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Socioeconomic Deprivation Weighs Heavily on Liver Fibrosis and Mortality After Hepatitis C Cure (ANRS CO22 Hepather)

Tangui Barré¹  | Lucia Parlati² | Marc Bourlière^{1,3} | Clémence Ramier¹ | Fabienne Marcellin¹  | Camelia Protopopescu¹  | Vincent Di Beo¹ | Cécile Moins⁴ | Céline Dorival⁵ | Jérôme Nicol⁵ | Jessica Zucman-Rossi^{6,7} | Philippe Mathurin⁸ | Dominique Larrey⁹ | Jérôme Boursier^{10,11} | Fabrice Carrat¹² | Patrizia Carrieri¹ | the ANRS/AFEF Hepather Study group

¹Aix Marseille Univ, Inserm, IRD, SESSTIM, Sciences Economiques & Sociales de la Santé & Traitement de l'Information Médicale, ISSPAM, Marseille, France | ²Département d'Hépatologie/Addictologie, Hôpital Cochin, Université de Paris Cité, INSERM U1016, AP-HP, Paris, France | ³Département D'hépatologie et Gastroentérologie, Hôpital Saint Joseph, Marseille, France | ⁴Department of Clinical Research, ANRS Emerging Infectious Diseases, Paris, France | ⁵Institut National de la Santé et de la Recherche Médicale (INSERM), Institut Pierre Louis d'Epidémiologie et de Santé Publique, Sorbonne Université, Paris, France | ⁶Centre de Recherche des Cordeliers, Sorbonne Université, Inserm, Université Paris Cité, Paris, France | ⁷Hôpital Européen Georges Pompidou, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France | ⁸Service des Maladies de l'Appareil Digestif, Université Lille 2 and Inserm U795, Lille, France | ⁹Liver Unit-IRB-INSERM 1183, Hôpital Saint Eloi, Montpellier, France | ¹⁰Hepato-Gastroenterology Department, Angers University Hospital, Angers, France | ¹¹HIFIH Laboratory, UPRES 3859, SFR 4208, Angers University, Angers, France | ¹²Sorbonne Université, Institut National de la Santé et de la Recherche Médicale (INSERM), Institut Pierre Louis d'Epidémiologie et de Santé Publique, Hôpital Saint-Antoine, Unité de Santé Publique, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France

Correspondence: Fabienne Marcellin (fabienne.marcellin@inserm.fr)

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Keywords: direct-acting antivirals | hepatitis C, chronic | liver disease | mortality | socioeconomic status

ABSTRACT

Although Hepatitis C virus (HCV) infection can be cured with direct-acting antivirals (DAA), some cured patients face a serious risk of advanced liver damage and early mortality. In order to avoid these two negative health outcomes, it is important to identify and assess related risk factors. Little is currently known about socioeconomic and behavioural factors in this context. Using data from the ANRS CO22 Hepather cohort, we tested for associations between socioeconomic and behavioural factors and (i) advanced liver fibrosis (defined as an FIB-4 > 3.25) assessed longitudinally using a mixed-effects logistic regression model (both the whole population and stratified on advanced liver fibrosis status at the time of HCV cure) and (ii) all-cause mortality (Cox proportional hazards model), during post-HCV cure follow-up. Among 5833 participants cured of HCV, living in poverty was associated with postcure advanced liver fibrosis in participants without this diagnosis at the time of HCV cure (population attributable fraction—PAF—of 8.6%) and with mortality in the whole study population (PAF of 10.6%). The detrimental effects of unhealthy alcohol use and heavy tobacco smoking, as well as the beneficial effect of living with a stable partner were also highlighted. We highlighted the major role of poverty and behavioural factors in advanced liver fibrosis and all-cause mortality

The ANRS/AFEF Hepather Study group is available in [Appendix](#).

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in patients cured of HCV. Encouraging linkage to social support services and healthy behaviours after successful DAA treatment could limit morbidity and increase survival in this population.

Clinical Trial Registration: [ClinicalTrials.gov](https://clinicaltrials.gov): NCT01953458

1 | Introduction

Hepatitis C virus (HCV) infection can now be cured with direct acting antivirals (DAA) [1]. HCV cure is associated with fibrosis regression, a lower risk of hepatocellular carcinoma in patients with advanced fibrosis and fewer extrahepatic manifestations of hepatitis C [2, 3]. Specifically, DAA treatment is associated with a substantial reduction in all-cause, liver- and drug-related mortality [4, 5]. As national DAA programmes continue to scale up, the public health benefits of HCV cure at the population levels are becoming increasingly evident [6–8]. For instance, in the DAA era, there has been a sharp decline in liver disease morbidity and mortality in New South Wales, Australia [8].

However, after DAA-related HCV cure, patients still have a high risk of adverse clinical events, as illustrated by costlier health management as compared to the general population in France [9]. One such effect is the serious risk of liver disease progression, potentially leading to severe complications including death [10]. A population-based cohort study conducted in British Columbia, Scotland and England found higher all-cause mortality risks in DAA-cured patients than in the general population, the leading causes of death being drug-related mortality, liver failure and liver cancer [11].

Given this context, it is important to identify and assess risk factors for post-HCV cure advanced fibrosis and early mortality in order to optimally monitor patients and avoid these two negative health outcomes. The most prominent risk factors for postcure liver disease progression include elevated body weight, metabolic disorders, unhealthy alcohol use, advanced liver fibrosis and persistently high alanine aminotransferase (ALT) and gammaglutamyltransferase (GGT) levels [10, 12]. Clinical factors associated with postcure all-cause mortality include high GGT levels [12], hepatocellular carcinoma development, a low estimated glomerular filtration rate and a high albumin–bilirubin grade [13].

Socioeconomic and behavioural factors affect liver fibrosis in people with HCV and/or HIV [14–16]. The importance of behavioural factors such as substance use on HCV-related mortality has already been highlighted for the HCV/HIV population [17]. Previous work in the US found that half the excess mortality risk for individuals with chronic HCV infection may be attributed to behavioural factors [18]. This suggests that modifying habits, such as diet and substance use, may lead to substantially lower mortality risk in people with HCV. To our knowledge, no study to date has examined the extent to which socioeconomic and behavioural factors affect liver fibrosis and survival in DAA-cured patients.

Using data from the French ANRS CO22 HEPATHER cohort, we aimed to identify socioeconomic and behavioural risk factors for advanced liver fibrosis and all-cause mortality in patients cured of HCV thanks to DAA.

