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# Hepatitis C virus cure from direct-acting antivirals and mortality: Are people with and without a history of injection drug use in the same boat? (ANRS CO22 Hepather cohort)

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## Abstract

**Introduction:** The risk of mortality in people with a history of injection drug use (PHID) is high, as is the prevalence of hepatitis C virus (HCV) infection. Although direct-acting antivirals (DAA) are effective in this population in terms of sustained virological response, it is not known whether PHID benefit as much as people with no history of injection drug use from DAA-related HCV cure in terms of reduced all-cause mortality.

**Methods:** Using Cox proportional hazards models based on the ANRS CO22 Hepather cohort data ( $n = 9735$ ), we identified factors associated with all-cause

Members of the ANRS/AFEF Hepather Study group are listed in Appendix.

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mortality among HCV-infected people. We tested for interaction effects between drug injection status, HCV cure and other explanatory variables.

**Results:** DAA-related HCV cure was associated with a 66% (adjusted hazard ratio [95% confidence interval]: 0.34 [0.29–0.39]) lower risk of all-cause mortality, irrespective of drug injection status. Detrimental effects of unhealthy alcohol use on mortality were identified in PHID only.

**Discussion and Conclusions.:** DAA-related HCV cure led to comparable benefits in terms of reduced mortality in PHID and people with no history of injection drug use. Policies and strategies to enhance DAA uptake among PHID are needed to lower mortality in this population.

Clinical trial registration details: [ClinicalTrials.gov](https://clinicaltrials.gov): NCT01953458.

#### KEYWORDS

direct-acting antivirals, drug injection, France, hepatitis C virus, mortality

#### Key Points

- The risk of mortality in people with a history of injection drug use (PHID) is high.
- Hepatitis C virus prevalence is high in PHID.
- Drug injection status had no effect on hepatitis C virus cure effect on mortality.
- Detrimental effects of alcohol use on mortality were identified in PHID only.

## 1 | INTRODUCTION

Compared with the general population, people with a history of injection drug use (PHID) have a higher risk of death, although mortality rates vary according to context [1, 2]. For instance, in their meta-analysis, Larney et al. estimated the all-cause standardised mortality ratio of people using extramedical opioids at 10 [2]. The prevalence of the hepatitis C virus (HCV) infection, one factor for higher death risk, may be as high as 60% among PHID [3, 4]. Moreover, drug-related deaths represent a large proportion of mortality in active PHID in industrialised countries [5–7]. Opioid substitution therapy can reduce mortality rates in this population [6, 8] by lowering the risks of HCV transmission and opioid overdose [9].

Although direct-acting antivirals (DAA) for HCV treatment have been associated with a sharp decrease in both liver disease prevalence and all-cause mortality in PHID [10, 11], no data exist comparing the impact of DAA-related HCV cure on mortality between PHID and people with no history of injection drug use. Testing the existence of such a putative difference may help orient and assess future public health strategies regarding DAA scale-up.

We tested the hypothesis that DAA-related HCV cure has a similar impact on all-cause mortality in both populations using data from the French ANRS C022 Hepather cohort.

## 2 | METHODS

### 2.1 | Participants

The ANRS CO22 Hepather is a French national, multicentre, prospective, observational cohort of adult patients infected with hepatitis B virus and/or HCV (NCT01953458). HCV-positive patients were defined as patients with positive HCV-RNA or positive anti-HCV antibodies, according to data retrieved from medical records. Patients with HIV co-infection and those who were currently receiving treatment (or had completed treatment within the last 3 months) were not included in the cohort (exclusion criteria). Implemented in 2012, enrolment in the cohort study took place in 32 hospital centres throughout France with a 10-year follow-up. Participants were recruited consecutively during a medical visit at their centre. The cohort design is described extensively elsewhere [12].

Patients included in the cohort received DAA treatment after enrolment, if eligible.

First- and second-generation DAA have been implemented throughout France since 2011 and 2014, respectively. Access was initially restricted (i.e., based on liver disease severity) until 2017 [13], when universal access was granted.

Written informed consent was obtained from each cohort participant before enrolment. The protocol was designed in accordance with the Declaration of Helsinki and the French law for biomedical research. It was approved by the Comité de Protection des Personnes Ile

de France 3 Ethics Committee (Paris, France) and the French Regulatory Authority.

## 2.2 | Study population

The present study population comprised patients with chronic HCV infection at enrolment in Hepather. We excluded patients with hepatitis B virus co-infection, persons whose drug injection status was unavailable, and individuals whose only available visit was the enrolment visit.

## 2.3 | Data collection

At cohort enrolment, physicians led a face-to-face interview and completed a structured questionnaire according to participating patients' answers. Anthropological measurements, urine and blood samples were also taken.

