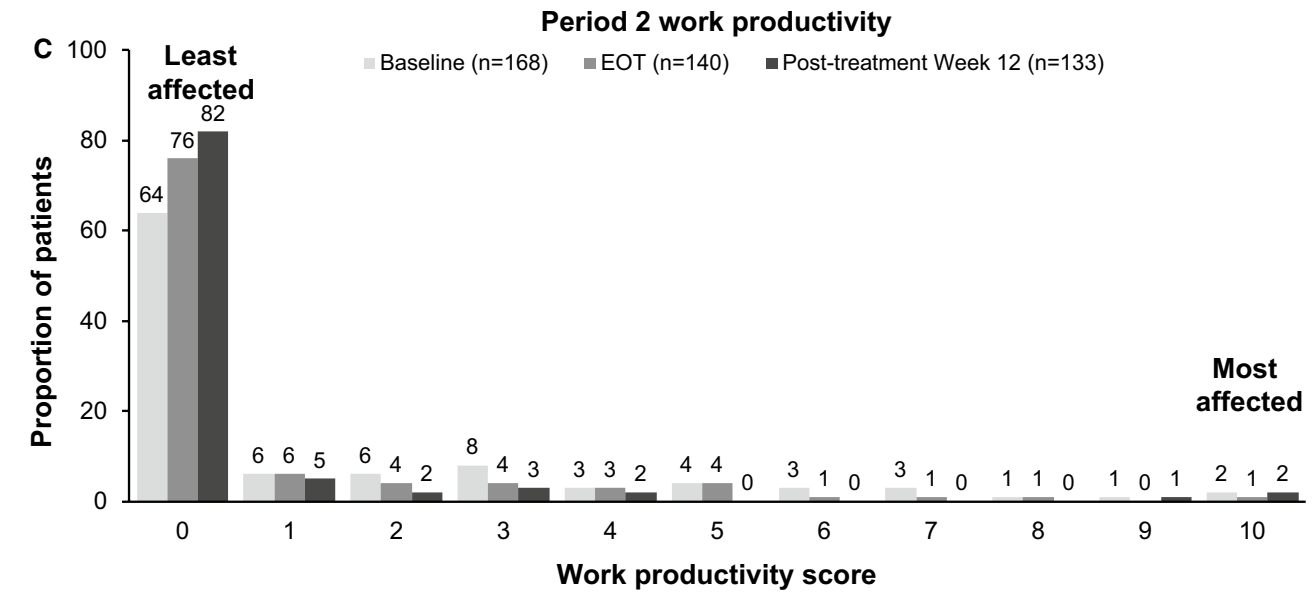
impairment with some SOF-based regimens. Presence of such predictors should also be considered when initiating HCV treatment in these patient groups to help inform caregivers of potential challenges.

HELIOS also provides insight into real-world adherence and treatment outcomes among a heterogeneous population. Overall adherence was high across this diverse group of patients, suggesting that perceptions regarding treating certain patient groups such as recreational drug users, patients on OST or those consuming excessive alcohol might be unfounded. Decisions regarding access to treatment by drug and alcohol users should be made according to clinical and public health requirements rather than coexisting disorders such as addiction [47]. Factors such as addiction, male sex and current unemployment were identified as independent predictors of poor treatment adherence in Period 1, when pangenotypic regimens such as SOF/VEL were not available. Baseline factors such as sex, employment status and substance abuse have previously been identified as predictors of suboptimal adherence in non-pangenotypic regimens [48, 49] and should be considered by healthcare professionals when initiating such HCV treatments in these patient groups. Conversely, no baseline factors included in the analysis were predictive of poor adherence to SOF/VEL \pm RBV in Period 2, providing further evidence that the use of pangenotypic regimens may be considered for simplified treatment, regardless of patient population. This is particularly important when prescribing treatment in injecting drug users, a population that has been identified as key if HCV elimination is to be achieved [50]. However, appropriate individual support should be offered to those who may have chaotic lifestyles, including moderate to heavy alcohol

use and require additional assistance to ensure appropriate adherence [51].