2 | Material and Methods

2.1 | Study Population

ANRS CO22 HEPATHER is a French, national, multicentre, prospective, observational cohort of adult patients living with hepatitis B virus (HBV) and/or HCV ([ClinicalTrials.gov](https://clinicaltrials.gov) registry number: NCT01953458). Implemented in 2012, enrolment in the cohort study took place in 32 hospitals throughout France, with an expected 10-year follow-up. Persons with HIV coinfection were not included. Patients with HCV received DAA treatment after enrolment, if eligible. The cohort design is described extensively elsewhere [19].

Written informed consent was obtained from each participant before cohort enrolment. The protocol was designed in accordance with the Declaration of Helsinki and French law for biomedical research and was approved by the *Comité de Protection des Personnes (CPP) Ile de France 3* Ethics Committee (Paris, France) and the French Regulatory Authority (ANSM).

The present study population comprised patients with chronic HCV infection at cohort enrolment who reached sustained virologic response (i.e., undetectable HCV RNA) 24 weeks after completing DAA treatment (SVR24 hereafter). Patients with HBV coinfection, those with a missing FIB-4 index data at the SVR24 visit, and persons with no follow-up data after the SVR24 visit were all excluded.

2.2 | Data Collection

At the cohort enrolment visit, physicians completed a structured questionnaire during a face-to-face interview with their patients. Anthropological measurements (i.e., height, weight) and urine and blood samples were also collected.

The questionnaire collected clinical, socioeconomic and behavioural data including sex, age, country of birth, educational level, civil/marital status, average monthly household income, number of adults and children in the household, HCV transmission mode, history of HCV treatment, past and current cannabis use, lifetime tobacco use (number of pack-years, obtained by multiplying the number of years the person had smoked by the average number of packs of cigarettes smoked per day), past and current drug injection, past and current opioid agonist therapy, past and current alcohol consumption (number of standard drinks per day) and current coffee consumption (number of cups per day).

Detailed clinical (including fibrosis stage and comorbidities) as well as biological data (including platelet count (platelets/L), ALT (IU/L) and aspartate aminotransferase (AST, IU/L) levels) were collected during the enrolment visit using an electronic

case report form. Follow-up included a visit once a year and supplementary visits for certain clinical events (e.g., decompensated cirrhosis and HCV treatment initiation). Clinical data were updated annually during follow-up visits. Vital status was ascertained through medical records at clinical centres. No linkage with a mortality registry was performed.

2.3 | Study Outcomes and Study Period

The baseline was defined as the visit during which SVR24 was ascertained and entered into the medical record. The study period corresponded to the time between baseline and the last available data point (whether a follow-up visit or death) or the 30th October 2022, or the eighth-year visit, whichever occurred first. The latter visit was chosen as very few participants had data beyond the eighth year. The primary study outcome was advanced liver fibrosis after HCV cure, measured longitudinally for the study period. Advanced fibrosis was defined as an FIB-4 > 3.25, based on the FIB-4 index calculated using the AST level, ALT level, age and platelet count [20, 21].

The secondary study outcome was the time between the SVR24 visit and all-cause deaths during the post-HCV cure study period.

2.4 | Explanatory Variables

The explanatory variables were assessed, as described in the following paragraphs.

Living in poverty was defined as a standard of living lower than the 2015 French poverty threshold (1015 euros per month) [22]. Standard of living was calculated as the disposable monthly income divided by the number of consumption units in the household. Educational level was dichotomised into having at least an upper secondary school certificate or not.

Tobacco smoking was quantified by a four-category variable, with the value 0 for people who had never smoked, and 1, 2 and 3 for lifetime smoking of 1–9, 10–19 and ≥ 20 pack-years, respectively. Cannabis use was coded into three categories: ‘current’, ‘former’ and ‘never’. Alcohol consumption was also coded into three categories as follows: ‘abstinent with no history of unhealthy alcohol use’, ‘current moderate alcohol use’ (i.e., non-abstinent and nonunhealthy use) and ‘current or past unhealthy alcohol use’. Unhealthy alcohol use was defined as >2 and >3 standard drinks per day for women and men, respectively, in accordance with the French National Authority for Health’s guidelines [23]. A dichotomous variable was created to test for a potential relationship between coffee consumption and both study outcomes. The three cups/day threshold was chosen based on previous results showing a potential protective effect of elevated coffee consumption on liver stiffness and mortality in patients likely to develop liver disease [17, 24].

To take into account the history of drug injection, we created a binary composite variable defined as follows: HCV infection through drug injection *or* reporting past or current opioid agonist therapy *or* past or current drug injection versus none of these. HCV treatment naivety was defined as not having

received HCV treatment before the DAA which cured the participant. Body mass index was categorised according to WHO cutoffs [25].

All explanatory variables were measured at cohort inclusion, except for treatment status, advanced liver fibrosis (for mortality analyses) and age, all three of which were assessed at the SVR24 visit.

2.5 | Statistical Analyses

Study population characteristics were compared according to advanced fibrosis status (yes/no) at the SVR24 visit using Pearson’s chi-squared test for categorical variables, and the Kruskal–Wallis test for continuous variables. We also compared persons included in the study population with those excluded because of no post-SVR24 follow-up visit, using similar statistical tests. Moreover, we compared participants lost to follow-up with those who were not. A participant was considered to be lost to follow-up if he/she had not died during the study period and his/her last follow-up visit was more than 3 years from the censoring date (30 October 2022).

The mortality rate was computed as the number of deaths recorded during the study period divided by the number of person-years (computed as the sum, for all patients, of the number of years between the SVR24 visit and the last available data point).

Factors associated with advanced liver fibrosis during post-HCV cure follow-up were identified using a mixed-effects logistic regression model. This choice of model ensured that the correlation of repeated measurements for individuals could be taken into account. The model included a single random effect (random intercept for patients), a fixed slope (time since HCV cure) and fixed effects for the other covariates. As participants’ characteristics and risk factors for advanced liver fibrosis post-HCV cure were likely to differ between persons with and without advanced liver fibrosis at baseline, we conducted stratified analyses by separating the study population into these two subpopulations. The baseline visit, which was used as the stratification criterion, was excluded from the stratified analyses. Nonstratified analyses were also performed on the whole study population and on the whole study period (including the baseline visit).

Factors associated with post-HCV cure mortality were identified using a Cox proportional hazards model. For both study outcomes (i.e., advanced liver fibrosis and mortality), explanatory variables were first tested in univariable analyses. Variables with a p value <0.20 (Wald test) were eligible for the multivariable analyses. Backward selection procedures were used to build the final multivariable models (significance threshold of $p \leq 0.05$). For both outcomes, we tested for an interaction effect between educational level and poverty.