The questionnaire collected clinical, socio-demographic and behavioural data including sex, age, country of birth, average monthly household income, the number of adults and children in the household, HCV transmission mode, lifetime tobacco use, and past and current alcohol consumption (number of standard drinks per day). Data on past and current drug injection as well as past and current opioid substitution therapy were also collected.

Detailed clinical (including body height, weight and comorbidities) and biological data were gathered during the enrolment visit using an electronic case-report form. Clinical data were updated annually during follow-up visits and in spontaneous reports for particular events (e.g., decompensated cirrhosis, DAA treatment initiation). HCV treatments were retrieved from medical records. Vital status was ascertained through medical records at clinical centres. No linkage with mortality registry was done.

## 2.4 | Study outcome and study period

The study outcome was the time between enrolment and all-cause death. The study period started at the enrolment visit and ended at the latest news date (i.e., the most recent available follow-up visit or death). Participants were censored at 9 years of follow-up.

## 2.5 | Explanatory variables

The main explanatory variable was drug injection status (i.e., PHID vs. people with no history of injection drug use), measured at the enrolment visit. Participants who self-reported past and/or active drug injection, past

and/or current opioid substitution therapy, or infection with HCV through injection drug use were defined as PHID. Active drug injection was defined as self-reporting 'current' injection drug use. Those statuses were not externally or objectively further validated. Participants who reported none of these elements were defined as people with no history of injection drug use.

Other explanatory variables tested were: sex, age, place of birth, living in poverty, alcohol use, tobacco use (the number of pack-years), body mass index (categorised according to World Health Organization cut-offs [14]), diabetes, advanced liver fibrosis (FIB-4 score >3.25 [15]), hypertension and HCV cure. HCV cure was defined as an undetectable viral load at 24 weeks after the end of HCV treatment. Living in poverty was defined as a standard of living lower than the 2015 French poverty threshold (1015 euros per month) [16]. 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 [17]. All variables were measured at enrolment, except for HCV cure, which was time-varying.

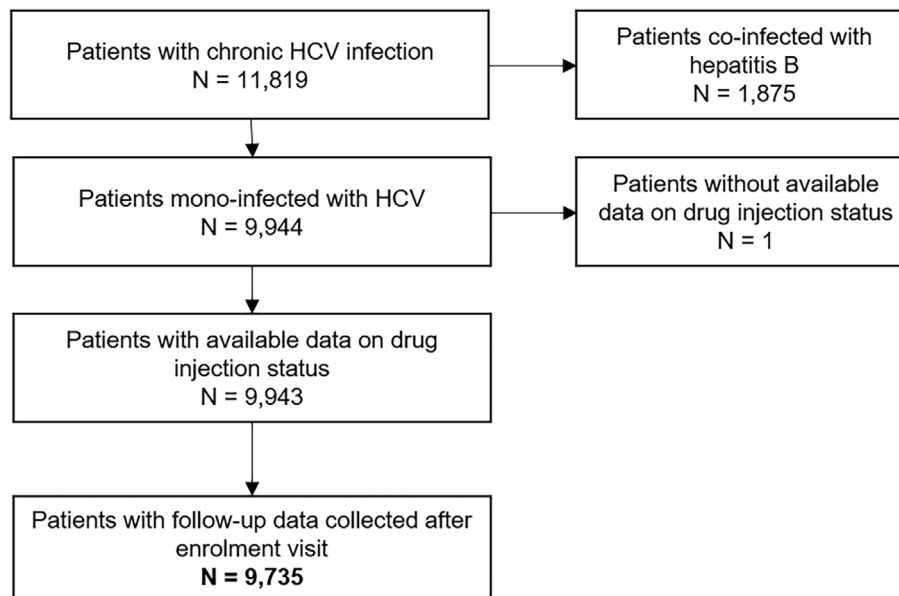
## 2.6 | Statistical analyses

The characteristics of the two sub-populations (PHID and people with no history of injection drug use) were compared using Pearson's chi-squared test or Student *t* test.

Mortality rates were computed, separately in PHID and people with no history of injection drug use, as the number of deaths occurring during the study period divided by the total number of person-years of follow-up. Mortality rates were compared between the two sub-populations using Fisher's exact test for incidence rates differences. Standardised mortality ratios (SMR) were then computed for each sub-population as the ratio between the mortality rate and the age- and sex-specific mortality rate in the general population (2019 data [18]).

Cox proportional hazards models were then used to identify factors associated with all-cause mortality. We tested for interaction between drug injection status and HCV cure (according to our hypothesis), as well as interactions between drug injection status and sex, age and alcohol use. As women who inject drugs face specific challenges [19], their benefits of HCV cure may differ from those observed for their men counterparts. We may expect age to interact with drug injection status, as younger PHID may engage in more risky behaviours [20]. Lastly, alcohol-related risks are more common and exacerbated in PHID [21].