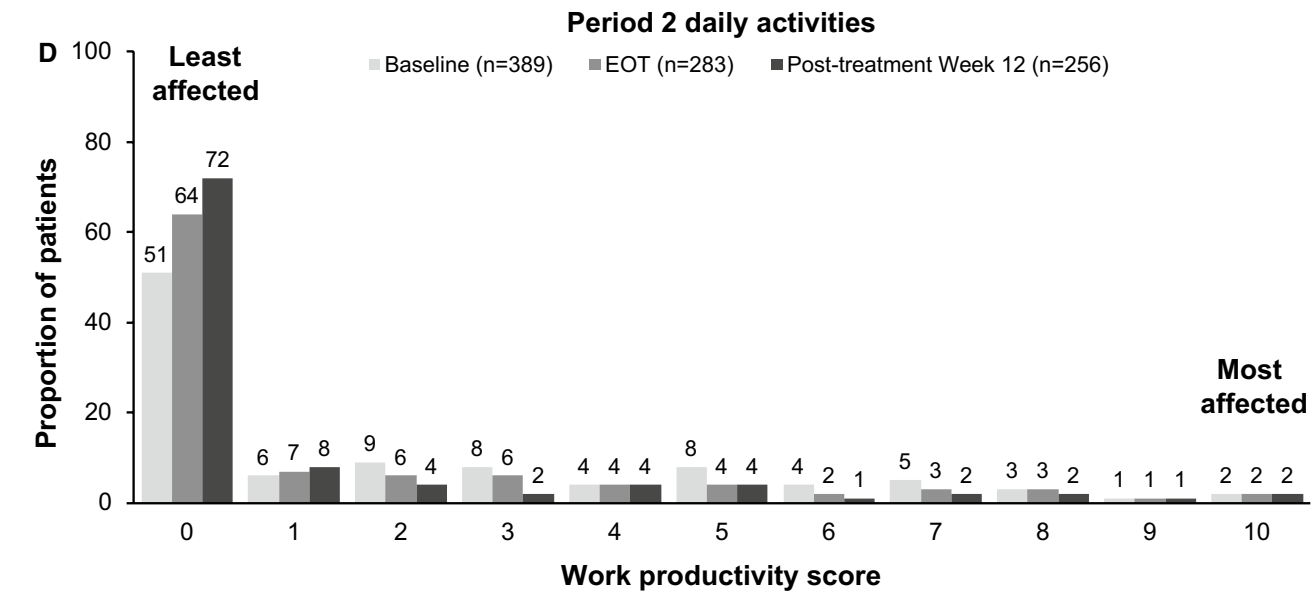
This prospective, observational study showed differences in the populations receiving DAA therapy for HCV infection in France between October 2015 and July 2018 after it became one of the first European countries to commit to goals to eliminate HCV. On their introduction in 2013, prescription of DAAs was initially restricted to patients with severe disease such as those with F3/F4 liver fibrosis, liver transplant or HCV/HIV coinfecting, with management in the specialist setting, reflective of Period 1 of HELIOS. By 2016, DAA prescription was extended to historically difficult-to-treat patients (genotype 3) and those with F2 liver fibrosis. In 2017, DAA reimbursement was extended to all HCV patients, including those with F0/F1 liver fibrosis; in 2019, prescription of DAAs was extended to non-specialists. Availability of simple, pangenotypic regimens has allowed an expanded focus on vulnerable populations infected with HCV, making HCV elimination a realistic goal. As such, the study population in Period 2 had a wider distribution of genotypes, less severe fibrosis stage at baseline, a higher proportion of treatment-naïve patients and fewer patients with extrahepatic manifestations or HIV/HCV coinfection. Additionally in Period 2, there were more reports of current excessive alcohol consumption and/or current recreational drug use and OST use, reflecting improved access to HCV treatment. The proportion of patients completing the study was higher in Period 2 (87%) than in Period 1 (59%), suggesting that simplified management with pangenotypic regimens resulted in fewer patients being retained within care to the end of follow-up. The baseline characteristics of patients enrolled during the two periods can again provide an indication of why fewer patients were retained in care up to the end of the follow-up period in Period 2. The high number of patients with serious liver disease in Period 1 means that these patients would be carefully retained in care to ensure that they achieved a favorable outcome. In contrast, the broader patient population included in Period 2, especially those with a history of alcohol or drug use, is recognized as a factor influencing engagement with care [40]. However, the successful initiation of therapy in this group is encouraging and, given the high response rates with these regimens, many patients will have been cured even if this is not captured during follow-up assessments.

The current study has several limitations. In a non-interventional study, all decisions on patient management are made solely by the treating physician. As such, some data or visits may be missing or visits delayed. In addition, selection bias for patient recruitment cannot be completely ruled out. Physicians at the recruiting sites might have selected one patient in preference to another owing to the small number of patients included per site.