The population attributable fractions (PAF) for the factors of the final multivariable models were computed (Stata commands *punaf* for advanced liver fibrosis and *punafec* for mortality [26]) as the percentages of the outcomes that could have been avoided had no individual been exposed to each risk factor. To avoid negative PAF, protective effects were quantified with the prevented

fraction (PF), computed as $PF = -PAF / (1 - PAF)$. PF corresponded to the percentage of outcomes that could be avoided if it were possible to expose everyone to this protective factor. The PAF for continuous variables are not provided here as they may be statistically biased and highly variable [27].

We tested for potential selection bias related to missing data on the advanced liver fibrosis outcome (i.e., missing data on the FIB-4 index) using a two-step Heckman method [28]. In the first step, we identified the factors associated with longitudinal missing data, using a multivariable mixed-effects probit model. We used the residuals of this model to calculate the inverse Mills ratio (IMR). Then, in the second step, we built a mixed-effects probit model for the outcome advanced liver fibrosis, adjusting for associated factors with a p value <0.05 and the IMR term (irrespective of the p value of this latter). Bias-corrected confidence intervals and p values based on 500 bootstrap replicates were used in the second step of the model. Here, a p value <0.05 for the IMR term indicated the presence of selection bias.

To assess the robustness of the findings in terms of the effects of the two main markers of socioeconomic deprivation (i.e., low education level and living in poverty), we estimated the corresponding E -values. The latter is defined as the minimum strength of association on the risk ratio scale that an unmeasured confounder would need to have with both the covariate and the outcome, in order to fully explain away their (i.e., covariate and outcome) association, conditional on the other measured covariates. For both covariates, we measured an E -value for the point estimate, and an E -value for the limit of the confidence interval (CI) closest to null [29, 30]. We used the Stata *eval* package to do this [31].

All analyses were performed with Stata version 17.0 for Windows (StataCorp LP, College Station, TX).

3 | Results

3.1 | Study Population Characteristics

The study population comprised 5833 participants (Figure 1), of whom 54.1% were men (Table 1). A comparison of included participants vs. individuals excluded because of no post-SVR24 follow-up visit is provided in Table S1.

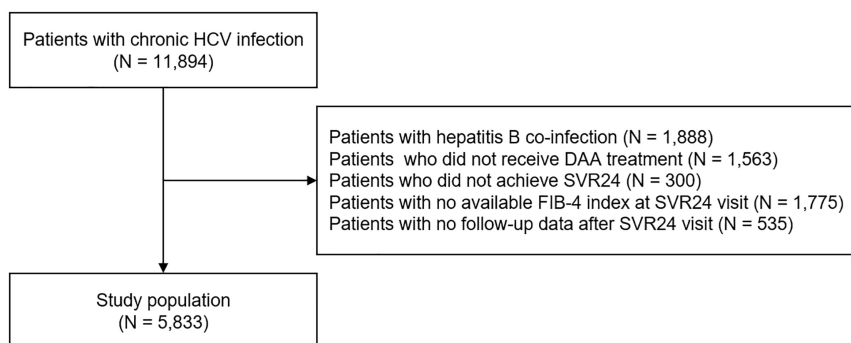


FIGURE 1 | Flow chart of the study population (ANRS CO22 Hepather cohort). DAA, direct-acting antivirals; HCV, hepatitis C virus; SVR24, sustained virologic response at Week 24.

The median [interquartile range (IQR)] age of study participants at SVR24 was 58 [52–67] years. The median [IQR] follow-up time was 4.25 [2.71–5.51] years (corresponding to 27,136 visits and 23,740.46 person-years).

More than half (56.8%) the study population did not have an upper secondary school certificate ('lower educational level', hereafter), and 28.7% lived in poverty. Participants cumulating a lower educational level and poverty represented 20.2% of the study population. Fifteen percent (15.3%) presented advanced liver fibrosis at baseline, and 22.2% at least once during the study period. A total of 584 deaths occurred during the study period. The mortality rate [95% confidence interval (CI)] was 2.46 [2.27–2.67] per 100 person-years in the whole study population, 6.43 [5.66–7.30] in participants with advanced liver fibrosis at baseline, and 1.73 [1.56–1.92] in participants without advanced liver fibrosis at baseline ($p < 0.001$ between the two latter rates).

At the censoring date, 16.1% of the study participants were considered lost to follow-up. Their characteristics are provided in Table S2.

3.2 | Factors Associated With Post-HCV Cure Advanced Liver Fibrosis

In participants with advanced liver fibrosis at baseline, after multivariable adjustment, having advanced liver fibrosis was associated with (i) previously (i.e., prior to baseline) experiencing HCV treatment failure (adjusted odds ratio (aOR) [95% CI] 2.02 [1.12–3.65], $p = 0.019$, PAF = 7.6%) and (ii) the time since HCV cure (aOR [95% CI] 0.75 [0.68–0.82] per year, $p < 0.001$; Table 2). No socioeconomic or behavioural factors were associated with this outcome.

In participants without advanced liver fibrosis at baseline, after multivariable adjustment, the following socioeconomic and behavioural factors were associated with advanced liver fibrosis: male sex, being over 70 years old, being born in sub-Saharan Africa/Caribbean, living in poverty (aOR [95% CI] 1.64 [1.09–2.47], $p = 0.017$) and unhealthy alcohol use (aOR [95% CI] 2.09 [1.29–3.37], $p = 0.003$). Diabetes and time since HCV cure were also associated with this outcome (Table 2). The highest PAF (or PF) were observed, in decreasing order, in persons aged over 70 years (PAF = 20.2%), persons of female sex (PF = 13.0%), those living in poverty and participants with unhealthy alcohol

TABLE 1 | Study population characteristics and post-HCV cure deaths, according to the liver fibrosis status at SVR24 visit (ANRS CO22 Hepather cohort, N = 5833).