Variables with a *p*-value <0.20 (Wald test) in the univariable analyses were eligible for the multivariable analysis. Interaction terms were tested using bivariate analyses with the same *p*-value criterion. A backward selection



**FIGURE 1** Flow-chart of the study population (ANRS CO22 Hephather cohort). HCV, hepatitis C virus.

procedure was used to build the final multivariable model, based on a  $p$ -value  $< 0.05$  for statistical significance. Proportional-hazard assumption was graphically verified using log–log survivor plots adjusted for the other variables in the final model, using the *stphplot* Stata command.

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

### 3 | RESULTS

#### 3.1 | Study population characteristics and mortality rates

The study population comprised 9735 cohort participants (Figure 1), of whom 53.9% were male (Table 1) and 29.0% were PHID (including 82 active injectors, or 0.8% of the whole study population). Median (interquartile range) age at enrolment was 56 (49–64) years. It was 51 (47–56) in PHID and 59 (51–68) in people with no history of injection drug use ( $p < 0.001$ ). Median (interquartile range) follow-up time was 6.10 (4.16–7.31) years, corresponding to 54,672.83 person-years. During the study period, of the 1121 deaths which occurred, 279 (24.9%) were among PHID (including seven active injectors) (Table 2).

At the last available visit, 1375 (14.1%) participants were not HCV cured. Among them, 52.1% did not receive any treatment. Among the 659 participants already treated but not cured, 321 received second generation DAA, 44 received first generation DAA, and 294 received interferon-based treatments without DAA. There was no difference between PHID and people with no history of injection drug use in terms of having received first,

second generation DAA or other treatments ( $p = 0.063$ , data not shown).

The crude mortality rate (95% confidence interval) was significantly higher in people with no history of injection drug use than in PHID (2.16 [2.02–2.31] and 1.79 [1.59–2.01] per 100 person-years, respectively,  $p = 0.006$ ). The SMR was lower in people with no history of injection drug use than in PHID (1.81 [1.69–1.94] and 3.30 [2.94–3.71], respectively). The same was true when considering only post-cure period (Table 2).

#### 3.2 | Factors associated with all-cause mortality in people with and without a history of injection drug use

Table 3 provides the factors associated with all-cause mortality in the study population. After multivariable adjustment, HCV cure was associated with a 66% (adjusted hazard ratio [95% confidence interval] 0.34 [0.29–0.39],  $p < 0.001$ ) lower risk of mortality. Drug injection status was not significantly associated with mortality risk (0.71 [0.40–1.27],  $p = 0.250$ ), after accounting for its interaction effects. Interaction terms with drug injection status were statistically significant for both age and alcohol use, but not for HCV cure. The adjusted hazard ratio of being  $\geq 60$  years was 1.94 [1.36–2.78] ( $p < 0.001$ ) in people with no history of injection drug use. It was not statistically significant in PHID (0.80 [0.52–1.25],  $p = 0.334$ ). In people with no history of injection drug use, moderate alcohol use was associated with a lower risk of mortality. Past or current unhealthy use was not associated with mortality (Table 2). In PHID, moderate

**TABLE 1** Study sample characteristics according to drug injection status (ANRS CO22 Heparther cohort,  $N = 9735$ ).

Characteristics <sup>a</sup> (% of missing values)	Study population ( $N = 9735$ )		People with no history of injection drug use ( $N = 6913$ )		PHID ( $N = 2822$ ) $N$ (%) or median [IQR]	$p$ -value <sup>b</sup>	Person-years
	$N$ (%) or median [IQR]	$N$ (%) or median [IQR]	$N$ (%) or median [IQR]	$N$ (%) or median [IQR]			
Sex (0)							
Male	5250 (53.9)	3150 (45.6)	2100 (74.4)	28,871.2	<0.001	28,871.2	
Female	4485 (46.1)	3763 (54.4)	722 (25.6)	25,801.6	<0.001	25,801.6	
Age (0), years							
Age (0), years	56 [49–64]	59 [51–68]	51 [47–56]		<0.001		
<50	2450 (25.2)	1395 (20.2)	1055 (37.4)	8639.9	<0.001	8639.9	
50–59	3645 (37.4)	2141 (31.0)	1504 (53.3)	18,882.0		18,882.0	
≥60	3640 (37.4)	3377 (48.8)	263 (9.3)	27,150.9		27,150.9	
Place of birth <sup>c</sup> (0.2)							
France	7158 (73.6)	4742 (68.7)	2416 (85.6)	40,197.1	<0.001	40,197.1	
Europe (outside France)/Latin and North America/Australia	744 (7.7)	570 (8.3)	174 (6.2)	3986.7		3986.7	
North Africa and Middle East	928 (9.5)	778 (11.3)	150 (5.3)	5062.2		5062.2	
Sub-Saharan Africa/Caribbean	622 (6.4)	590 (8.6)	32 (1.1)	3561.2		3561.2	
Asia	267 (2.7)	218 (3.2)	49 (1.7)	1388.2		1388.2	
Living in poverty <sup>d</sup> (3.4)							
No	6521 (69.3)	4794 (71.8)	1727 (63.2)	37,200.8	<0.001	37,200.8	
Yes	2884 (30.7)	1880 (28.2)	1004 (36.8)	15,682.0		15,682.0	
Alcohol use <sup>e</sup> (0.5)							
Abstinent without past unhealthy use	4148 (42.8)	3561 (51.7)	587 (21.0)	23,621.3	<0.001	23,621.3	
Moderate use	3792 (39.1)	2607 (37.8)	1185 (42.4)	21,546.1		21,546.1	
Past or current unhealthy use	1746 (18.0)	724 (10.5)	1022 (36.6)	9237.9		9237.9	
Tobacco use <sup>f</sup> (pack-years) (5.3)							
0	3685 (40.0)	3539 (53.5)	146 (5.6)	21,246.8	<0.001	21,246.8	
1–10	1554 (16.9)	1074 (16.2)	480 (18.4)	8766.8		8766.8	
11–20	1534 (16.6)	794 (12.0)	740 (28.4)	8700.2		8700.2	
>20	2448 (26.5)	1209 (18.3)	1239 (47.6)	13,179.7		13,179.7	
Body mass index <sup>g</sup> (0.8)							
Normal	4907 (50.8)	3315 (48.4)	1592 (56.8)	27,544.8	<0.001	27,544.8	
Underweight	319 (3.3)	180 (2.6)	139 (5.0)	1677.4		1677.4	