Number at:

Baseline	107	10	10	14	5	6	5	5	1	1	4
EOT	107	9	5	5	4	5	1	2	1	0	1
Week 12	109	7	3	4	3	4	0	0	0	1	1



Number at:

Baseline	199	24	36	29	14	30	17	18	11	5	6
EOT	180	20	18	16	10	11	5	8	8	1	6
Week 12	184	20	11	6	9	9	1	4	6	1	5

Fig. 4 (continued)

However, because of the large number of sites involved, no changes in overall results of the study were expected. To get a good representation of the patients treated with SOF-based regimens in France, sites were selected from all over the French metropolitan territory, including university hospitals, general hospitals and private practice. However, non-inclusion criteria de facto excluded some patients from the study, and patients at risk of not being available for follow-up over the 2-year course of the study were unlikely to be enrolled. In this study, 1029 patients were enrolled and 885 patients were included in the PP analysis at post-treatment Week 12. The remaining 144 patients were excluded due to loss to follow-up or because data relating to HCV RNA were unavailable at the time of analysis for SVR. This reflects everyday clinical practice; however, the proportion of patients with missing data could compromise the effectiveness analysis and the relationship between effectiveness and HRQoL. Although the baseline demographics of patients with and without data relating to HCV RNA at the SVR time point were similar in Period 2, the proportion of patients with experience of addiction was higher in the group without SVR data than the group with SVR data in Period 1. This further highlights the need to ensure appropriate treatment choice and support is given to optimize engagement and adherence among vulnerable populations. With many clinical studies reporting the effectiveness of pangenotypic regimens in up to 99% of patients [13, 14, 52–55], including a high rate of SVR in those without full adherence to therapy [56], clinical practice is evolving to redefine the parameters of success in HCV treatment. If adequate compliance is attained, which has been reported in diverse populations, it could be assumed that SVR is achieved in the majority of patients and HCV RNA assessment post-treatment may not be needed for some patients. Thus, simplification of HCV care with pangenotypic regimens reduces the burden of healthcare utilization for both the patient and healthcare professionals. With less focus on patient management after HCV diagnosis and linkage to care, more resources can be used to identify people who are unaware of their HCV status and maintain momentum towards achieving HCV elimination.

In conclusion, SOF-based regimens are associated with high response rates, favorable safety profiles, as well as improvements in parameters associated with HRQoL. The effectiveness and safety results with these regimens in clinical practice are similar to the efficacy reported in clinical trials. Data from HELIOS support the findings from clinical studies and demonstrate benefits of achieving an SVR beyond the liver. The study puts the evolution of DAA therapy into perspective, seeing the added benefits of pangenotypic regimens since they became universally available in France in 2017, with SOF/VEL the most frequently

prescribed regimen at the time of writing. Continued use of simplified HCV management algorithms, multistakeholder engagement with care and bringing national policy in line with evidence-based recommendations, France is on track for eliminating HCV in line with WHO targets.

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Compliance with Ethical Standards

Conflict of interest Denis Ouzan has served as a speaker for AbbVie and Gilead Sciences, reports research funding from Gilead Sciences, and reports financial support for attending symposia and sponsorship for educational meetings from AbbVie, Gilead Sciences and Merck Sharp & Dohme. Dominique Larrey has served as a speaker/advisor for AbbVie, Gilead Sciences and Merck Sharp & Dohme. Dominique Guyader has served as a speaker for and reports financial support for attending symposia from AbbVie, Gilead Sciences, Merck Sharp & Dohme, and Janssen, and also reports research funding from Janssen. André-Jean Remy has served as a speaker/consultant/advisor for Gilead Sciences. Ghassan Riachi has served as a speaker and advisor for Gilead Sciences. Frédéric Heluwaert, Jean-Marc Combis, Isabelle Rosa, Dominique Roulot, Bruno Roche and Jérôme Dumortier have no conflicts of interest to declare. Régine Truchi has served as a speaker and clinical investigator for Gilead Sciences. François Bailly has served as a speaker/advisor for AbbVie, Bristol-Myers Squibb, Gilead Sciences and Merck Sharp & Dohme, and reports financial support for attending symposia from AbbVie, Gilead Sciences and Merck Sharp & Dohme. Christophe Hézode, Denise Glorian-Petaud, Olivier Libert and Heribert Ramroth is an employee of Gilead Sciences. Tarik Asselah has served as a clinical investigator and speaker for AbbVie, Gilead Sciences, Janssen and Merck Sharp & Dohme. Gérard Thieffin has served as a speaker for and reports financial support for attending symposia from Gilead Sciences. Vincent Leroy has served as a speaker/advisor and clinical investigator for Gilead Sciences. Dominique Thabut reports financial support for attending symposia from AbbVie and Gilead Sciences. Stanislas Pol has served as a speaker/consultant for AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck Sharp & Dohme, and Roche, and reports research funding from Bristol-Myers Squibb, Gilead Sciences, Merck Sharp & Dohme, and Roche.

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