Variables (% missing)	Study population (N = 5833)		Deaths (N = 584)		Participants without advanced liver fibrosis ^a at baseline (N = 4941)		Participants with advanced liver fibrosis ^a at baseline (N = 892)		p ^b
	N (%)	or Median [IQR]	N (%)	or Median [IQR]	N (%)	or Median [IQR]	N (%)	or Median [IQR]	
Sex (0)									0.037
Male	3155 (54.1)		369 (63.2)		2644 (53.5)		511 (57.3)		
Female	2678 (45.9)		215 (36.8)		2297 (46.5)		381 (42.7)		
Age, in years (0)									<0.001
<50	1015 (17.4)		43 (7.4)		926 (18.7)		89 (10.0)		
50–59	2202 (37.8)		157 (26.9)		1924 (38.9)		278 (31.2)		
60–69	1544 (26.5)		173 (29.6)		1286 (26.0)		258 (28.9)		
≥70	1072 (18.4)		211 (36.1)		805 (16.3)		267 (29.9)		
Place of birth ^c (0.2)									0.104
France	4422 (75.9)		442 (76.0)		3771 (76.4)		651 (73.1)		
Europe (excluding France), North America, Latin America, Australia	419 (7.2)		42 (7.2)		339 (6.9)		80 (9.0)		
North Africa, Middle East	543 (9.3)		66 (11.3)		450 (9.1)		93 (10.4)		
sub-Saharan Africa, Caribbean	306 (5.3)		23 (3.9)		257 (5.2)		49 (5.5)		
Asia	134 (2.3)		9 (1.6)		116 (2.4)		18 (2.0)		
Living with a stable partner ^d (0.3)									0.027
No	2371 (40.8)		267 (45.9)		1979 (40.2)		392 (44.1)		
Yes	3442 (59.2)		315 (54.1)		2946 (59.8)		496 (55.9)		
Living in poverty ^e (3.0)									0.001
No	4034 (71.3)		361 (63.8)		3457 (72.1)		577 (66.6)		
Yes	1625 (28.7)		205 (36.2)		1335 (27.9)		290 (33.4)		
Educational level (1.0)									<0.001
<Upper secondary school certificate	3277 (56.8)		390 (67.5)		2686 (54.9)		591 (67.1)		

(Continues)

TABLE 1 | (Continued)

Variables (% missing)	Study population (N = 5833)		Deaths (N = 584)		Participants without advanced liver fibrosis ^a at baseline (N = 4941)		Participants with advanced liver fibrosis ^a at baseline (N = 892)		p ^b
	N (%)	or Median [IQR]	N (%)	or Median [IQR]	N (%)	or Median [IQR]	N (%)	or Median [IQR]	
≥ Upper secondary school certificate	2495 (43.2)		188 (32.5)		2205 (45.1)		290 (32.9)		
Past or current drug injection (0.0)									0.085
No	4209 (72.2)		432 (74.0)		3544 (71.7)		665 (74.6)		
Yes	1623 (27.8)		152 (26.0)		1396 (28.3)		227 (25.4)		
Alcohol use ^f (0.4)									<0.001
Abstinent with no history of unhealthy use	2514 (43.3)		257 (44.0)		2095 (42.6)		419 (47.1)		
Moderate use	2262 (38.9)		186 (31.9)		2006 (40.8)		256 (28.8)		
Unhealthy use (history or current)	1032 (17.8)		141 (24.1)		817 (16.6)		215 (24.2)		
Coffee consumption, in cups per day (1.3)									<0.001
<3	4034 (70.0)		434 (75.2)		3299 (67.6)		735 (83.8)		
≥3	1725 (30.0)		143 (24.8)		1583 (32.4)		142 (16.2)		
Cannabis use (1.8)									<0.001
Never	3971 (69.3)		408 (71.6)		3317 (68.3)		654 (75.0)		
Former	1113 (19.4)		94 (16.5)		977 (20.1)		136 (15.6)		
Current	645 (11.3)		68 (11.9)		563 (11.6)		82 (9.4)		
Tobacco smoking, in pack-years ^g (4.9)									0.044
0	2229 (40.2)		212 (38.6)		1855 (39.5)		374 (44.2)		
1–9	804 (14.5)		58 (10.6)		700 (14.9)		104 (12.3)		
10–19	904 (16.3)		67 (12.2)		774 (16.5)		130 (15.3)		
≥20	1610 (29.0)		212 (38.6)		1371 (29.2)		239 (28.2)		

(Continues)

TABLE 1 | (Continued)

Variables (% missing)	Study population (N = 5833)		Deaths (N = 584)		Participants without advanced liver fibrosis ^a at baseline (N = 4941)		Participants with advanced liver fibrosis ^a at baseline (N = 892)		p ^b
	N (%) or Median [IQR]	N (%) or Median [IQR]	N (%) or Median [IQR]	N (%) or Median [IQR]	N (%) or Median [IQR]	N (%) or Median [IQR]	N (%) or Median [IQR]		
Body mass index ^{c,h} (0.6)									0.009
Normal weight or underweight	3049 (52.6)		275 (47.4)		2620 (53.4)		429 (48.3)		
Overweight	1945 (33.5)		196 (33.5)		1630 (33.2)		315 (35.4)		
Obesity	804 (13.9)		111 (19.1)		659 (13.4)		145 (16.3)		
Diabetes (0.0)									<0.001
No	5023 (86.1)		432 (74.0)		4328 (87.6)		695 (77.9)		
Yes	810 (13.9)		152 (26.0)		613 (12.4)		197 (22.1)		
Treatment-naïve (0.2)									<0.001
No	3213 (55.2)		375 (64.4)		2613 (53.0)		600 (67.3)		
Yes	2608 (44.8)		207 (35.6)		2316 (47.0)		292 (32.7)		
Time from HCV diagnosis to HCV cure, in years (2.2)	16.5 [9.6–22.1]		19.0 [11.4–24.4]		16.5 [9.6–22.2]		16.6 [10.1–21.5]		0.814

Abbreviations: HCV, hepatitis C virus; IQR, interquartile range; SVR24, 24-week sustained virologic response.

^aAdvanced liver fibrosis was defined as an FIB-4 index >3.25 [1, 2].

^bChi-squared test for categorical variables, and Kruskal–Wallis test for continuous variables.

^cThere were 12 participants from South America, 8 from North America, 2 from Central America, 26 from Russia and 5 from the Caribbean.

^d‘Living with a stable partner’ included living with one’s partner, having a spouse and being in a civil partnership.

^e‘Living in poverty’ was defined as a standard of living lower than the 2015 French poverty threshold (1015 euros per month). The standard of living was calculated as the disposable monthly income divided by the number of

consumption units in the household [3].

^fUnhealthy alcohol use was defined as >2 and >3 standard drinks per day for women and men, respectively, in accordance with the French National Authority for Health [4].

^gThe number of pack-years was obtained by multiplying the number of years the person had smoked by the average number of packs of cigarettes smoked per day.

^hBody mass index was categorised according to the WHO cut-offs: overweight: ≥25 and <30 kg/m²; obesity: ≥30 kg/m² [5].