TABLE 1 (Continued)

Characteristics <sup>a</sup> (% of missing values)	Study population (N = 9735) N (%) or median [IQR]	People with no history of injection drug use (N = 6913) N (%) or median [IQR]	PHID (N = 2822) N (%) or median [IQR]	p-value <sup>b</sup>	Person-years
Overweight	3152 (32.6)	2340 (34.1)	812 (29.0)		17,897.9
Obesity	1276 (13.2)	1018 (14.9)	258 (9.2)		7141.7
Diabetes (0)					
No	8449 (86.8)	5859 (84.8)	2590 (91.8)	<0.001	47,623.7
Yes	1285 (13.2)	1053 (15.2)	232 (8.2)		7047.3
Advanced liver fibrosis <sup>b</sup> (6.5)					
No	6732 (74.0)	4717 (72.9)	2015 (76.6)	<0.001	38,349.9
Yes	2367 (26.0)	1750 (27.1)	617 (23.4)		12611.9
Hypertension (0.1)					
No	6874 (70.7)	4493 (65.0)	2381 (84.4)	<0.001	38,840.2
Yes	2854 (29.3)	2414 (35.0)	440 (15.6)		15,807.3
HCV cure (0)					
No	1375 (14.1)	960 (13.9)	415 (14.7)	0.462	14,679.0
Yes by first generation DAA and/or interferon	81 (0.8)	55 (0.8)	26 (0.9)		1213.4
Yes by second generation DAA	8279 (85.1)	5898 (85.3)	2381 (84.4)		38,780.4
HCV cure (0)					
No	1375 (14.1)	960 (13.9)	415 (14.7)	0.292	14,679.0
Yes	8360 (85.9)	5953 (86.1)	2407 (85.3)		39,993.8

Abbreviations: DAA, direct-acting antivirals; HCV, hepatitis C virus; IQR, interquartile range; PHID, people with a history of injection drug use.

<sup>a</sup>Characteristics are given for cohort enrolment, except for HCV cure (time-varying variable), which was provided at the last available visit.

<sup>b</sup>Pearson's chi-squared test or Student *t* test.

<sup>c</sup>The category 'Europe and America' included participants from Europe (excluding France), South America (N = 20), North America (N = 32), Central America (N = 2) and Russia (N = 45). The category 'Sub-Saharan Africa' included participants from the Caribbean (N = 10).

<sup>d</sup>Living in poverty was defined as a standard of living lower than the 2015 French poverty threshold (1015 euros per month) [16].

<sup>e</sup>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 [17].

<sup>f</sup>The 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.

<sup>g</sup>Body mass index was categorised according to World Health Organization cut-offs: overweight: ≥25 and <30 kg/m<sup>2</sup>; obesity: ≥30 kg/m<sup>2</sup> [14].

<sup>h</sup>Advanced liver fibrosis was defined as an FIB-4 score >3.25 [15].

TABLE 2 Mortality rates and standardised mortality ratios according to drug injection status (ANRS CO22 Hepather cohort).