TABLE 2 | Factors associated with post-HCV cure advanced liver fibrosis, stratified on liver fibrosis status at baseline, mixed-effects logistic regression model, multivariable analyses.

	Participants with advanced liver fibrosis at baseline ^a (N= 827)			Participants without advanced liver fibrosis at baseline ^a (N= 4108)		
	aOR [95% CI]	<i>p</i>	PAF or PF ^b (%)	aOR [95% CI]	<i>p</i>	PAF or PF ^b (%)
Sex						
Male (ref.)				1		
Female				0.58 [0.40–0.85]	0.005	13.0 ^a
Age, in years					<0.001	
<50 (ref.)				1		
50–59				1.17 [0.68–2.01]	0.570	3.1
60–69				1.37 [0.77–2.42]	0.283	4.3
≥70				5.45 [3.01–9.85]	<0.001	20.2
Place of birth					0.034	
France (ref.)				1		
Europe (excluding France), North America, Latin America, Australia				1.75 [0.92–3.33]	0.088	2.5
North Africa, Middle East				0.85 [0.47–1.53]	0.592	1.0 ^a
Sub-Saharan Africa, Caribbean				2.74 [1.30–5.79]	0.008	3.3
Asia				0.90 [0.25–3.20]	0.875	0.1 ^a
Living with a stable partner ^c						
No (ref.)						
Yes						
Living in poverty ^d						
No (ref.)				1		
Yes				1.64 [1.09–2.47]	0.017	8.6
Educational level						
<Upper secondary school certificate						
≥Upper secondary school certificate (ref.)						
Past or current drug injection						
No (ref.)						
Yes						
Alcohol use ^e					0.001	
Abstinent with no history of unhealthy use (ref.)				1		
Moderate use				0.84 [0.56–1.26]	0.397	3.4 ^a
Unhealthy use (history or current)				2.09 [1.29–3.37]	0.003	8.6

(Continues)

TABLE 2 | (Continued)

	Participants with advanced liver fibrosis at baseline ^a (N = 827)			Participants without advanced liver fibrosis at baseline ^a (N = 4108)		
	aOR [95% CI]	<i>p</i>	PAF or PF ^b (%)	aOR [95% CI]	<i>p</i>	PAF or PF ^b (%)
Coffee consumption, in cups per day						
<3 (ref.)						
≥3						
Cannabis use						
Never (ref.)						
Former						
Current						
Tobacco smoking, in pack-years ^f						
0 (ref.)						
1–9						
10–19						
≥20						
Body mass index ^g						
Normal weight or underweight (ref.)						
Overweight						
Obesity						
Diabetes						
No (ref.)				1		
Yes				1.88 [1.20–3.97]	0.006	6.5
Treatment-naïve						
No	2.02 [1.12–3.65]	0.019	7.6			
Yes (ref.)	1					
Time from HCV diagnosis to HCV cure, in years						
Time since HCV cure, in years	0.75 [0.68–0.82]	<0.001	—	1.18 [1.10–1.28]	<0.001	—

Note: Bold values indicate global *p*-values for variables with more than two modalities.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; HCV, hepatitis C virus; PAF, population attributable fraction; PF, prevented fraction.

^aAdvanced liver fibrosis was defined as an FIB-4 index >3.25 [1, 2].

^bMarked values are PF (not PAF). The prevented fraction (PF) was computed as $PF = -PAF / (1 - PAF)$. PAF for continuous variables are not provided as it may be both statistically biased and highly variable [6].

^c‘Living with a stable partner’ included living with one’s partner, having a spouse and being in a civil partnership.

^d‘Living in poverty’ was defined as a standard of living lower than the 2015 French poverty threshold (1015 euros per month). The standard of living was calculated as the disposable monthly income divided by the number of consumption units in the household [3].

^eUnhealthy alcohol use was defined as >2 and >3 standard drinks per day for women and men, respectively, in accordance with the French National Authority for Health [4].

^fThe number of pack-years was obtained by multiplying the number of years the person had smoked by the average number of packs of cigarettes smoked per day.

^gBody mass index was categorised according to the WHO cut-offs: overweight: ≥25 and <30 kg/m²; obesity: ≥30 kg/m² [5].

use (PAF = 8.6% for both the latter). The *E*-value for the point estimate for living in poverty was 2.68 and 1.42 for the limit of the CI closest to null.

Results from the nonstratified analyses are provided in Table S3. Advanced liver fibrosis was associated with the

following socioeconomic and behavioural factors: being born in Europe (excluding France), North America, Latin America, Australia, not living with a stable partner, living in poverty, a lower educational level, unhealthy alcohol use (moderate use was protective compared with abstinence) and no elevated coffee consumption.

No selection bias related to missing data on the FIB-4 index was identified in the Heckman mixed-effects probit models (data not shown).

3.3 | Factors Associated With Post-HCV Cure All-Cause Mortality

The following socioeconomic and behavioural factors were associated with all-cause mortality after multivariable adjustment: not living with a stable partner (adjusted hazard ratio (aHR) [95% CI] 0.81 [0.68–0.98], $p=0.027$ for living with a stable partner), living in poverty (aHR [95% CI] 1.42 [1.17–1.72], $p<0.001$) and heavy tobacco smoking (aHR [95% CI] 1.65 [1.33–2.06], $p<0.001$; Table 3). The E-value for the point estimate of living in poverty was 2.20 and 1.63 for the limit of the CI closest to null. Male sex, being aged over 59, obesity, diabetes and advanced liver fibrosis were also associated with this outcome. The highest PAF (or PF) were observed, in decreasing order, for advanced liver fibrosis (PAF=28.9%), being aged over 70 years (PAF=20.5%), heavy tobacco smoking (≥ 20 pack-years, PAF=15.5%), female sex (PF=14.9%), living with a stable partner (PF=11.0%) and living in poverty (PAF=10.6%).

4 | Discussion

In this large national French cohort, we found that socioeconomic and behavioural factors weighed heavily on the risk of advanced liver fibrosis and all-cause mortality after HCV cure. Specifically, living in poverty was associated with both outcomes.

The relationship between socioeconomic deprivation and poor liver outcomes has already been documented [32–36]. For instance, in their meta-analysis, Lu et al. concluded that socioeconomic risk factors greatly impact hepatocellular carcinoma incidence [37]. In HCV populations in various countries, determinants such as neighbourhood poverty, lower educational level and language barriers, have been consistently linked to poorer HCV-related outcomes [38]. Our results on poverty and mortality are also consistent with previous findings in the general population [39–41].

After adjusting for behavioural factors, living in poverty was associated with both liver fibrosis and mortality. This might be partly explained by preexisting health problems acting as a barrier to employment and therefore causing both poverty and health issues. Another hypothesis is that a lack of disposable financial means impacts the health expenditure burden for people living in poverty and fosters inequality in the use of healthcare providers [42, 43]. More specifically, despite the low out-of-pocket payments for health care in France [44], people with the lowest disposable income may not have enough means to seek appropriate care. Although all our cohort participants were followed in hospital hepatology services, unequal access to care prior to their enrolment in the cohort may have had detrimental effects [45]. Furthermore, socioeconomic deprivation is likely to be associated with poorer diet [46, 47], a known risk factor for both liver fibrosis and mortality. In addition, people living in poverty are more likely to be exposed to the detrimental

effects of stress [48–50]. Finally, the protective effect of being in a relationship which we found on mortality, and the detrimental effect of social isolation, echo previous findings in the general population [51, 52].

Contrary to what was found in a Spanish study [53], in our study, people with a lower educational level (versus those with a higher level) who were cured of HCV through DAA did not have a higher postcure mortality risk. This may be because the effect of a lower educational level was captured by the living in poverty and behavioural variables [54]. The fact that the association between advanced liver fibrosis and lower educational level was only found in the unstratified analyses (which included more visits and more cases of advanced fibrosis) suggests that greater statistical power was needed to identify this association. Similarly, the protective effect of elevated coffee consumption on advanced liver fibrosis was highlighted in the unstratified analyses only. This effect was previously highlighted in meta-analyses in patients with nonalcoholic fatty liver disease [16, 55], alcoholic liver disease, hepatitis B virus [56] and HCV infection [57].

In participants with advanced liver fibrosis at the time of HCV cure, no socioeconomic or behavioural factors were associated with postcure advanced liver fibrosis. In terms of mortality, advanced liver fibrosis displayed the highest aHR and PAF. Our results therefore emphasise the prominent role of liver fibrosis prevention and management, as well as the importance of monitoring it post-HCV cure [55]. After adjusting for liver fibrosis, some socioeconomic and behavioural factors were still associated with our outcome.

In people without advanced liver fibrosis at the time of HCV cure, living in poverty and unhealthy alcohol use were as strongly associated (according to aOR) with postcure advanced liver fibrosis as diabetes, and all three variables had comparable PAF. The same was true for the mortality analyses in the whole study population. For mortality, heavy (≥ 20 pack-years) smoking was associated with a higher absolute PAF than for diabetes.

Tobacco and alcohol use can be readily targeted by prevention interventions, and HCV cure may represent a teachable moment to do so [56, 57]. However, because of sociodemographic characteristics, substance use pattern, comorbidities and tobacco-related beliefs, the implementation of effective tobacco treatment in this population is challenging and may require specific tailoring [58–60]. Our results therefore advocate integrated HCV care including substance use-related services [61], as previous results showed a favourable impact on alcohol-related outcomes in people living with HCV [62, 63]. In Australia, social workers identified support for access to substance and alcohol services as one of the needs of people attending HCV treatment centres [64].

While poverty cannot directly be addressed by medical staff, linkage with social workers could help patients to better deal with issues interlinked and related to it, such as poor housing conditions, asylum-seeking, difficulties in accessing financial support and social isolation [65]. All these factors may directly impact the continuum of care and health status. Better linkage with social workers could be integrated in comprehensive and/or community-based care systems [66–68].

TABLE 3 | Factors associated with post-HCV cure all-cause mortality, Cox proportional hazard model, univariable and multivariable analyses (ANRS CO22 Hepather cohort, $N = 5833$).

	Univariable analyses ($N = 5833$)		Multivariable analysis ($N = 5371$)		PAF or PF ^a (%)
	HR [95% CI]	<i>p</i>	aHR [95% CI]	<i>p</i>	
Sex					
Male (ref.)	1		1		
Female	0.72 [0.61–0.85]	<0.001	0.68 [0.56–0.84]	<0.001	14.9 ^a
Age, in years		<0.001		<0.001	
<50 (ref.)	1		1		
50–59	1.23 [0.93–1.63]	0.152	1.20 [0.88–1.63]	0.253	5.2
60–69	1.50 [1.12–2.00]	0.007	1.44 [1.04–1.98]	0.026	7.7
≥70	2.63 [1.98–3.49]	<0.001	2.75 [1.98–3.82]	<0.001	20.5
Place of birth		0.237			
France (ref.)	1				
Europe (excluding France), North America, Latin America, Australia	1.01 [0.73–1.38]	0.966			
North Africa, Middle East	1.18 [0.91–1.53]	0.207			
Sub-Saharan Africa, Caribbean	0.75 [0.50–1.15]	0.189			
Asia	0.64 [0.34–1.22]	0.174			
Living with a stable partner ^b					
No (ref.)	1		1		
Yes	0.77 [0.66–0.91]	0.002	0.81 [0.68–0.98]	0.027	11.0 ^a
Living in poverty ^c					
No (ref.)	1		1		
Yes	1.45 [1.22–1.72]	<0.001	1.42 [1.17–1.72]	<0.001	10.6
Educational level					
<Upper secondary school certificate	1.53 [1.29–1.82]	<0.001			
≥Upper secondary school certificate (ref.)	1				
Past or current drug injection					
No (ref.)	1				
Yes	0.94 [0.78–1.12]	0.477			
Alcohol use ^d		<0.001			
Abstinent with no history of unhealthy use (ref.)	1				
Moderate use	0.88 [0.73–1.06]	0.188			
Unhealthy use (history or current)	1.41 [1.15–1.73]	0.001			
Coffee consumption, in cups per day					
<3 (ref.)	1				
≥3	0.83 [0.69–1.00]	0.055			
Cannabis use		0.197			

(Continues)

TABLE 3 | (Continued)