Characteristics <sup>a</sup>	Deaths (N = 1121) N (%)	People with no history of injection drug use (N = 703)		PHID (N = 242)		People with no history of injection drug use (N = 842)		PHID (N = 279) Standardised mortality ratios [95% CI]
		Mortality rates per 100 person-years [95% CI]	Mortality rates per 100 person-years [95% CI]	Mortality rates per 100 person-years [95% CI]	Mortality rates per 100 person-years [95% CI]	Standardised mortality ratios [95% CI]	Standardised mortality ratios [95% CI]	
Overall		2.16 [2.02–2.31]	1.79 [1.59–2.01]	0.006	1.81 [1.69–1.94]	3.30 [2.94–3.71]		
Sex								
Male	717 (64.0)	2.73 [2.50–2.99]	2.11 [1.86–2.39]	0.001	2.01 [1.84–2.20]	3.40 [3.00–3.86]		
Female	404 (36.0)	1.69 [1.53–1.88]	0.89 [0.65–1.24]	<0.001	1.60 [1.45–1.78]	2.77 [2.01–3.83]		
Age, years								
<50	91 (8.1)	0.72 [0.53–0.99]	1.64 [1.25–2.16]	<0.001	8.10 [5.94–11.04]	15.28 [11.62–20.11]		
50–59	314 (28.0)	1.50 [1.28–1.75]	1.86 [1.59–2.17]	0.062	4.98 [4.24–5.83]	5.06 [4.34–5.90]		
≥60	716 (63.9)	2.78 [2.58–3.01]	1.74 [1.37–2.21]	<0.001	1.51 [1.40–1.63]	1.34 [1.05–1.71]		
Place of birth <sup>c</sup>								
France	829 (74.1)	2.20 [2.03–2.38]	1.73 [1.52–1.97]	0.002	1.76 [1.63–1.91]	3.23 [2.85–3.68]		
Europe (outside France)/Latin and North America/Australia	87 (7.8)	2.29 [1.81–2.89]	1.84 [1.14–2.96]	0.502	1.92 [1.52–2.43]	3.54 [2.20–5.69]		
North Africa and Middle East	140 (12.5)	2.79 [2.33–3.34]	2.66 [1.75–4.04]	0.948	2.14 [1.78–2.56]	3.80 [2.50–5.77]		
Sub-Saharan Africa/Caribbean	44 (3.9)	1.19 [0.87–1.62]	2.14 [0.80–5.70]	0.398	1.55 [1.14–2.12]	3.96 [1.49–10.54]		
Asia	19 (1.7)	1.36 [0.84–2.23]	1.39 [0.45–4.32]	1.000	1.71 [1.05–2.79]	3.50 [1.13–10.85]		
Living in poverty <sup>d</sup>								
No	699 (64.7)	2.04 [1.87–2.21]	1.44 [1.22–1.70]	<0.001	1.60 [1.47–1.74]	2.51 [2.13–2.96]		
Yes	381 (35.3)	2.43 [2.15–2.75]	2.43 [2.04–2.88]	1.000	2.46 [2.17–2.78]	5.00 [4.21–5.95]		
Alcohol use <sup>e</sup>								
Absinent without past unhealthy use	499 (44.6)	2.29 [2.09–2.51]	1.08 [0.78–1.49]	<0.001	1.81 [1.65–1.99]	2.00 [1.45–2.76]		
Moderate use	341 (30.5)	1.64 [1.45–1.86]	1.45 [1.19–1.77]	0.335	1.47 [1.30–1.66]	2.70 [2.21–3.30]		
Past or current unhealthy use	278 (24.9)	3.52 [2.97–4.17]	2.65 [2.25–3.12]	0.022	3.15 [2.66–3.73]	4.84 [4.11–5.70]		
Tobacco use <sup>f</sup> , pack-years								
0	404 (38.6)	1.92 [1.74–2.12]	1.43 [0.81–2.52]	0.380	1.48 [1.34–1.63]	2.25 [1.28–3.96]		
1–10	133 (12.7)	1.64 [1.35–1.99]	1.24 [0.88–1.74]	0.188	1.72 [1.41–2.09]	2.48 [1.76–3.49]		
11–20	140 (13.4)	1.79 [1.44–2.23]	1.42 [1.11–1.83]	0.204	2.04 [1.64–2.55]	2.94 [2.29–3.78]		
>20	369 (35.3)	3.51 [3.08–3.99]	2.12 [1.80–2.50]	<0.001	2.78 [2.44–3.16]	3.63 [3.08–4.28]		
Body mass index <sup>g</sup>								
Normal	501 (45.2)	1.95 [1.76–2.16]	1.54 [1.30–1.82]	0.020	1.66 [1.49–1.84]	2.88 [2.44–3.41]		
Underweight	44 (4.0)	2.72 [1.85–4.00]	2.49 [1.57–3.95]	0.896	2.82 [1.92–4.13]	5.43 [3.42–8.62]		
Overweight	373 (33.6)	2.15 [1.92–2.42]	1.89 [1.53–2.33]	0.318	1.71 [1.52–1.92]	3.29 [2.66–4.06]		
Obesity	191 (17.2)	2.68 [2.29–3.14]	2.64 [1.91–3.66]	1.000	2.36 [2.01–2.76]	5.15 [3.71–7.14]		