	Univariable analyses (N = 5833)		Multivariable analysis (N = 5371)		PAF or PF ^a (%)
	HR [95% CI]	p	aHR [95% CI]	p	
Never (ref.)	1				
Former	0.84 [0.68–1.06]	0.138			
Current	1.11 [0.86–1.43]	0.441			
Tobacco smoking, in pack-years ^e		<0.001		<0.001	
0 (ref.)	1		1		
1–9	0.80 [0.60–1.06]	0.121	1.00 [0.74–1.36]	0.983	0.0
10–19	0.79 [0.60–1.03]	0.086	1.02 [0.76–1.37]	0.895	0.2
≥20	1.43 [1.18–1.73]	<0.001	1.65 [1.33–2.06]	<0.001	15.5
Body mass index ^f		0.003		0.046	
Normal weight or underweight (ref.)	1		1		
Overweight	1.05 [0.88–1.27]	0.568	0.97 [0.79–1.18]	0.744	1.1 ^a
Obesity	1.47 [1.18–1.83]	0.001	1.31 [1.03–1.67]	0.030	4.5
Diabetes					
No (ref.)	1		1		
Yes	2.08 [1.73–2.51]	<0.001	1.55 [1.25–1.91]	<0.001	9.2
Treatment-naïve					
No	1.22 [1.03–1.45]	0.021			
Yes (ref.)	1				
Time from HCV diagnosis to HCV cure, in years	1.01 [1.00–1.02]	0.150			
Advanced liver fibrosis ^g					
No (ref.)	1		1		
Yes	3.66 [3.09–4.32]	<0.001	3.24 [2.69–3.90]	<0.001	28.9

Note: Bold values indicate global *p*-values for variables with more than two modalities.

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; HCV, hepatitis C virus; PAF, population attributable fraction; PF, prevented fraction.

^aMarked values are PF (not PAF). The prevented fraction (PF) was computed as $PF = -PAF / (1 - PAF)$.

^b‘Living with a stable partner’ included living with one’s partner, having a spouse and being in a civil partnership.

^c‘Living in poverty’ was defined as a standard of living lower than the 2015 French poverty threshold (1015 euros per month). The standard of living was calculated as the disposable monthly income divided by the number of consumption units in the household [3].

^dUnhealthy alcohol use was defined as >2 and >3 standard drinks per day for women and men, respectively, in accordance with the French National Authority for Health [4].

^eThe number of pack-years was obtained by multiplying the number of years the person had smoked by the average number of packs of cigarettes smoked per day.

^fBody mass index was categorised according to the WHO cut-offs: overweight: ≥25 and <30 kg/m²; obesity: ≥30 kg/m² [5].

^gAdvanced liver fibrosis was defined as an FIB-4 index >3.25 [1, 2].

Our results indicate that the social inequalities in health outcomes among people with HCV exist even after HCV cure. Markers of deteriorated health status at the SVR24 visit were strongly associated with our outcomes (i.e., previous treatment failure for the advanced liver fibrosis outcome and advanced liver fibrosis for the mortality outcome). We can hypothesise that poverty, and more broadly, socioeconomic deprivation, leads to late presentation for HCV care (defined as presenting with advanced liver fibrosis at first consultation for HCV care [69])—a risk factor for mortality [70]—through unequal access to care [45]. The same is true for diabetes [71]. Although multiple adjustment partly took into account pretreatment effects

of socioeconomic deprivation, potential posttreatment effects cannot be excluded (as indicated by the presence of the living in poverty variable in our multivariable results).

We showed that screening for substance use is essential for patients with HCV, even after HCV cure, as tobacco and alcohol use were associated with detrimental outcomes. Clinicians should be made aware that HCV cure may provide a suitable opportunity to encourage individuals to reduce or stop addictive behaviours [56, 72]. Screening for socioeconomic deprivation by medical staff may be of clinical usefulness if linkage to social services is implemented.

The main strength of our study is its large sample size. Moreover, the fact that we collected a range of demographic, socioeconomic, behavioural and clinical factors is very valuable, as clinical factors alone fail to capture major health determinants. In terms of limitations, some behavioural factors, such as dietary habits and physical activity level [73] were not collected. While we can suppose that the factors we did investigate partially captured their effects [46, 74, 75], confounding effects of unmeasured variables cannot be ruled out, as indicated by the E-values we provided. Moreover, data on behavioural factors were only collected at cohort inclusion, and may not have reflected participants' long-term habits. Participants in Hepather were, by design, already in care, and had already agreed to medical follow-up in hospital centres. Our results may therefore not be generalisable to individuals who were cured with DAA through other care pathways, such as community-based programmes. Postcure follow-up in the Hepather cohort lasted only 4.25 years in median. The lack of linkage with mortality registry may have led to some deaths being missed, especially patients lost to follow-up. The characteristics of individuals lost to follow-up differed slightly (in magnitude) from others, which may have introduced bias. For instance, the former were slightly more likely to have ever smoked, which may have led to an underestimation of the tobacco-related mortality risks. Additionally, people with no follow-up data available after SVR24 were excluded from the analyses, which may have introduced selection bias within the Hepather population. Future studies should consider liver- and nonliver-related mortality separately. This could provide a more precise picture of the mechanisms involved in the socioeconomic deprivation–mortality relationship which we observed.

5 | Conclusion

We highlighted the major role of poverty and behavioural factors in advanced liver fibrosis and all-cause mortality in patients cured of HCV. Encouraging healthy behaviours after successful DAA treatment and linkage to social support services could help limit morbidity and increase survival in this population.

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Ethics Statement

The study protocol was designed in accordance with the Declaration of Helsinki and with French law for biomedical research. It was approved by the Comité de Protection des Personnes (CPP) Ile de France 3 Ethics Committee (Paris, France) and the French Regulatory Authority (ANSM).

Consent

Participate: Written informed consent was obtained from each cohort participant before enrolment. Publication: The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data are available upon request to tanguibarre@inserm.fr, due to privacy/ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

APPENDIX

ANRS/AFEF Hepather Study Group

Investigators

Laurent Alric, Delphine Bonnet, Virginie Payssan-Sicart, Chloe Pomes (CHU Purpan, Toulouse, France), Fabien Zoulim, Marianne Maynard,