TABLE 2 (Continued)

Characteristics <sup>a</sup>	Deaths (N = 1121) N (%)	People with no history of injection drug use (N = 703)		People with no history of injection drug use (N = 842)		PHID (N = 242) Mortality rates per 100 person- years [95% CI]	p-value <sup>b</sup>	PHID (N = 279) Standardised mortality ratios [95% CI]	
		Mortality rates per 100 person-years [95% CI]	Mortality rates per 100 person- years [95% CI]	Standardised mortality ratios [95% CI]	Standardised mortality ratios [95% CI]				
Diabetes									
No	840 (74.9)	1.81 [1.67–1.96]	1.67 [1.47–1.89]	1.59 [1.47–1.72]	0.316	3.14 [2.77–3.56]		3.14 [2.77–3.56]	
Yes	281 (25.1)	4.19 [3.69–4.75]	3.10 [2.27–4.22]	2.78 [2.45–3.16]	0.084	4.76 [3.49–6.49]		4.76 [3.49–6.49]	
Advanced liver fibrosis <sup>b</sup>									
No	454 (43.2)	1.25 [1.12–1.39]	1.03 [0.86–1.23]	1.24 [1.12–1.38]	0.079	2.00 [1.66–2.39]		2.00 [1.66–2.39]	
Yes	598 (56.8)	4.84 [4.41–5.31]	4.47 [3.80–5.25]	2.73 [2.49–3.00]	0.427	7.19 [6.11–8.46]		7.19 [6.11–8.46]	
Hypertension									
No	612 (54.6)	1.56 [1.42–1.72]	1.60 [1.40–1.83]	1.71 [1.55–1.88]	0.792	3.14 [2.75–3.60]		3.14 [2.75–3.60]	
Yes	508 (45.4)	3.28 [2.99–3.61]	2.80 [2.21–3.56]	1.91 [1.74–2.10]	0.247	3.92 [3.09–4.98]		3.92 [3.09–4.98]	
HCV cure									
No	429 (38.3)	3.10 [2.78–3.46]	2.49 [2.06–3.01]	5.10 [4.57–5.69]	0.053	11.77 [9.73–14.24]		11.77 [9.73–14.24]	
Yes by first generation DAA and/or interferon	7 (0.6)	0.70 [0.32–1.57]	0.28 [0.04–1.97]	2.27 [1.02–5.04]	0.669	1.59 [0.22–11.31]		1.59 [0.22–11.31]	
Yes by second generation DAA	685 (61.1)	1.85 [1.69–2.01]	1.56 [1.35–1.81]	1.29 [1.18–1.40]	0.061	2.30 [1.98–2.67]		2.30 [1.98–2.67]	
HCV cure									
No	429 (38.3)	3.10 [2.78–3.46]	2.49 [2.06–3.01]	5.10 [4.57–5.69]	0.053	11.77 [9.73–14.24]		11.77 [9.73–14.24]	
Yes	692 (61.7)	1.81 [1.66–1.98]	1.52 [1.31–1.77]	1.29 [1.19–1.41]	0.049	2.29 [1.97–2.66]		2.29 [1.97–2.66]	

Abbreviations: CI, confidence interval; DAA, direct-acting antivirals; HCV, hepatitis C virus; PHID, people with a history of injection drug use.

<sup>a</sup>Characteristics are given at cohort enrolment, except for HCV cure (time-varying variable), which was provided at the last available visit.<sup>b</sup>Fisher's exact test for incidence rates difference.<sup>c</sup>The category 'Europe and America' included participants from Europe (excluding France), South America (N = 32), North America (N = 20), Central America (N = 2) and Russia (N = 45). The category 'Sub-Saharan Africa' included participants from the Caribbean (N = 10).<sup>d</sup>Living in poverty was defined as a standard of living lower than the 2015 French poverty threshold (1015 euros per month) [16].<sup>e</sup>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 [17].<sup>f</sup>The 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.<sup>g</sup>Body mass index was categorised according to World Health Organization cut-offs: overweight: ≥25 and <30 kg/m<sup>2</sup>; obesity: ≥30 kg/m<sup>2</sup> [14].<sup>h</sup>Advanced liver fibrosis was defined as an FIB-4 score >3.25 [15].

**TABLE 3** Factors associated with all-cause mortality, univariable and multivariable analyses (Cox proportional hazards models, ANRS CO22 Hepather cohort,  $N = 9735$ ).

Explanatory variables	Univariable analyses ( $N = 9735$ )		Interactions adjusted for principal effects		Multivariable analysis ( $N = 8287$ )	
	HR [95% CI]	<i>p</i> -value	aHR [95% CI]	<i>p</i> -value	aHR [95% CI]	<i>p</i> -value
Drug injection status						
People with no history of injection drug use (ref.)	1				1	
PHID	0.83 [0.72–0.95]	0.008			0.71 [0.40–1.27]	0.250
Sex						
Male (ref.)	1				1	
Female	0.63 [0.56–0.71]	<0.001			0.58 [0.50–0.67]	<0.001
Sex*PHID interaction						
Male (ref.)			1			
Female			0.69 [0.47–1.00]	0.047		
Age, years <sup>a</sup>						
<50 (ref.)	1	<0.001			1	<0.001
50–59	1.53 [1.22–1.94]	<0.001			1.42 [0.97–2.07]	0.071
≥60	2.33 [1.87–2.90]	<0.001			1.94 [1.36–2.78]	<0.001
Age*PHID interaction						
<50 (ref.)			1	<0.001	1	<0.001
50–59			0.52 [0.33–0.84]	0.007	0.81 [0.48–1.36]	0.428
≥60			0.25 [0.15–0.41]	<0.001	0.41 [0.24–0.72]	0.002
Place of birth <sup>b</sup>						
France (ref.)	1	<0.001			1	<b>0.002</b>
Europe (outside France)/Latin and North America/Australia	1.07 [0.86–1.34]	0.514			0.87 [0.67–1.11]	0.261
North Africa and Middle East	1.36 [1.13–1.62]	0.001			0.87 [0.70–1.09]	0.221
Sub-Saharan Africa/Caribbean	0.60 [0.44–0.81]	0.001			0.54 [0.38–0.76]	>0.001
Asia	0.68 [0.43–1.07]	0.094			0.54 [0.31–0.95]	0.034
Living in poverty <sup>c</sup>						
No (ref.)	1				1	
Yes	1.30 [1.15–1.48]	<0.001			1.29 [1.11–1.50]	0.001
Alcohol use <sup>d</sup>						
Abstinent without past unhealthy use (ref.)	1	<0.001			1	<0.001
Moderate use	0.76 [0.66–0.87]	<0.001			0.69 [0.58–0.83]	>0.001
Past or current unhealthy use	1.44 [1.25–1.67]	<0.001			0.94 [0.74–1.19]	0.581
Alcohol use*PHID interaction						
Abstinent without past unhealthy use (ref.)			1	<b>0.011</b>	1	<b>0.010</b>
Moderate use			1.87 [1.24–2.82]	0.003	1.99 [1.27–3.11]	0.003

TABLE 3 (Continued)

Explanatory variables	Univariable analyses (N = 9735)		Interactions adjusted for principal effects		Multivariable analysis (N = 8287)	
	HR [95% CI]	p-value	aHR [95% CI]	p-value	aHR [95% CI]	p-value
Past or current unhealthy use			1.59 [1.06–2.40]	0.026	1.69 [1.06–2.69]	0.026
Tobacco use <sup>e</sup> , pack-years						
0 (ref.)	1	<0.001			1	<0.001
1–10	0.80 [0.66–0.98]	0.029			1.00 [0.80–1.25]	0.991
11–20	0.85 [0.70–1.03]	0.101			1.03 [0.82–1.29]	0.804
>20	1.49 [1.30–1.72]	<0.001			1.53 [1.27–1.84]	<0.001
Body mass index <sup>f</sup>						
Normal (ref.)	1	<0.001			1	<b>0.016</b>
Underweight	1.46 [1.06–1.99]	0.019			1.57 [1.09–2.26]	0.015
Overweight	1.14 [1.00–1.30]	0.054			0.92 [0.79–1.07]	0.297
Obesity	1.47 [1.24–1.73]	<0.001			1.12 [0.93–1.36]	0.233
Diabetes						
No (ref.)	1				1	
Yes	2.26 [1.98–2.59]	<0.001			1.37 [1.15–1.62]	<0.001
Advanced liver fibrosis <sup>g</sup>						
No (ref.)	1				1	
Yes	4.03 [3.57–4.55]	<0.001			3.71 [3.21–4.29]	<0.001
Hypertension						
No (ref.)	1				1	
Yes	2.04 [1.81–2.29]	<0.001			1.65 [1.42–1.92]	<0.001
HCV cure <sup>a</sup>						
No (ref.)	1				1	
Yes	0.44 [0.39–0.50]	<0.001			0.34 [0.29–0.39]	<0.001
HCV cure*PHID interaction						
No (ref.)			1			
Yes			1.08 [0.82–1.43]	0.567		

Note: P-values in bold are global p-values.

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; HCV, hepatitis C virus; PHID, people with a history of injection drug use.

<sup>a</sup>All explanatory variables are fixed, except for age and HCV cure, which were time-varying variables.

<sup>b</sup>The category 'Europe and America' included participants from Europe (outside France), South America (N = 34), North America (N = 20), Central America (N = 2), and Russia (N = 47). The category 'Sub-Saharan Africa' included participants from the Caribbean (N = 11).