Roxane Bai, Lucie Hucault, François Bailly (Hospices Civils de Lyon, Lyon, France), François Raffi, Eric Billaud, David Boutoille, Maeva Lefebvre, Elisabeth André-Garnier (Hôpital Hôtel-Dieu, Nantes, France), Paul Cales, Isabelle Hubert, Adrien Lannes, Françoise Lunel, Jérôme Boursier (CHU Angers, Angers, France), Tarik Asselah, Nathalie Boyer, Nathalie Giully, Corinne Castelnau, Giovanna Scoazec (Hôpital Beaujon, Clichy, France), Stanislas Pol, Hélène Fontaine, Emilie Rousseaud, Anaïs Vallet-Pichard, Philippe Sogni (Hôpital Cochin, Paris, France), Victor de Ledinghen, Juliette Foucher, Jean-Baptiste Hiriart, Jancell M’Bouyou, Marie Irlès-Depé (Hôpital Haut-Lévêque, Pessac, Bordeaux, France), Marc Bourlière, Si Nafa Si Ahmed, Valérie Oules (Hôpital Saint Joseph, Marseille, France), Albert Tran, Rodolphe Anty, Eve Gelsi, Régine Truchi (CHU de Nice, Nice, France), Dominique Thabut, Saloua Hammeche, Joseph Moussali (Hôpital de la Pitié Salpêtrière, Paris, France), Xavier Causse, Barbara De Dieuleveult, Brahim Ouarani, Damien Labarrière (CHR La Source, Orléans, France), Nathalie Ganne, Véronique Grando-Lemaire, Pierre Nahon, Séverine Brulé, Betul ULKER (Hôpital Jean Verdier, Bondy, France), Dominique Guyader, Caroline Jezequel, Audrey Brener, Anne Laligant, Aline Rabot, Isabelle Renard (CHU Rennes, Rennes, France), François Habersetzer, Thomas F. Baumert, Michel Doffoel, Catherine Mutter, Pauline Simo-Noumbissie, Esma Razi (Hôpitaux Universitaires de Strasbourg, Strasbourg, France), Jean-Pierre Bronowicki, Hélène Barraud, Mouni Bensenane, Abdelbasset Nani, Sarah Hassani-Nani, Marie-Albertine Bernard (CHU de Nancy, Nancy, France), Georges-Philippe Pageaux, Dominique Larrey, Magda Meszaros (Hôpital Saint Eloi, Montpellier, France), Sophie Metivier, Christophe Bureau, Thibault Morales, Jean Marie Peron, Marie Angèle Robic (CHU Purpan, Toulouse, France), Thomas Decaens, Marine Faure, Bruno Froissart, Marie-Noëlle Hilleret, Jean-Pierre Zarski (CHU de Grenoble, Grenoble, France), Ghassan Riachi, Odile Gorla, Fatima Paris, Hélène Montialoux (CHU Charles Nicolle, Rouen, France), Vincent Leroy, Giuliana Amadeo, Anne Varaut, Mélanie Simoes, Rachida Amzal (Hôpital Henri Mondor, Créteil, France), Olivier Chazouillères, Tony Andreani, Bénédicte Angoulevant, Azeline Chevance, Lawrence Serfaty (Hôpital Saint-Antoine, Paris, France), Didier Samuel, Teresa Antonini, Audrey Coilly, Jean-Charles Duclos Vallée, Mariagrazia Tateo (Hôpital Paul Brousse, Villejuif, France), Armand Abergel, Maud Reymond, Chanteranne Brigitte, Buchard Benjamin, Léon Muti (Hôpital Estaing, Clermont-Ferrand, France), Claire Geist, Guillaume Conroy, Raphaëlle Riffault (Centre Hospitalier Régional, Metz, France), Isabelle Rosa, Camille Barrault, Laurent Costes, Hervé Hagège (Centre Hospitalier Intercommunal, Créteil, France), Véronique Loustaud-Ratti, Paul Carrier, Maryline Debette-Gratien (CHU Limoges, Limoges, France), Philippe Mathurin, Guillaume Lassailly, Elise Lemaitre, Valérie Canva, Sébastien Dharancy, Alexandre Louvet (CHRU Claude Huriez, Lille, France), Anne Minello, Marianne Latournerie, Marc Bardou, Thomas Mouillot (Dijon University Hospital, Dijon, France), Louis D’Alteroche, Didier Barbereau, Charlotte Nicolas, Laure Elkrief, Anaïs Jaillais (CHU Trousseau, 37044 Tours, France), Jérôme Gournay, Caroline Chevalier, Isabelle Archambeaud, Sarah Habes (CHU de Nantes, Nantes, France), Isabelle Portal (CHU Timone, Marseille, France), Moana Gelu-Simeon, Eric Saillard, Marie-Josée Lafrance, Lucie Catherine (CHU de Pointe-à-Pitre, Pointe-à-Pitre, Guadeloupe).

Methodology and Coordinating Centre

Fabrice Carrat (coordinator), Frederic Chau, Céline Dorival, Isabelle Goderel, Clovis Lusivika-Nzinga, Jonathan Bellet, Jessica Chaneteng, Grégory Pannetier, Jérôme Nicol, Florian Sebal, Rafika Bekhti (Sorbonne University & INSERM U1136—IPLESP, Paris, France).

Sponsor

Carole Cagnot, Anaïs Boston, Laura Nailler, Guillaume Le Meut (INSERM-ANRS-MIE, Paris, France), Alpha Diallo (Pharmacovigilance coordinator), Ventzislava Petrov-Sanchez (coordinator).

Scientific Committee

Voting Members

Marc Bourlière (Hôpital St Joseph, Marseille), Jérôme Boursier (CHU Angers, Angers, France), Fabrice Carrat (Scientific Coordinator, Hôpital Saint-Antoine, Paris, France), Patrizia Carrieri (INSERM U912, Marseille, France), Elisabeth Delarocque-Astagneau (Inserm UMR1181, Paris), Victor De Ledinghen (Hôpital Haut-Lévêque, Pessac, Bordeaux, France), Céline Dorival (UPMC & INSERM U1136, Paris, France), Hélène Fontaine (Hôpital Cochin, Paris, France), Slim Fourati (Hôpital Henri Mondor, Créteil, France), Chantal Housset (Inserm UMR-S938 1 IFR65, Paris), Dominique Larrey (Hôpital Saint Eloi, Montpellier, France), Pierre Nahon (Hôpital Jean Verdier, Bondy, France), Georges-Philippe Pageaux (Hôpital Saint Eloi, Montpellier, France), Ventzislava Petrov-Sanchez (ANRS, Paris, France), Stanislas Pol (Principal Investigator, Hôpital Cochin, Paris, France), Mathias Bruyand (Agence Nationale de Santé Publique, Saint Maurice, France), Linda Wittkop (ISPED-INSERM U897, Bordeaux, France), Fabien Zoulim (Hospices Civils de Lyon, Lyon, France), Jessica Zucman-Rossi (Inserm U674/1162, Paris).

NonVoting Members

Marianne L'hennaff (ARCAT-TRT-5-CHV, France), Michèle Sizorn (SOS hépatites, France); one representative from the INSERM-ANRS-MIE Pharmacovigilance team, Paris, France (Anaïs Boston, Alpha Diallo), Carole Cagnot (INSERM-ANRS-MIE, Paris, France), one member from Inserm Transfert, Paris, France (Alice Bousselet, Mireille Caralp) and one representative from each pharmaceutical company (MSD, Gilead, Abbvie).