<sup>c</sup>Living in poverty was defined as a standard of living lower than the 2015 French poverty threshold (1015 euros per month) [16].

<sup>d</sup>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 [17].

<sup>e</sup>The 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.

<sup>f</sup>Body mass index was categorised according to World Health Organization cut-offs: overweight:  $\geq 25$  and  $< 30$  kg/m<sup>2</sup>; obesity:  $\geq 30$  kg/m<sup>2</sup> [14].

<sup>g</sup>Advanced liver fibrosis was defined as a FIB-4 score  $> 3.25$  [15].

alcohol use was not associated with the study outcome, while unhealthy use was (1.58 [1.06–2.37],  $p = 0.026$ ).

## 4 | DISCUSSION

In this study, DAA-related HCV cure was associated with a 66% lower risk in all-cause mortality, irrespective of drug injection status. This result shows that expanded access to DAA resulted in an equitable reduction in mortality for PHID, who nevertheless still had a higher SMR than people with no history of injection drug use.

Furthermore, this result suggests that the decrease in HCV-related mortality—and therefore in infectious disease-related mortality overall—among PHID could be strengthened by adequately scaling up DAA [11, 22, 23]. Currently, too many barriers exist [24–26] to this scale-up, yet hope lies in innovative multilevel interventions and outreach strategies that have proven efficient in reaching and engaging PHID in HCV testing and prevention [27–31]. It has been shown that multidisciplinary, people-centred strategies improves HCV linkage to care and adherence to treatment in a variety of settings [32]. For instance, providing HCV treatment in primary care rather than in hospital facilities may increase treatment uptake and cure rates [33], and receiving treatment at a peer-led needle and syringe program was estimated as acceptable by people who inject drugs [34].

While PHID equally benefited from DAA-related HCV cure in terms of reduced mortality, past or current alcohol use prevalence was three times higher among PHID than people with no history of injection drug use; moreover, its effect was only significant among the former. Unhealthy alcohol use is a risk factor for liver fibrosis and cirrhosis, which may lead to liver-related death. As advanced liver fibrosis is a major risk factor for mortality among HCV-infected people [11, 35] (adjusted hazard ratio = 3.71 in our study sample), we may expect unhealthy alcohol use to increase all-cause and liver-related mortality in this population [36, 37]. The protective effect of moderate alcohol use on mortality we found in people with no history of injection drug use has previously been found in some general population studies [38–40]. This effect, which is more present in the context of cardiovascular mortality [41], may be the result of confounding effects of health behaviours [42, 43] not present in PHID. As treatment of potential alcohol use disorder may benefit patients, substance use services should include comprehensive care for HCV-infected people [44, 45].

The mortality rates higher in our study population than what would have been expected in the general

population is in line with a recent population-based cohort study. Hamill et al. found SMRs between 2.96 and 13.61 (according to the setting and liver disease severity) among their sample of DAA-cured participants [35]. They also found a protective effect of being a woman in some sub-populations and, while differently assessed, detrimental effects of recent unhealthy alcohol use and past or recent substance use (in most of their sub-populations).

Our study has several strengths. First, it had a large sample size. Second, we collected data on demographic, clinical and socio-behavioural variables. Third, we were able to compare PHID with people with no history of injection drug use in the same context. One limitation is that only a small number of participants were active injectors; accordingly, replication of our results is needed in samples with more active injectors, as drug-related mortality may be important in this sub-population. We did not make the distinction between first and second generation DAA in our survival analyses because of the low number of cases of first generation DAA-related cure. Future analyses exclusively including second generation DAA treatment era should be performed to inform on the generalisability of our findings. Another limitation is that deaths that were not reported in the cohort context (i.e., for participants lost to follow-up) were missed. As we may expect PHID to be lost to follow-up more frequently than people with no history of injection drug use, this may have led to underestimation of mortality among PHID. Moreover, causes of deaths were not available. Therefore, we were not able to separately estimate for instance COVID-, liver- or drug-related mortality, and highlight specific patterns of mortality in each sub-population.

To conclude, DAA-related HCV cure led to comparable benefits in terms of mortality reduction in PHID and people with no history of injection drug use. Policies and strategies to enhance DAA uptake among PHID are needed to lower mortality in this population.

### AUTHOR CONTRIBUTIONS

Conceptualisation: Tangui Barré, Marc Bourlière, Camelia Protopopescu, Fabrice Carrat and Patrizia Carrieri. Methodology: Clémence Ramier and Camelia Protopopescu. Formal analysis: Clémence Ramier. Investigation: Marc Bourlière, Lucia Parlati, Carole Cagnot, Celine Dorival, Jérôme Nicol, Fabien Zoulim and Fabrice Carrat. Writing—original draft: Tangui Barré. Writing—review and editing: all authors.

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### CONFLICT OF INTEREST STATEMENT

No conflict declared.

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## APPENDIX

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